Obstructive sleep apnea syndrome in end stage renal disease patients undergoing hemodialysis

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ABSTRACT: Obstructive Sleep Apnea Syndrome (OSAS) is very prevalent among End Stage Renal Disease (ESRD) patients. The syndrome is considered to be an important cardiovascular risk factor for the general population and for Chronic Kidney Disease (CKD) patients, as well. The augmented cardiovascular morbidity and mortality in ESRD patients makes the early diagnosis and treatment of the syndrome in this population a necessity. The present review focuses on the clinical presentation and the signs and symptoms of the syndrome in ESRD patients that in many cases differ from the ones on the general population. Furthermore, it attempts to explain the special conditions and mechanisms related to CKD that lead to the pathogenesis of the syndrome and explain its augmented relation to cardiovascular risk. It aims to help nephrologists understand the syndrome, be aware of its high prevalence and impact on this population, achieve an early referral and accurate diagnosis of the syndrome and consider the therapeutic options suitable for this population.

Key words: OSAS, hemodialysis, CKD, cardiovascular risk

INTRODUCTION

Cardiovascular disease and its complications is the major cause of the augmented morbidity and mortality that characterizes patients suffering from chronic kidney disease (CKD) (1). According to Go et al cardiovascular risk elevates as renal function declines and is dramatically high in patients with end stage renal disease (ESRD) (2). Indeed, CKD patients are more likely to die from cardiovascular disease than to reach ESRD and undergo dialysis (3). In 1998, the USRDS (United States Renal Data System) reported that cardiovascular disease was responsible for 40-50% of death causes in ESRD patients and that its prevalence was 10 to 20 times higher than in the general population even after adjustment for age, sex, race and diabetes mellitus (4).

Traditional and non-traditional, urea related, risk factors have been described in an attempt to explain the augmented cardiovascular morbidity and mortality (5). Over the past few years, newer risk factors have emerged and nephrologists have focused on the role that inflammation and oxidative stress play in ESRD patients (6). Obstructive sleep apnea syndrome (OSAS) is an established cardiovascular risk factor in the general population that lately has been included among the newer risk factors in ESRD patients, as well (5-7). It is reported that in this population its prevalence is over 50% (8). The extremely high prevalence of the syndrome and its relation to the augmented cardiovascular morbidity and mortality makes its understanding and recognition a necessity for the nephrologist.

DEFINITION AND EPIDEMIOLOGY

OSAS is characterized by repeated episodes of partial or complete obstruction of upper airway during sleep (9). The full-blown syndrome includes many different
symptoms, with excessive daytime sleepiness, loud snoring and non-refreshing sleep being the most common ones. In many cases, choking during sleep, witnessed apneas, morning headaches, as well as, nocturia and decreased libido are described. Additionally, symptoms related to sleep deprivation, such as decreased concentration, memory loss and irritability, are included. Clinically, the diagnosis of OSAS is established when at least 5 obstructive episodes (apneas, hypopneas or respiratory effort related arousals) are recorded, combined with daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or choking.

In the general population it is estimated that 9% of women and 24% of men have Apnea Hypopnea Index (AHI) ≥5 episodes per hour of sleep and that 2% of women and 4% of men meet the minimal criteria for the diagnosis of OSAS (10). In 2002, Young et al, reported that one of 5 adults with Body Mass Index (BMI) 25-28kg/m² suffers from at least mild OSAS and that one of 15 from at least moderate syndrome (11). Already in 1982 the first study related to sleep problems in hemodialysis patients was published (12). According to this study 14 out of the 22 patients that participated referred reduced and fragmented sleep. Since then many studies were conducted in ESRD patients and it is estimated that the prevalence of the syndrome, as already mentioned, is over 50% and is surprisingly high in this population. Indeed, this high prevalence concerns ESRD patients on hemodialysis, on peritoneal dialysis and transplanted patients, as well (8).

Unfortunately, the majority of the studies conducted in this field have severe limitations (13). More precisely, the diagnosis of OSAS in many studies is based on the results of the Berlin Questionnaire and the Epworth Scale (14, 15). Both of those questionnaires are considered to be reliable for the diagnosis of the syndrome in the general population but have not been yet validated in patients suffering from CKD. In any case, it must be highlighted that the gold standard for OSAS’s diagnosis is a full polysomnography study (9). Moreover, in many studies there was a selection bias, as patient selection was based only on the presence or absence of clinical symptoms indicative of OSAS. Finally, one more significant limitation that must be mentioned is the presence of different comorbidities, beyond CKD, that could predispose to OSAS, such as cardiovascular diseases, diabetes mellitus and obesity (14). Even though all of those limitations plus the small sample size could not be overlooked, still it is clear that the prevalence of the syndrome in CKD patients is extremely high (15).

Unruh et al, in an attempt to overcome the aforementioned limitations, randomly selected ESRD patients undergoing hemodialysis 3 times per week and compared them to a group of patients selected from the ones that participated in the Sleep Heart Health Study (13). More precisely, 46 elderly hemodialysis patients were compared to 137 patients of the Sleep Heart Health Study matched for age, sex, BMI and race. According to the results of the study, the prevalence of OSAS was 4 times higher in the group of hemodialysis patients. Moreover, hemodialysis patients presented more severe hypoxia during sleep, shorter sleep duration and greater sleep fragmentation than the controls.

The prevalence of OSAS seems to be augmented not only in ESRD patients undergoing hemodialysis but in patients with milder degree of CKD, as well (15). Markou et al found that 54.3% of patients with glomerular filtration rate (GFR) <40ml/min that did not undergo hemodialysis suffer from OSAS and that in those patients AHI correlated negatively with GFR (16). Roumelioti et al confirmed the augmented prevalence of the syndrome in patients with mild degree of CKD (17), while Agrawal et al published that in obese patients the severity of OSAS correlates positively with serum creatinine elevation (18) and Sakaguchi et al that there is a negative correlation between AHI and GFR (19). In the latter study, participated 100 patients with GFR <89ml/min and it was found that the prevalence of OSAS in this population was 65% and that there was a 42% elevation of this prevalence for every 10ml/min reduction of GFR, even after adjusting for age, BMI and diabetes mellitus.

**RISK FACTORS**

In the general population the prevalence of OSAS is closely related to sex, age and ethnicity. It is known that the prevalence of the syndrome is 2 to 3 times higher in men than in women and its severity is worst in men compared to women of the same age (20). Furthermore, the prevalence is higher in post than pre menopause women or post menopause women receiving hormonal replacement therapy (20). It is believed that hormonal, structural and factional differences between the two sexes could explain this observation (21). One the other hand, the prevalence of OSAS elevates in co-ordination to the age of the...
patients and reaches its peak levels between the ages of 50 and 60, while it seems to decrease in the elderly ones (10). Probably the elderly patients that live alone or suffer from hearing loss cannot provide a detailed history in order to diagnose accurately the syndrome (22). Another explanation focuses on natural selection and the survival of the elderly ones that do not suffer from OSAS (22). Finally, race seems to be related to the risk and the severity of OSAS, a correlation attributed to obesity, differences in social and economical status and environmental factors (21).

The most important risk factor for OSAS in the general population is obesity (10). It is believed that even small augmentation of body weight could result in augmentation of the risk for OSAS. Moreover, it is believed that obesity correlates not only with the presence of the syndrome but with its rapid rate of progression, as well (23). The narrow upper airway is another very important risk factor for the development of the syndrome. More precisely, obesity, tonsilar and tongue hypertrophy, enlarged uvula, retrognathia or even family predisposition are considered factors that could reduce the size of the pharynx and lead to OSAS occurrence (24). One the other hand, alcohol consumption and smoking play fundamental role on the occurrence of OSAS (11). It seems that alcohol consumption before sleep correlates negatively with the patency of the upper airway, while smoking could deteriorate OSAS and even more its cessation could reverse the syndrome.

Although it is obvious that age, male sex and obesity play fundamental role in the occurrence of OSAS in the general population, when it comes to CKD patients the risk factors of OSAS are not fully understood. Indeed, in many studies the risk factors of this specific population present great differences to the ones of the general population (8, 14, 25, 26) and the correlation of OSAS with age, sex and obesity present controversial results (27, 28). One possible explanation in this discrepancy is the weakness of the studies already conducted in the field to reveal strong correlations, though the sample of CKD patients was in most cases quite small (14). Another possibly explanation is that this controversy could be attributed to special characteristics and conditions of the sample that result from CKD itself (25). Regarding BMI, its correlation with OSAS occurrence is not always strong and in many cases the OSAS patients with ESRD are not as obese as the ones in the general population. It is proposed that in this population it is not BMI that leads to the high prevalence of OSAS but the fact that BMI may reflect fluid overload or even high levels of uremic toxins. One the other hand, the prevalence of both CKD and OSAS increases as the age of the population increases. So the likelihood of suffering from both as the age increases is high. Finally, it is known that after menopause the prevalence of OSAS in women in the general population increases. In CKD patients many hormonal changes take place and women usually have anovulation and amenorrhea that diminish the expected differences that characterize sexes.

Clinical presentation of OSAS in CKD patients seems to be unique, as well. Loud snoring, witnessed episodes of apneas during sleep and morning headaches are not considered reliable clinical criteria in order to diagnose OSAS in ESRD patients undergoing dialysis (29). Snoring seems to be less common and less loud in this population than in the general population. Furthermore, partners of ESRD patients with OSAS do not report as usual episodes of apneas during sleep. One the other hand, many of the clinical symptoms that characterize OSAS patients, such as daytime somnolence, fatigue, depression, mental and sexual dysfunction are symptoms closely related to uremia itself (25, 26). The altered clinical presentation of the syndrome in ESRD patients and the common symptoms between OSAS and uremia make its diagnosis quite a challenge for a nephrologist.

**PATHOPHYSIOLOGY**

Pharynx is a complex structure that maintains its function thanks to the balance of opposite forces of dilation and collapse (24). Any disruption of this balance during sleep could lead to obstruction episodes such as the ones described in patients suffering from OSAS, although during day dilation muscles, especially genioglossus, seem to dominate and preserve the upper airway patency. The anatomic structure of pharynx and factors such as obesity, tonsilar and tongue hypertrophy, enlarged uvula, retrognathia that have been already mentioned seem to play key role in its predisposition to collapse during sleep. In OSAS patients, to these mechanical problems that lead to an easier collapse of the pharynx one must add the altered function of the dilation muscles. The inflammation and denervation of the dilation muscles resulting from vibration during snoring could disrupt their function during sleep (30). At the same time the ventilation instability described in OSAS patients jeopardize the
upper airway patency (31). Finally, the translocation of water from the lower extremities to upper body during sleep leads to augmentation of the neck circumference and predisposes to obstruction, as well (32).

Regarding ESRD patients it seems that the high prevalence of OSAS is the result of the combined effect of many different factors that characterize this unique population. Uremia and uremic toxins, hypocapnia due to metabolic acidosis, edema of the upper airway due to fluid overload, reduced muscle tone and neuropathy of the autonomic nervous system are some of the factors believed to play an important role and explain this high prevalence (8, 14, 15, 25, 26, 33). Furthermore, anemia, cardiovascular disease and other comorbidities that are usually found in ESRD patients, use of specific medicines, such as sedatives, pain killers and some antihypertensives, psychological factors and special factors reflecting the way of life of those patients are believed to play a prominent role, as well. Finally, the role of the augmented levels of many different cytokines that are described in ESRD patients and are believed to be closely related to the occurrence of sleep disturbances must be mentioned (34).

Beecroft et al described in ESRD patients many significant alternations of the sensitivity of the respiratory center and the central and peripheral chemoreceptors. Indeed, they found enhanced responsiveness to hypercapnia of both central and peripheral chemoreceptors that control the respiratory drive. Those changes are believed to result from uremia and hypopnea due to metabolic acidosis of CKD. Some years later the same researchers published a study that confirmed their past results and surprisingly demonstrated reduction of chemoreceptors hyper-sensitivity and reduction of the severity of the syndrome in ESRD patients that instead of daytime hemodialysis during the study underwent nocturnal hemodialysis (29).

Oedema of the upper airway due to fluid overload, as has already been mentioned, is one of the factors responsible for OSAS pathogenesis in ESRD. There is evidence supporting that the pharynx of CKD patients is narrower than in the general population (35). One the other hand, it is believed that during the nighttime sleep fluid is transferred from the lower extremities to the neck, resulting in augmentation of its circumference and in augmentation of the duration of the obstructive episodes (36). In a recent published study the authors report that the fluid overload and its translocation during sleep are related to augmentation of the jugular volume and edema of the upper airway mucosal (37). The role of the edema in the pathogenesis of the syndrome in ESRD patients is highlighted by the findings of Beecroft et al (38). The authors found that the size of the pharynx increases after initiation of nocturnal instead of daytime hemodialysis. The same results were found in peritoneal dialysis patients. More precisely, the authors using MRI (Magnetic Resonance Imaging) of the upper airway found that after transition from CAPD (Continuous Automated Peritoneal Dialysis) to NPD (Nocturnal Peritoneal Dialysis) the size of the pharynx increased and the prevalence of OSAS reduced (39).

**CARDIOVASCULAR DISEASE**

The repeated episodes of obstruction during sleep cause hypoxia that resemble the ischemia reperfusion syndrome, sleep fragmentation and negative endothromic pressure, leading finally to the activation of the autonomous nervous system and to hemodynamic fluctuations during the episodes of apnea (40). Typically, 5-7 seconds after each obstructive episode the cardiac rhythm and the arterial pressure elevate in contrast to the expected reduction during normal sleep. It seems that each obstructive episode is a stressful event during a period of time that the parasympathetic nervous system should normally dominate. Those pathways that are triggered during sleep in OSAS patients are the ones that lead to the augmented cardiovascular morbidity and mortality that characterizes the general population.

Nowadays, many longitudinal studies proved the strong correlation of OSAS to the augmented risk for cardiovascular events even after adjusting for age, BMI, smoking, systolic and diastolic arterial pressure (41, 42). Moreover, according to the Sleep Heart Health Study (43) and the Wisconsin Sleep Cohort Study (44) the syndrome is strongly related to arterial hypertension and it is considered as a curable cause of secondary hypertension (45) and the most common cause of drug resistant hypertension (46). Cardiac failure, ischemic heart disease, stroke and arrhythmias during bedtime are related to OSAS, as well (47, 48).

In ESRD patients the nocturnal hypoxia has been related to a non-dipping profile and to concentric left ventricular hypertrophy and remodeling (49), through the activation of the autonomous nervous system (50). Nocturnal hemodialysis seems to be able to reduce the frequency of apnea and hypoxia episodes and to
balance the action of sympathetic and parasympathetic nervous system (51). Furthermore, Abdel-Kader et al reported that resistant hypertension and severe OSAS were more prevalent among patients with CKD and especially among patients undergoing hemodialysis (52), while Jung et al reported strong correlation of OSAS and severe calcification of coronary arteries in dialysis patients (28). Nocturnal hypoxia has been closely related to morbidity and mortality in this population and Zoccali et al reported that even 1% reduction of the mean SpO₂ during sleep could lead to an 33% augmentation of fatal and non-fatal cardiovascular events risk (53).

**TREATMENT**

OSAS is a complex disease and its treatment is complex, as well. According to the American Academy of Sleep Medicine, its treatment could be medical, behavioral and surgical in some cases (9). The therapeutic use of positive airway pressure devices (Continuous positive airway pressure-CPAP, Bilevel positive airway pressure-BPAP, Autotitrating positive airway pressure-APAP) that manage to maintain the patency of the upper airway is considered the treatment of choice for patients suffering from OSAS. Behavioral changes on the other hand could be useful and include body weight reduction, exercise, avoidance of alcohol and sedatives before sleep and of supine position during sleep. In some cases the use of oral devices can improve the pharynx patency and finally in some cases the surgical treatment is required in order to deal and overcome anatomical problems.

When it comes to ESRD patients with OSAS the optimal treatment is not still known. Only few studies have focused on the beneficial effect of the therapeutic use of CPAP devise (54) or nocturnal oxygen administration in this population (55), while other authors focused on the role that the buffer of the hemodialysis dialysate could play and found that acetate and not bicarbonate were correlated to central apnea episodes. Finally, nocturnal dialysis (hemodialysis or peritoneal dialysis) instead of daytime was investigated and it seems to benefit ESRD patients suffering from OSAS. It is believed that its beneficial role is based not only in the fluid removal during sleep that has already been described but in the effective clearance of uremic toxins, as well (56). Besides the dysfunction of the upper airway muscles is the result of neuropathy and myopathy that characterizes ESRD patients and is closely related to uremia (57). For these reasons nocturnal dialysis is proposed to be an effective treatment for patients with severe OSAS.

Transplantation is considered to be another possible treatment for patients with OSAS and ESRD. Indeed, there have been reports of patients that were improved or even cured after transplantation (58-60). Surprisingly, recently published studies claim that the prevalence of OSAS in transplanted patients is equal to the one of ESRD patients under dialysis (15). So it is believed that transplantation can be a treatment of the syndrome and at the same time a predisposing condition to the syndrome occurrence. The transplanted patients develop clinical features that resemble Cushing syndrome, such as weight gain, obesity, abnormal fat distribution and metabolic syndrome. Those clinical features are the result of the immunosuppressive therapy administered to transplanted patients and could lead to the high prevalence of the syndrome in this population (15).

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**ABBREVIATIONS**

CKD: Chronic kidney disease
ESRD: End stage renal disease
USRDS: United States renal data system
OSAS: Obstructive sleep apnea syndrome
BMI: Body mass index
GFR: Glomerular filtration rate
MRI: Magnetic resonance imaging
CAPD: Continuous automated peritoneal dialysis
NPD: Nocturnal peritoneal dialysis
CPAP: Continuous positive airway pressure
BPAP: Bilevel positive airway pressure
APAP: Autotitrating positive airway pressure
Σύνδρομο αποφρακτικών απνοιών ύπνου σε ασθενείς με χρόνια νεφρική νόσο
tελικού σταδίου, υπό αιμοκάθαρση
Ολγα Νικητίδου, Νικόλαος Ντόμπρος

ΠΕΡΙΛΗΨΗ: Το Σύνδρομο Αποφρακτικών Απνοιών Ύπνου είναι ένα σύνδρομο το οποίο παρουσιάζει ιδιαίτερα αυξημένο επιπολασμό μεταξύ των ασθενών με Χρόνια Νεφρική Νόσο (XNN) τελικού σταδίου υπό αιμοκάθαρση. Το σύνδρομο φαίνεται να σχετίζεται άμεσα με τον αυξημένο καρδιαγγειακό κίνδυνο των ασθενών με XNN. Η αυξημένη καρδιαγγειακή θνητότητα και θνησιμότητα που χαρακτηρίζει τους ασθενείς με XNN καθιστά την έγκαιρη διάγνωση και θεραπεία του συνδρομού στο συγκεκριμένο πλήθυσμο αναγκαία. Η παρούσα βιβλιογραφική ανασκόπηση εστιάζει στην κλινική εικόνα και τη συμπτωματολογία του συνδρομού στο συγκεκριμένο πλήθυσμο καθώς φαίνεται να είναι διαφορετική από αυτήν που χαρακτηρίζει το γενικό πλήθυσμο. Επιπλέον, προσπαθεί να εξηγήσει τους μηχανισμούς εκείνους που σχετίζονται με τη XNN εμφάνιση του παθογενετικού μηχανισμού του συνδρομού στους ασθενείς αυτούς και τη σχέση του με τον αυξημένο καρδιαγγειακό κίνδυνο. Στόχος τού τα ιδιαίτερα αυξημένου χαρακτηρίζει το ΣΑΑΥ οι νεφρολόγοι, να αντλήσουν τον αυξημένο επιπολασμό και την επίπτωση που έχει στους ασθενείς με XNN, να επιτευχθεί έγκαιρη και ακριβής διάγνωση του συνδρομού και να γίνουν κατανοητές οι θεραπευτικές επιλογές που ταιριάζουν στον πληθυσμό αυτό.

Α Latinox kleidia: ΣΑΑΥ, XNN, Αιμοκάθαρση, καρδιαγγειακός κίνδυνος

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