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Creatinine Clearance in Patients with Obstructive Sleep Apnea

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Abstract: During an apnea, hemodynamic complications such as hypoxemia, a rise in systemic and pulmonary arterial pressure, and changes in heart rate occur in patients with obstructive sleep apnea (OSA). Potential mechanisms of OSA-associated renal dysfunction include renal hypoxia, hypertension, endothelial dysfunction. Hypertension is common in patients with OSA. This study aims to assess OSA patients' renal functions and investigate the creatinine clearance (CC) values across OSA patients with and without hypertension. The study included 530 individuals with OSA and 60 individuals with an apnea-hypopnea index (AHI) of <5. CC was calculated with the Cockcroft-Gault Equation. Patients with OSA were divided into two groups as the group of patients with hypertension (HT) (group 1) and without HT (group 2). The study included 339 (64%) male and 191 (36%) female patients. It was found that 32.4% of OSA patients had HT (Group 1). There was a significant difference in CC and urea levels between groups 1 and 2 ($p<0.001$; $p=0.005$). While CC was low in the OSA group, CC values were not statistically significantly different between the OSA patients and the control group ($p>0.05$). A statistically significant difference was detected in urea and creatinine levels between the OSA and control groups ($p=0.005$; $p=0.012$). Creatinine clearance decreases in patients with OSA in the presence of HT. Patients with OSA often experience cardiovascular disorders, and glomerular endothelial dysfunction occurs in OSA patients.
Keyword: Creatinine; hypertension; obstructive sleep apnea; renal dysfunction

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder (Schwab RJ et al., 1998). OSA results from collapses of the upper airway leading to recurrent interruptions of breathing during sleep. Breathing can be interrupted by complete or partial obstructions in the upper airway (Lindberg E et al., 2000). The disorder is characterized by snoring, excessive daytime sleepiness, and apnea. In the literature, the reported prevalence of obstructive sleep apnea in the population varies from 0.3% to 15% affecting approximately 1-5% of adults (Koktürk O et al., 1997). During apneas, hemodynamic complications such as hypoxemia, a rise in systemic and pulmonary arterial pressure, and changes in heart rate occur in patients with OSA. As a result, emerging cardiac risks are high. The significant complications arising in patients with OSA reports associated with the cardiovascular system.

Systemic arterial hypertension accounts for 30-40% of such complications (James M et al., 2004; Shahar E et al., 2001). The severity of hypertension finds out to correlate to the severity of OSA in such patients. Furthermore, studies have shown that 22-30% of patients diagnosed with idiopathic hypertension have OSA concurrently (Lavie P et al.,1984). It's known that the pathophysiology of the relationship is not clear

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enough. The relationship between OSA and the cardiovascular system has been associated with increased sympathetic nerve traffic, vagal activity, insulin resistance. In one study, albumin excretion was associated with cardiovascular events, and it interpreted as an indicator of endothelial dysfunction (Faulx M et al., 2007).

Limitation of this study was obesity and hypertension. In the study of Inal BB et al., 2009, CC was lower in OSA patients with HT than in OSA patients without HT. However, OSA patients were not classified according to OSA severity, and the study sample was too small. Our study aimed to evaluate the renal function of OSA patients by assessing the value of creatinine clearance (CC) of OSA patients with and without hypertension.

MATERIALS AND METHOD

A total of 590 people; who had undergone polysomnography (PSG) in Kartal Dr. Lutfi Kirdar Training and Research Hospital were evaluated retrospectively. The study included 530 individuals with OSA and 60 individuals with an apnea-hypopnea index (AHI) of < 5 as a control group. Patients diagnosed with diabetes, rheumatic diseases, acute and or chronic renal failure, or nephropathy were excluded from the study. Age, body weight, height, gender, apnea index(AI), oxygen desaturation index (ODI) of patients, and oxygen saturation values of <90 (TS90%) were recorded from the medical files. CC was calculated using the Cockcroft-Gault equation as follows: CC = (140-age) (ideal weight)/Serum creatinine (mg/dl) X72. For women, the value were adjusted by multiplying the results by 0.85. Video images and PSG recordings of patients taken for the entire night were obtained to diagnose obstructive sleep apnea.

Apneas measured by a thermal sensor and described as a ≥90% reduction in the airflow signal for at least 10 seconds, with ≥90% of that period meeting the amplitude criterion. A prolonged and increased respiratory effort in the absence of airflow describes as obstructive apnea. Hypopnea was described as a decrease of ≥30% in the nasal pressure signal compared to the baseline for at least 10 seconds, resulting in 3% desaturation or arousal compared to the baseline and meeting the amplitude criterion during ≥90% of the time. AHI values of 5-14.9 consider indicating mild OSA, AHI values of 15-29.9 considered to indicate moderate OSA, and AHI values of ≥30 considered severe OSA. Patients diagnosed with OSA divided into two groups as patients with and without hypertension, accounting for hypertension (HT) group (group 1) and the non-HT group (group 2), respectively. Patients in the HT group were previously diagnosed with HT and were taking antihypertensive medications. The study approved by an institutional ethics committee

Statistical Analysis

For the statistical analysis of the results, SPSS 20.0 software was used. The Kolmogorov-Smirnov test uses to determine whether continuous variables conformed to a normal distribution. For continuous variables of normal distribution, the independent t-test uses to compare the means of two groups, and the one-way ANOVA was used to compare the means of more than two groups. Pearson's chi-square test uses to assess the relationship between two continuous variables. For categorical variables, percentage and frequency values use as descriptive statistics. Mean and standard deviation was used to describe continuous variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study included 530 OSA patients consisting of 339 (64%) men and 191 (36%) women. In addition, 60 individuals were included in the study as the control group. The mean age was 49 ± 12 years. CC values were found see as 67.78 ± 27.4 ml/min and 73.79 ± 25.3 ml/min in the OSA and control groups, respectively. CC was low in the OSA population, but there was no statistically significant difference in CC between the OSA and control groups (p> 0.05). Urea and creatinine levels were statistically significantly different between the OSA and control groups (p = 0.005; p = 0.012, respectively). Age and gender were not different between the OSA group and the control group (p> 0.05). The demographic characteristics of patients were shown in table 1. In the OSA group, a statistically significant but weak correlation of CC was found in the same direction with AHI, AI, and minimum saturation (p: 0.032, r: 0.093; p: 0.003, r: 0.130; p: 0.009, r: 0.113).

When the patients were stratified by OSA severity, there were no significant differences in CC between the mild-moderate and severe OSA patients (p> 0.05). In our study, we found out that 32.4% of OSA patients had concomitant HT. CC and urea levels were significantly different between groups 1 and 2 (p<0.001) (Figure 1). Body mass index (BMI) was not significantly different between groups 1 and 2. When AHI, AI, and ODI compare between group 1 and group 2, no significant differences were observed (p> 0.05) (Table 2).

Table 1. Demographic Characteristics of OSA and Control Patients

	OSA	**Control**	**p value**
Male/Female	339/191	38/22	0,328
Age(years)	49±12	48±11	0,614
Urea (mg/dl)	33,6±10,8	29,5±8	**0,005**
Creatinine Clearance (ml/dk)	67,78±27,4	73,79±25,3	0,392
Body mass index (kg/m²)	31,63±5,54	30,66±4,21	0,491
Apnea hypopnea index	32,21±21,36	3,4±2,1	<0,001

Table 2. Demographic Characteristics of OSA Patients with and without Hypertension

	OSA HT+	**OSA HT -**	**p value**
Male/Female	92/80	247/111	0,086
Age(years)	51±10	46±11	0,079
Urea (mg/dl)	35,81±13,51	32,56±9,01	**0,005**
Creatinine Clearance (ml/dk)	58,03±25,63	69,50±27,55	**0,005**
Body mass index (kg/m²)	32,66±5,33	31,14±5,58	0,297
Apnea hyponea index	33,42±23,24	32,21±26,96	0,596
Apnea index	18,10±17,14	18,21±16,54	0,398
Oxygen desaturation index	25,01±24,12	26,17±12,66	0,172

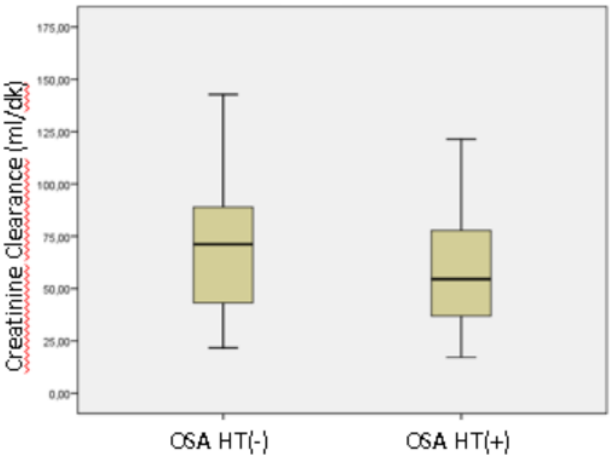

Figure 1. Creatinine Clearance in OSA Patients with and without Hypertension

OSA, generally characterized by hypoxemia resulting from recurrently obstructed upper airways during sleep. There is a strong relationship between OSA and cardiovascular diseases. Of cardiovascular disorders, HT occurs at a rate of 30-40% in OSA patients (Shahar E et al., 2001)). Similarly, we found out that the frequency of HT in OSA patients was 32.4% in our study. When we compared the CC and urea levels in OSA patients between the HT and non-HT groups in our study, we found out that the HT group had significantly lower CC and urea levels compared to the non-HT group. This situation indicates that patients; who suffer from sleep apnea have cardiovascular issues contributing to glomerular endothelial dysfunction. Faulx et al. conducted a study on 496 OSA patients to evaluate OSA severity, GFR, and albumin excretion. They found out that albumin excretion was higher in patients with severe OSA. When patients were grouped by OSA severity, GFR was normal in all groups (Faulx M et al., 2007). Similarly, CC was not found to be different by OSA severity in our study. However, there was a significant difference in CC between the HT and non-HT groups.

In one study, 91 morbidly obese OSA patients were assessed for renal functions before bariatric surgery. OSA was found in 55 patients. Creatinine values in the group with OSA were observed to be significantly higher than in patients without OSA (Agrawal V et al., 2009). In a study on 858 patients, the effects of nocturnal hypoxemia on renal functions investigate, and patients were followed up for an average of 2.1 years. Patients with OSA had a higher rate of deterioration in renal functions compared to the control group (Ahmed SB et al., 2011). Urinary albumin excretion was higher in hypertensive patients with OSA than hypertensive patients without OSA (Tsioufis C et al., 2008).

In the study by Inal BB et al., CC was 72.3 ± 9.9 ml/min in OSA patients with HT and 84.33 ± 16.98 ml/min in OSA patients without HT. Between those two groups of patients, CC was statistically significantly different (İnal BB et al., 2009). Similarly, CC was statistically significantly lower in the HT group than the non-HT group in our study. In a survey of 9000 OSA patients, chronic kidney disease was found in 30.5% of the study population (Iseki K et al., 2008). The mechanisms of OSA-related chronic renal failure have not been elucidated. The majority of studies indicate that hypertension, oxidative stress, endothelial dysfunction, and hypoxemia-related activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system resulting from a sleep- related breathing disorder induce kidney damage or

chronic kidney disease indirectly (Adeseun GA et al., 2010; Abdel-Kader K et al., 2012; Di Murro A et al.,2010).

In a study on 634 OSA patients and 62 individuals in the control group, GFR was lower in the group of OSA patients with metabolic compared to the OSA patients without metabolic (Uyar M et al.,2016). In a study on 93 OSA patients, patients group by OSA severity. That study found that CC values were not statistically significantly different between the patient and the control groups. Furthermore, OSA severity and CC were not correlated (Karakaş S et al.,2012). Hypertension and diabetes rank the first as the predisposing factors for chronic kidney failure. In OSA patients without hypertension or diabetes, it has been shown that increased sympathetic activity at night and endothelial dysfunction act as risk factors for developing chronic kidney disease (Mallamaci F et al.,2011). Although renal dysfunction in OSA patients considers the risk factors involved in the development of OSA, it is thought that pathophysiological effects of OSA such as hypoxemia, systemic inflammation, and oxidative stress could be involved in the development of renal dysfunction, too. A meta-analysis examining different study designs showed the importance of poor renal function in OSA patients (Hwu, DW et al., 2017).

Meta-analysis of 12 studies including 3344 people to investigate the relationship between eGFR and OSAS showed that the decrease of eGFR was related to moderate and severe OSAS, and the levels of eGFR decreased significantly in OSAS patients with hypertension and diabetes (Liu, T et al., 2021). A study on 27 OSA patients evaluating renal functions reported that serum creatinine levels decreased and GFR rose from 72.9 mg/dl to 79.3 mg/dl after a three-month, short-term continuous positive airway pressure (CPAP) therapy (Koga S et al.,2013). Another study found that the glomerular filtration rate improved with short-term CPAP therapy (Kinebuchi S et al., 2004).

The retrospective design, the impossibility to evaluate urinary albumin excretion of patients, and the inclusion of patients undergoing PSG in the control group can suggest the limitations of our study.

CONCLUSION

This study aimed to evaluate the creatinine clearance (CC) values in OSA patients with and without hypertension. Creatinine clearance was lower in OSA patients with HT than in OSA patients without HT in our study. This condition can attribute to glomerular endothelial dysfunction. Kidney failure may remain asymptomatic as long as GFR does not drop to very low levels (30-50 ml/min). In light of these findings and the respective literature, it is critical to follow up with OSA patients for hypertension and kidney function in clinical practice.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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