Editorial

Obstructive sleep apnea and chronic kidney disease: open questions on a potential public health problem

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The relationship between obstructive sleep apnea (OSA) and chronic kidney disease (CKD) is the object of an increasing interest. OSA and CKD share some common risk factors, like older age and obesity, and both of them have complex interrelationships with conditions like systemic hypertension or diabetes, so that to some extent their joint occurrence may be expected. However, several mechanisms, like sympathetic hyperactivity, apnea-related hypertensive peaks, and oxidative stress with subclinical inflammation and endothelial dysfunction, could account for an independent harmful effect of OSA on the kidney, in addition to effects of comorbidities (1). In the last years, evidence has accumulated from both epidemiological and pathophysiological studies supporting some independent pathogenetic role of OSA in kidney disease.

About 30 years ago, based on small case series, a relationship was proposed between end-stage renal disease and sleep apnea (2). Thereafter, several epidemiological studies have been published which explored the association between OSA and CKD from different perspectives (OSA in CKD, CKD in OSA, OSA and CKD in diabetes) and with different experimental designs (cross-sectional, longitudinal, pre-post therapy, randomized controlled trial).

Cross-sectional studies, mostly performed in patients recruited in sleep laboratories for suspected OSA, analysed estimated glomerular filtration rate (eGFR), albumin excretion, or, more rarely, both of them (3-9). Some relationship between OSA and CKD was found in most studies, but discordant data were often reported, especially about the possible correlates of CKD in OSA [apnea/hypopnea index (AHI) or severity of nocturnal hypoxemia].

Longitudinal studies have mostly shown an increased incidence of CKD, or a faster decline in eGFR, in patients with OSA than in controls (10-14). However, they often lacked important information, i.e., data on severity of OSA and CKD, or on OSA treatment.

Studies on effects of OSA treatment by continuous positive airway pressure (CPAP) provided interesting additional data, mostly supporting some positive effects of treatment. Some studies demonstrated a decrease in albumin excretion after CPAP (15,16). GFR was reported to decrease after CPAP when it was high and associated with glomerular hyperfiltration before OSA treatment (17,18), and to increase (19), or decrease at a slower rate (20), when it was low. At variance with these studies, a recent randomized controlled trial has shown non-significant differences in eGFR decline between treated and untreated OSA subjects, although this negative result could be due to an insufficient sample size or to mild nocturnal hypoxemia at baseline (21).

Pathophysiological studies support a detrimental role of OSA. In patients with OSA, impaired renal vasodilating capacity (22) and increased renal vascular resistance (23,24) and filtration fraction (17,18) were reported, which could be related to increased intrarenal renin-angiotensin system (RAS) activation (18,25). While some alterations

were already observed in mild-moderate OSA (23), severe hypoxemia was associated with worse hemodynamic and functional renal impairment (17,25).

In their study, Adams *et al.* cross-sectionally analysed the association between OSA, defined as AHI ≥10, and CKD in a large sample of men (26). Polysomnographic findings were typical of general population studies, i.e., a high prevalence of OSA (52.1%) with mild nocturnal hypoxemia [highest tertile of time spent with oxygen saturation (SaO_2) <90%: ≥2.21%]. For their analyses, the authors accurately collected extensive information, including demographic data, clinical history (comorbidities, symptoms, drug therapy), and data on socioeconomic condition (workforce participation, household income, education) that had been disregarded in previous studies on this subject. They divided their population into three groups: normal kidney function (eGFR ≥90 mL/min/1.73 m^2), mildly reduced kidney function (eGFR 60–89) and CKD (albumin/creatinine ratio ≥3 mg/mmol and/or eGFR <60). Among demographic and biomedical factors, age, diabetes and smoking were significantly and independently associated to CKD. When considering polysomnographic indices, factors independently associated with CKD were AHI values exceeding different thresholds, the highest tertile of the respiratory arousal index (≥7.63), but not total arousal index or hypoxia parameters.

One peculiarity of this study is that the subjects under analysis did not come from a sleep laboratory, but from the general population, unlike in most previous cross-sectional studies. One consequence was that in most subjects under investigation OSA, when present, was mild or moderate and, more than else, characterised by mild oxygen desaturations. Studies that found a relationship between hypoxemia and kidney function usually had populations where severe or protracted hypoxic levels were reached (6,7,9,10,16). Conversely, other studies reporting no effect of hypoxemia mainly included subjects with mild respiratory disorders and desaturations (8). One experimental study in humans demonstrated that the more severe hypoxemia, the greater the activation of the RAS and, therefore, the more likely a renal impairment (25). Longitudinal studies used a threshold of 12% night time with SaO_2 <90% as cut-off to separate patients with and without accelerated eGFR decline (10). The only longitudinal study that did not find detrimental influence of OSA on eGFR decline was based on the Wisconsin cohort, which included only a small percentage of subjects with severe OSA (27). Therefore, the mild desaturations could explain the lack of a relationship between hypoxemia and CKD in Adams' study.

The question arises whether OSA may be a risk factor for CKD in the absence of significant hypoxemia. OSA could exert some of its harmful effects through mechanisms like, for example, sleep fragmentation associated with apnea recurrence. However, in Adams' study it remains unclear why AHI and respiratory arousal index were associated to CKD while total arousal index was not. Some studies observed significant associations between AHI and some parameters of kidney damage or dysfunction even when no effect of hypoxemia was found (5,12), whereas the opposite was reported by others (10,16). Further studies are needed to explore possible non-hypoxic mechanisms that may endanger the kidney in OSA.

An important aspect of the OSA-CKD relationship evaluated by Adams and coworkers was the clinical presentation of OSA in CKD. Loud snoring in OSA was more often reported by patients without than by those with CKD. Besides, among patients with CKD, as opposed to patients without CKD, witnessed apneas and loud snoring were reported similarly by patients with and without OSA. Likewise, a score corresponding to a high OSA risk at the STOP questionnaire was more frequently found in OSA than in non-OSA patients only if they were not affected by CKD (26).

Similar findings were reported in another study (28) where, however, the OSA patients had been taken from a sleep laboratory population, so that they could represent a group preselected for OSA symptoms and risk factors. Instead, in Adams' study all OSA subjects came from the general population (26), which demonstrates that OSA with coexistent CKD is really associated with fewer symptoms than isolated OSA, particularly as concerns snoring and witnessed apneas. Mild symptoms were already observed in OSA diagnosed after stroke or heart failure (29,30). That arises the question whether OSA symptoms are not perceived equally in patients with cardiovascular or renal diseases as opposed to OSA patients without comorbidities. Alternatively, obstructive apneas in these diseases may have different characteristics than in the general or in sleep laboratory populations, and generate more soft snoring that may make them less evident to bed partners. The most common OSA screening questionnaires proved poorly performant in CKD (31), and other screening tools have been advocated, as it was the case in other diseases, like stroke or diabetes (32,33). Developing new tools could have clinically important consequences, since the clinical course of CKD might improve if OSA is recognised and

treated. Although data in that respect are still uncertain, a preliminary analysis of our data suggests a benefit of treatment by fixed CPAP on eGFR in OSA (34).

In clinical populations of suspected OSA patients, the link between OSA and CKD appeared stronger in female subjects (9,14). One limitation of Adams' study is that it cannot provide any information on possible gender-related differences in the general population, since it included only male subjects (26).

To conclude, the study by Adams *et al.* may open perspectives for new investigations on OSA, both from a pathophysiological and a clinical point of view. It suggests the need of new studies on the role of non-hypoxic risk factors for CKD in OSA and on their pathophysiological mechanisms. Besides, it could open the way to the study of a new phenotype of OSA. Today, much interest is aroused by the variability of the clinical presentation of many diseases, including OSA, and by the management required by each of them. Several analyses have been performed in OSA that have identified highly different clinical clusters, often characterised by presence of comorbidities with poor OSA symptomatology (35). While some studies have underscored a decreased risk for hypertension in non-hypersomnolent OSA patients (36), other investigations have shown that OSA after stroke is characterised by poor symptoms but, in spite of that, may worsen life expectancy (37). OSA characterised by the association of CKD with rarely reported loud snoring and witnessed apneas could be a new phenotype with prognostic implications as regards the evolution of kidney dysfunction. The importance of paucisymptomatic OSA is still poorly understood and deserves great attention due to its very high prevalence. Results of new studies on poorly symptomatic OSA and on its therapy in patients with different comorbidities may have important implications for public health.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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