ORIGINAL ARTICLE

Sleep apnea in kidney transplant patients: Clinical correlates and comparison with pretransplant patients

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Abstract *Background:* Sleep disordered breathing (SDB) is a prevalent, but forgotten, cardiovascular (CV) risk factor in end-stage renal disease patients. Studies of SDB in renal transplant patients are few with mixed results.

Objectives: To assess the prevalence and clinical correlates of SA in patients who received a kidney transplant, and to compare the prevalence of SA between waiting list and transplant patients.

Subjects and methods: Our study included 40 clinically stable renal transplant patients and 15 patients awaiting transplantation. Patients with morbid obesity, diabetes, pulmonary disease or symptomatic heart failure were excluded from the study. All patients underwent overnight polysomnography, demographic and clinical data were also collected.

Results: We found that the prevalence of SA was high in both the transplant and the waiting list groups (38% *vs* 47%). The severity of SA didn't show significant difference in both groups (AHI = 9.6 *vs* 16.2). Moreover, we found a significant association between impaired renal function and the AHI in Tx patients. Also, SA was associated with difficult-to-treat hypertension in Tx patients as we found a significant association between the AHI and the systolic blood pressure as well as the number of prescribed antihypertensive drugs.

Conclusion: SA is as highly prevalent in Tx as in WL patients. Moreover, this high prevalence in the transplant patients could be a consequence of declining renal function. In addition, we propose that sleep apnea is a new risk factor for hypertension and cardiovascular events in kidney-transplanted patients.

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Introduction

Sleep apnea (SA) is a surprisingly common disorder in end-stage renal disease (ESRD) and chronic renal failure [1]. Previous studies have shown high prevalence of SA (16–60%) in patients with ESRD [2,3]. Although the underlying mechanisms linking these two conditions remain to be better defined, it is likely that multiple factors are involved [2].

The symptoms of sleep apnea frequently go unreported or may be misdiagnosed as uremia, depression, chronic illness, or insomnia. Sleep apnea is reportedly associated with higher risk for stroke, hypertension, diabetes, congestive heart failure, arrhythmias, metabolic syndrome and also with fatal and non-fatal cardiovascular events [4].

Although it has been claimed that renal transplantation may improve the SA in patients with ESRD, consistent information about SA in patients who have received a kidney transplant is scarce [5,6].

Among patients who receive kidney transplants, cardiovascular disease is the leading cause of mortality [7]. Since SA may contribute to the increased cardiovascular risk in transplant patients we chose to study the prevalence and clinical correlates of SA in these patients.

Aim of the work

The objectives of the study were to assess the prevalence and clinical correlates of SA in patients who received a kidney transplant, and to compare the prevalence of SA among waiting list and transplant patients.

Subjects and methods

Patients attending the Transplant Clinic at Alexandria Main University Hospital were invited to participate in the study. Potential recruits were either patients on hemodialysis for at least 3 months and awaiting kidney transplantation or post transplant patients. All transplant patients underwent living donor kidney transplantation at least 3 months before enrollment. Following transplantation all patients were taking prednisone and a combination of two other immunosuppressive drugs and were free of acute rejection, infectious and acute cardiovascular events.

Both groups of patients were included regardless of sleep complaints. In order to exclude sleep disorders not directly related to their underlying renal dysfunction, patients with class III obesity (BMI $\geqslant 40$), previous diagnosis of SA, recent start (< 3 months) on dialysis or transplantation, diabetes, pulmonary disease, symptomatic heart failure, hospitalization within 1 month, and surgery within 3 months, were excluded from the study. Therefore, 40 clinically stable renal transplant patients and 15 patients awaiting transplantation participated in the study. All patients were enrolled in the study after a written informed consent according to a protocol approved by the Ethics Committee of Alexandria Main University Hospital (Faculty of Medicine).

Data were collected regarding anthropometric and demographic factors, medication use, co-morbid conditions, and laboratory parameters.

Pretransplant patients underwent polysomnography after a hemodialysis session. All had to have their dry weight assessed to be included in the study. Prior to polysomnography clinical examination, weight, height and BMI were assessed for both groups. Just after polysomnography blood samples were taken for laboratory parameters.

Assessment of daytime sleepiness

The Epworth Sleepiness Scale (ESS) was used for assessing daytime sleepiness. This is a commonly used self-administered scale with eight items about how easily the respondent would fall asleep in different situations. The items are scored on a 0–3 scale, which are added to give an overall score of 0–24. Higher scores indicate more sleepiness. ESS score 2–10 is considered 'normal' and > 10 indicative of pathological sleepiness [8].

Polysomnography

All patients underwent overnight polysomnography in the chest department, Faculty of Medicine, Alexandria University, using RESMED Apnea LinkTM System which measured the following cardiorespiratory data; respiratory sounds, airflow, oxygen saturation and heart rate [9].

The analysis was carried out automatically and manually. Respiratory events were scored using standard criteria. The apnea hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep. As indices of nocturnal hypoxemia we considered the oxygen desaturation index (the number of O2 desaturation episodes per hour of sleep), T90 (the fraction of sleep time spent below an oxygen saturation of 90 percent), minimal SaO2 (the minimal value recorded during sleep), and the average oxygen saturation (calculated from the oxygen saturation values measured during sleep) [10,11].

The presence of SA was defined as an AHI of $\geqslant 5$ events/h and patients were further subdivided into three categories of severity: mild; AHI $\geqslant 5$ and < 15, moderate; AHI $\geqslant 15$ and < 30, and severe; AHI $\geqslant 30$ [10].

Laboratory measurements

Serum urea, creatinine, cholestrol, triglycerides, glucose, albumin, and hemoglobin were measured by standard methods in the routine clinical laboratory. Estimated GFR (eGFR) was calculated using the Cockroft and Gault formula: creatinine clearance (ml/min/1.73m2) = (140-age in years) $\times$ weight (kg) $\times$ K/ (serum creatinine $\times$ 72) [12].

Transplantation data and immunosuppressive therapy

Transplantation-related information collected included current medications, transplant and dialysis "vintage" (i.e., time elapsed since transplantation or since the initiation of dialysis treatment), time spent on dialysis before transplantation. Standard maintenance immunosuppressive therapy generally consisted of prednisolone, plus either cyclosporin A microemulsion formulation or tacrolimus, combined with mycophenolate mofetil or azathioprine.

BP measurement

BP was measured in the clinic three times after 10 min of rest. The average of the three measurements was tabulated. The number of antihypertensive medications was also collected.

Statistical analysis

Data were collected, tabulated, then analyzed using SPSS Ver.13. Qualitative data were presented as numbers and percentage. Quantitative data were expressed as means and standard deviation. The prevalence of SA was compared among

the 2 groups using the Z test of proportion. The severity of SA among the studied groups was compared using the chi square test. Demographic, clinical and laboratory data between groups were compared by the chi square test and the Student's t-test when appropriate. The Pearson correlation coefficient (r) was used to assess the relation between AHI and numerical variables. A 5% level was chosen as a level of significance in all statistical tests used in the study

Results

Demographic data and baseline characteristics of the sample

Fourty clinically stable renal transplant patients (Tx patients) and 15 patients awaiting transplantation (WL patients) were enrolled in the study. Baseline patient characteristics are shown in Table 1. Demographic, clinical and laboratory variables did not show any statically significant difference between the Tx and WL groups (Table 1).

All of the Tx patients were taking steroids, 75% were administered cyclosporin A, 65% were on mycophenolate mofetil, 25% patients were administered tacrolimus, and 35% were on azathioprine.

Prevalence and severity of SA in Tx versus WL dialysis patients

Fifteen patients (38%) of the Tx and seven patients (47%) of WL patients had SA (AHI $\geqslant$ 5; showing no statistically significant difference) (Table 2). The respiratory sleep parameters did not show significant differences between the two studied groups as shown in Table 2. There was no significant difference in the severity of SA among the two studied groups, where the prevalence of mild, moderate, and severe SA in the Tx and WL groups were: 23%, 10%, and 5% in the Tx group and 13%, 27%, and 7% in the WL group, respectively (Fig. 1).

Correlates of SA in the Tx group

The AHI was significantly correlated with the eGFR ($p = 0.040$), systolic blood pressure ($p = 0.003$), as well as the number of prescribed antihypertensive drugs ($p = 0014$) (Table 3). Otherwise, the AHI did not show any significant correlation with other demographic, clinical or laboratory data.

Discussion

In this study we aimed to assess the prevalence of SA in patients who received a kidney transplant, in comparison to patients with ESRD who are on the transplant waiting list. We found that the prevalence of SA was comparably high in the transplant and the waiting list patients, (38% and 47%, respectively, NS). Moreover, the AHI did not show significant difference between the transplant and the waiting list groups (9.6 and 16.2, respectively) where the severity of SA was the same in both groups. Previous studies have yielded mixed results; few patients have been described to have their SA cured with renal transplant [5,6]. On the other hand, other studies, suggested that SA may not show significant improvement after transplantation. A recent study found that 27% of renal transplant patients had a high likelihood for SA based on the Berlin questionnaire, this was comparable to the 33% who were on the transplant waiting list, including dialysis patients [13]. Also, Molnar et al. in a cross-sectional study of 100 Tx and 50 WL patients who underwent one-night polysomnography, showed that the prevalence of OSA was similarly high in both groups [7]. Therefore our results adds further evidence that the post-transplant state also appears to be a risk factor for SA.

The exact pathophysiologic factors linking ESRD and SAHS remain unclear and controversial, and there may be multiple independent factors impacting the association.

Table 1 Patient characteristics.

Characteristic	Tx Patients (n = 40)	WL Patients (n = 15)	P
Male (n, %)	27 (68)	17 (73)	NS
Age (yr)	39 ± 8.29	34 ± 5.66	NS
Tobacco use (n, %)	11 (28)	5 (33)	NS
BMI (kg/m^2)	28 ± 3	24 ± 2	NS
Prevalence of hypertension (n, %)	36 (90)	11 (73)	NS
Number of antihypertensive drugs used (n, %)			
1	2 (5)	1 (7)	NS
2	24 (60)	8 (53)	
$\geqslant$3	10 (25)	2 (13)	
Hb (g/dl)	11.9 ± 1.12	10.95 ± 1.5	NS
Systolic pressure (mmHg)	140 + 14.14	135 + 33.17	NS
Diastolic pressure (mmHg)	78 ± 11.55	80 ± 7.36	NS
Serum albumin (g/dl)	3.5 ± 0.4	3.6 ± 0.6	NS
Serum cholesterol(mg/dl)	211.5 ± 44.75	148 ± 32.12	NS
Serum triglycerides(mg/dl)	143.25 ± 43.11	147 ± 38.5	NS
Serum urea(mg/dl)	29 ± 9.77	76.5 ± 27.38	P = 0.031
Serum creatinine(mg,dl)	1.65 ± 0.79	5.15 ± 4.13	NS
eGFR(ml/min/1.73m^2)	58.3 ± 30.16	NA	
Transplant or dialysis vintage (months)	56 ± 37.7	14 ± 5.7	NS

Results are expressed as mean + standard deviation unless otherwise specified. Definition of abbreviations: n: number of patients, BMI:body mass, HB: hemoglobin, eGFR: estimated glomerular filtration rate.

Table 2 Sleepiness and respiratory sleep parameters in Tx and WL patients.

Parameter	Tx patients	WL patients	
Patients with SA n (%)	15 (38)	7 (47)	NS
AHI	9.6 ± 7.64	16.2 ± 5.83	NS
ODI	4.3 ± 6.16	4 ± 1,41	NS
Minimum oxygen saturation during sleep (%)	84.3 ± 8.50	75 ± 16.97	NS
Average oxygen saturation during sleep (%)	95 ± 1.73	90.5 ± 4.95	NS
T 90%	5.02 ± 8.65	6.4 ± 4.81	NS
ESS	6.5 ± 0.71	7.8 ± 3.54	NS

Results are expressed as mean + standard deviation. Definition of abbreviations: AHI: apnea hypopnea index, ODI: oxygen desturation index, T90: fraction of sleep time spent below an oxygen saturation of 90 percent, ESS: Epworth sleepiness scale.
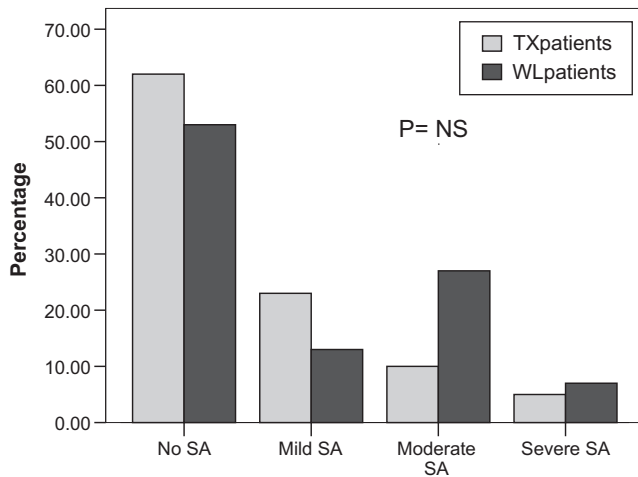
Figure 1 Prevalence and severity of OSA in Tx and WL patients.

Table 3 Correlation between AHI and selected variables in Tx patients.

Parameter	AHI	
	r	p
eGFR	0.326	0.040*
Systolic pressure	0.452	0.003*
Number of antihypertensive drugs	0.387	0.014*

^{n}P: p value for pearson correlation. *: Statistically significant at $p \leqslant 0.05$.

Volume overload, a common problem in patients with ESRD, causes redistribution of body water during the recumbent position and gives rise to upper airway edema causing pharyngeal narrowing that predispose to upper airway collapse during sleep leading to obstructive sleep apnea [14]. Accumulation of uremic toxins induces metabolic acidosis and hypocapnea increases chemosensitivity to carbon dioxide leading predominantly to central sleep apnea [15]. Uremia has also been theorized to contribute to SAHS through uremic-related myopathy and neuropathy. Myopathy related to uremia can involve the muscles of the respiratory system and thus predispose to upper airway collapse during sleep [16]. Peripheral and autonomic neuropathies, by affecting the innervation of the pharyngeal dilators, could also lead to upper airway collapse during sleep. However, unlike uremic myopathy, uremic neuropathy is generally irreversible and sleep apnea would thus persist post-

transplantation [17]. Other factors pertinent to patients with ESRD may affect the control of ventilation during sleep, as shown in animal studies, severe anemia enhances hypoxia-induced ventilatory responses and could thus predispose to periodic breathing [6]. Finally, cytokines could have a role in both ESRD and SA. Tumor necrosis factor-alpha (TNF-α), a cytokine that is elevated in individuals with chronic renal failure [18], might have a role in the underlying pathophysiologic course of SAHS, as a study found TNF-α levels abnormally elevated in patients with SAHS compared with controls [19]. Several of these underlying factors for SA in ESRD persist after kidney transplantation, and therefore should be considered as possible contributors for the high prevalence of SA in Tx patients [20].

Moreover, we found a significant association between impaired renal function in Tx patients and the AHI. It is possible, that the surprisingly high prevalence of SA observed in the Tx population is the consequence of declining renal function in these patients. This result lends further support to the hypothesis that uremia-related factors may be involved in the pathogenesis of ESRD-associated SA [21].

On the other hand, other factors typically associated with sleep disordered breathing (SDB) appear following kidney transplantation. SDB have been described as being related to cushing disease and to corticosteroid effect [22], so the contribution of immunosuppressive therapy to the high prevalence of SA in the Tx patients in our study cannot be excluded. Since recent weight gain is common in patients with newly diagnosed SDB [23], therefore weight gain that occurs following transplantation could be another confounding factor for the increased risk for new-onset OSA. Although, we didn't find a significant correlation between the AHI and the BMI in our studied Tx patients, the effect of this risk factor cannot be excluded. Therefore, the post transplant state due to multiple factors such as medications along with improved nutrition and appetite may represent another risk factor for SA [24]. Finally, extracellular water may increase in at least some of the Tx patients [25,26], which may also be associated with increased risk for OSA [27].

In the general population, SA is associated with male gender [28] and older age [29]. These relationships are less evident in ESRD related SA and posttransplantation, findings from previous studies have been controversial [7,21,30–32]. In our study, the majority of our patients were young, which could be contributing factors to our lack of demonstrating similar associations. And since, SDB is also associated with diabetes, [33] pulmonary diseases [34] and heart failure [35], therefore we excluded patients with these comorbidites to avoid confounding factors that could cause SA.

In our study, SA was associated with difficult-to-treat hypertension in Tx patients as we found a significant association between the AHI and the systolic blood pressure as well as the number of prescribed antihypertensive drugs. The association of OSA and hypertension is well documented in other patient populations [36,37]. This result has important clinical implications, as hypertension is an independent risk factor for allograft dysfunction [38,39] and cardiovascular mortality [40] in kidney transplant recipients. Therefore, we propose that the higher BP in Tx patients with SA may contribute to the high cardiovascular morbidity and mortality of Tx patients.

Cardiovascular disease remains the leading cause of mortality in this patient population [40]. Recent findings suggest that sleep apnea is associated with increased mortality in dialysis-dependent patients [41]. Obstructive sleep apnea which persists following transplantation may therefore contribute to the increased risk of cardiovascular disease and reduced life expectancy among kidney transplant recipients [42,43]. Our findings highlight the potential clinical consequences of persistent sleep apnea in this patient population and the need for comprehensive re-evaluation of sleep apnea following kidney transplantation.

From our study we conclude that SA is as highly prevalent in Tx as in WL patients. Moreover, this high prevalence in the transplant patients could be a consequence of declining renal function. In addition, we propose that sleep apnea is a new risk factor for hypertension and cardiovascular events in kidney-transplanted patients. And since, recognition and treatment of sleep-related breathing disorders has the potential to both improve the quality of life and decrease morbidity and mortality in this patient population [44]. Therefore, we suggest that screening for SA should be routinely performed, and appropriate treatment should be offered for Tx patients.

Declaration of interest

Funding

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