ORIGINAL ARTICLE

Sleep disordered breathing in patients with chronic kidney diseases: How far the problem?

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Abstract *Background:* Sleep-disordered breathing (SDB) is highly prevalent in patients with advanced chronic kidney diseases (CKDs).

Objective: To describe and compare the prevalence, severity, and patterns of SDB and associated nocturnal hypoxia among patients with advanced CKD, hemodialysis (HD) patients, and control group.

Methods: Forty patients were recruited from outpatient nephrology clinics and hemodialysis units. Patients were stratified into two groups: conservative ($n = 25$), and HD ($n = 15$). 30 healthy individual enrolled as the control group. All participants completed polysomnography (PSG).

Results: Case control study of forty CKD patients (15 HD and 25 conservative) [13(86.7%) and 20 (80%) men, mean age 62.73 ± 5.43 and 55.76 ± 9.03 year, BMI 40.83 ± 8.75 and 36.12 ± 16.53 kg/m, mean ESS 18.46 ± 3.20 and 17.84 ± 2.79), respectively, and 30 healthy participants served as the control. The prevalence of SDB in CKD was 33/40(82.5%). In the conservative group, AHI was 148.84 ± 147/h, [80% obstructive, 13% central, and 5% mixed apnea]. Among these conservative groups with OSA patients, 56% had severe, 31% moderate, and 12.5% mild OSA. While in the HD group, AHI 133.26 ± 111/h, [84.6% obstructive, 7.7% central, and 7.7% mixed apnea]. Among these HD groups with OSA, 63% had severe, 27% moderate, and 9% mild OSA. GFR was significantly correlated with AHI and ODI ($r = -0.315$, $P < 0.05$, $r = -0.506$, $P < 0.001$) respectively. AHI correlated with urea concentration ($r = -0.094$, $P < 0.05$). Increased creatinine, and decreased eGFR were significant risk factors of severe OSA. Predictors that reduced renal function were, decreased TST, delayed latency to REM sleep, and increased AHI.

Conclusions: Severe OSA was highly prevalent among CKD. Urea was the stronger predictor of increased AHI.

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Introduction

The prevalence of chronic kidney diseases (CKDs) is increasing worldwide, and there is increasing evidence linking sleep-disordered breathing (SDB) with kidney disease [1]. Sleep-disordered breathing refers to a wide spectrum of sleep-related breathing abnormalities; those related to an increase in upper airway resistance include snoring, upper airway resistance syndrome, and obstructive sleep apnea–hypopnea syndrome [2]. CKD describes patients with a chronically decreased glomerular filtration rate (GFR) or other evidence of kidney damage. There are different levels of CKD, which provide the basis of an international classification system [3]. Sleep disorders are common in patients with chronic renal failure [4,5]. Sleep apnea occurs in 50% of patients with end stage renal disease (ESRD); [6] which is considerably higher than in the general population [7]. The potential importance of sleep disordered breathing in the CKD population is highlighted by the worldwide mortality in end stage renal disease (ESRD) patients as high as 20 per cent per annum. It is also possible that sleep apnea accelerates the deterioration of kidney function in patients with CKD either indirectly by increasing systemic BP, inflammatory cytokines and sympathetic nervous system activity all of which have been proposed to reduce kidney function [8–10] or directly through the effect of hypoxia on the kidney [11,12]. Severe hypoxic events in obstructive sleep apnea (OSA) might lead to kidney damage [13]. Sleep disorders tend to be under-recognized by renal healthcare providers [13]. Polysomnography remains the gold standard for diagnosing sleep-disordered breathing. Monitoring should be done in conjunction with a comprehensive sleep medicine evaluation. Portable monitoring can be performed in a patient who cannot be safely transported for laboratory polysomnogram [14].

Subjects and methods

Forty patients with CKD, stages 5 as defined by an estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m according to the National Kidney Foundation Staging System [15], attended outpatient nephrology clinics and the hemodialysis unit of the Internal Medicine Department of the Menoufiya University Hospital from January 2011 to 2013. And 30 apparent healthy control subjects [eGFR] > 90 mL/min/1.73 m were invited to participate in the study. Exclusion criteria included supplemental oxygen use, tracheostomy, CPAP therapy and inability to give informed consent. The study was approved by the Health Research Ethics Board of the Menoufia University. Informed consent was obtained from all participants. Patients were stratified according to their estimated glomerular filtration rate (eGFR) at the time of the study visit and classified into two groups based on the National Kidney Foundation staging system as follows: CKD (eGFR < 13 mL/min/1.73 m^2 not on dialysis, $n = 25$), ESRD (on hemodialysis, $n = 15$), eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [15]. All patients completed a standardized sleep history questionnaire which included a history of snoring, witnessed apnea during sleep and nocturnal choking, un-refreshing sleep, morning headaches, insomnia, and memory impairment. Additionally,

the questionnaire surveyed demographic information and medical history, including a history of obesity (body mass index [BMI] $\geqslant$ 30 kg/m), hypertension, cardiovascular disease (angina, myocardial infarction, coronary artery bypass surgery, or congestive heart failure), cerebrovascular disease (stroke or transient ischemic attack), diabetes, chronic obstructive pulmonary disease (COPD), and medications. All patients completed the Epworth sleepiness score (ESS) [16]. The ESS is a self-administered questionnaire designed to measure the general level of daytime sleepiness. Patients rate on a scale of 0–3 how likely they are to fall asleep in 8 different situations that are commonly encountered. Total ESS scores range from 0 to 24, with higher scores indicating more subjective daytime sleepiness. Specifically, an ESS score > 10 is considered indicative of subjective daytime sleepiness [16]. All CKD patients performed an attended, overnight PSG in the sleep laboratory unit in chest Department Menoufia University. Dialysis patients were asked to perform the overnight study on a dialysis-free day. Overnight PSG was performed using (Embla S4000 Medcare, Iceland).The system has Somnologica studio 3.3.2 software, electrodes and cablestor record the electroencephalogram (EEG), electrooculogram (EOG),electromyogram (EMG) of the chin and bilateral tibialis anterior muscles, and electrocardiogram (ECG). Airflow was measured using nasal and oral thermistors, and a nasal pressure transducer. Respiratory effort was monitored with respiratory inductive polysomnography belts with thoracic and abdominal locks. Oximetry was measured using a disposable finger probe (oximeter flex sensor 8000J) placed on the index finger. Snoring was recorded using snore microphones (piezo snoring sensor) attached to the neck. Body position was monitored using a body position sensor. All studies were analyzed by trained PSG technicians and sleep physicians using the criteria of Rechtscaffen and Kales [17], and in close concordance with scoring updates given by the American Academy of Sleep Medicine [18].The traditional Rechtscaffen and Kales terminology for the 5 sleep stages (i.e. stages 1, 2, 3, 4, and REM sleep, with stages 1 and 2 collectively referred to as "light sleep", stages 3 and 4 collectively referred to as "deep sleep") were used in this study. Apneas were scored when there was a complete cessation of airflow or $\geqslant$90% drop in the peak thermal sensor excursion for at least 10 s. Hypopneas were scored when there was a drop in nasal pressure by $\geqslant$30% of baseline lasting at least 10 s with a $\geqslant$4% desaturation from pre-event baseline, or when there was a drop in nasal pressure signal excursion by $\geqslant$50% of baseline lasting at least 10 s with a $\geqslant$3% desaturation from pre-event baseline. The apnea–hypopnea index (AHI) which is the number of apnea–hypopnea events per hour was determined after the exclusion of periods with movements, which were considered to be wake periods. An apnea without chest or abdominal movements was classified as CSA and apnea with chest and abdominal movements was classified as OSA. Hypopneas were considered to be obstructive when there was evidence of upper airway obstruction, such as snoring, paradoxical respiratory band movement or inspiratory flow limitation through the nasal cannula; central hypopnea, in contrast, was associated with in-phase respiratory movements and no evidence of inspiratory flow limitation. SDB was considered to be central if greater than 50% of apnea/hypopnea events were central and obstructive if greater than 50% were obstructive [19].

Statistical data

Data were collected, tabulated, statistically analyzed by the computer using SPSS version 16, two types of statistics were done:

1- *Descriptive statistics:* Quantitative data are expressed to measure the central tendency of data and diversion around the mean, mean (*x*) and standard deviation (SD) Qualitative data are expressed in number and percentage.
2- *Analytic statistics:* ANOVA test was used for comparison of more than two groups of normally distributed variables;

Kruskal–Wallis test was used for comparison of more than two groups of normal distributed variables; Student *t* test was used to compare between two groups of quantitative data normally distributed; Mann–Whitney test was used to compare between two groups of quantitative data not normally distributed; Chi square test and chi-square (χ^2) tests were used to compare categorical outcomes. Pearson correlation (*r*) was used to detect association between quantitative variables.

Binary logistic regression was done for significant risk factors) *P* value > 0.05 was considered statistically non significant. – *P* value ⩽ 0.05 was considered statistically significant. – *P* value ⩽ 0.001 was considered statistically highly significant).

Results

The characteristics for all studied participants are shown in (Table 1). 15 patients attending HD unit and 25 patients with stage 4 kidney disease (conservative group) were completed the study (13/15 (86.7%) and 20/25 (80%) men, 8/15 (53.3%) and 15/25 (60%) current smokers, mean age 62.73 ± 5.4 and 55.76 ± 9.03 year, neck circumference 41.63 ± 3.22 and 39.06 ± 3.76 cm, BMI 40.83 ± 8.75 and 36.12 ± 16.53 kg/m², the mean ESS 18.46 ± 3.204 and 17.84 ± 2.79) respectively (Table 1). 30 apparent healthy participants served as control (23/30 (76.7%) men, mean age 54.83 ± 11.25 year, neck circumference 30.07 ± 2.66 cm, BMI 30.63 ± 9.47 kg/m², the mean ESS 6.50 ± 2.59). There were statistically significant differences between the studied groups regarding socio-demographic and anthropometric measurements. Sex distribution was statistically insignificant among the studied group. Patients with the conservative group were the youngest and the greatest proportion of current smokers (*P* < 0.001), while the HD group had significantly higher BMI, neck circumference and ESS (*P* < 0.05), compared with control group (Table 1). Among patients group, 20 (50%) were diabetic, 22 (55%) hypertensive, 24 (60%) IHD, 15(37.5%) cerebrovascular disease, and 20 (50%) COPD. The prevalence of hypertension, DM, and cardiovascular diseases were highly significant *P* < 0.001 in those with the conservative group (Table 2). Sleep related symptoms for all patients groups are displayed in (Table 2). The most common symptoms were EDS 22(55%), snoring 20(50%), insomnia 18(45%), while morning headache and nocturea were the least encountered symptoms 12(30%). There were highly significant differences *P* < 0.001 in the prevalence of reported snoring, EDS, insomnia, morning headaches, and nocturea among HD compared with the conservative group (Table 2).The laboratory characteristics for all studied patients groups (HD and conservative) are displayed in Table 3. There were statistically significant differences between the HD and conservative group regarding serum urea, creatinine, Ionized Ca + +, % of HCT, and eGFR. Sleep efficiency and monitoring time were sufficiently long to capture important respiratory events. Polysomnography Parameters and their unadjusted differences across study groups are shown in (Table 4). Total sleep time (TST), REM latency from sleep onset, AHI in supine position, PLM index, (%) of lowest oxygen saturation, AHI, oxygen desaturation index (ODI), % of snoring time in TST, % of REM in TST, total AHI in NREM, and Total AHI in REM were significantly different in the HD and conservative groups compared with control group. There were no significant differences in sleep onset, Sleep latency to S1 or S2, deep sleep latency (SWS), total arousal index, flow limitation index, % of sleep in supine position, total limb movement, and average oxygen saturation across three groups (Table 4). The prevalence of SDB in CKD was 33/40 (82.5%).Conservative group had more participants with SDB compared with the HD (20/25 [80%]; vs. 13/15 [86.6%]; *P* < 0.05), respectively. 5/25(20%); and 2/15(13.4%) were normal (AHI < 5) across both groups, respectively (Table 5). Sleep apnea was predominantly obstructive; very few central and/or mixed apneas were recorded among any of the participants (Table 6). In the conservative group, Mean AHI was 148.84 ± 147.79/h, (16/20 (80%) obstructive

Table 1 Showed socio-demographic data, anthropometric measurement, and Epworth sleepiness score (ESS).

Parameter	Dialysis $N = 15$	Conservative $N = 25$	Control $N = 30$	ANOVA	P value
Age (years)	62.73 ± 5.43	55.76 ± 9.03	54.83 ± 11.25	3.716	< 0.05
Male (No & %)	13(86.7%)	20(80%)	23(76.7%)	0.625*	> 0.05
Female (No & %)	2(13.3%)	5(20%)	7(24.3%)		
Smoker (No & %)	8(53.3%)	15(60%)	–	16.6	< 0.001
Non smoker (No & %)	7(47.7%)	10(40%)			
BMI (kg/m)	40.83 ± 8.75	36.12 ± 16.53	30.63 ± 9.47	3.633	< 0.05
Neck circumference	41.63 ± 3.22	39.06 ± 3.76	30.07 ± 2.66	2.21	< 0.05
ESS (0–24)	18.46 ± 3.204	17.84 ± 2.79	6.50 ± 2.59	146.39	*P* < 0.001
					Post hoc LCD
					P1 > 0.05
					P2 < 0.001
					P3 < 0.001

P1 between dialysis and conservative group, P2 between dialysis and control group, P3 between control and conservative group.

Table 2 Showed co-morbid diseases and symptoms of patients group.

Parameter (No&%)		Dialysis (n = 15)	Conservative (n = 25)	Total	X^2	P value
DM	Yes	6(40%)	14(56%)	20(50%)	32.7	<0.001
	No	9(60%)	11(44%)	20(50%)		
Hypertension	Yes	6(40%)	16(64%)	22(55%)	32.7	<0.001
	No	9(60%)	9(36%)	18(45%)		
Cardiovascular	Yes	9(60%)	15(60%)	24(60%)	0.0	1.0
	No	6(40%)	10(40%)	16(40%)		
Cerebrovascular disease	Yes	5(33.7%)	10(40%)	15(37.5%)	0.18	>0.05
	No	10(67.3%)	15(60%)	25(62.5%)		
COPD	Yes	7(46.7%)	13(52%)	20(50%)	0.11	>0.05
	No	8(53.3%)	12(48%)	20(50%)		
Snoring	Yes	6(40%)	14(56%)	20(50%)	32.7	<0.001
	No	9(60%)	11(44%)	20(50%)		
Excessive daytime sleepiness	Yes	6(40%)	16(64%)	22(55%)	32.7	<0.001
	No	9(60%)	9(36%)	18(45%)		
Insomnia	Yes	9(60%)	9(36%)	18(45%)	32.7	<0.001
	No	6(40%)	16(64%)	22(55%)		
Morning headache nocturia	Yes	12(80%)	0(0)	12(30%)	31.7	<0.001
	No	3(20%)	25(100%)	28(70%)		

Table 3 Showed laboratory characteristics of the studied patients group.

Parameter	Dialysis N = 15	Conservative N = 25	T test	P value
Creatinine (mg/dl)	3.606 ± .955	2.564 ± .591	4.278	<0.001
Urea (mg/dl)	218.667 ± 73.070	156.08 ± 78.52	2.503	<0.05
Na+ (mmol/l)	134.973 ± 6.316	135.960 ± 5.898	0.499	>0.05
K+ (mmol/l)	4.5133 ± .691	4.544 ± .834	0.12	>0.05
Ionized Ca++ (mg/dl)	3.906 ± .648	4.572 ± .382	4.09	<0.001
HCT (%)	30.106 ± 2.322	32.756 ± 2.280	3.533	<0.05
GFR mL/min/1.73 m	6.613 ± 2.350	13.52 ± 4.102	7.31	<0.001

apnea, 3/20 (13%) central apnea, 1/20 (5%) mixed apnea). Among these conservative groups with OSA patients, 9/16 (56%) had severe OSA (AHI >30/h), 5/16 (31%) had moderate OSA (AHI 15–30/h), and 2/16 (12.5%) had mild OSA (AHI 5–15/h).While in the HD group, Mean AHI was 133.26 ± 111.48/h, 11/13 (84.6%) obstructive apnea, 1/13 (7.7%) central apnea, and 1/13 (7.7%) mixed apnea). Among these HD groups with OSA patients, 7/11 (63%) had severe OSA (AHI >30/h), 3/11 (27%) had moderate OSA (AHI 15–30/h), 1/11 (9%) had mild OSA (AHI 5–15/h) (Tables 5–7). Age correlated with urea concentration (r = 0.353, P < 0.05), serum creatinine (r = 0.337, P < 0.05) and GFR (r = 0.615, P < 0.001), GFR significantly correlated with BMI, AHI or ODI (r = −0.351, P < 0.05, r = −0.315, P < 0.05, r = −0.506, P < 0.001), respectively (Table 11). Regarding correlation between AHI and markers of renal function, significant negative correlations were found between AHI and eGFR mL/min per 1.73 m^2 (r = −0.032, P < 0.05) (Table 9). AHI correlated with urea concentration (r = −0.094, P < 0.05), but interestingly, not serum creatinine (r = 0.120, P < 0.05) (Table 9). There was highly significant positive correlation between AHI and DI (r = 0.612, <0.001) (see Table 10). PLM significantly correlated with Serum K level (r = −0.100, P < 0.05) (Table 8). Serum Na level correlated with AHI, ODI and hypopnea(r = 0.323, P < 0.05, r = 0.394, P < 0.05, r = −0.411, P < 0.001), respectively (Table 11). Using Binary logistic regression model including risk factors regarding CKD, advanced age, increase BMI, diabetes, hypertension, smoking, elevated serum urea and creatinine level, decrease ionized Ca, HCT and decreased GFR were risky by: 0.940, 0.960, 0.030, 0.004, 0.032, 0.999, 0.464, 0.652, 1.145, 1.035, respectively (Table 12). Other Independent variables included TST,REM Latency from sleep onset, AHI, ODI, % of snoring time from TST, % of REM in TST, AHI in REM and NREM, PLM and lowest oxygen saturation. Predictors that accelerate the deleterious effect on the renal system included, decrease in total sleep time. Delayed sleep latency to the REM sleep, increase in AHI relative to supine position, low (eGFR), smoking, and decreased HCT%, while at older age, higher body mass index, diabetes, hypertension and other sleep parameters were not significant across ourmodels (Tables 13 and 14). The relationship between severe OSA (AHI >30 and ODI >30) on one side and risk factors on the other side was tested by multivariate logistic regression analysis, AHI and oxygen desaturation were regarded as dependant variables. And the independent variables included age, BMI, diabetes, hypertension, Smoking, serum urea and creatinine level, ionized Ca level, HCT, and GFR were risky by 1.007, 1.043, 0.488, 0.818, 0.402, 1.070, 0.996, 1.042, 0.839, and 3.68 times, respectively. Among traditional risk factors, advanced age, and increased BMI were all associated with severe obstructive sleep apnea. Additionally, increased serum creatinine, decreased ionized calcium and decrease eGFR were associated with severe OSA (Table 15).

Table 4 Polysomnography parameters across all studied groups.

Parameters	Hemodialysis (HD) $N = 15$	Conservative (CKD) $N = 25$	Control $N = 30$	Kruskal–Wallis test	P value	Post hoc
Total sleep time (TST) (min)	254.27 ± 71.165	288.21 ± 91.046	352.90 ± 114.433	5.856	<0.05	P1 > 0.05 P2 < 0.05 P3 < 0.05
Sleep onset (minute)	61.366 ± 66.209	51.020 ± 43.119	63.800 ± 18.744	0.681	>0.05	
Sleep latency to S1 (min)	33.140 ± 57.887	22.326 ± 26.838		0.649	>0.05	
Sleep latency to S2(minute)	37.806 ± 60.548	35.174 ± 40.639		0.027.	>0.05	
Deep sleep latency SWS (min)	99.580 ± 113.176	263.05 ± 830.224		0.569	>0.05	
REM latency from sleep onset (min)	33.13 ± 114.388	66.91 ± 90.413	114.10 ± 116.583	3.320	<0.05	P1 > 0.05 P2 < 0.05 P3 > 0.05
Spontaneous arousals index	27.760 ± 29.562	40.124 ± 26.920	34.733 ± 30.31	0.859	>0.05	
Flow limitation index % total	13.98 ± 16.511	9.980 ± 13.503	11.213 ± 10.92	0.435	>0.05	
% of sleep in supine position	44.41 ± 29.510	50.05 ± 31.905	50.60 ± 34.512	0.197	>0.05	
A + H/h in supine position	50.50 ± 30.526	39.96 ± .9.211	2.303 ± .1.867	30.608	<0.001	P1 > 0.05 P2 < 0.05 P3 < 0.05
Total limb movement	15.82 ± 170.360	11.97 ± 124.607	–	0.678	>0.05	
PLM movement	39.00 ± .62.249	30.52 ± 59.719	.100 ± ..402	4.798	<0.05	P1 > 0.05 P2 < 0.05 P3 < 0.05
Average oxygen saturation (%)	90.33 ± .7.239	89.93 ± 16.807	92.63 ± .5.542	0.451	>0.05	
Lowest oxygen saturation (%)	77.93 ± .11.732	79.08 ± 8.484	85.266 ± .8.76	4.344	<0.05	P1 > 0.05 P2 < 0.05 P3 < 0.05
AHI	133.266 ± .111.480	148.840 ± .147.791	2.303 ± .1.867	16.389	<0.001	P1 > 0.05 P2 < 0.001 P3 < 0.001
Oxygen desaturation events (OD)	203.33 ± .137.832	157.96 ± .148.999	3.880 ± .3.186	21.847	<0.001	P1 > 0.05 P2 < 0.001 P3 < 0.001
% of snoring time in TST	133.35 ± .155.843	181.11 ± .218.921	2.563 ± .6.499	10.416	<0.001	P1 > 0.05 P2 < 0.001 P3 < 0.001
%of REM in TST	11.820 ± .12.553	21.240 ± .19.902	9.700 ± .8.259	4.725	<0.05	P1 < 0.05 P2 > 0.05 P3 < 0.001
Total AHI in NREM	25.273 ± .22.806	30.704 ± .26.364	3.760 ± .7.297	14.330	<0.001	P1 > 0.05 P2 < 0.001 P3 < 0.001
Total AHI in REM	25.053 ± .17.273	31.384 ± .26.436	6.833 ± .11.169	12.008	<0.001	P1 > 0.05 P2 < 0.05 P3 < 0.001

P1 between dialysis and conservative group, P2 between dialysis and control group, P3 between control and conservative group.

Table 5 Showed different types of sleep related breathing disorders among studied patient's group (mean ± SD).

Parameters	Dialysis $n = 15$	Conservative $n = 25$	T test	P value
CKD with SDB $N = 33/40(82.5\%)$	13/15(86.6%)	20/25(80%)		<0.05
CKD without SDB $N = 7/40(7.5\%)$	2/15(13.4%)	5/25(20%)	0.29	>0.05
Light sleep 1 (mean ± SD)	59.767 ± 18.790	57.952 ± 24.553	0.246	>0.05
Deep sleep 1 (mean ± SD)	28.433 ± 22.318	20.296 ± 23.561	1.078	>0.05
OSA (mean ± SD)	60.400 ± 73.889	67.440 ± .82.712	0.073	>0.05
Central apnea (mean ± SD)	1.666 ± .2.894	6.680 ± .24.867	0.599	>0.05
Mixed apnea (mean ± SD)	3.133 ± .5.370	15.520 ± .43.202	1.209	>0.05
Hypopnea	68.066 ± .65.238	59.200 ± .60.678	0.189	>0.05

Table 6 Showed different types of sleep related breathing disorders among studied patient's group (No & %).

CKD	OSA	CSA	Mixed	Chi square test	P value
Conservative	16/20 (80%)	3/20 (13%)	1/20 (5%)	29.85	<0.001
(HD)	11/13 (84.6%)	1/13 (7.7)	1/13 (7.7%)	23.08	<0.001

Table 7 Showed different grades of OSA among studied patient's group (No&%).

CKD	Mild OSA AHI >5	Moderate OSA AHI 15–30	Severe OSA AHI >30	Chi square test	P value
Conservative	2/16 (12.5%)	5/16 (31%)	9/16 (56%)	6.94	<0.05
(HD)	1/11 (9%)	3/11 (27%)	7/11 (63%)	7.93	<0.05

Table 8 Showed correlation between PLM and different KFT, serum electrolytes and sleep parameters.

PLM	R	P value
Creatinine (mg/dl)	−0.185	>0.05
Urea (mg/dl)	−0.164	>0.05
Na (mmol/l)	−0.362	>0.05
K (mmol/l)	−0.100	<0.05
Ca (mg/dl)	−0.163	>0.05
HCT%	−0.179	>0.05
GFR mL/min per 1.73 m^2	0.146	>0.05
AHI	−0.012	>0.05
DI	0.044	>0.05

Table 10 Showed correlation between DI and different parameters.

DI	R	P value
Creatinine (mg/dl)	0.069	>0.05
Urea (mg/dl)	0.045	>0.05
Na (mmol/l)	0.394	<0.05
K (mmol/l)	0.068	<0.05
Ca (mg/dl)	0.221	>0.05
HCT (%)	−0.207	>0.05
GFR mL/min per 1.73 m^2	−0.153	<0.05
PLM	0.044	>0.05
AHI	0.612	<0.001

Table 9 Showed correlation between AHI and different parameters.

AHI	R	P value
Creatinine (mg/dl)	0.120	>0.05
Urea (mg/dl)	−0.094	<0.05
Na (mmol/l)	0.210	>0.05
K (mmol/l)	−0.002	>0.05
Ca (mg/dl)	−0.055	>0.05
HCT%	−0.133	>0.05
GFR mL/min per 1.73 m^2	−0.032	<0.05
PLM	−0.12	>0.05
DI	0.612	<0.001

Discussion

Sleep related breathing disorders (SDB) tend to be under-recognized by renal healthcare providers [13]. The aim of our study is to describe and compare the prevalence, severity, and patterns of SDB and associated nocturnal hypoxia among patients with advanced CKD, hemodialysis (HD) patients, and the control group (see Figs. 1 and 2).

In the current work the prevalence of SDB in CKD was 33/40(82.5%). Sleep apnea was predominantly obstructive; very few central and/or mixed apneas were recorded among any of the participants. In the conservative group, mean AHI was 148.84 ± 147.79/h, (80%) obstructive apnea, and (13%) central apnea, (5%) mixed apnea. Among these conservative groups with OSA patients, 56% had severe OSA (AHI >30/h), 31% had moderate OSA (AHI 15–30/h), and 12.5% had mild OSA (AHI 5–15/h).While in the HD group, mean AHI was 133.26 ± 111.48/h, (84.6%) obstructive apnea, (7.7%) central apnea, and (7.7%) mixed apnea. Among these HD groups with OSA patients, 64% had severe OSA (AHI >30/h), 27% had moderate OSA (AHI 15–30/h), and 9% had mild OSA (AHI 5–15/h). A systematic review of 17 studies in patients with end stage renal disease (ESRD) indicated that ''sleep disordered breathing'' was one of their most common

Table 11 Showed the correlation between kidney function testes and different sleep parameters.

GFR r P value	HCT r P value	Ca r P value	K r P value	Na r P value	Urea r P value	Creatinine r P value	Parameter
0.615	−0.274	−0.299	−0.141	0.094	0.353	0.337	Age
<0.001	>0.05	>0.05	>0.05	>0.05	<0.05	<0.05	
−0.351	−0.036	−0.225	0.102	−0.084	−0.053	−0.102	BMI
<0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
−0.315	−0.111	−0.100	0.013	0.323	−0.106	−0.004	Apnea−hypoapnea index
<0.05	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05	
−0.146	−0.066	−0.212	−0.011	0.189	−0.185	−0.069	Obstructive apnea
>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
0.162	−0.036	0.103	−0.211	−0.044	0.200	0.083	Central apnea
>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
0.077	0.164	0.236	−0.231	0.112	0.040	−0.061	Mixed apnea
>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
−0.114	−0.237	−0.112	0.239	0.411	0.114	0.087	Hypoapnea
>0.05	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05	
−0.506	−0.207	−0.125	0.068	0.394	0.045	0.069	Oxygen desaturation
<0.001	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05	
0.039	−0.193	0.003	−0.167	0.001	0.013	0.272	Flow limitation index
>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
0.143	0.080	−0.031	0.009	0.152	0.192	0.004	Light sleep
>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
0.020	−0.276	−0.003	0.040	−0.104	0.173	0.143	Deep sleep
>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	

comorbidities, with a mean prevalence of 44 percent [20]. Kraus [21] reported that the prevalence of sleep apnea in such patients ranges from 50 to 70 percent. Previous studies have evaluated the prevalence of sleep apnea in CKD. Markou et al. [22] reported a 31.4% prevalence of sleep apnea in a cross-sectional study of 35 patients with CKD, but their study was limited by a small sample size and the absence of comparative groups with eGFR <60 and ESRD. Further, patients with cardiovascular disease were excluded; limiting the generalizability of their findings because cardiovascular comorbidities are common in this patient population [23,24]. Sim et al. [25] reported an increased risk for sleep apnea in patients with mildly reduced eGFR. However, the prevalence of sleep apnea was low (2.5%), and the absence of BMI data precluded adjustment for the known association between obesity and sleep apnea [26], Canales et al. [27] declared an increased prevalence (27%) of sleep apnea in a cohort of elderly men but found no association with kidney function. Sakaguchi et al. [28] reported an increased prevalence (32%) of sleep apnea in 100 patients with CKD in Japan, which may not be generalizable to non-Asian populations. Roumelioti et al. [29] reported a high prevalence (22.5%) of severe sleep apnea in 89 patients with CKD but used historical control data where kidney function was undefined. Finally, in all of these studies, eGFR was determined using the Modification of Diet and Renal Disease Study equation, which is unreliable at eGFR ≥60, introducing potential misclassification bias [30–33]. Two recent American studies investigated the prevalence of SDB in patients with different degrees of chronic kidney disease and reported a prevalence of 26–57% [32]. Cornette et al. [32] had evaluated the prevalence of SDB in a large group of European patients undergoing CHD. 71 patients attending six CHD centers in the western part of Switzerland completed the study (50 men, mean age 61.8 ± 15.4, neck circumference 40.6 ± 4.6 cm, BMI 25.7 ± 4.8 kg/m^2). Mean AHI was 23.9 ± 20.4/h, (18% obstructive apnea, 8.5% central apnea,

and 2.4% mixed apnea). Among these 71 patients, 31% had severe SDB (AHI >30/h), 23.9% had moderate SDB (AHI 15–30/h), 31% had mild SDB (AHI 5–15/h) and 14.1% were normal (AHI <5/h). Our study had limitations. First, the potential for selection bias exists as patients attending the nephrology clinics may have been more likely to participate if they suspected they had sleep apnea. We tried to limit the potential impact of this on our findings by emphasizing that sleep related complaints were not required for recruitment. Although such a bias existed, a higher prevalence of sleep related breathing disorders (SDB) in CKD patients was the case. Second, we did not examine patients with the full spectrum of kidney function, ranging from those with eGFR ≥60 to ESRD. Third, we recruited a relatively small sample from a renal population representative of the CKD (stage 4–5) and ESRD populations only. Forth cardiovascular, cerebrovascular diseases, hypertension, and DM were not excluded, expanding generalizability of their findings because these comorbidities are common in this CKD population and had a potential effect on SDB. Markou et al., Canales et al., Roumelioti et al., and Young et al. [22,27,29,26] showed that the prevalence of OSA in this population has ranged from 27% to 54%, which is considerably higher than the general population [7]. These findings were in harmony with our results. Kimmel et al. [20] postulated that there was growing evidence that obstructive sleep apnea (OSA) was common in patients with chronic kidney disease who do not require chronic dialysis (CKD) 1. Unruh [34] mentioned that OSA is exceedingly common among individuals with end-stage renal disease, affecting an estimated 50% of patients [34]. But in a cross-sectional study of 158 individuals with suspected OSA, Fleischmann et al. [35] found that stage 3 CKD (defined as an eGFR <60 ml/min/1.73 m^2) was a statistically significant predictor of central sleep apnea events but not OSA events. However, data are limited by small sample size and selection bias because study participants were drawn from individuals with suspected

Table 12 Showed binary logistic regression between risk factors regarding dialysis and conservative group.

Variables	Exp (B)	95.0% CI for EXP (B)	
		Lower	Upper
Age (year)	.940	.823	1.075
BMI (weight/hight)	.960	.896	1.029
DM	.726	.030	17.873
HTN	.231	.004	14.847
Smoking	2.409	.032	183.660
Creatinine mg/dl	.464	.079	2.734
Urea mg/dl	.999	.987	1.011
Ionized Ca	.652	.074	5.776
HCT%	1.145	.761	1.723
GFR (mL/min per 1.73 m)	1.035	.616	1.738
Constant	403.74		

Table 15 Showed Binary logistic regression between risk factors.

Parameters	Exp (B)	95.0% C.I. for EXP (B)	
		Lower	Upper
Age (year)	1.007	.883	1.149
BMI (weight/hight)	1.043	.966	1.125
Diabetes	.488	.006	38.426
Hypertension	.818	.011	63.016
Smoking	.402	.005	29.486
Creatinine mg/dl	1.070	.165	6.947
Urea mg/dl	.996	.983	1.010
Ionized Ca mg/dl	3.683	.411	32.990
HCT%	.839	.536	1.312
GFR (mL/min/1.73 m^2)	1.042	.587	1.850
Constant	.768		

OSA. The coexistence of OSA in patients with CKD is likely to have clinical relevance. In addition to causing impairment of sleep quality and daytime function [9], furthermore, OSA may accelerate the deterioration of kidney function in patients with CKD either directly, through the effect of hypoxia on the kidney [9], or indirectly, by increasing systemic blood pressure, inflammatory cytokines, and sympathetic nervous system activity [11,12]. Gbemisola and Sylvia [36] concluded that OSA is associated with hypoxemia and sleep fragmentation, which activates the sympathetic nervous system, the renin angiotensin-aldosterone system, alters cardiovascular hemodynamics, and results in free radical generation. In turn, a variety of deleterious processes such as endothelial dysfunction, inflammation, platelet aggregation, atherosclerosis, and fibrosis are triggered, predisposing individuals to adverse cardiovascular events and likely renal damage [37]. Independent of obesity, OSA is associated with glomerular hyperfiltration and may be an independent predictor of proteinuria, a risk factor for CKD progression. OSA may mediate renal damage via several mechanisms, and there is a need to better elucidate the impact of OSA on incident renal disease and CKD progression [38]. Fluid retention may lead to airway edema nocturnal

Table 13 Showed multivariate analysis between dialysis group and the control group.

Variables	B	Wald	Sig.	Exp (B)	95.0% C.I. for EXP (B)	
					Lower	Upper
Total sleep time	.000	.000	.999	1.000	.953	1.049
REM latency from sleep onset	.009	.059	.807	1.009	.939	1.084
Apnea–Hypopnea (AH)	−.047	−.209	.648	.955	.782	1.165
Oxygen desaturation events	−.012	−.112	.738	.988	.919	1.061
%snoring time in TST	−.029	−.432	.511	.971	.891	1.059
%of REM in TST	−.062-	−.037	.848	.940	.497	1.776
Total AHI NREM index	−.079	−.096	.757	.924	.561	1.523
AHI relative to supine position	.004	.000	.983	1.004	.672	1.500
PLM movement	−.049	−.257	.612	.952	.789	1.150
Lowest oxygen saturation	−.072	−.015	.902	.930	.295	2.933

Table 14 Showed multivariate analysis between the conservative group and the control group.

| Variables	B	Wald	Sig.	Exp (B)	95.0% C.I. for EXP (B)	
					Lower	Upper
Total sleep time	.000	.000	.992	1.000	.952	1.051
REM latency from sleep onset	.006	.038	.846	1.006	.947	1.068
Apnea–Hypopnea (AH)	−.054	−.269	.604	.948	.774	1.161
Oxygen desaturation events	−.013	−.123	.726	.987	.919	1.061
Snoring time of TST	−.027	−.435	.510	.973	.898	1.055
% REM of TST	−.083	−.060	.807	.921	.475	1.786
Total AHI REM index	−.058	−.066	.798	.943	.603	1.475
AH/h in supine position	−.007	−.001	.972	.993	.678	1.456
PLM movement	−.048	−.284	.594	.953	.799	1.137
Lowest oxygen saturation	−.118	−.024	.878	.889	.198	3.989
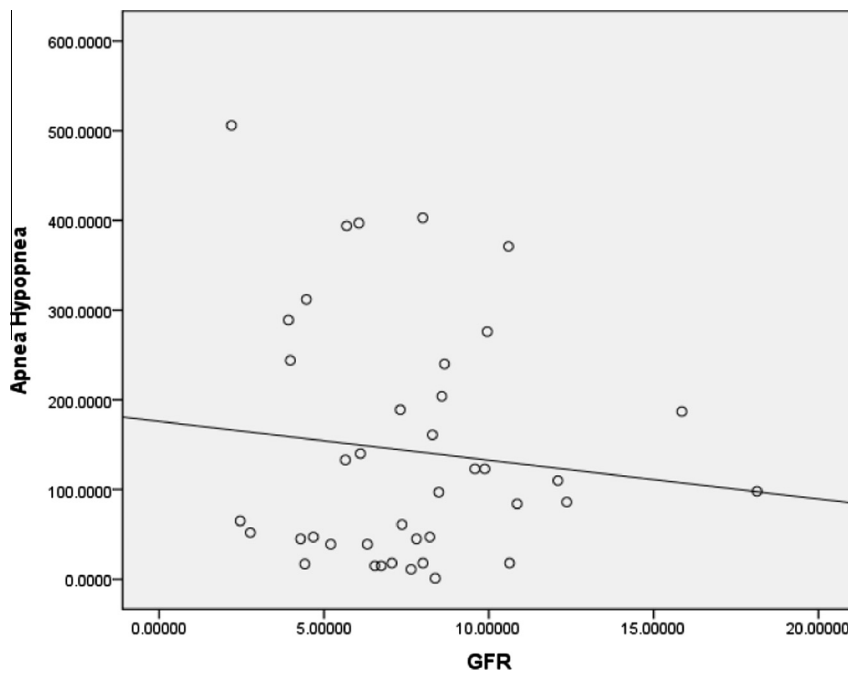
Figure 1 Showed significant negative correlation between GFR and AHI.
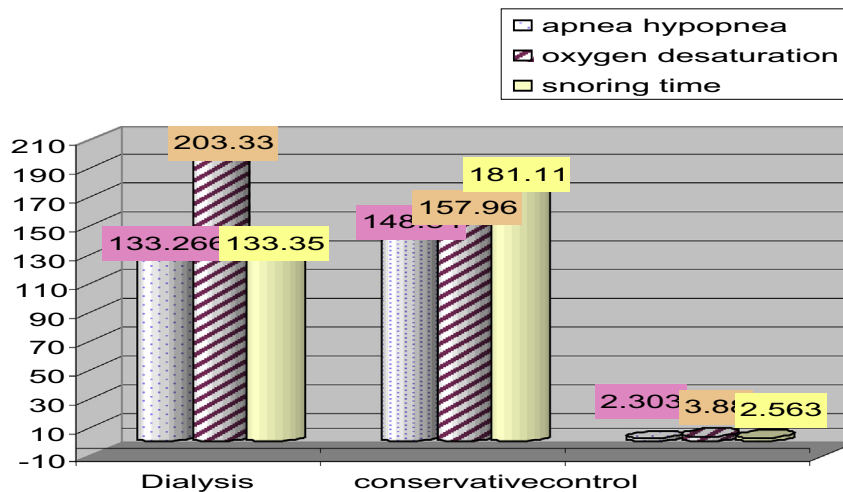

Figure 2 AHI, DI, and snoring time in three different studied groups.

hypoxemia, and the observed severity and obstructive patterns of SDB (5), Roumelioti et al. [5] found that potential pathophysiological mechanisms and mediators for the higher prevalence of SDB in the CKD and HD population included, increased pharyngeal cross-sectional area and abdominal circumference, over hydration, metabolic acidosis, high levels of proinflammatory cytokines, C-reactive protein, and triglycerides. Moreover sleep apnea increases the risk of hypertension [39], cardiovascular disease, and cerebrovascular disease [40,41], all of which are important and highly prevalent complications of both CKD and ESRD [42–44]. These complications of sleep apnea are predominantly mediated through nocturnal hypoxia, which has been associated with elevated nocturnal BP [38], left ventricular hypertrophy [37], and adverse cardiovascular outcomes in patients with ESRD [42,38]. Although it is likely that sleep apnea may have a

similar impact on clinical outcomes in patients with CKD, Shahar et al. [45] announced that the OSA has been independently associated with cardiovascular diseases, including hypertension [46], coronary heart disease, heart failure, and stroke [47]. Each of these factors can have a deleterious impact on renal function; thus, it is not surprising that OSA is a common clinical problem for patients with chronic kidney disease (CKD). Nieto et al. [46] postulated that the OSA is also associated with hypertension, another important risk factor for CKD progression, particularly proteinuric CKD. In the present work AHI correlated with urea concentration ($r = 0.094$, $P < 0.05$), and GFR ($r = -0.032$, $P < 0.05$) but interestingly, not serum creatinine level ($r = 0.120$, $P > 0.05$). However oxygen desaturation index (ODI) had been demonstrated to be independently associated with declined eGFR and accelerated loss of kidney function ($r = -0.153$, $P < 0.05$). This

finding was concordant with Markou et al. [22] they conducted a cross-sectional cohort study of 35 individuals with stable CKD, defined by a creatinine clearance less than 40 mL/min, AHI correlated with urea concentration ($r = 0.35$, $P = 0.037$), but not creatinine clearance ($r = -0.12$, $P = 0.506$). After excluding diabetic patients, Markou et al. [22] found that urea became an even stronger predictor of AHI ($r = 0.608$, $P = 0.001$), and a statistically significant relationship between creatinine clearance and AHI emerged ($r = -0.5$, $P = 0.012$). An important limitation of that study was the small sample size and absence of a control group. In another study of obese adults, increasing severity of OSA was associated with higher serum creatinine [47]. Agrawal et al. [47] emphasized that the markers of renal function, including serum urea concentration and creatinine clearance, also has been associated with OSA in CKD. Thus, there may be an association between renal function and sleep apnea. Marrone's group [48] analyzed 8,112 patients in the European Sleep Apnea Database (ESADA) seen for suspected OSA at 24 centers with polysomnography or cardiorespiratory polygraphy and who had data available to calculate eGFR. Overall, 8.5% of the cohort had an eGFR below 60 ml/min/1.73 m^2, all in the range of stage 3 kidney disease. That measure of kidney function correlated with Apnea–Hypopnea Index by home polygraphy ($P = 0.008$) but not by the more rigorous sleep study. The opposite was true for oxygen desaturation index, which correlated with eGFR on polysomnography ($P = 0.013$) but not polygraphy. Mean and lowest oxygen saturation were significantly linked with eGFR by both types of sleep study [48] the chronic hypoxia hypothesis suggests that chronic ischemic damage in the tubule-interstitium of the kidney is the final common pathway for the development of ESRD [12,49] if such a process is already under way in patients with CKD, it is possible that ongoing nocturnal hypoxia will amplify the effect and accelerate the decline in kidney function. If so, identification and treatment of nocturnal hypoxia may provide a potential disease-modifying intervention that could delay or halt the progression of CKD to ESRD. Controversially, an observational study showed that Severe hypoxic events in obstructive sleep apnea (OSA) might lead to kidney damage, though the sleep disorder appeared to be only a minor contributor overall, and the researchers reported that Mean oxygen saturation was not a significant predictor overall in the multivariate analysis, nor were there consistent correlations between eGFR and Apnea–Hypopnea Index [50]. These data imply that reduced kidney function may contribute to the pathogenesis of sleep apnea independently of traditional risk factors for sleep apnea and coexisting vascular disease. Both fluid overload [50] and altered chemical control of breathing [51,52] have been proposed to cause sleep apnea in patients with ESRD. It is possible that similar mechanisms contribute to the pathogenesis of sleep apnea in patients with CKD prior to starting dialysis. In the present work, the striking finding was the high prevalence of nocturnal hypoxia 203.33 ± 37.832 in patients with HD. Furthermore, only a portion of the nocturnal hypoxia in the HD groups was attributed to sleep apnea (mean AHI was 133.26 ± 11.48), suggesting that the pathogenesis was partly due to non-apneic factors. Co morbid pulmonary and cardiac diseases are possible mechanisms that can alter the mechanics and control of respiration, where 7/15(46.7%) of HD participants were COPD and 9/15(60%) were IHD. In other studies [51,53,54] multivariate

analysis revealed that COPD was associated with nocturnal hypoxia, but cardiovascular disease and use of sedatives and narcotics were not. Other potential causes, such as fluid overload, should be considered in future studies. We can expect that if a patient has a very important drop in oxygen saturation, it may in some way worsen his kidney function, especially if he has comorbidities. In the present work, among traditional risk factors, advanced age, and increased BMI were all associated with severe obstructive sleep apnea. Additionally, increased serum creatinine, decreased ionized calcium and decreased eGFR were associated with severe OSA. Predictors that accelerate the deleterious effect on the renal system included, decrease in total sleep time. Delayed sleep latency to the REM sleep, increase AHI relative to the supine position, low (eGFR), smoking, and decreased HCT%, while older age, higher body mass index, diabetes, hypertension and other sleep parameters were not significant across our models. Marrone [55] noted that, predictors of a low estimated glomerular filtration rate (eGFR) included older age, female gender, and higher body mass index across most models, while diabetes was significant in polysomnography-tested patients, and hypertension was significant in nocturnal cardiorespiratory polygraphy-tested patients. Marrone [55] noted that, potential mechanisms for a causal link to kidney damage could be intermittent hypoxia, metabolic abnormalities, hypertension, and sympathetic hyperactivity, the most likely explanation was via vascular damage in kidneys from hypoxic events. He announced that kidney is a vulnerable area of the body provided that there were comorbid conditions like diabetes and hypertension; it could accelerate the deleterious effect on the renal system. Our data revealed that, the most common sleep symptoms were EDS 22(55%), insomnia 20(50%), and snoring 20(50%) among CKD patients. The lack of excessive daytime sleepiness in a significant proportion of OSA patients with CKD18 (45%) has been reported in other specific OSA populations, including those with stroke [56], heart failure [57], hypertension [57,33], and end-stage renal disease [58]. There are a number of potential explanations for this observation that we can speculate on. First, it may reflect selection bias if the presence of sleep symptoms is not equally important in the recruitment of patients to the groups that are compared. Second, the complaint of subjective sleepiness may be overshadowed by other symptoms associated with chronic disease, such as anxiety or chronic fatigue, or side effects of their treatment such as medications. Third, the comorbid disease itself may hinder the development of excessive sleepiness through competing biologic mechanisms, such as augmented sympathetic activity in patients with chronic heart failure. Regardless of the explanation, the cumulative evidence indicates that daytime sleepiness is not a reliable diagnostic criterion for OSA in patients with many chronic medical disorders including CKD. Further, the absence of daytime sleepiness should not dissuade the clinician from considering a diagnosis of OSA in this patient population. In the present work, Sleep disorders among CKD patients, included, insomnia 20(50%), and periodic limb movement (PLM) disorder, it was significantly different in the HD and conservative groups compared with the control group ($P < 0.05$). Contributors to insomnia include periodic limb movement (PLM);and sleep apnea [59,60]; metabolic factors, including uremia, anemia, hypercalcemia [61,62], bone pain, and pruritus; anxiety and depression [63,64]; circadian rhythm disorders, such as delayed sleep phase syndrome [65]; the use of

medications that prevent sleep; and poor sleep hygiene, including frequent napping during daytime dialysis. Elevated plasma levels of orexin (a neuropeptide that promotes wakefulness) [66] and systemic inflammation [67,68] may also contribute to poor sleep among ESRD patients. The diurnal rhythm of melatonin is disturbed in patients with ESRD, and it is also related to the degree of kidney dysfunction in patients with chronic kidney disease (CKD) [69] Some studies have suggested that the timing of the dialysis shift alters the severity of insomnia, such that insomnia is worse among patients who are dialyzed in the morning [70,71], but this has not been shown in all studies [72]. Lugaresi et al. declared that Snoring would affect 19% to 37% of the CKD population and more than 50% of ESRD [73]. In our work 20(50%) of CKD were snorers, There were highly significant differences $P < 0.001$ in the prevalence of reported snoring, among HD compared with the conservative group. while% of snoring time in TST was significantly higher in the HD and conservative groups compared with the control group ($P < 0.001$). Present work revealed that older age was strongly associated with increased likelihood of severe SDB in the HD and CKD groups. This finding extends established knowledge from the general population; SDB occurs in 24% of older men and 56% of older women [74]. Differences in fat distribution, upper airway anatomy, neurochemical control mechanisms, arousal response, and hormones may underline these age differences in the general population [74] and are possibly operational in patients with renal dysfunction.

In conclusion, sleep related breathing disorders (SDB) tend to be under-recognized by renal healthcare providers. Objective polysomnography is required to reliably identify sleep apnea in the CKD population. Severe OSA is highly prevalent among advanced CKD & HD. Urea became a stronger predictor of increased AHI. Patients with CKD are commonly exposed to nocturnal hypoxia related to both unrecognized sleep apnea and other factors. Further studies are required to determine whether treatment of sleep apnea and nocturnal hypoxia improves these clinical outcomes in patients with CKD. A longitudinal follow-up study is needed to better characterize the natural history of SDB in patients with progressive CKD. Nephrologists should have a high index of suspicion for the diagnosis and treatment of SDB in symptomatic CKD and HD patients. OSA is treatable condition; therefore, additional studies are necessary to better define the role of OSA in renal injury and to identify ways of improving renal outcomes in CKD.

Conflict of interest

None declared.

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Further reading

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