Original Article

Risk of obstructive sleep apnea among Saudis with chronic renal failure on hemodialysis

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Abstract:

AIM: The prevalence of obstructive sleep apnea (OSA) in end-stage renal disease (ESRD) patients was reported to be 10-fold that in the general population. OSA can worsen the clinical symptoms and cardiovascular complications of ESRD. We aimed to investigate the prevalence of symptoms and risk of OSA among Saudi patients with ESRD.

SETTINGS AND DESIGN: This multi-center, cross-sectional study was conducted in Jeddah, Saudi Arabia, between June 2012 and September 2013.

METHODS: The prevalence of OSA was assessed using the Berlin questionnaire. The presence of daytime sleepiness was evaluated using the Epworth sleepiness scale. Data were also collected on the medical history, clinical, and laboratory findings of participants.

RESULTS: In all, 355 patients (61% male) were enrolled (mean age: 45.5 ± 15.4 years). The overall prevalence of high-risk of OSA was 44.2% (males, 47.3%; females, 44.8%; $P = 0.65$). The prevalence of excessive daytime sleepiness (EDS) was 74%. Controlling for age, gender and body mass index, multivariate analysis revealed that hypertension and hepatitis C infection were the only comorbidities significantly associated with OSA (odds ratio [OR]: 3.827 and 0.559; confidence interval [CI]: 2.120-6.906 and 0.324-0.964; $P < 0.0001$ and 0.036, respectively). OSA was also strongly associated with EDS (OR: 3.054; CI: 1.676-5.565; $P < 0.0001$).

CONCLUSIONS: In Saudi Arabia, the risk of OSA is more common in ESRD patients than in the general population. OSA is strongly associated with EDS. Interestingly, a significant negative correlation between OSA and hepatitis C infection was noted, which warrants further investigation.

Key words:

Chronic renal failure, excessive daytime sleepiness, prevalence, risk of obstructive sleep apnea

Obstructive sleep apnea (OSA) refers to repetitive episodes of absent respiration during sleep despite a continuous effort to breath and is characterized by excessive daytime sleepiness (EDS), disruptive snoring, and nocturnal hypoxemia.[1] OSA is associated with serious health consequences, such as increased risk of hypertension (HTN), cardiovascular disease, cerebrovascular disease, glucose intolerance, decreased functional ability, and motor vehicle accidents. Even a mild degree of sleep-disordered breathing may adversely affect overall health.[2-5]

In end-stage renal disease (ESRD), OSA may aggravate the cardiovascular complications, which are the leading causes of morbidity and mortality in such cases.[6-8] OSA has been shown to be associated with increased all-cause mortality independent of age, gender, and presence of diabetes.[9] Furthermore, OSA may compromise the quality of life and worsen the clinical symptoms of ESRD patients, such as fatigue, daytime sleepiness, and impaired cognitive function.[10] These findings highlight the importance of early recognition and treatment of OSA.

In general, sleep disorders are common in ESRD patients (mean prevalence, 44%).[11] However, the prevalence of OSA in ESRD patients (up to 50%)[12-14] was reported to be about 10-fold

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that in the general population (2-20%).[15,16] Regionally, the prevalence of OSA symptoms among Egyptian hemodialysis (HD) patients was reported as 21-32%.[17,18] However, a cross-sectional study in two dialysis centers of Saudi Arabia was the only one published thus far on the prevalence of OSA in Saudi ESRD patients, as defined by the Berlin questionnaire.[19] The study yielded an extremely high overall prevalence of OSA risk, at 70% (males, 69%; females, 73.3%).[19] The aim of our study is to reevaluate this considerably high prevalence of OSA symptoms on a larger population of HD patients across multiple centers and identify associated risk factors.

Methods

This was a cross-sectional, multicenter, descriptive study. Subjects were recruited from the HD centers at King Abdulaziz University Hospital, King Abdulaziz Hospital, and King Fahd General Hospital, Jeddah, Saudi Arabia between June 2012 and September 2013. The study protocol complied with the Declaration of Helsinki and was approved by the hospital ethical committee. All participants provided written informed consent.

The target population comprised stable ESRD patients undergoing regular HD between 0700 and 2300 h. Patients were excluded if they were confused, demented, or unwilling/unable to participate. Trained physicians interviewed all patients individually. The administered questionnaire collected the following data: Demographic features; comorbidities; dialysis protocol, including the cause of ESRD, weekly frequency of dialysis, duration of each dialysis session, and dialysis adequacy using urea reduction ratio (URR);[20] medications; Epworth sleepiness questionnaire to assess daytime sleepiness;[21,22] Berlin[23,24] and STOP-Bang[25] questionnaires to evaluate the risk of OSA; serum levels of hemoglobin, calcium, creatinine, urea before and after dialysis, and glycated hemoglobin.

Berlin is widely used a reliable questionnaire that is composed of 11 self-reported questions used to identify individuals at high-risk for sleep apnea. These questions focus on three categories of apnea signs and symptoms, namely: Snoring, daytime sleepiness, and obesity/high blood pressure. It was originally designed as a mean for clinicians to establish quickly apnea risk factors and has been validated in patients 18 years or older. The scoring process includes evaluating "yes or no" responses as well as multiple-choice selections, and also includes space for calculating body mass index (BMI) based on respondent measurements. For "yes or no" questions, one point is given to an answer of "yes." While in the case of multiple choice questions, the two answers that correspond with the highest severity of apnea both receive one point. Categories 1 and 2 are considered high-risk if the individual scores 2 or more points. Category 3 is considered high-risk, if either BMI is greater than> 30 kg/m2 or blood pressure, is found to be high (a score of 2 is assigned for each item). The respondent is then considered high-risk for OSA if there are 2 or more categories where the score is 2 or above.[23,24]

STOP-Bang questionnaire screens for symptoms of OSA and has been validated for subjects with a mean age of 57 + 16. It was originally designed for use in a preoperative setting, as untreated OSA is associated with increased postoperative complications and longer hospital stays. The questionnaire is represented by the mnemonic "STOP Bang": S — "Do you snore loudly?" T — "Do you often feel tired, fatigued, or sleepy during the daytime?" O — "Has anyone observed you stop breathing during you sleep?" P — "Do you have or are you being treated for high blood pressure?" In order to improve the accuracy of the scale, B — BMI, A — age, N — neck circumference, and G — gender are recorded. The STOP Bang questionnaire is scored as follows: For the first four yes/no questions, a response of "yes" is given one point. An additional one point is awarded for each of the following conditions: A BMI of more than 35 kg/m^2, an age of 50 years or greater, a neck circumference >40 cm, and a final point for patients who are male. When using the complete STOP-Bang, a total score of 3 or more places the individual at a high-risk.[25]

Statistical analysis

Continuous data were summarized as means and standard deviations (SDs) and nominal data, as frequencies and percentages. Unpaired *t*-test was used to evaluate differences in means, and the Chi-square test, for independence or association of categorical data. In case of violation of statistical assumptions needed to perform the parametric tests, nonparametric tests were used.

Data are expressed as mean ± SD unless stated otherwise. The association between investigated sleep disorders and other baseline characteristics was assessed using Pearson's or Spearman's correlation. Odds ratios (OR) were taken as approximations of relative risk and expressed with 95% confidence interval (CI). $P < 0.05$ was considered statistically significant.

We explored the relations of OSA with different risk factors individually while controlling for variables such as demographics like age, gender and possible confounders like BMI. These relations were best presented as correlation coefficients (*r*) with significance values, and as ORs with CIs. Logistic regression was used to model the likelihood of OSA when considering multiple predictors simultaneously. The analysis was performed using the Statistical Package for Social Science (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.).

Results

Three hundred and fifty-five patients (males: 216, 61%) were enrolled (mean age: 48.5 ± 15.4 years). The mean duration of dialysis was 78.8 ± 72.4 months (6.6 ± 6 years). Thirty-eight percent were smokers or ex-smokers. Most (90%) of the patients underwent 3-4 h sessions of dialysis 3 times/week. Differences in demographic data between high-risk and low-risk groups are presented in Table 1.

According to the Berlin questionnaire, 157 patients had high-risk of OSA, and the overall prevalence of OSA was 44.2% (males, 47.3%; females, 44.8%; $P = 0.65$). According to the STOP-Bang criteria, 64.2% had high-risk of OSA (males, 67%; females, 33%; $P = 0.001$).

Based on the URR, 60% of the patients had adequate dialysis. OSA showed no significant correlation with age, gender, smoking status, or dialysis adequacy. Surprisingly, the only dialysis-related criterion that differed significantly between groups with high- and low-risk of OSA was the frequency of dialysis: The high-risk group underwent more frequent dialysis.

Obstructive sleep apnea was significantly associated with BMI, ($r = 0.19$; $P < 0.0001$) with the risk of OSA for obese (BMI ≥30) patients being 3.5 times that in normal weight individuals [Table 2].

The following comorbidities were recorded: Diabetes mellitus (DM 28.6%), (HTN; 73.5%), anemia (86%), stroke (7%), ischemic heart disease (6.5%), chronic obstructive pulmonary disease (1.4%), hepatitis B virus (HBV) infection (1.1%), hepatitis C virus (HCV) infection (28.2%), and human deficiency virus infection (1.1%). In the high-risk OSA group, the prevalence rates were 35%, 86.6%, 87.3%, and 21.7% for DM, HTN, anemia, and HCV infection, respectively. OSA showed significant positive correlation with DM and HTN, negative correlation with HCV infection ($r = 0.14$, 0.28, and −0.16; $P = 0.01$, < 0.0001, and 0.003, respectively), and no correlation with anemia, and other comorbidities.

Other sleep disorders noted were restless legs syndrome (RLS; 20.2%) and EDS (21.5%). High-risk of OSA was significantly correlated with RLS ($r = 0.137$; $P < 0.012$) and daytime somnolence ($r = 0.22$; $P < 0.0001$) [Table 3].

Univariate regression analysis revealed the following risk factors for OSA: BMI, EDS, RLS, DM, and HTN. Patients with HTN had 4-7 times greater risk of OSA than patients without HTN. EDS also tripled the odds of OSA. However, it also revealed a protective effect of HCV infection [Table 4].

Multivariate regression analysis controlling for traditional variables such as, age, gender, and BMI showed good correlation of OSA with HTN, EDS, BMI, and HCV infection. However, positive HCV serology significantly lowered the risk of OSA by 50% [Table 5].

Table 1: Difference in demographic data between high-and low-risk

Variable	High-risk	Low-risk	*P*
@ (%)			
Male	97 (61.8)	108 (59.3)	0.65
Female	60 (38.2)	74 (40.7)	
Age (years)	50.26±14.71	46.27±15.54	0.17
BMI (kg/m^2)	26.6±7.33	23.94±6.21	<0.0001*
Years on dialysis	6.16±5.79	7.23±6.32	0.11
Frequency of dialysis per week	2.97±0.24	2.88±0.36	0.009*
Duration of dialysis per session (h)	3.08±0.28	3.08±0.3	1.000
Dialysis adequacy	67.7±72.25	62.34±21.92	0.34

BMI = Body mass index, @Data of 16 cases (11 males and 5 females were not complete and hence excluded), **P* value of less than 0.05 is considered statistically significant

Table 2: Effect of BMI on the probability of OSA symptoms

BMI	*P*	OR	95% CI	
			Lower	Upper
Underweight	0.002	Ref		
Normal	0.464	1.283	0.659	2.497
Overweight	0.201	1.627	0.771	3.431
Obese	0.001*	3.498	1.671	7.321

BMI = Body mass index, CI = Confidence interval, OR = Odds ratio, OSA = Obstructive sleep apnea, **P* value of less than 0.05 is considered statistically significant

Table 3: The association of OSA risk with other sleep disturbances

Sleep disorders	Correlation coefficient	High-risk (%)	Low-risk (%)	*P*
EDS	*r*=0.22	31	13	<0.0001*
RLS	*r*=0.14	26	15	0.012*

EDS = Excessive daytime sleepiness, RLS = Restless legs syndrome, OSA = Obstructive sleep apnea, **P* value of less than 0.05 is considered statistically significant

Table 4: Univariate analysis of OSA risk factors

Variable	OR	CI	*P*
BMI	1.06	1.026-1.097	0.001*
EDS	2.99	1.730-5.157	<0.0001*
RLS	1.99	1.16-3.423	0.013*
Adequate dialysis	1.002	0.997-1.008	0.40
Anemia	1.36	0.739-2.51	0.32
DM	1.86	1.15-3.001	0.01*
HTN	4.05	2.3-7.007	<0.0001*
HCV	0.486	0.299-0.789	0.004*

BMI = Body mass index, EDS = Excessive daytime sleepiness, RLS = Restless legs syndrome, OSA = Obstructive sleep apnea, HCV = Hepatitis C virus, DM = Diabetes mellitus, HTN = Hypertension, OR = Odds ratio, CI = Confidence interval, **P* value of less than 0.05 is considered statistically significant

Discussion

This study clearly showed that almost one-half to two-thirds of ESRD patients are at high-risk for OSA. The prevalence determined in this study is close to that reported in previous studies based on the Berlin questionnaire [Table 6].[19,26-31] The wide range of prevalence previously reported (23-71%) may be related to the size and ethnicity of the study population and the validity of the questionnaire used. OSA symptoms were more frequent in our ESRD population (males, 47.3%; females, 44.8%) than in the general Saudi population (males, 33.3%; females, 39%).[32,33] This agrees with reports indicating a higher prevalence of OSA among ESRD patients than in the general population.[13-16] In addition, the severity of OSA was also found to be greater in HD patients than the general population (OR: 4.07; CI: 1.83-9.07).[14] This high prevalence was reported in ESRD patients, irrespective of whether they underwent peritoneal dialysis or HD,[13] implying that the pathophysiology of OSA is related to renal failure than its treatment. Our prevalence rates were remarkably lesser than those reported by Al-Jahdali.[19] No clear explanation is apparent for this disparity; however, it may be because the mean age group in our study was 10 years less than that in the previous one.[19]

Our study confirmed that neither age nor gender was a significant risk factor for OSA in ESRD patients.[12,34] However, obesity was highly associated with OSA risk, as reported in

Table 5: Multivariate analysis of OSA risk factors

Variable	OR	95% CI for OR		*P*
		Lower	Upper	
Age	1.013	0.997	1.029	0.125
Gender	0.919	0.556	1.521	0.743
BMI	1.052	1.014	1.091	0.006*
HTN	3.827	2.120	6.906	<0.0001*
HCV	0.559	0.324	0.964	0.036*
EDS	3.054	1.676	5.565	<0.0001*

EDS: Excessive daytime sleepiness, BMI = Body mass index, HTN = Hypertension, HCV = Hepatitis C virus, OR = Odds ratio, OSA = Obstructive sleep apnea, CI = Confidence interval, **P* value of less than 0.05 is considered statistically significant

Table 6: Comparison of the prevalence of OSA reported in different studies, as determined by validated questionnaires

Study	Population	Size of study population	Prevalence of OSA (%)
Kuhlmann *et al.*, 2000[29]	Germany	77	31
Mucsi *et al.*, 2004[26]	Hungary	78	32
Chen *et al.*, 2006[27]	Taiwan	700	20
Merlino *et al.*, 2006[30]	Italy	883	27
Argekar *et al.*, 2007[28]	USA	270	28
Szentkiralyi *et al.*, 2011[31]	Canada	823	28
Al-Jahdali 2012[19]	Saudis	227	71
Wali *et al.* (current study)	Saudis	355	44.2

OSA = Obstructive sleep apnea

both the general population[35,36] and ESRD patients.[19,37,38] Furthermore, the significant association between BMI and OSA held true even in multivariate analysis (OR: 1.052; CI: 1.014-1.091; $P = 0.006$).

As reported previously,[19,37,39] OSA risk was significantly associated with both HTN and DM ($r = 0.14$ and 0.28; $P = 0.01$ and < 0.0001, respectively). This relationship was observed (OR: 1.86 and 4.05; CI: 1.15-3.001 and 2.30-7.01; $P = 0.01$ and < 0.0001, respectively) in univariate analysis, but only HTN showed significant positive correlation with OSA (OR: 3.827; CI: 2.120-6.906; $P < 0.0001$) in multivariate analysis. However, other studies found no such correlations.[26-28,40] This may be explained by the differences in the ethnicity of the population in our study and previous ones. Interestingly, a negative association was noted between OSA and HCV infection ($r = -0.16$; $P = 0.003$), which held true in multivariate analysis (OR: 0.559; CI: 0.324-0.964; $P = 0.036$). This negative correlation, introducing HCV infection as a protective factor for OSA, has not been reported hitherto and appears inexplicable. Considering the increased OSA risk in cirrhotic patients, HCV infection is also expected to increase the OSA risk, possibly via the subsequent liver cirrhosis, portal HTN, and ascites.[41] Moreover, this negative association was not seen for HBV infection.

The dialysis data, including dialysis adequacy, duration of dialysis, and duration of each dialysis session had no correlation with the prevalence of OSA risk among ESRD patients. However, more frequent dialysis was associated with increased OSA risk in our study. This is probably because such patients are susceptible to fluid overload that causes interstitial edema affecting the pharynx and contributing to pharyngeal narrowing and hence requiring increasing frequency of dialysis.[42] Nevertheless, subsequent univariate analysis showed no such link between OSA risk and dialysis frequency (OR: 1.002; CI: 0.997-1.008; $P = 0.40$).

In this study, multivariate analysis revealed that EDS was three-fold more frequent in patients at high-risk of OSA than those at low-risk of OSA (OR: 3.054; CI: 1.676-5.565; $P < 0.0001$). Furthermore, OSA is not the only cause of EDS in dialysis patients; RLS can also cause sleepiness. As reported previously,[19,39] RLS was closely associated with OSA (OR: 1.99; CI: 1.16-3.423; $P = 0.013$). Moreover, the significance of daytime sleepiness as a marker of OSA in ESRD patients may be questioned, since fatigue and sleepiness are often attributed to renal failure rather than OSA. Conversely, ESRD patients who generally experience sleepiness and get used to it, may undermine the importance of daytime sleepiness and fail to report this.[34]

Both the Berlin and STOP-Bang questionnaires are well validated in assessing OSA risk. A significant difference was noted in the OSA risk assessed by the two questionnaires (46.3%, Berlin questionnaire and 64.2%, STOP-Bang). Abrishami *et al.* conducted a systematic review of screening questionnaires for OSA and concluded that the accuracy of OSA questionnaires is promising, but inconsistent due to the heterogeneity of methods.[43] The two questionnaires have been reported to have similar levels of sensitivity (86%, Berlin questionnaire; 85%, STOP-Bang). However, their specificities differ greatly, with the Berlin questionnaire being more specific (95%) than STOP-Bang (56%).[43] Nunes *et al.*, compared the data of the two questionnaires with polysomnography data and reported sensitivities of 95% and 82% for the Berlin questionnaire and STOP-Bang and specificities of 13% and 62%, respectively.[44] Furthermore, unlike the Berlin questionnaire, STOP-Bang considers male gender a risk factor for OSA. This may explain the significant difference in gender found in our study by STOP-Bang and not by Berlin. Over all, the Berlin questionnaire has good sensitivity and relatively high specificity and is more widely used than STOP-Bang, and hence our data interpretation and discussion were dependent on Berlin questionnaire outcomes.[43]

Despite the use of validated questionnaires and personal interviews of patients, this study is limited by its dependency on questionnaires rather than objective tools, namely polysomnography. In addition, a recent study on ESRD patients undergoing dialysis reported that the accuracy of both Berlin and STOP-Bang questionnaires remain suboptimal (62% and 51%, respectively) which again emphasis the limitation of our study.[40]

Conclusions

The symptoms and risk of OSA are more common in ESRD patients than in the general population and affects both genders equally. The high-risk of OSA is associated with RLS and EDS. This calls for a comprehensive treatment of sleep disturbances, particularly OSA, in ESRD patients. Interestingly, we noted a significant negative correlation between OSA and HCV infection, which warrants further investigation.

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Conflicts of interest

There are no conflicts of interest.

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