ORIGINAL ARTICLES

Sleep Disorders in Patients on a Kidney Transplant Waiting List

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OBJECTIVE: To evaluate the prevalence of sleep disorders in patients awaiting kidney transplants compared to a control group.

PATIENTS AND METHODS: We carried out an observational study of 23 patients on a kidney transplant waiting list in comparison with 20 healthy volunteers matched for age, sex, and body mass index (BMI). Overnight polysomnography was performed and a diagnosis of sleep apnea-hypopnea syndrome (SAHS) established when the apnea-hypopnea index (AHI) was 10 or higher.

RESULTS: Eighty-two percent of the patients awaiting kidney transplants (16 men and 7 women with a mean [SD] age of 51 [15] years and a mean BMI of 25 [3.8] kg/m^2) had some type of sleep disorder. The most frequent disorders were SAHS (48%) and insomnia and periodic limb movement disorder (30%). Patients showed poorer sleep efficiency compared to the control group (75.4% vs 87.8%; *P*=.01) and a lower percentage of slow-wave and rapid eye movement sleep (24.5% vs 40%; *P*=.001). Those with sleep-disordered breathing had a higher AHI (17.7 vs 3.6; *P*=.001) and oxygen desaturation index (31.5 compared to 8.2; *P*=.001).

CONCLUSIONS: Sleep disorders are common in patients awaiting kidney transplants. Such patients show reduced quantity and quality of sleep compared to controls and a significantly elevated number of respiratory events that may affect morbidity and mortality.

Key words: *Apnea-hypopnea index. Oxygen desaturation index. Chronic renal failure. Kidney transplantation. Sleep disorders. Sleep-disordered breathing.*

Trastornos del sueño en pacientes en lista de espera de trasplante renal

OBJETIVO: Valorar la prevalencia de los trastornos del sueño en pacientes en lista de espera de trasplante renal, comparados con un grupo control.

PACIENTES Y MÉTODOS: Se ha realizado un estudio observacional en 23 pacientes en lista de espera para trasplante renal, cuyos resultados se compararon con los de 20 personas sanas que accedieron voluntariamente a participar en él. Se emparejaron por edad, sexo e índice de masa corporal. Se efectuó una polisomnografía de noche completa y el diagnóstico de síndrome de apneas-hipopneas durante el sueño se estableció cuando el índice de apneas-hipopneas era como mínimo de 10.

RESULTADOS: Los pacientes en lista de espera para trasplante renal (16 varones y 7 mujeres; edad media ± desviación estándar: 51 ± 15 años; índice de masa corporal: 25 ± 3,8 kg/m^2) presentaron en un 82% de los casos algún trastorno del sueño. Los más frecuentes fueron el síndrome de apneas-hipopneas durante el sueño (48%) e insomnio y síndrome de movimiento periódico de piernas (30%). Los pacientes presentaron, respecto al grupo control, una menor eficiencia del sueño (el 75,4 frente al 87,8%; p = 0,01) y un menor porcentaje de sueño de ondas lentas y REM (un 24,5 frente a un 40%; p = 0,001), mientras que los trastornos respiratorios del sueño mostraron un mayor índice de apneas-hipopneas (17,7 frente a 3,6; p = 0,001) e índice de desaturación (31,5 frente a 8,2; p = 0,001).

CONCLUSIONES: Los trastornos del sueño son frecuentes en pacientes en lista de espera para trasplante renal, quienes, respecto al grupo control, tienen una menor cantidad y calidad del sueño, con un número significativamente elevado de eventos respiratorios, que pueden influir en la morbimortalidad.

Palabras clave: *Índice de apneas-hipopneas del sueño. Índice de desaturación. Insuficiencia renal crónica. Trasplante renal. Trastornos del sueño. Trastornos respiratorios del sueño.*

Introduction

Sleep apnea-hypopnea syndrome (SAHS) is associated in the general population with increased cardiovascular morbidity and mortality.[1,2] As cardiovascular disease is the most frequent cause of death among patients in hemodyalisis,[3,4] SAHS may play a role in the continued high mortality rate among such patients.

Recent studies have described the importance of nocturnal hypoxemia associated with SAHS and the severity of coronary arteriopathy in patients with chronic renal failure (CRF) on hemodialysis.[5,6] Several studies have been conducted to determine a possible association between CRF and SAHS. While its mechanism has not been clearly determined, it has been suggested that

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uremic toxins may be involved in the appearance of SAHS.[7-9] This hypothesis has been supported by several reports of improvement in sleep-disordered breathing once kidney function has been successfully restored following transplantation.[10-12] Such observations have increased interest in sleep disorders in patients with CRF.[13]

Studies show considerable disparity concerning the prevalence of SAHS in patients with CRF, with rates ranging from 14.5% to 80%.[7,9,14] This is probably due to differences in research designs, as many of the studies were carried out in selected populations with small samples and with diagnostic techniques other than polysomnography (PSG), the gold-standard diagnostic test for sleep disorders.[15] There have been even fewer studies of populations with distinct clinical characteristics, such as patients awaiting kidney transplants,[16] in whom quality of sleep and possible sleep-disordered breathing have not been adequately evaluated. The aim of our study, then, was to evaluate quality of sleep and respiratory disorders using overnight PSG in a group of patients on a kidney transplant waiting list compared to sleep quality in a control group of healthy subjects.

Patients and Methods

Study Subjects

The study was carried out in the Sleep-Disordered Breathing Unit of the Hospital Universitario Reina Sofía in Cordoba, Spain. All patients on a hemodialysis program in a satellite unit of our hospital's nephrology department who were on a kidney transplant waiting list were considered eligible. All had hemoglobin levels higher than 11 g/L and hemodialysis was adequate (equilibrated Kt/V>1.3). Hemodialysis using a bicarbonate dialysis fluid was performed 3 times a week in sessions lasting between 3.5 and 5 hours. Blood flow rates varied between 300 and 400 mL/min and the dialysis fluid flow rates ranged from 500 to 800 mL/min.

The control group consisted of volunteers who were either hospital staff members or relatives of the patients studied. Part of this cohort belonged to a previous study.[12] None had any known respiratory disease, kidney disease, or sleep disorder. In all cases, the results of the physical examination were normal and waking arterial oxygen saturation measured by pulse oximetry (SpO_2) was at least 95%. The mean (SD) creatinine concentration was 0.92 (0.23) mg/dL and creatinine clearance was 123 (9.70) mL/min.

A medical history, based on a standardized questionnaire to determine sleeping habits and detect possible sleep disorders, was taken of all participants, who also underwent a complete physical examination. Daytime sleepiness was assessed using a validated Spanish version of the Epworth scale,[17] which evaluates the propensity to fall asleep in certain everyday situations.[18] A score higher than 11 indicates a significant degree of sleepiness.[19] SpO_2 was determined with the patient awake, after a rest period of at least 10 minutes.

The study protocol was approved by the hospital ethics committee.

Sleep Study

None of the participants had any acute disease at the time PSG was performed. In the case of patients, PSG was performed the night before their midweek hemodialysis session. The method used for the PSG has been described previously.[12] In summary, signals were recorded from 2 electroencephalographic channels (C4/A1 and C3/A2), electrooculogram and electromyogram (submental and anterior tibialis). Thermal sensors were used to monitor airflow. We also recorded snoring, chest and abdominal effort using impedance bands, electrocardiogram, and SpO_2 by digital pulse oximetry (Pulxox-7, Minolta, Osaka, Japan). All the recordings were analyzed manually according to the recommendations of Rechtschaffen and Kales.[20]

Apnea was defined as the absence of oronasal airflow lasting at least 10 seconds, and hypopnea as a clearly discernible reduction of more than 30% and less than 90% in the airflow signal accompanied by a decrease in SpO_2 of at least 3% and/or arousal.[15] An arousal was defined as a sudden change in electroencephalogram frequencies, including θ and α waves and frequencies higher than 16 Hz, lasting more than 3 seconds.[21] The apnea-hypopnea index (AHI) was calculated by dividing the total number of apneas and hypopneas by the number of hours of sleep.

During PSG we analyzed sleep efficiency, sleep latency in minutes, nocturnal awakenings, rapid eye movement (REM) and non-REM sleep stages, and arousal and periodic limb movement indexes. Sleep efficiency was expressed as the ratio of total sleep time to time in bed, expressed as a percentage. As an indicator of the stability and quality of sleep, we determined the sum of percentage of sleep time spent in slow wave sleep (stages III and IV) and the percentage of sleep time spent in REM sleep. The following respiratory variables were analyzed: waking SpO_2 and lowest SpO_2 during sleep, number of decreases in SpO_2 of 3% or more per hour of sleep, percentage of sleep time with SpO_2 less than 90%, percentage of sleep time spent in apnea and hypopnea, and the number of apneas and hypopneas per hour of sleep.

AHI was the main variable used in the study, and we considered a score of 10 or more to be diagnostic of SAHS. For the diagnosis of restless legs syndrome, the currently accepted criteria were used.[22] A diagnosis of periodic limb movement disorder was established when the patient presented insomnia or daytime sleepiness and had a periodic limb movement index of 15 or more per hour in PSG, provided the movements were not associated with respiratory events. A diagnosis of insomnia was established on the basis of a medical history suggestive of insomnia (poor quality or insufficient quantity of sleep perceived by the patient) and a PSG result showing sleep latency longer than 30 minutes and sleep efficiency less than 60%. A diagnosis of primary snoring was made if snoring was the main symptom recorded and if PSG did not show 5 or more respiratory events.

Statistical Analysis

Qualitative variables were expressed as absolute numbers and percentages, and quantitative variables as means (SD). Qualitative variables were analyzed using the χ^2 test. Means were compared using the nonparametric Mann-Whitney *U* test, 95% confidence intervals were calculated, and statistical significance was set at $P<.05$. The statistical analysis was carried out using SPSS software, version 11.1 (SPSS Inc, Chicago, Illinois, USA).

Results

At the time of the study, 25 of the 60 patients (41%) enrolled in the hemodialysis program were on a kidney transplant waiting list. Of those, one refused to undergo PSG and another could not discontinue sleeping pills. The remaining 23 patients (92%) agreed to participate in the study.

Table 1 shows the characteristics of the 2 groups studied (patient and control). No between-group differences in

TABLE 1
Characteristics of the 2 Study Groups[a]

	Awaiting Kidney Transplants (n=23)	Control Group (n=20)	*P*
Age, y	51.1 (15.7)	52.4 (14.00)	NS
Sex			NS
Men	16	13	
Women	7	7	
BMI, kg/m^2	25.7 (3.86)	26.0 (4.03)	NS
Smokers	3 (13%)	4 (20%)	NS
Waking SpO_2, %	96.4 (2.04)	96.7 (1.86)	NS

Abbreviations: BMI, body mass index; NS, not significant; SpO_2, arterial oxygen saturation measured by pulse oximetry.
[a]Data are expressed as number of patients (%) or mean (SD).

TABLE 2
Comparison of Mean (SD) Values for the Main Variables of the Sleep Study in Patients Awaiting Kidney Transplants and in Healthy Controls

	Patients Awaiting Transplant (n=23)	Control Group (n=20)	*P*
Total sleep time, min	277.1 (76.16)	320.3 (48.31)	.035[a]
Latency, min	32 (29.45)	13 (14.42)	.048[a]
Sum of sleep stages III + IV + REM, %	24,5 (13.63)	40 (6.49)	.001[a]
Efficiency, %	75.4 (17.93)	87.8 (10.49)	.010[a]
Nocturnal awakenings, %	19.2 (13.25)	6.9 (7.40)	.001[a]
REM, %	8.9 (6.76)	17 (4.61)	.001[a]
Stage I, %	14.2 (12.84)	5.1 (2.51)	.003[a]
Stage II, %	61.2 (9.84)	54.8 (9.92)	.042[a]
Stage III, %	9.1 (6.40)	14 (5.46)	.012[a]
Stage IV, %	6.5 (5.92)	9 (3.66)	.250
Arousal index	33.6 (19.29)	10.5 (4.9)	.001[a]
PLM/h	33.6 (19.29)	8.5 (4.90)	.001[a]

Abbreviations: PLM, periodic limb movements; REM, rapid eye movement.
[a]Statistically significant (*P*<.05)

TABLE 3
Respiratory Events, Expressed as Means (SD), in Patients Awaiting Kidney Transplants Compared to Control Subjects

	Patients Awaiting Transplants (n=23)	Control Group (n=20)	*P*
AHI	17.7 (15.40)	3.6 (2.87)	.001[a]
Time in apnea, % of TST	6.1 (9.20)	0.2 (0.43)	.006[a]
Time in apnea or hypopnea, % of TST	7.9 (10.04)	1.4 (1.72)	.007[a]
ODI3	31.5 (26.74)	8.2 (6.52)	.001[a]
Minimum SpO_2, %	85 (8.02)	83 (13.87)	.490
T90, %	2 (4.28)	0.3 (0.65)	.076

Abbreviations: AHI, apnea-hypopnea index; ODI3, oxygen desaturations index, indicating number of decreases in arterial oxygen saturation of 3% or more, measured by pulse oximetry and expressed per hour of sleep; SpO_2, arterial oxygen saturation measured by pulse oximetry; T90, percentage of sleep time with SpO_2 less than 90%; TST, total sleep time.
[a]Statistically significant (*P*<.05)

age, sex, body mass index, smoking habit, or waking SpO_2 can be seen. The comparison of the sleep study variables between the 2 groups are shown in Table 2. Significant differences were found in all the values related to quality of sleep, except in the percentage of stage IV sleep. Sleep latency in the group of patients awaiting kidney transplants was 32 minutes and the percentage of time in bed corresponding to nocturnal awakenings was 19%. Significant differences were found for both of these variables, and sleep efficiency was significantly poorer in patients with CRF (P=.010). The sum of the percentages of deep sleep and REM sleep was also less in patients than in controls (24% compared to 40%; *P*=.0001). Finally, the arousal and periodic limb movement indexes (*P*=.0001) were significantly higher in the group with CRF.

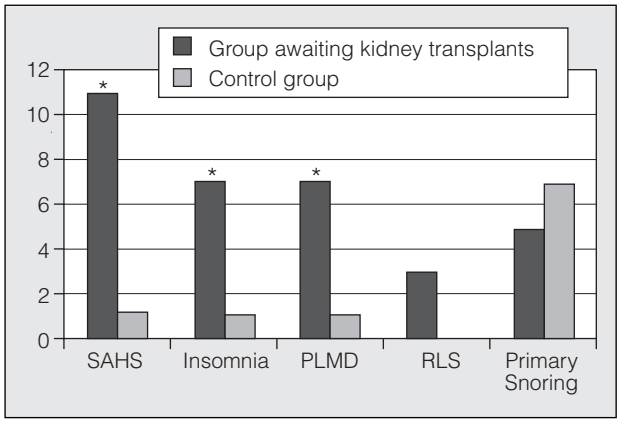

Figure. Diagnoses based on medical history and results of polysomnography in the 2 study groups. SAHS indicates sleep apnea-hypopnea syndrome; PLMD, periodic limb movement disorder; RLS, restless legs syndrome. *P<.05.

Table 3 shows the comparison of respiratory sleep disorders between the 2 groups. Patients awaiting kidney transplants had a higher AHI than controls (*P*=.001), as well as higher percentages of time in apnea (*P*=.006) and time in apnea or hypopnea (*P*=.007). The patient group had a significantly higher percentage of decreases in SpO_2 of 3% or more per hour of sleep (*P*=.001). A higher percentage of sleep time with SpO_2 less than 90% was also recorded for patients than control subjects, although the difference was not significant (*P*=.076).

The Figure shows the diagnoses established according to the results of PSG and symptoms. Significant differences were observed in the frequency of SAHS, insomnia, and periodic limb movement disorder. It must be emphasized that some participants presented more than a single sleep disorder and that 82% of the patients awaiting kidney transplants had some such disorder, most frequently SAHS (n=11; 48%), insomnia (n=7; 30%), periodic limb movement disorder (n=7; 30%), restless legs syndrome (n=3; 13%), and primary snoring (n=4; 21%).

Discussion

Our study, using the gold standard technique for sleep studies and with a high level of participation, showed a high prevalence of sleep disorders in patients on a kidney transplant waiting list. The most frequent disorders were SAHS, insomnia, and periodic leg movement disorder.

These disorders resulted in poor quality of sleep. An important finding was that the patients presented a significantly elevated number of respiratory events and episodes of nighttime hypoxemia. Such complications should be avoided in this population with a high rate of cardiovascular mortality.[3,4]

The prevalence of sleep disorders in patients with CRF is high.[7-9,12,23] In our study, 82% of such patients presented at least 1 sleep disorder. This high percentage is similar to that obtained in a cohort of patients in a hemodialysis program.[12] There were differences, however, compared to other groups, probably due to differences in study design.[9,16,23-25] Patients on a kidney transplant waiting list tend to be younger than those excluded from the list and also tend not to present severe comorbidity, such as liver disease, respiratory failure, or cardiovascular disease. This may have affected the results of our study.

Insomnia has been reported in 50% of patients on hemodialysis.[26] In our series, as many as 30% of patients were affected and, as is usual, insomnia was associated with other sleep disorders[25] The most frequent of these, after SAHS, was restless legs syndrome, diagnosed in 13% of patients. This is similar to the percentage found in other studies.[27-29]

Sleep-disordered breathing has been associated, as in our study, with CRF.[7-9,13] Patients on a kidney transplant waiting list had a mean AHI of 17.7 and a significantly elevated percentage of sleep time in apnea and in apnea or hypopnea. These data confirm the severity of sleep-disordered breathing in this population. Other findings also point to disease severity. Respiratory events had considerable repercussions on SpO_2, as 31 significant decreases in SpO_2 were observed per hour of sleep in our patients. This point is of great interest. Firstly, such episodes of hypoxemia-reoxygenation favor the production of free radicals, and this has been suggested as a possible mechanism of atherogenesis.[30-32] Furthermore, sudden decreases in nocturnal SpO_2 have been associated in the general population with increased morbidity and mortality due to vascular disease.[1,2,33] The effect that such desaturations may have on patients awaiting kidney transplants is unknown. We do know, however, that despite advances in hemodialysis and improved control of some cardiovascular risk factors, mortality due to vascular disease remains high. There must therefore be other risk factors that are not yet adequately accounted for. It is reasonable to hypothesize that the presence of sleep-disordered breathing may be one of these. Although this has not yet been fully elucidated, several recent studies support such a hypothesis.[5,6,34,35]

One of the mechanisms most frequently involved in the appearance of sleep-disordered breathing in patients with CRF is an increase in levels of uremic toxins.[7,8,9,13] Daily nocturnal hemodialysis has been seen to improve sleep-disordered breathing compared to conventional hemodyalisis.[36,37] Another mechanism that has been proposed to explain sleep-disordered breathing in these patients is inadequate central respiratory control due to altered chemoresponsiveness.[38]

In any event, while these aspects are being studied, special attention should be paid to symptoms such as snoring and apneas noticed by someone living with the patient. Such symptoms are frequently associated with SAHS both in the general population[39,40] and in patients with CRF.[12] Obviously, clinical suspicion will facilitate early diagnosis and adequate control of SAHS through the use of continuous positive airway pressure (CPAP) treatment.[15,41] However, while there is consensus regarding the indication of CPAP in the general population,[15,42] there is no such consensus regarding its use in patients with CRF, in whom adaptation to therapy is poor.[12,43] While this question is being settled, CPAP therapy should be considered for patients with cardiovascular comorbidity.[15,44]

It has been suggested that kidney transplantation can improve breathing during sleep.[10,11] In the 4 patients in our series studied before and after successful kidney transplants, we observed a decrease in the number of respiratory events and an improvement in parameters related to nocturnal SpO_2.[12] In addition to offering overall improvement, measured in terms of the patient's health and quality of life, kidney transplantation can correct sleep-related breathing disorders.

The present study, carried out on the total population of patients on a kidney transplant waiting list, provides further evidence of the prevalence and potential seriousness of sleep-disordered breathing. However, some limitations of the study should be borne in mind. Firstly, although 92% of the eligible population was included in the study, the number of patients was small. Nevertheless, it was sufficient to establish comparisons and obtain conclusive results. Secondly, the sensation of nonrestorative sleep in such patients may be due to multiple factors, and physical fatigue may be attributable to CRF itself. For this reason, we chose to use an AHI of 10 or higher to establish a diagnosis of SAHS, so as to avoid overdiagnosing SAHS by using the currently recommended cutoff point of 5.[15] Thirdly, the control group consisted of volunteers, although as these were selected from among health care workers and relatives of the patients studied and were people who showed a high level of collaboration and reliability, selection bias was unlikely.

In conclusion, sleep disorders, of which SAHS is the most common, are frequent in patients with CRF awaiting kidney transplants. Such patients show reduced quality and quantity of sleep and this in turn affects their quality of life. Furthermore, respiratory events and sudden episodes of nocturnal hypoxemia, which are numerous in such patients, may lead to increased morbidity and mortality. However, more studies are needed to show that proper diagnosis and treatment of SAHS can modify morbidity and mortality due to cardiovascular disease in this population.

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