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ORIGINAL ARTICLE

Sleep Disordered Breathing in Patients with Chronic Kidney Diseases

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Abstract

Background: **The incidence of chronic kidney disease (CKD) is rising globally, and there are raised proofs connecting sleep disordered breathing (SDB) with kidney diseases. Those proofs are attributed to increased upper airway resistance in such patients leading to a disturbed sleeping rhythm.**

Aim of the work: **To evaluate the incidence, severity, and patterns of SDB and related nocturnal hypoxia among people with advanced CKD, hemodialysis (HD), and healthy individuals.**

Patients and methods: **This case−control research was performed in the Departments of Chest Diseases and Nephrology Unit at Al-Azhar University Hospitals from January 2022 to December 2022. The study involved 60 participants diagnosed as CKD, either on regular follow-up in outpatients' clinics or attending to the HD unit. Twenty participants who appeared to be in good health served as a control group.**

Results: **The occurrence of SDB in CKD patients was 81.7 % and detected sleep apneas were predominantly obstructive. Severe obstructive sleep apnea (OSA) was frequent among different CKD patients. A significant strong positive correlation of periodic limb movement with serum K+ level was found. Moreover, significant good negative correlations of apnea−hypopnea index with estimated glomerular filtration rate (eGFR) and urea concentration were noticed. Blood urea, serum creatinine, and estimated glomerular filtration rate are independent variables associated with severe OSA.**

Conclusion: **SDB is frequently overlooked by renal healthcare providers. Severe OSA and nocturnal hypoxia are highly prevalent among advanced CKD and HD cases.**

Keywords: sleep disordered breathing (SDB), Hemodialysis (HD), Obstructive sleep apnea (OSA)

1. Introduction

Renal function declines in individuals with chronic kidney disease (CKD) over the course of several months to a year.[1]

Originally, patients may be completely symptomless. Later, emerging symptoms may contain leg swelling, tiredness, vomiting, and anorexia up to confusion in critical situations. Complicated patients may suffer from high blood pressure, higher risk of heart disease, bone disease, and anemia.[2]

The main causes of CKD are diabetes, hypertension, glomerulonephritis, vasculitis, immunologic disorders, and polycystic kidney disease. A family history of CKD is a vital risk factor. Diagnosis of CKD depends on measuring estimated glomerular filtration rate (eGFR), by Cockcroft method together with microscopic urine for albuminuria. Ultrasonography and renal biopsy are valuable tools that may uncover the underlying etiology.[3] The term 'sleep disordered breathing (SDB)' encompasses a wide variety of problems with breathing when sleeping. Recent studies suggested strong associations between SDB and a variety of chronic medical conditions including CKD.[4]

2. Patients and methods

This case−control research was performed at the Departments of Chest Diseases and Internal Medicine (nephrology and hemodialysis (HD) unit) in Al-

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Azhar University Hospitals from January 2022 to December 2022. The study involved 60 patients diagnosed as CKD, either on regular follow-up in outpatients' clinics or attending to the HD unit. Twenty apparently healthy subjects were enrolled as a control group. They were selected as the best match for patient groups in age, sex, and BMI. All participants were briefed on the nature of the investigation and provided verbal consent.

All patients were diagnosed with chronic kidney disease according to their eGFR (expressed in ml/min/1.73 m^2) at the time of enrollment in the research. According to the National Kidney Foundation's classification method, they were divided as follows: HD (Stage-5) group: comprised 20 cases with eGFR less than 15 ml/min/1.73 m^2. They were under regular HD for 12 h/week divided into 3 equal sessions. The onset of dialysis varied from 6 months to 5 years, while Stage-3 group involved 20 participants with eGFR = 30–59 ml/min/1.73 m^2, Stage-4 group consisted of 20 cases with eGFR = 15–29 ml/min/1.73 m^2. Cases in Stage-3 and -4 groups have never undergone dialysis and they were on conservative treatment when enlisted in the study.

While patients on supplemental oxygen, tracheostomy, and those previously diagnosed to have SDB or being on continuous positive airway pressure (CPAP) therapy for any reason were totally excluded from the study.

All included subjects were submitted to detailed medical history taking, Epworth Sleepiness Score (ESS) estimation that is a self-administered questionnaire designed to measure the general level of daytime sleepiness and vital sign measurement (pulse, blood pressure, temperature, and weight) (in kilograms)/height (in square meters), and also head and neck were carefully tested for craniofacial morphology, neck circumference, thyroid swelling, and any mandibular or maxillary malformation. The otorhinolaryngological examination was done to detect deviated nasal septum, turbinate hypertrophy, polyps, or adenoid hypertrophy if present. The cautious oropharyngeal examination was applied, including measuring uvula length and width, tonsils assessment according to Mallampati score (T0–T4), palatal position identification depending on Fisher et al. criteria, and finally, tongue position was graded enlightened by Friedman tongue position (FTP) classification (FTPI–FTPIV), plain chest radiograph, resting electrocardiogram (ECG), transthoracic echocardiography, abdominal ultrasound with special stress on both kidneys using the 2–6 MHz curvilinear probe of the ultrasound machine SonoScape-SS1 (SonoScape Medical Manufacturer, Shenzhen, Guangdong, China), and overnight polysomnography by means of Embla S 4000 device (Embla Systems, Inc., Missouri, USA) were performed to all study populations. Laboratory investigations counting complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) titer, liver enzymes, and renal function tests (blood urea and serum creatinine) were also implemented. eGFR and creatinine clearance were both calculated using Cockcroft and Gault equation:

$$\{(140-\text{age}) \times \text{weight}) / (72 \times \text{serum creatinine})\} \times 0.85 \ (\text{if female})$$

3. Results

Conservative patients' groups (Stage 3, Stage 4) were younger than the HD group Fig. 1.

They show the greatest proportion of current smokers ($P < 0.05$). Furthermore, CKD patients exhibited significant ESS ($P < 0.05$) in contrast to the control group Table 1.

The prevalence of common comorbidities among the patients groups was 66.6 % for hypertensive, 61.6 % for diabetes, 33.4 % for ischemic heart disease (IHD), and 38.3 % for cerebrovascular diseases Table 2.

In our study, the most commonly reported sleep-related symptoms were insomnia in 36 (60 %) patients, snoring in 34 (56.6 %) patients, and excessive daytime sleepiness (EDS) in 33 (55 %) patients, while morning headache and nocturia were the least-encountered symptoms, being watched in 32 (53.3 %) patients. There were significant variations ($P < 0.05$) among the frequency of all former symptoms in the HD group and the control group Table 3.

Considering laboratory results, there were significant distinctions in serum urea, creatinine, ionized Ca++, hematocrit (HCT) percentage, and eGFR among the HD and conservative groups Table 4.

Total sleep time (TST), periodic limb movement (PLM) index, % of the lowest oxygen saturation, apnea–hypopnea index (AHI), oxygen desaturation

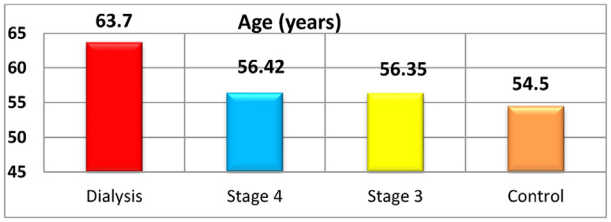

Fig. 1. Age distribution in different study groups.

Table 1. Sociodemographic data, anthropometric measurement, and Epworth Sleepiness Score in different studied groups.

Parameters	Dialysis $N = 20$	Stage 4 $N = 20$	Stage 3 $N = 20$	Control $N = 20$	Statistical analysis P value
Age (y)	63.7 ± 10.8	56.42 ± 8.4	56.35 ± 9.2	54.5 ± 6.7	$F = 2.8 < 0.05$
Sex					
Male	17 (85 %)	15 (75 %)	16 (80 %)	15 (75 %)	$X^2 = 0.82 > 0.05$
Female	3 (15 %)	5 (25 %)	4 (20 %)	5 (25 %)	
Smoking					
Smoker	11 (55 %)	14 (70 %)	12 (60 %)	1 (5 %)	$X^2 = 20.2 < 0.05$ *P*1, *P*2; *P*6>0.05 *P*3, *P*4, *P*5 <0.05
Nonsmoker	9 (45 %)	6 (30 %)	8 (40 %)	19 (95 %)	
BMI (kg/m^2)	32.2 ± 9.2	34.7 ± 8	32.6 ± 7.9	33 ± 10.2	$F = 3.2 > 0.05$
Neck circumference	38.4 ± 3.6	39.1 ± 2.9	39.38 ± 2.4	37.9 ± 2.8	$F = 1.9 > 0.05$
ESS (0–24)	18.9 ± 3.2	17.2 ± 4.1	17.1 ± 3.9	8.2 ± 2.8	$F = 16.6 < 0.001$ *P*1, *P*2; *P*6>0.05 *P*3, *P*4, *P*5 <0.05

Table 2. Comorbid diseases of studied patients' groups.

Parameter (No)	Dialysis $N = 20$	Stage 4 $N = 20$	Stage 3 $N = 20$	Total	X 2	P value
Hypertension						
Yes	18	12	10	40 (66.6 %)	7.8	<0.05
NO	2	8	10	20 (33.4 %)		
DM						
Yes	17	11	9	37 (61.6 %)	7.33	<0.05
NO	3	9	11	23 (38.4 %)		
Cardiovascular						
Yes	11	5	4	20 (33.4 %)	6.45	<0.05
NO	9	15	16	40 (66.6 %)		
Cerebrovascular disease						
Yes	6	9	8	23 (38.3 %)	0.98	>0.05
NO	14	11	12	37 (61.7 %)		

Table 3. Symptom diseases of studied patients' groups.

Parameter (No)	Dialysis $N = 20$	Stage 4 $N = 20$	Stage 3 $N = 20$	Total	X 2	P value
Snoring						
Yes	16	10	8	34 (56.6 %)	7.05	**<0.05**
NO	4	10	12	26 (43.4 %)		**0.029**
Excessive daytime sleepiness						
Yes	15	12	6	33 (55 %)	8.48	**<0.05**
NO	5	8	14	27 (45 %)		**0.014**
Insomnia						
Yes	15	14	7	36 (60 %)	7.91	**<0.05**
NO	5	6	13	24 (40 %)		**0.019**
Morning headache nocturia						
Yes	14	12	6	32 (53.3 %)	6.96	**<0.05**
No	6	8	14	28 (46.7 %)		**0.03**

Table 4. Laboratory characteristics of the studied patients' group.

Parameter	Dialysis $N = 20$	Stage 4 $N = 20$	Stage 3 $N = 20$	Anova	P value
Creatinine (mg/dl)	4.69 ± 1.69	2.66 ± 0.703	2.99 ± 0.502	5.1	<0.001
Urea (mg/dl)	218.609 ± 73.90	156.35 ± 76.5	160.50 ± 77.51	2.40	<0.05
K+ (mmol/l)	4.52 ± 0.691	4.54 ± 0.550	4.60 ± 0.630	0.15	>0.05
Ionized Ca++ (mg/dl)	3.8 ± 0.58	4.5 ± 0.37	4.7 ± .47	4.22	<0.001
HCT (%)	30.80 ± 2.3	32.75 ± 2.8	31.80 ± 2.9	3.6	<0.05
GFR ml/min/1.73 m^2	9.22 ± 3.3	38.5 ± 7.33	20.23 ± 5.2	6.2	<0.001

Table 5. Polysomnography parameters across all examined groups.

Parameters	Dialysis $N = 20$	Stage 4 $N = 20$	Stage 3 $N = 20$	Control $N = 20$	P value	Post hoc
Total sleep time (TST) (min)	230 ± 61.2	264 ± 93.01	271 ± 86.16	352 ± 101	<0.05	*P*1, *P*2, *P*6>0.05, *P*3, *P*4, *P*5<0.05
Spontaneous arousal index	42.670 ± 30.5	39.5 ± 27.2	37.50 ± 28.50	35.06 ± 32.05	**>0.05**	
PLM	38.05 ± 63.5	34.5 ± 58.8	32.5 ± 57.9	.109 ± 0.415	**<0.05**	*P*1, *P*2, *P*6>0.05, *P*3, *P*4, *P*5<0.05
Average oxygen saturation (%)	89.90 ± 6.89	88.87 ± 8.9	88.56 ± 7.9	92.50 ± 5.20	**>0.05**	
Lowest oxygen saturation (%)	78.50 ± 11.50	79.05 ± 9.5	80.50 ± 8.7	85.88 ± 8.65	**<0.05**	*P*1, *P*2, *P*6> 0.05, *P*3, *P*4, *P*5<0.05
AHI	55.5 ± 33.20	53.06 ± 29.78	52.08 ± 28.07	2.5 ± 2.10	**<0.001**	*P*1, *P*2, *P*6>0.05, *P*3, *P*4, *P*5<0.001
Oxygen desaturation events (OD)	203.37 ± 133.2	162.78 ± 145.52	160.96 ± 146.87	3.88 ± 3.21	**<0.001**	*P*1, *P*2, *P*6> 0.05, *P*3, *P*4, *P*5<0.001
% of snoring time in TST	186.45 ± 160.21	184.5 ± 210.05	182.24 ± 215.68	2.563 ± 6.452	**<0.001**	*P*1, *P*2, *P*6> 0.05, *P*3, *P*4, *P*5<0.001
Total AHI in NREM	35.273 ± 23.80	28.073 ± 28.50	27.50 ± 29.30	3.760 ± 7.29	**<0.001**	*P*1, *P*2, *P*6>0.05, *P*3, *P*4, *P*5<0.001
Total AHI in REM	30.384 ± 17.101	25.561 ± 29.10	23.58 ± 32.85	6.833 ± 11.161	**<0.001**	*P*1, *P*2, *P*6>0.05, *P*3, *P*4, *P*5<0.001

Table 6. Prevalence and type of sleep disordered breathing among the studied (patient's and control) group.

Parameters	Dialysis $N = 20$	Stage 4 $N = 20$	Stage 3 $N = 20$	Chi-square test	P value
CKD without SDB $N = 11/60$ (18.3 %)	3/20 (15 %)	3/20 (15 %)	5/20 (25 %)	**0.89**	**>0.05**
CKD with SDB $N = 49/60$ (81.7 %)	17/20 (85 %)	17/20 (85 %)	15/20 (75 %)		

index (ODI), % of snoring time in TST, total AHI in nonrapid eye movement (NREM) sleep, and total AHI in rapid eye movement (REM) sleep were substantially distinct in the CKD groups in comparison with the control group. While there were no variations among the same three groups in terms of spontaneous arousal index or average oxygen saturation, there was a variance among the three groups in terms of heart rate variability Table 5.

In the present research, the frequency of SDB in CKD cases was 49/60 (81.7 %). On a detailed face, this prevalence was 32/40 (80 %) in the conservative groups and 17/20 (85 %) in the HD group Table 6.

Our data demonstrated an established positive connection between PLM and serum K+ level ($r = -0.6$, $P < 0.05$) Table 7.

Age was observed to be positively linked to urea concentration ($r = 0.52$, $P < 0.05$), serum creatinine ($r = 0.41$, $P < 0.05$), and eGFR ($r = -0.812$, $P < 0.001$) Fig. 2.

Table 7. Correlation among periodic limb movement and various KFT, serum electrolytes, and sleep parameters.

PLM	r	P value
Creatinine (mg/dl)	−0.196	>0.05
Urea (mg/dl)	−0.165	>0.05
K (mmol/l)	−0.6	<0.05
Ca (mg/dl)	−0.163	>0.05
GFR mL/min/1.73 m^2	0.166	>0.05
AHI	−0.311	>0.05

KFT, kidney function test.

eGFR showed a significant negative correlation with BMI Fig. 3.

AHI, and ODI ($r = -0.432$, $P < 0.05$, $r = -0.411$, $P < 0.05$, $r = -0.807$, $P < 0.001$) correspondingly. As well, serum Na + levels denoted significant positive correlations with AHI, ODI, and hypopnea ($r = 0.422$, $P < 0.05$, $r = 0.322$, $P < 0.05$, $r = -0.312$, $P < 0.05$) correspondingly Table 8.

4. Discussion

Sleep disturbances and CKD are common comorbid conditions, especially in the elderly.[5] It is still unobvious whether the link between SDB and CKD is single or double-directional.[6]

In this work, statistically significant differences were observed among the examined groups as regards age and anthropometric measurements. Conservative patients' groups (Stage 3, Stage 4) were younger than the HD group, and they show the greatest proportion of present smokers ($P < 0.05$). Furthermore, CKD patients exhibited significant ESS ($P < 0.05$) contrasted with the control group.

The distribution of common comorbidities among our patients' groups was 66.6 % for hypertensive, 61.6 % for diabetes, 33,4 % for IHD, and 38.3 % for

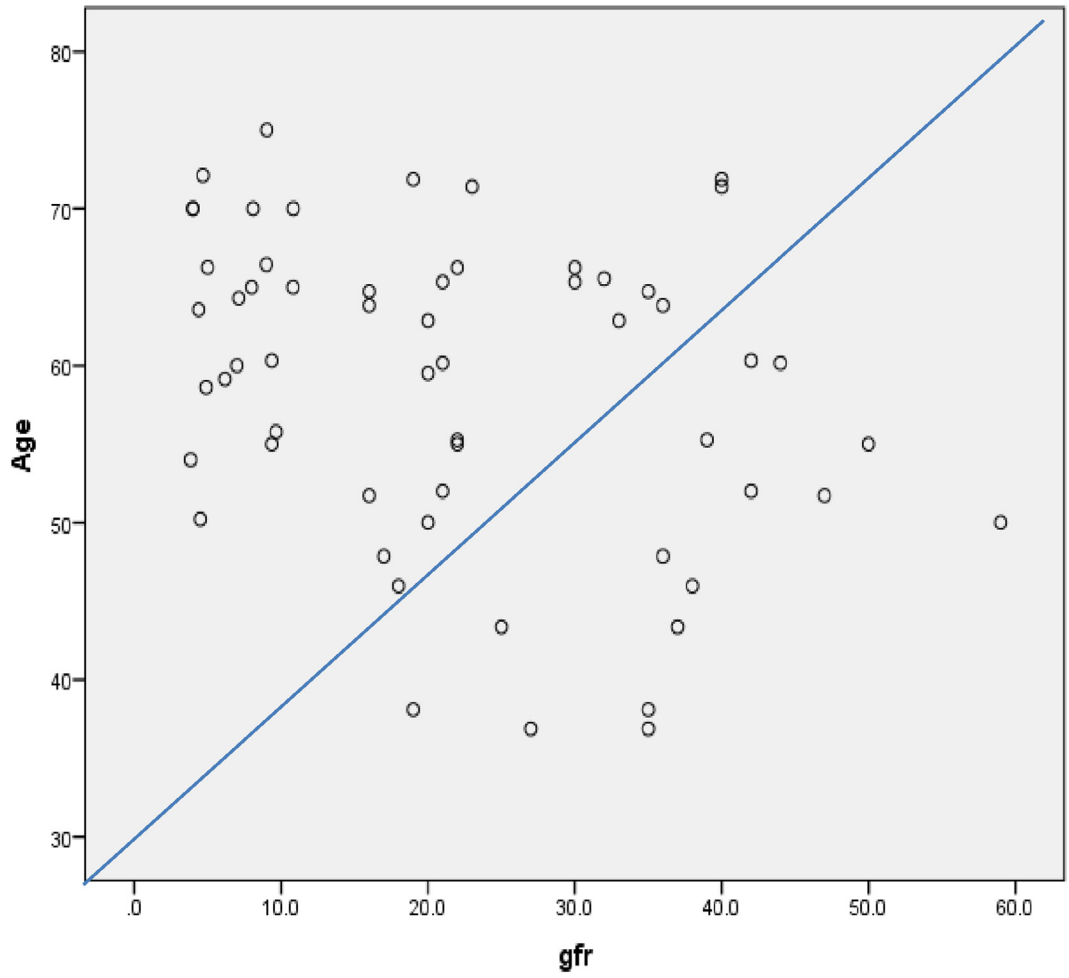

Fig. 2. Correlation between glomerular filtration rate and age.

cerebrovascular diseases. These results are compatible with Redline et al. who revealed that hypertension, diabetes, and cardiovascular diseases were highly prevalent in both CKD and end-stage renal disease (ESRD) patients.[7]

In our study, the most common reported sleep-related symptoms were insomnia in 36 (60 %) patients, snoring in 34 (56.6 %) patients, and EDS in 33 (55 %) patients, while morning headache and nocturia were the least-encountered symptoms, being watched in 32 (53.3 %) patients.

Those findings are not far from those of Sabbatini et al., who show that 45 % of cases with ESRD were influenced by insomnia.[8]

On the contrary, a large study that included 883 patients on maintenance dialysis demonstrated that daytime somnolence has been anecdotally reported in dialysis patients.[9] It was the first study performed with the purpose of quantifying subjective daytime sleepiness in a large number of cases with ESRD.

In this study, the prevalence of SDB in CKD patients was 49/60 (81.7 %). On a detailed face, this prevalence was 32/40 (80 %) in the conservative groups and 17/20 (85 %) in the HD group. The vast majority of recorded sleep apneas were obstructive.

This overall percentage is almost identical to that observed by Menofiea and colleagues who reported that the prevalence of SDB in CKD was 33/40 (82.5 %).[10] However, it appears low when compared with the 96 % demonstrated by another study.[11]

This finding is in line with the findings of a meta-analysis of 17 studies that found SDB to be one of the most prevalent comorbidities among those with ESRD, with a mean prevalence of 44 %.[12] Half of the way, Kraus found that 50–70 % of the individuals with this condition also suffered from sleep apnea.[13] Additionally, Individuals with mildly impaired eGFR were shown to have an increased risk of sleep apnea, as reported by Sim et al.[14]

On the opposite side, Cornette et al. documented a SDB prevalence of 26–57 % in cases with different degrees of CKD.[15] Similarly, Markou and colleagues revealed a prevalence of sleep apnea of 31.4 % in a cross-sectional investigation of 35 individuals with

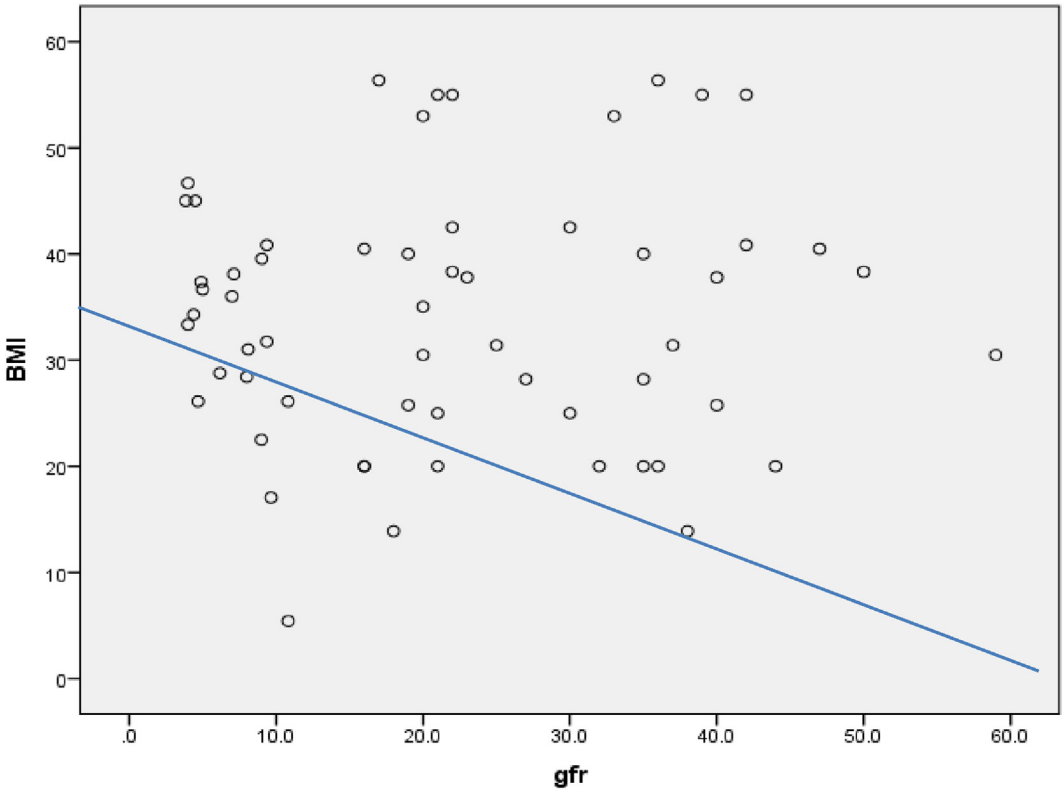

Fig. 3. Negative correlation between glomerular filtration rate and BMI.

CKD, however, their analysis was constrained by a lack of comparison groups with eGFR less than 60 and ESRD.[16]

An Egyptian study shows that all of the participants in the study reported having issues with sleep, which involves daytime sleepiness, waking up too early, and jerky leg movements. Total sleep time, oxygen desaturation, respiratory distress, and PLM indices were all lower in individuals with CKD than in controls. Leg jerk complaints were more common and ESS was higher in HD patients than in non-dialysis individuals.[17] Total sleep time and oxygen saturation were adversely connected with a patient's age, while the respiratory distress index was positively correlated with age.

In this study, severe OSA (AHI >30) was predominant among different CKD patients. This finding agrees with Roumelioti and colleagues who

Table 8. Correlation among kidney function testes and different sleep parameters.

Parameter	Creatinine	Urea	Na	K	HCT	GFR
	r	r	r	r	r	r
	P value	*P* value	*P* value	*P* value	*P* value	*P* value
Age	0.41	0.52	0.084	−0.131	−0.294	0.812
	<0.05	<0.05	>0.05	>0.05	>0.05	<0.001
BMI	−0.103	−0.053	−0.094	0.112	−0.036	−0.432
	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05
Apnea–hypoapnea index	−0.003	−0.106	0.422	0.031	−0.141	−0.411
	>0.05	>0.05	<0.05	>0.05	>0.05	<0.05
Obstructive apnea	−0.068	−0.195	0.179	−0.021	−0.066	−0.156
	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Hypoapnea	0.097	0.124	0.312	0.249	−0.247	−0.114
	>0.05	>0.05	<0.05	>0.05	>0.05	>0.05
Oxygen desaturation index	0.079	0.055	0.322	0.078	−0.217	−0.807
	>0.05	>0.05	<0.05	>0.05	>0.05	<0.001

reported that 80 % of participants with different stages of CKD had moderate or severe sleep apnea.[11]

Directly, by the effect of hypoxia on the kidney, or indirectly, through the increase in systemic blood pressure, inflammatory cytokines, and sympathetic nerve activity, OSA may hasten the decline of renal function in individuals with CKD.[18]

The hypoxemia and sleep fragmentation caused by obstructive sleep apnea stimulate the sympathetic nervous system, the renin angiotensin–aldosterone system, change cardiovascular hemodynamics, and generate free radicals. Endothelial dysfunction, inflammation, platelet aggregation, atherosclerosis, and fibrosis are all downstream effects, putting people at risk for cardiovascular problems and possibly kidney injury.[18] Nocturnal hypoxemia, fluid retention, and the severity and obstructive patterns of SDB all have been linked to OSA, which may mediate renal injury.[11]

Our research has some caveats. To start, there is the possibility of selection bias, as patients visiting the nephrology clinics may have been more inclined to participate if they felt they had sleep apnea. We sought to mitigate this by stressing that participants did not need to be experiencing sleep problems in order to be recruited. Second, we did not look at patients with a wide range of kidney function, from those with an eGFR of greater than or equal to 60 to those with ESRD. Third, we only included people who had kidney failure (Stages 3–5) or ESRD in our sample.

4.1. Conclusion

SDB tends to be under-recognized by renal healthcare providers. Severe OSA is highly prevalent among advanced CKD and HD patients. Nighttime hypoxia, brought on by both undiagnosed sleep apnea and other reasons, is a common risk among individuals with CKD. Increased serum creatinine and urea, together with decreased ionized calcium and eGFR, could be strong predictors of increased AHI.

4.2. Recommendations

The diagnosis and management of SDB among individuals with symptomatic CKD and HD should raise the nephrologist's index of suspicion. All cases with CKD should be screened for the presence of associated SDB, especially if there is a history of EDS. Large sample sizes are needed, to enable the detection of SDB in patients with CKD.

Conflicts of interest

There is no any conflict of interest.

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