Sleep-disordered breathing changes after kidney transplantation: a polysomnographic study

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Abstract

Background: Sleep disorders are common in patients with end-stage renal disease (ESRD) and are not improved by either conventional haemodialysis or peritoneal dialysis. Sleep-disordered breathing (SDB) is associated with cardiovascular disease and contributes to high mortality found in patients with ESRD. Cure of SDB after transplantation has been anecdotally reported.

Methods: Thirty-four non-diabetic patients with ESRD were studied, and clinical, laboratory test and polysomnographic features were determined and compared prior to and after transplantation and between groups with or without SDB, defined as having an apnoea–hypopnoea index (AHI) ≥5.

Results: An AHI ≥5 was present in nine patients (26.5%) prior to and seven (21%) after transplantation, and no significant reduction of mean AHI was found between study phases (5.3 ± 7.3 vs 3.1 ± 4.5; P > 0.05). Transplantation was associated with a significant improvement in sleep architecture.

Conclusions: Kidney transplantation is associated with an improvement in sleep architecture, but does not cure SDB in all patients.

Keywords: kidney transplantation; sleep-disordered breathing

Introduction

Cardiovascular disease is the leading cause of mortality and morbidity, both in patients with end-stage renal disease (ESRD) and in those after kidney transplantation [1].

Poor sleep is common in dialysis patients and is associated with lower quality of life [2], and this is an independent predictor of mortality [3]. Sleep-disordered breathing (SDB) is characterized by intermittent episodes of breathing cessation during sleep. The severity of SDB is measured by the apnoea–hypopnoea index (AHI), obtained by counting the total number of apnoeas and hypopnoeas during sleep and dividing that by the hours of sleep. An AHI >5 is considered pathological [4]. Although the prevalence of SDB in the general population is 2% to 4% [5], this percentage goes as high as 30% to 80% in patients with ESRD [6]. SDB has been associated with left ventricular hypertrophy [7], hypertension [8] and increased cardiovascular events [9] in patients with ESRD. The high prevalence of coronary disease, stroke and congestive heart failure in ESRD patients could be partially related to the high prevalence of SDB [10].

Although dialysis does not reduce the prevalence of sleep disorders in ESRD patients [11], previous case reports have described instances of SDB reversal after kidney transplantation [12,13]. Two longitudinal case series have shown discrepant results [14,15], and a single study suggested that the prevalence of SDB in transplant patients does not differ from that in the general population [16]. We conducted this study to further clarify the effects of kidney transplantation on SDB by analysing physical and biochemical parameters and objective measures of sleep disorders.

Subjects and methods

Patients on chronic haemodialysis thrice a week for at least 6 months and awaiting kidney transplantation were enrolled in the study. They were included regardless of sleep complaints. In order to exclude sleep disturbances not directly associated with renal dysfunction, patients with diabetes, pulmonary disease, evidenced by clinical, radiological and functional alterations and symptomatic heart failure were excluded. The Ethics Committee of the Federal University of São Paulo approved the protocol, and written informed consent was obtained from each participant. The study was conducted in accordance with the Declaration of Helsinki and with Brazilian National Ministry of Health Resolution CNS 196/96.

The patients underwent a polysomnographic evaluation at night after a haemodialysis session. All of them had to have their dry weight assessed to be included in the protocol. Prior to polysomnography, clinical examination was made, and weight, height and blood pressure (BP) were recorded, according to recommendations of the VII Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [17]. Body mass index (BMI = weight / square of height) was calculated according to World Health Organization classification [18]. Just after polysomnography, blood samples were taken for glucose, creatinine, urea, alkaline phosphatase, haematocrit, haemoglobin, intact parathormone (PTH), pH and bicarbonate. KvU index was calculated by the formula -log (R − 0.03) + [(4 − 3.5 × R) × (UF:W)], where UF is ultrafiltration volume (litre), W is weight (kilogram) after dialysis and R is the pre- and post-dialysis urea ratio. The glomerular filtration rate (GFR) was estimated using the equations described in the Modification of Diet in Renal Disease study [19]. All patients underwent a living
donor kidney transplantation. The same protocol was repeated in all patients 3 to 6 months after transplantation.

The polysomnography recording started at the patient’s usual bedtime and was carried out using a Polysmith Neurotronics Inc. System, with 14 channels distributed as follows: three for electroencephalography, two for electrocardiography, one for airflow, two for thoracic–abdominal movements, one for pulse oximetry, one for tracheal sound (snoring) and one for detection of body position. The system automatically analyses sleep stages using Rechtschaffen and Kales criteria [20] and arousals according to American Sleep Disorders Association criteria [21].

A physician, blinded to the protocol and well trained in polysomnography, re-analysed the computer-generated staging according to these criteria.

The normal values used for analysis of sleep variables were those proposed by Carskadon and Dement [22]. The respiratory events (apnoeas and hypopnoeas) were classified according to the American Academy of Sleep Medicine Task Force criteria [23].

The variables analysed during polysomnography were: sleep efficiency (ratio of total sleep time to total time spent in bed), sleep stages: 1, 2, 3, 4, rapid eye movement (REM) sleep and slow-wave sleep (stages 3 and 4) (percentage of total sleep time), REM sleep + slow-wave sleep, number of arousals per hour of sleep and apnoea/hypopnoea index (AHI).

We studied the prevalence of SDB (defined as AHI ≥5) and compared clinical, laboratory test and polysomnographic features prior to and after kidney transplantation. Differences in clinical and laboratory test features between groups with AHI ≥5 and AHI <5 were assessed in each study phase. In a separate analysis, we examined the effect of kidney transplantation on AHI in patients with and without SDB prior to transplantation.

Statistical analysis was performed using SPSS 15.0. Comparisons of groups with and without SDB were made with Student’s t-test. Paired t-tests were done to examine AHI changes in both groups with and without SDB prior to transplantation. Relationships between variables were analysed with Pearson’s correlation when both variables were numerical and normal or Spearman’s rank correlation when numerical variables were not normally distributed. Significance was accepted as a P-value <0.05.

### Results

Of the original sample of 46 patients, nine with diabetes, one with pulmonary disease and one with symptomatic heart failure were excluded. One patient refused to participate after kidney transplantation and was also excluded from the analysis. The remaining 34 patients (aged 35 ± 10.4 years, 58% male) completed the study and are presented here. Chronic glomerulonephritis was the main cause of chronic renal failure (44%), and median time on dialysis was 16 months.

Prior to kidney transplantation, 85% had BP >140/90 mmHg, although the great majority (71%) were taking antihypertensive medications. Similarly, anaemia was a usual finding; only 53% had a haematocrit >33%, as recognized for ESRD patients [24]. Metabolic acidosis was also frequent (78% had pH <7.35), and mean Kt/V was 1.32 ± 0.4.

Following kidney transplantation, all subjects were taking corticosteroids and a combination of two other immunosuppressive drugs and were free of acute rejection and infectious or acute cardiovascular events. Three patients developed diabetes, and seven were treated for episodes of acute rejection. Four participants had BMI ≥30 kg/m². The prevalence of hypertension remained high, and 56% were taking antihypertensive drugs. Metabolic acidosis was observed in half of the population. Mean weight, BMI, haemoglobin, haematocrit and pH were significantly increased, and significant reductions in DBP, creatinine, urea and PTH were observed after transplantation. Clinical and laboratory findings prior to and after transplantation are shown in Table 1.

Table 1 shows polysomnographic findings prior to and after transplantation. The prevalence of SDB was 26.5% [95% confidence interval (12.9%; 44.4%)] prior to and 21% [95% confidence interval (8.7%; 37.9%)] after transplantation. Mild cases predominated in both phases of the study, where only three patients before and two after transplantation had an AHI ≥15. Kidney transpl-

### Table 1. Clinical and laboratory test findings pre- and post-kidney transplantation

<table>
<thead>
<tr>
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<th>Pre</th>
<th>Post</th>
<th>P-value</th>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>153.4 ± 20.8</td>
<td>144.9 ± 16.4</td>
<td>0.088</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>100.8 ± 16.2</td>
<td>93.1 ± 11.2</td>
<td>0.030</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>61.2 ± 11.5</td>
<td>66.9 ± 12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.3 ± 4.1</td>
<td>24.4 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>10.7 ± 2.1</td>
<td>12.4 ± 2.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>32.3 ± 6.0</td>
<td>37.1 ± 6.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>10.9 ± 2.6</td>
<td>1.7 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>153.6 ± 31.1</td>
<td>57.7 ± 20.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>298.0 ± 316.1</td>
<td>179.5 ± 134.6</td>
<td>0.016</td>
</tr>
<tr>
<td>Alkaline phosphatase (UI)</td>
<td>106.0 ± 95.8</td>
<td>92.1 ± 50.4</td>
<td>0.406</td>
</tr>
<tr>
<td>pH</td>
<td>7.29 ± 0.07</td>
<td>7.34 ± 0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>22.2 ± 4.7</td>
<td>23.5 ± 2.5</td>
<td>0.191</td>
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</tbody>
</table>

Data are shown as mean ± standard deviation; Student’s t-test.

### Table 2. Polysomnographic findings pre- and post-kidney transplantation (n = 34)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P-value</th>
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<tbody>
<tr>
<td>AHI</td>
<td>5.3 ± 7.3</td>
<td>3.1 ± 4.5</td>
<td>0.132</td>
</tr>
<tr>
<td>Central apnoea (%)</td>
<td>7.6 ± 13.5</td>
<td>4.9 ± 10.8</td>
<td>0.301</td>
</tr>
<tr>
<td>AHI in REM (%)</td>
<td>16.6 ± 21.3</td>
<td>24.8 ± 28.3</td>
<td>0.122</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>80.2 ± 19.4</td>
<td>89.0 ± 22.5</td>
<td>0.072</td>
</tr>
<tr>
<td>Wake stage (%)</td>
<td>19.3 ± 19.4</td>
<td>14.7 ± 12.9</td>
<td>0.205</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>20.5 ± 21.2</td>
<td>9.0 ± 6.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>41.0 ± 14.8</td>
<td>46.6 ± 13.8</td>
<td>0.067</td>
</tr>
<tr>
<td>Stage 3 (%)</td>
<td>7.5 ± 4.7</td>
<td>10.5 ± 3.7</td>
<td>0.008</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>18.8 ± 11.0</td>
<td>18.9 ± 8.3</td>
<td>0.952</td>
</tr>
<tr>
<td>Slow-wave sleep (%)</td>
<td>20.9 ± 13.7</td>
<td>25.4 ± 8.5</td>
<td>0.082</td>
</tr>
<tr>
<td>Slow-wave sleep + REM (%)</td>
<td>38.3 ± 14.9</td>
<td>44.0 ± 12.6</td>
<td>0.041</td>
</tr>
<tr>
<td>O2 desaturation episodes per hour</td>
<td>2.5 ± 5.5</td>
<td>2.1 ± 6.9</td>
<td>0.751</td>
</tr>
<tr>
<td>Arousals per hour</td>
<td>26.6 ± 19.5</td>
<td>19.3 ± 11.3</td>
<td>0.072</td>
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</tbody>
</table>

Data are shown as mean ± standard deviation; Student’s t-test.

### Table 3. AHI pre- and post-kidney transplantation (n = 34)

<table>
<thead>
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<th></th>
<th>Pre</th>
<th>Post</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>AHI &lt;5</td>
<td>25 (73.5%)</td>
<td>27 (79.4%)</td>
<td></td>
</tr>
<tr>
<td>AHI ≥5</td>
<td>9 (26.5%)</td>
<td>7 (20.6%)</td>
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</table>

AHI = apnoea–hypopnoea index; McNemar test: P = 0.754.
tation was associated with significantly higher percentages of deep stages of sleep in contrast to a reduction in sleep stage 1. Sleep efficiency tended to increase, and a reduction in the number of arousals was also observed. Although a reduction in the number of patients with SDB was demonstrated, there was no statistical significance in this improvement (Table 3). There was no correlation between AHI or variation in AHI with the clinical and laboratory variables. There were also no correlations between changes in AHI with modifications in the sleep stages.

Figures 1 and 2 show the development of patients with AHI ≥5 in the two phases of the study. Of the nine individuals with AHI ≥5 before kidney transplantation, eight demonstrated some reduction in AHI, while one individual showed a worse picture. On the other hand, of the seven individuals with AHI ≥5 after kidney transplantation, five showed lower levels in the dialysis phase. In the group as a whole, 22 patients showed a reduction in AHI, and 12 had an increase in AHI. When we analysed only the group with AHI ≥5 prior to transplantation, there was a significant reduction in AHI (15.4 ± 7.8 vs 4.4 ± 4.4, pre- and post-transplantation, respectively; P = 0.008). Considering only patients with AHI <5 prior to transplantation, the difference was not significant (1.6 ± 1.3 vs 2.7 ± 4.5, pre- and post-transplantation, respectively; P = 0.21).

Discussion

Sleep disturbances show a high prevalence in dialysis patients. Subjective sleep complaints are reported in up to 80% of those surveyed. SDB, restless syndrome and periodic limb movement disorder are much more prevalent than in the general population [6]. Thirty-four ESRD patients on chronic haemodialysis who received a living donor kidney transplant and underwent polysomnographic studies prior to and after that are described. They served as their own controls, prior to and after transplantation. We found a high prevalence of SDB in the population while undergoing dialysis (26.5% of the patients with AHI ≥5), regardless of sleep complaints, confirming other studies [25–28].

Sleep deprivation has been implicated as a cause of impaired immune function [29,30] and cardiovascular disease [31]. Our findings about sleep quality are similar to those of previous studies that have demonstrated a short and fragmented sleep in patients on chronic dialysis [11,32–34], with increased amounts of stage 1 and decreased sleep efficiency and slow-wave sleep. In our study, kidney transplantation was associated with an increase in slow-wave sleep and a decrease in stage 1 sleep, with a trend for higher sleep efficiency. Various factors have been proposed as being associated with the improvement of sleep architecture after transplantation, such as the reduction in periodic limb movements during sleep (PLMS) and restless legs syndrome (RLS), correction of anaemia and disturbances in calcium and phosphorus metabolism, and the recovery of renal function [35,36]. In our study, there were no correlations between improvement in sleep pattern and the modifications of clinical parameters or AHI, such that we could not determine which factors were responsible for the better quality of sleep after transplantation. The improvement in sleep architecture could possibly explain part of the better quality of life after kidney transplantation.

Previous case reports have demonstrated an improvement in SDB after kidney transplantation in three patients [12,13]. More recently, a study of 841 patients submitted to kidney transplantation demonstrated, through the use of self-administered questionnaires, that such individuals show a high risk for sleep apnoea syndrome [37]. However, no polysomnographic examinations were performed that could prove these alterations. Two longitudinal studies were able to analyse the presence of sleep apnoea in renal transplantation utilizing polysomnographic examinations, but with discrepant results. While one study demonstrated a reduction in AHI in eight of nine of the individuals studied [14], another, evaluating 18 patients before and after living donor renal transplantation [15], yielded findings similar to ours, in that, transplantation does not lead to the cure of alterations, since of the eleven patients with AHI >10 in the first phase of the study, only three showed improvement after transplantation. In both studies, the groups consisted of individuals with some type of clinical suspicion, which in a way tend to demonstrate an elevated prevalence of alteration. The authors of the aforementioned studies did not mention possible new cases of alterations arising after transplantation. Later, a report of
47 patients also demonstrated a high prevalence of SDB in a transplantation group, but without demonstrating data before transplantation [38].

In the general population, SDB is clearly associated with male gender [5], older age [39] and obesity [40]. Such relationships are less evident in ESRD-related SDB, and findings from previous studies have been controversial [6,25,41]. In our study, the majority of patients were young, which could have contributed to a lower prevalence of changes in relation to similar studies. SDB is also associated with diabetes [42], cardiac disorders [43] and pulmonary diseases [44]. In our study, patients with these diagnoses were excluded to avoid confounding factors that could be causes of sleep disturbances.

In our study, AHI declined in most subjects with pre-transplant SDB while it increased in some subjects without pre-transplant SDB. Of the nine individuals with SDB before kidney transplantation, three persisted with alterations after transplantation, and four others showed SDB only in the second phase of the study. The results of our study confirm that the prevalence of SDB still persists at a high level after kidney transplantation. In fact, twelve patients had even higher indices than during chronic haemodialysis. The heterogeneous distribution of the changes reinforces the possibility of multifactorial mechanisms in which different factors may be involved in each situation.

It is well known that conventional haemodialysis does not reduce the prevalence or severity of SDB in ESRD patients, but previous studies have described improvements in subjects undergoing nocturnal haemodialysis [45] and cycle-assisted peritoneal dialysis [46]. The authors of the aforementioned studies and a recent review of the association between SDB and peritoneal dialysis [47] did consider that such reduction of sleep disturbances could be related to a better clearance of uraemic toxins, supporting a direct effect of uraemia on respiratory control, or to a better fluid clearance. Recent studies have demonstrated a high prevalence of SDB in non-dialysed chronic renal failure patients [48,49]. Other factors such as metabolic acidosis, uraemic myopathy or neuropathy, anaemia, hormonal imbalance, fluid overload, inflammatory cytokines and the dialytic process itself have been considered as possibly associated with the high prevalence of SDB in ESRD patients [6,10,12,50]. Several of these factors persist after transplantation and should be considered as possible contributors to the high frequency of SDB.

On the other hand, other factors typically associated with SDB appear with kidney transplant. SDB and disrupted sleep have been described as being related to Cushing’s disease and to corticosteroid effects [51], so a contribution of immunosuppressive drugs to the high frequency of SDB in our study cannot be excluded. A recent Italian study compared polysomnographic data of 163 kidney transplant patients with two control groups [16]. In the first case, the data utilized were from pulse oximetry of individuals matched by weight, age and sex. Also compared were data from the Wisconsin study cohort which included 602 North Americans. In both cases, the authors did not find any differences in prevalence of SDB in relation to the control groups. There are no data of polysomnographic studies before transplantation that allow the comparison of the development of changes. The authors concluded that the prevalence of SDB in transplanted patients did not differ from that in the general population. The high prevalence of SDB in transplanted patients could be associated to weight gain. In fact, in our study, there was substantial weight gain after kidney transplantation. Although we did not find any association between changes in BMI and in AHI, the possible contribution of weight gain after kidney transplantation cannot be excluded and warrants better future investigations.

Considering the important association of SDB with cardiovascular events and high cardiovascular mortality in kidney transplant patients, new studies are needed to determine which factors are involved in the persistence of SDB in this population.

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