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Risk of obstructive sleep apnea and hemodialysis efficacy

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ABSTRACT

Background: Obstructive sleep apnea (OSA) occurs frequently in hemodialysis (HD) patients with important consequences and increased mortality. However the role of adequacy of HD on the prevalence of OSA is less studied.

Objectives: Our aim was to screen OSA and evaluate the effect of HD adequacy on the risk of OSA.

Patients and Methods: This is a cross-sectional study on adult HD patients. Clinical and laboratory parameters were collected. The risk of OSA was assessed by STOP-BANG and Berlin questionnaire (BQ). Excessive daytime sleepiness (EDS) was evaluated with Epworth Sleepiness Scale (ESS). Kt/V index was applied for determining HD adequacy. Mortality followed after 2 years.

Results: Sixty-five patients (63% men, with a mean age of 53 ± 16.5 years) were included in the study. Most of the subjects were categorized as high risk by Berlin (68.3%) and STOP-BANG (84.6%) questionnaires and 25.8% had EDS. Participants who were categorized as high risk of OSA showed lower Kt/V ($P = 0.018$ based on BQ, $P = 0.002$ based on STOP-BANG). OSA risk was significantly correlated with Kt/V (OR: 0.007; CI: 0-0.36; p: 0.01). Two-year mortality was not significantly correlated with OSA.

Conclusion: OSA was prevalent in our HD patients and correlated with less adequacy of HD. Screening for this common disease by nephrologists using simple questionnaires is recommended.

Implication for health policy/practice/research/medical education:
Obstructive sleep apnea (OSA) is a common problem in hemodialysis (HD) patients with negative consequences. Our study suggested OSA is prevalent in our HD patients and could be correlated with adequacy of HD. So screening of OSA by STOP-BANG and Berlin questionnaire (BQ) and proper management of this problem is recommended to improve hemodialysis efficacy.

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1. Background

End-stage renal disease (ESRD) is a worldwide health problem with increasing prevalence and incidence globally and also in Iranian population. Nearly 47.7% of Iranian ESRD patients undergo hemodialysis (HD) as their renal replacement therapy with variable efficacy according to clinical and laboratory parameters. HD is accompanied by many health problems (1,2). Sleep disorder as a prevalent health problem can adversely affect the quality of life in ESRD patients (3,4).

Obstructive sleep apnea (OSA) is defined as repetitive obstructive respiratory pauses (each lasting at least 10 seconds) during sleep. OSA is a common respiratory sleep disorder in HD patients affecting 30%-80% of this

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population compared to 3%-7% in general population (3,5). In addition to impaired sleep quality and decreased daytime function, OSA can induce important morbidities (like hypertension, coronary artery disease, and stroke) and higher mortality in HD and other patients (6-10).

2. Objectives

We conducted this study to evaluate the prevalence of OSA in our HD patients and to assess the variables correlated with risk of OSA and long term mortality.

3. Patients and Methods

This was a prospective cross-sectional study. ESRD patients with at least 3 months (thrice-weekly) maintenance HD referred to Imam Reza university hospital, Mashhad, Iran were included in the study between April 2013 and April 2014. Those with a history of concurrent peritoneal dialysis, serious neurological and psychiatric disorders, history of opium or alcohol abuse, concurrent use of sedatives, uncontrolled hypothyroidism, and history of upper airway surgery, severe craniofacial abnormalities and those who did not accept to participate were excluded from the study.

After explaining designs and objectives of the study and receiving informed consent, demographic and anthropometric data of the subjects were gathered by a hemodialysis nurse trained in sleep apnea. History of systemic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease along with HD duration was recorded. Anthropometric variables included height, weight, neck, waist circumferences and body mass index (BMI) were collected.

Adequacy of HD was evaluated with urea kinetic modeling and expressed as Kt/V.

Hence, Kt/V ≥1.2 used as the marker of efficient dialysis according to 2006 KDOQI guidelines (11).

Other laboratory data including serum urea, creatinine, calcium, phosphorus, sodium, potassium, uric acid, hemoglobin concentration (HB), iron, total iron binding capacity (TIBC), ferritin, albumin, fasting blood sugar, cholesterol, triglyceride, and parathyroid hormone were gathered from dialysis chart review.

3.1. Obstructive sleep apnea assessment

Upper airway examination was evaluated by Mallampati scale (mouth opening amount classified from class-1 with visible soft palate, uvula and pillars to class-4 with only hard palate visible) and tonsillar hypertrophy. Subjects were also categorized as low and high risk for OSA by Persian versions of STOP-BANG (12) and Berlin questionnaire (BQ). STOP-BANG is a validated popular questionnaire consisting of 8 items used for screening of OSA: Snoring, daytime tiredness, observed pauses in breath, hypertension, BMI>35 kg/m^2, age>50 years, neck circumference>40 cm and male gender. A total STOP-BANG score ≥3 was considered as high risk for OSA (13). BQ is a validated and accurate questionnaire including 11 questions, which is divided into three sections. It addresses snoring and witnessed apnea, daytime fatigue and sleepiness and history of hypertension, height, weight, gender and body mass index (BMI). Individuals with positive results in ≥2 out of 3 categories were considered as high risk for OSA (14).

Excessive daytime sleepiness (EDS) was evaluated by Epworth Sleepiness Scale (ESS) which is an 8 items questionnaire. It asks patients to estimate their dozing propensity in different situations. Results are summed to a final score 0 to 24. ESS greater than 10 categorizes the subject as sleepy (15).

3.2. Follow up

Subjects were followed up by phone call 2 years after enrollment in the study in order to assess mortality rate.

3.3. Ethical issues

The research followed the tenets of the Declaration of Helsinki. After explaining designs and objectives of the study the informed consent was obtained. The patients' medical records were used anonymously for data gathering and this process was secret.

3.4. Statistical analysis

Normal distribution of variables was assessed by Kolmogorov-Smirnov test. Chi-square test was used to determine differences in the frequency of variables between two groups (low risk and high risk for OSA). Continuous variables according to normal distribution were tested via independent sample *t* test or Mann-Whitney U test. Two-sided *P* value ≤0.05 was considered statistically significant. Correlation of OSA risk with HD efficacy, demographic and anthropometric data was assessed. Univariable and multivariable logistic regression with backward method was used to determine the independent association of Kt/V on high-risk category OSA. SPSS (version 16, SPSS Inc., IL, USA) was used for statistical analysis.

4. Results

4.1. Descriptive analysis

A total number of 65 HD patients (63% men) with mean ± SD age of 53.0 ± 16.5 years were enrolled in the

study. Among them 49 patients (75.4%) were hypertensive and 21 (32.3%) had diabetes type 2. Mean ± SD for BMI and waist circumference was 23.1 ± 4.2 kg/m² and 89.4 ± 13.2 cm, respectively. Eleven patients (19%) were anemic (Hb <10 g/dL) with mean ± SD hemoglobin concentration of 11.2 ± 1.9 g/dL in all patients.

HD duration was ranged from 3 to 255 months. HD was efficient in 41 (67.2%) of patients with mean ± SD Kt/V of 1.33 ± 0.29. Grade 2 and 3 tonsillar enlargement were seen in 21.5% and 1.5%, respectively. Mallampati grade 3-4 was observed in 29 patients (44.6%).

The range of STOP-BANG and BQ scores were 1-6 and 0-32, respectively. High risk OSA was determined in 55 subjects (84.6%) and 43 (68.3%) according to STOP-BANG and BQ, respectively.

ESS score ranged from 0 to 16. Most of the subjects were in non-EDS group (74.2%) and 25.8% had EDS. Patients' demographic data are summarized in Table 1.

4.2. Correlation analysis

Subjects in high risk group (based on STOP-BANG) was significantly older (mean age 58.6 vs. 41 years, $P < 0.001$). Chi-square analysis showed male predominance (70.9% versus 20%, $P = 0.004$) and higher diabetes prevalence (38.2% versus 0.0%, $P = 0.024$) in high-risk versus low-risk group (based on STOP-BANG).

STOP-BANG questionnaire screening showed high risk OSA is associated with age, neck, waist circumference, Kt/V, male gender and diabetes. BQ screening showed high risk OSA is correlated with waist circumference, Kt/V and erythropoietin administration (Table 1).

Efficient HD was more prevalent in low-risk group (based on BQ) (90% versus 56.1%, $P = 0.009$) and also in no EDS group (73.8% versus 43.8%, $P = 0.031$).

Although anemia was not more prevalent in high risk group (according to BQ), using erythropoietin was more frequent in them (88.6% versus 66.7% in low-risk, $P = 0.04$). Lower hemoglobin concentrations were observed in EDS group (10.2 ± 2.01 versus 11.6±1.85, $P = 0.032$). Other clinical and laboratory variables were not significantly different in OSA (Table 1) and EDS groups. Univariable analysis for prediction of OSA based on STOP-BANG showed significant correlation with age, male gender, waist circumference and Kt/V (Table 2). However, after multivariable logistic regression we found only Kt/V and age were associated with OSA based on STOP-BANG (Table 2). Based on BQ, we found that waist circumference significantly associated with OSA risk after controlling for EDS, dialysis duration and Kt/V (OR: 1.96; 95% CI: 1.01-1.12, $P = 0.02$) (Table 3).

4.3. Follow up data

Total case fatality rate after 2-year follow-up was 21/65 (32.3%). Mortality was non-significantly more prevalent in high risk OSA group according to both STOP-BANG

Table 1. Comparison of variables between low risk and high risk OSA groups based on BQ and STOP-BANG

Characteristics[a]	Questionnaire					
	BQ			STOP BANG		
	Low risk OSA	High risk OSA	*P* value[b]	Low risk OSA	High risk OSA	*P* value[b]
Age (years)	50.24 ± 17.63	54.36 ± 16.03	0.35	41 ± 7.69	58.67 ± 15.71	<0.001[c]
Neck circumference (cm)	36.33 ± 3.79	37.48 ± 4.42	0.31	34.7 ± 3.23	37.55 ± 4.26	0.028[c]
Waist Circumference (cm)	84.67 ± 11.83	91.84 ± 13.47	0.04[c]	81.7 ± 8.58	90.93 ± 13.57	0.01[c]
BMI (kg/m²)	22.43 ± 6.57	24.59 ± 6.69	0.22	21.88 ± 2.82	23.38 ± 4.67	0.30
Dialysis duration (months)	59.17 ± 6.44	58 ± 6.3	0.09	68.2 ± 6.75	55.08 ± 6.17	0.15
Kt/V	1.44 ± .18	1.28 ± .32	0.018[c]	1.56 ± .21	1.29 ± .29	0.002[c]
Hemoglobin (g/dL)	11.67 ± 1.75	11 ± 2.02	0.23	11.6 ± 1.26	11.2 ± 2.07	0.48
BUN (mg/dL)	120.62 ± 30.98	126.66 ± 30.41	0.46	118.2 ± 32.85	125.89 ± 30.21	0.46
Male gender[d]	15 (71.4)	26 (59.1)	0.41	2 (20)	39 (70.9)	0.004[c]
Hypertension[d]	13 (61.9)	36 (81.8)	0.12	7 (70)	42 (76.4)	0.69
Diabetes[d]	4 (19)	17 (38.6)	0.15	0 (0)	21 (38.2)	0.02[c]
Kt/V[d] ≥1.2	18 (90)	23 (56)	0.009[c]	9 (90)	32 (62.7)	0.14
EDS[d]	7 (9.5)	13 (34.1)	0.06	7 (14.3)	42 (85.7)	0.12
Anemia[d] (Hb<10g/dL)	1 (5.6)	10 (25)	0.14	0	11 (22.9)	0.18
Erythropoietin use[d]	14 (66.7)	39 (88.6)	0.04[c]	7 (70)	46 (83.6)	0.37
2 years mortality[d]	4 (19)	17 (38.6)	0.15	2 (20)	19 (34.5)	0.48

[a] Values are expressed as mean ± SD.
[b] *P* values were tested by *t* test and Mann-Whitney U test.
[c] *P* value ≤0.05 was considered as statistically significant.
[d] Values were analyzed by chi-square test and expressed as number (percent).

Table 2. Univariable and multivariable logistic regression of variables associated to OSA (based on STOP-BANG)

Variable	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age	1.08 (1.02-1.14)	0.008*	1.09 (1.02-1.16)	0.01*
Waist circumference	1.07 (0.99-1.38)	0.05*	1.02 (0.94-1.12)	0.55
Diabetes	4.75 (0.77-9.31)	0.99	-	-
Kt/V	0.01 (0.001-0.35)	0.01*	0.007 (0.0-0.36)	0.01*
BUN	1.009 (0.99-1.03)	0.46	-	-
Hb	0.88 (0.61-1.26)	0.48	-	-
EDS	0.99 (0.86-1.14)	0.92	-	-

Table 3. Univariable and multivariable logistic regression of variables associated to OSA (based on Berlin Questionnaire)

Variable	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age	1.02 (0.98-1.05)	0.35	-	-
Male gender	1.73 (0.56-5.31)	0.34	-	-
Waist circumference	1.05 (1.00-1.09)	0.04[a]	1.06 (1.00-1.12)	0.025[a]
Diabetes	2.67 (0.77-9.31)	0.12	-	-
Kt/V	0.12 (0.01-1.03)	0.05[a]	0.22 (0.01-2.75)	0.24
Hb	0.83 (0.61-1.12)	0.23	-	-
Dialysis duration	0.99 (0.98-0.99)	0.02[a]	0.99 (0.98-1)	0.05[a]
EDS	1.13 (1.005-1.28)	0.04[a]	1.09 (0.95-1.24)	0.23

[a] *P* value ≤0.05 was considered as statistically significant.

(34.5% in OSA group versus 20%) and BQ (38.6% versus 19%) ($P=0.47$ and $P=0.15$ respectively). EDS group also showed non-significant higher mortality (50% versus 28.3% in non-EDS group) ($P=0.13$).

5. Discussion

Nocturnal HD has been shown to improve OSA severity (16). Volume overload and night time rostral fluid shift have been suggested as the pathogenic mechanisms for the high prevalence of OSA in HD patients (17). Our study reproduced the results of other studies in terms of high prevalence of OSA risk in HD patients (3, 18-20). Using STOP-BANG most of our patients (84.6%) were assessed as high risk of OSA which is much higher than general Iranian population (21). This high prevalence has been observed in other studies with a range of 64% to 80.6% (20, 19). Wali et al highlighted that BQ is a less sensitive tool for screening OSA in 44.2% of HD patients (21) while 68.3% of our patients were screened as high risk of OSA.

Univariable analysis showed a significant correlation between waist circumference and Kt/V. In multivariable analysis OSA was significantly associated with age and waist circumference (OR: 1.09, 95% CI: 1.02-1.16, $P=0.01$ and OR: 1.06, 95% CI: 1.00-1.12, $P = 0.025$, respectively).

Patients who were screened as high risk of OSA had lower Kt/V in comparison to the low risk of OSA group (Table 1).

Multivariate analysis revealed a significant negative independent correlation of OSA with Kt/V (OR=0.007, CI 95%: 0.0-0.36) which can be interpreted as a protective role of adequate dialysis for OSA. Similar results were observed in a Chinese cohort with reported lower dialysis dose (single-pool Kt/V) increases the risk of sleep apnea and likelihood of daytime sleepiness (EDS) (22).

Although EDS was not common in our patients (25.8%), a wide range of EDS prevalence has been reported in individuals undergoing HD (22.2 and 77%) (23, 18). This wide range of EDS can be explained by the subjective nature of ESS questionnaire. EDS can also be explained by day-night sleep reversal due to uremic encephalopathy and abnormal metabolism (24). This study showed anemia is significantly more prevalent in the EDS group. In other studies EDS was also correlated to older age, upper airways obstruction and Erythropoietin use (25). OSA is considered as a well-known independent risk factor for all-cause mortality (8-9,26). Our results showed no significant increase in mortality of high risk OSA subjects. Survey of a larger cohort with the use of polysomnography as the gold standard of OSA diagnosis can be more informative in terms of mortality.

6. Conclusions

Nephrologists should be more vigilant about early diagnosis of OSA in ESRD subjects in order to improve HD efficacy and prevent cardiovascular complications of OSA. STOP-BANG and BQ are simple tools for

screening OSA and referral for polysomnography in this population.

Study limitations

Small sample size and not using polysomnography as the most accurate tool for OSA diagnosis are some of our limitations.

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Authors' contribution

MA and FN designed the study. FR, MA, FN and AH conducted the research. NM and AH performed the statistical analyses. AH and MA prepared the final draft. All the authors studied and approved the final paper.

Conflicts of interest

The authors declare that they have not any conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. United States Renal Data System. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases; 2010.
2. Mousavi SS, Soleimani A, Mousavi MB. Epidemiology of end-stage renal disease in Iran: A review article. Saudi J Kidney Dis Transpl. 2014;25 (3):697-702.
3. Merlino G, Gigli GL, Valente M. Sleep disturbances in dialysis patients. J Nephrol. 2008;21 (Suppl 13):S66–70.
4. Merlino G, Piani A, Dolso P, et al. Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. Nephrol Dial Transplant. 2006;21:184-90. doi: 10.1093/ndt/gfi144.
5. Abuyassin B, Sharma K, Ayas NT, Laher I. Obstructive sleep apnea and kidney disease: a potential bidirectional relationship? J Clin Sleep Med. 2015;11 (8):915–924. doi: 10.5664/jcsm.4946.
6. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ. 2009;108 (5):246–249.
7. Mirrakhimov A.E. Obstructive sleep apnea and kidney disease: is there any direct link? Sleep Breath. 2012;16 (4):1009-16. doi: 10.1007/s11325-011-0624-8.
8. Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. J Am Soc Nephrol. 2002;13 (3):729-33.
9. Masuda T, Murata M, Honma S, Iwazu Y, Sasaki N,Oqura M et al. Sleep-disordered breathing predicts cardiovascular events and mortality in hemodialysis patients. Nephrol Dial Transplant. 2011;26 (7):2289-95. doi: 10.1093/ndt/gfq756.
10. Tuohy CV, Montez-Rath ME, Turakhia M, Chang TI, Winkelman JW, Winkelmayer WC. Sleep disordered breathing and cardiovascular risk in older patients initiating dialysis in the United States: a retrospective observational study using medicare data. BMC Nephrol. 2016;17:16. doi: 10.1186/s12882-016-0229-3.
11. National Kidney Foundation (NKF), "KDOQI clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. Am J Kidney Dis. 2006;48 (suppl 1):S1-322.
12. Sadeghniiat-Haghighi K, Montazeri A, Khajeh-Mehrizi A, Ghajarzadeh M, Alemohammad ZB, Aminian O. The STOP-BANG questionnaire reliability and validity of the Persian version in sleep clinic population. Qual Life Res. 2015; 24 (8):2025-30. doi: 10.1007/s11136-015-0923-9.
13. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S. STOP questionnaire a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008; 108 (5):812-21. doi: 10.1097/ALN.0b013e31816d83e4.
14. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131 (7):485-91.
15. Johns MW. "Daytime sleepiness, snoring, and obstructive sleep apnea: The Epworth Sleepiness Scale. Chest. 1993; 103 (1):30–36.
16. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med. 2001;344:102-7. doi: 10.1056/NEJM200101113440204.
17. White LH, Bradly TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnea. J Physiol. 2013;591 (5):1179-93. doi: 10.1113/jphysiol.2012.245159.
18. Sabry AA, Abo-Zenah H, Wafa E, Mahmoud K, El-Dahshan K, Hassan A, et al. Sleep disorders in hemodialysis patients. Saudi J Kidney Dis Transpl. 2010;21 (2):300-5.
19. Zibar L, Kristić A, Krnjeta D, Dogas Z. Risk for

sleep apnea syndrome and excessive daily sleepiness in chronic hemodialysis patients. Acta Med Croatica. 2011;65 (Suppl 3):30-5.
20. Wali SO, Alkhouli A, Howladar M, et al. Risk of obstructive sleep apnea among Saudis with chronic renal failure on hemodialysis. Ann Thorac Med. 2015;10 (4):263-8. doi: 10.4103/1817-1737.164300.
21. Amra B, Farajzadegan Z, Golshan M, Fietze I, Penzel T. Prevalence of sleep apnea-related symptoms in a Persian population. Sleep Breath. 2011;15 (3):425-9. doi: 10.1007/s11325-010-0353-4.
22. Chen WC, Lim PS, Wu WC, Chiu HC, Chen CH, Kuo HY, et al. Sleep behavior disorders in a large cohort of chinese (Taiwanese) patients maintained by long-term hemodialysis. Am J Kidney Dis. 2006;48 (2):277-84.
23. Brekke FB, Amro A, Hortemo Østhus TB, Dammen T, Waldum B, Os I. Sleep complaints, depression and quality of life in Norwegian dialysis patients. Clin Nephrol. 2013;80 (2):88-97. doi: 10.5414/CN107916.
24. Perl J, Unruh ML, Chan CT. Sleep disorders in end-stage renal disease: 'Markers of inadequate dialysis?' Kidney International. 2006;-70:-1687-93. doi: 10.1038/sj.ki.5001791 .
25. Abassi MR, Safavi A, Haghverdi M, Saedi B. Sleep Disorders in ESRD Patients Undergoing HemodialysisActa Med Iran. 2016;54 (3):176-184.
26. Tang SC1, Lam B, Yao TJ, Leung WS, Chu CM, Ho YW, et al. Sleep apnea is a novel risk predictor of cardiovascular morbidity and death in patients receiving peritoneal dialysis. Kidney Int. 2010;77 (11):1031-8. doi: 10.1038/ki.2010.76.