COMMENTARY

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Consider the Kidney when Managing Obstructive Sleep Apnea

Commentary on Abuyassin et al. Obstructive sleep apnea and kidney disease: a potential bidirectional relationship? J Clin Sleep Med 2015;11:915–924.

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The first description of obstructive sleep apnea (OSA) in patients with end stage renal disease (ESRD) was published 30 years ago.[1] The authors' "discovery of sleep apnea in 2 patients on maintenance hemodialysis" prompted them to study "all 29 male patients undergoing outpatient dialysis." Ultimately, 6 of the 8 patients who agreed to have overnight polysomnography were found to have OSA, and ESRD and dialysis became recognized risk factors for OSA. These observations were subsequently supported by multiple descriptive studies, and the relationship between ESRD and OSA is now well established. Furthermore, many of the pathogenic mechanisms whereby ESRD patients develop OSA have also been investigated, with evidence for changes in both the control of breathing and upper airway mechanics.

It was not until 2006 that investigators began to look for a potential association between OSA and non-dialysis-dependent chronic kidney disease (CKD), predominantly focusing on patients with stage 3 and 4 CKD.[2] Most of these studies fall into one of two groups, namely CKD patients who were investigated for sleep apnea, and sleep apnea patients who were investigated for CKD. Notwithstanding the limitations of these studies with regard to sample size, study design and confounding variables, they have shown a high prevalence of OSA in patients with CKD. Unlike the ESRD population, the pathogenesis of OSA in CKD has not been systematically investigated. However, it would be naive to assume that the pathogenesis of OSA is the same in CKD as in ESRD since the latter represents a very different physiologic milieu, particularly with the additional impact of chronic dialysis.

The clinical relevance of OSA in patients with CKD arises from its potential to influence the pathogenesis of renal failure. The first hint of this came from a case report in 1987 in which the findings in a kidney biopsy were attributed to sleep disordered breathing.[3] Although many of the histopathological changes may have been due to comorbid obesity, there has been growing interest in the potential for OSA and associated hypoxemia to contribute to kidney injury and thereby accelerate kidney failure. The mechanisms proposed to explain kidney failure, are the "glomerular hyperfiltration theory,"[4] which causes glomerular hypertension, and the "chronic hypoxia hypothesis,"[5] which results in tubulointerstitial injury, thought to be the final common pathway and best predictor of progression to ESRD. OSA has the potential to influence both of these mechanisms through its effect on hypertension, sympathetic nervous system activation, inflammation, oxidative stress, and activation of the renal renin-angiotensin system. In addition, experimental animal models and in vitro studies have shown that the kidney, particularly the renal medulla, is vulnerable to hypoxemia and that tissue hypoxia plays a prominent role in kidney injury.[6,7]

The potential association between nocturnal hypoxemia and a decline in kidney function has been explored by 2 recent studies. Ahmed et al. studied 858 patients who were referred for diagnostic sleep testing and correlated nocturnal hypoxemia with the change in glomerular filtration rate (GFR) over 2 years.[8] Baseline GFR was mildly reduced (71 ± 12 mL/min per 1.73 m^2) since CKD was not a selection criterion. Forty-four percent of the patients had nocturnal hypoxemia, and 5.7% had an accelerated decline in GFR. Multivariate logistic regression showed a significant association between nocturnal hypoxemia and rapid loss of kidney function with an odds ratio of 2.89 (1.25–6.67) following adjustment for RDI, age, BMI, diabetes, and heart failure. In contrast, Sakaguchi et al. evaluated 161 patients with stage 3–4 CKD (GFR: 31 mL/min per 1.73 m^2).[9] Fifty percent of patients had nocturnal hypoxemia, reflected by the oxygen desaturation index (ODI). The decline in GFR over 1 year was 3–4 times greater in patients with ODI ≥ 15 than those with ODI < 15. These studies indicate an association between nocturnal hypoxemia and kidney injury, but they cannot imply causality and the hypothesis that OSA accelerates the progression of CKD remains to be proven.

The review by Abuyassin and colleagues provides a comprehensive account of the literature to date.[10] However, many important questions remain. Central to determining the relevance of OSA in ESRD is to evaluate how OSA impacts clinical outcomes such as sleep quality, daytime function, and cardiovascular morbidity and mortality. The high prevalence of coexisting medical and sleep disorders in ESRD patients make it challenging to assess how much OSA contributes to these outcomes. Secondly, the optimum therapy for OSA in this setting requires further study. Despite the high prevalence of OSA in patients with ESRD there have been no large studies to determine the efficacy and adherence with CPAP therapy. The effectiveness of renal function replacement therapy, such as different modes of dialysis and kidney transplantation, on OSA and related outcomes needs to be systematically

evaluated. Finally, alternative therapies, such as manipulation of rostral fluid shift and blood pressure control[11] could also be evaluated in this patient population.

Future studies of the impact of OSA on kidney function present a different challenge. First and foremost, the appropriate patient population needs to be studied. The demonstration that OSA can alter renal physiology in patients without kidney disease[12,13] needs to be applied to patients with CKD to determine whether these physiologic changes contribute to an accelerated deterioration in kidney function. Secondly, OSA is often not clinically apparent in patients with CKD,[14] and conventional screening tools for OSA are not reliable.[15] More effective risk stratification tools to identify those CKD patients who should have diagnostic sleep testing would be helpful. Thirdly, it is likely that OSA and hypoxemia will not cause kidney injury in all CKD patients; consequently, biomarkers (genetic, cardiovascular, and renal) would be helpful to identify those who are at greatest risk.

The benefits of meeting and overcoming these challenges are obvious and significant. Patients with ESRD have a high prevalence of sleep complaints, improvement of which would greatly improve their quality of life. Cardiovascular disease is their single biggest cause of mortality and any reduction in that outcome would be meaningful. Treatment of OSA in patients with CKD may delay or stop their progression to ESRD, which would have significant medical and financial benefits both for the patient and the healthcare system. Realization of these goals will require collaboration between clinical researchers in sleep medicine and nephrology on a scale that has not happened up to now.

CITATION

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DISCLOSURE STATEMENT

Dr. Hanly has consulted for Dream Sleep Respiratory Services and has received the use of equipment for research from Philips Respironics.