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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

A systematic review of central sleep apnea in adult patients with chronic kidney disease

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Abstract
Background Obstructive sleep apnea has been widely studied in patients with chronic renal insufficiency; however only a limited number of studies have reviewed the association between central sleep apnea (CSA) and chronic kidney disease (CKD). The objectives of this systematic review were to assess the prevalence of CSA in and its association with CKD in adult patients and to determine if inclusion of the central hypopnea index affected the reported rates for the prevalence of CSA in CKD.
Methods Medline, Web of Science, Google Scholar, Scopus, and Cochrane Library were searched through October 2015 without any language limitations.
Results Of 188 articles searched, 8 articles met our study inclusion criteria. Of a cumulative total of 313 patients with CKD undergoing sleep study, a total of 30 patients were diagnosed with central sleep apnea. Three studies had patients with coexistent congestive heart failure, six studies included some patients on dialysis and at least 3 studies included central hypopneas while calculating central sleep apnea index.
Conclusion The aggregate point prevalence of CSA in CKD is 9.6 %, although the estimated range is highly variable between 0 and 75 %. Limited evidence suggested that even after adjustment for cardiovascular comorbidities, CKD is independently associated with CSA. It is unknown if patients on dialysis are at increased risk compared to patients without end-stage renal disease. Standardization of polysomnographic criteria used to define CSA and sleep disordered breathing (SDB) as well as inclusion of central hypopneas in the overall CSA index will limit the heterogeneity and allow better estimation of the prevalence of CSA in patients with CKD.

Keywords Prevalence · Central sleep apnea · Chronic kidney disease · Hemodialysis · Congestive heart failure · Sleep disordered breathing · Apnea-hypopnea index

Introduction

Central sleep apnea (CSA) has been commonly associated with cardiovascular comorbidities like congestive heart failure (CHF) and atrial fibrillation as well as neurologic disorders such as stroke, multiple sclerosis, and brain neoplasm [1, 2]. The role of chronic kidney disease (CKD) in development of CSA has not been discussed widely in the literature. The Kidney Disease Improving Global Outcomes (KDIGO) Work Group defines CKD as the presence of any marker of kidney damage (including albuminuria) or a reduction in glomerular filtration rate to a value lower than 60 mL/min per 1·73 m^2 for 3 months or longer [3]. The prevalence of CKD in the USA has been on the rise in the last few decades [4]. There is an impending need to specifically identify if these patients are at increased risk for development of CSA syndromes given CSA has several important clinical implications [1]. Untreated CSA can lead to excessive daytime sleepiness. It can also contribute to non-restorative sleep patterns where patients experience multiple nocturnal awakenings with shortness of breath, apneas, or insomnia. When monitored in a hospital setting or sleep laboratory, these patients may demonstrate episodic oxyhemoglobin desaturation and nocturnal

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arrhythmias such as atrial fibrillation [5]. The bed partner may experience poor quality of sleep due to the patient's CSA-associated snoring. CSA has been associated with increased mortality in patients with CHF [6]. In many instances, CHF and CKD are coexisting comorbidities in patients with central sleep apnea. In instances where patients have CKD, it would be helpful to investigate if patients have concurrent CSA, given some of their symptoms can improve with treatment of central sleep apnea.

Multiple factors make determination of prevalence of CSA in patients with CKD challenging. Identifying selectively the role of CKD severity (as evidenced by glomerular filtration rate reduction) in development of CSA is a difficult task, given the influence of coexisting comorbidities that inevitably accompany CKD progression. In particular, progression of CKD insidiously increases the risk of developing cardiovascular disease [7]. Therefore, the contribution of CHF in precipitating central apneas in patients with advancing kidney disease cannot be dismissed. Pre-existing cardiovascular disease by itself is a prominent and independent risk factor for development of CKD [8]. Cardiovascular events and mortality seem to be a far more likely outcome than progression to end-stage renal disease in all stages of CKD, further compromising efforts to establish prevalence of CSA in a given patient as CKD evolves [3, 7].

What is the pathophysiology behind development of CSA in patients with chronic kidney disease? Evidence suggests that there are multiple biochemical mechanisms at play, which promote "exaggerated chemoreflex sensitivity" leading to unstable ventilatory control of breathing during sleep. First, in end-stage renal disease, there is often fluid overloading of lungs leading to interstitial pulmonary edema [9]. This leads to activation of pulmonary mechanoreceptors leading to an unstable, high loop gain ventilatory control system [10]. Second, metabolic acidosis associated with CKD can mediate left shift of the rebreathing hypercapnic ventilatory response curve [11]. Third, overactivation of the sympathetic nervous system due to decreased clearance of uremic toxins such as beta-2 microglobulin and endogenous opiates could be manifested as exaggerated chemoreflex sensitivity [12, 13]. This systematic review explores the prevalence of CSA in adult patients with CKD irrespective of their dialysis status or presence of coexisting cardiovascular comorbidities.

Methods

This review was conducted utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. Authors (GN, CP, and MR) carried out a systematic search of electronic databases that included MEDLINE, Scopus, Google Scholar, Web of Science and Cochrane Central, Register of Controlled Trials, from inception through October 2015 with an update through December 31, 2015. The search included Mesh terms, key words, and phrases in combinations to accommodate for any differences in select terminology in the different databases. Hand searches of the reference lists of relevant articles were completed to identify other pertinent articles. Extensive gray literature searches were completed to identify relevant publications that may have been missed by the electronic database search. No language limits were applied. An example of MEDLINE search strategy is as follows: ((("Kidney Failure, Chronic"[Mesh])) AND "Sleep Apnea Syndromes"[Mesh]), "Kidney Failure, Chronic"[Mesh] AND "Sleep Apnea Syndromes"[Mesh]) AND "Prevalence"[Mesh], (((((("Kidney Failure, Chronic"[Mesh])) AND "Sleep Apnea Syndromes"[Mesh])) AND "Renal Dialysis"[Mesh], "Sleep Apnea Syndromes"[Mesh])) "Renal Dialysis"[Mesh]) AND "Prevalence"[Mesh], sleep disordered breathing*[tiab] AND chronic kidney disease* [tiab]. All three investigators independently performed data extraction utilizing a standard data extraction form to determine the eligibility for inclusion. Disagreements amongst investigators were resolved by consensus opinion.

All articles that discussed sleep disordered breathing (SDB) in CKD patients were reviewed. Articles meeting the inclusion criteria were included in the systematic review. Inclusion criteria included studies assessing CSA prevalence and/or risk factors in adult patients with CKD or end-stage renal disease or on dialysis. Exclusion criteria included (1) all studies on SDB in CKD patients not assessing CSA prevalence or associated risk factors and (2) studies discussing CSA in CKD in pediatric patients. The primary outcome of the review was to determine the prevalence of CSA in patients with established diagnosis of CKD. The secondary outcomes were to explore if the presence of CKD independent of heart failure is associated with increased risk for developing CSA and to assess if inclusion of central hypopnea index significantly affects the reported rates for the prevalence of CSA in patients with CKD.

Results

The search yielded a total of 188 articles (with constituent studies in 6 different languages), and after applying exclusion and inclusion criteria, 8 studies were included in the review (Fig. 1) [15–22]. These studies included patients with CKD and at least some description of an assessment for CSA. All eight studies included patients with CKD and these were conducted globally. These included four studies in USA, one in Canada, one in Austria, one in Greece, and one in Japan. Hence, this review represents estimates of global prevalence. Table 1 describes demographic characteristics and CSA prevalence in patients with CKD while Table 2 describes the polysomnographic characteristics and dialysis status of the studied

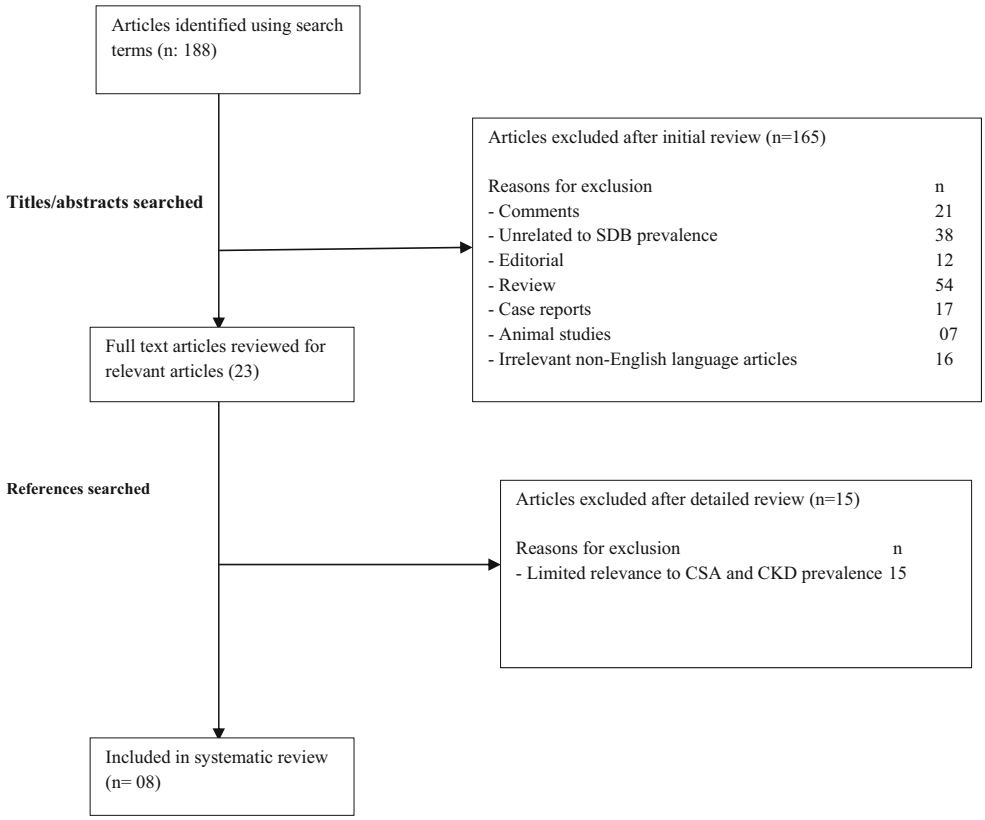

Fig. 1 Study selection flow diagram for evaluating CSA in CKD

subjects. Two studies (Markou et al. and Fleischmann et al.) totally excluded patients on dialysis, two studies (Kimmel et al. and Roumelioti et al.) included patients with and without hemodialysis, and one study (Stepanski et al.) exclusively considered patients on continuous ambulatory peritoneal dialysis (CAPD). The remaining three studies considered patients exclusively on hemodialysis (HD).

Global prevalence of CSA in patients with CKD varied between 0 % (Roumelioti et al. and Markou et al.) and 75 % (Pressman et al.). In summation, a total of 313 patients underwent a sleep study (either in-laboratory or home sleep apnea testing), of which 30 patients met the criteria for central sleep apnea. This gives an aggregate point prevalence (percentage of the total number of CKD patients that had CSA at the time of undergoing the sleep study) of 9.58 %. Studies that included subjects on HD (either some or all patients) still varied widely with regard to prevalence of CSA between 0 and 75 %. Kimmel et al. did not find any difference in overall apnea-hypopnea index (AHI) in CKD patients who were predialysis versus patients undergoing regular dialysis. Within the dialysis cohorts, Tada et al. noted that in CSA patients, AHI on the hemodialysis night was significantly lower when compared to the non-hemodialysis night. Hanly et al. found that central apneas were remarkably suppressed by nocturnal hemodialysis compared to conventional hemodialysis.

The criteria used to define SDB varied between AHI >5 and AHI >30. Similarly, criteria defining CSA varied widely across the studies. All eight studies reported polysomnographically identified central apneas, with three (Hanly et al., Kimmel et al., and Pressman et al.) out of the eight studies doing meticulous work of reporting even central hypopneas. Three studies (Tada et al., Kimmel et al., and Fleischmann et al.) included patients with coexisting CHF when calculating prevalence of CSA. All studies were relatively good quality that fulfilled at least 5 criteria on NICE quality assessment tool (Table 1).

Discussion

There are three main findings in this review that deserve detailed discussion.

First, the aggregate point prevalence of CSA in patients with CKD is about 10 %, although the global range of prevalence varies widely between 0 and 75 %. This heterogeneity is attributed to the use of varying and non-standardized polysomnographic criteria to diagnose CSA and SDB, inconsistencies around incorporating central hypopnea index in overall CSA index calculation, and varying proportion of patients with heart failure, restless legs, and periodic limb movement disorder in the sleep study cohorts. Two studies reported a

Table 1 Demographic parameters and CSA prevalence in patients with CKD undergoing sleep studies

Study author, study year, country	Number of patients with CSA/total no. of CKD patients undergoing PSG (% of CKD patients with CSA)	Number of patients with SDB/total no. of CKD patients (% of CKD patients with SDB)	Mean age ± SEM	Percent of male patients	Inclusion of subjects with coexistent heart failure	Study quality assessment[a]							
						1	2	3	4	5	6	7	8
Fleischmann et al. 2004–2007, Austria	4/18 (22 %)	17/18 (94 %)	61.2 ± 12.7	39	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
Hanly et al. 1993–1998, Canada	1/14 (7 %)	8/14 (57 %)	45 ± 9	71	NM	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Kimmel et al. 1984–1988 USA	7/26 (27 %)	16/26 (62 %)	56.7 ± 3.2	73	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Markou et al. 2002–2004 Greece	0/35 (0 %)	19/35 (54 %)	57.3 ± 12	54	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pressman et al. 1993 and prior USA	6/8 (75 %)	8/8 (100 %)	52.4 ± 15.5	75	NM	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Roumelioti et al. 2004–2008 USA	0/164 (0 %)	39/164 (24 %)	51 (43–64)/58 (46–67) (CKD/HD)	66	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Stepanski et al. 1993 and prior USA	4/18 (22 %)	11/18 (61 %)	48.7 ± 15.2	67	NM	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Tada et al. 2005 Japan	8/30 (27 %)	41/119 (35 %) (based on 4 % ODI >5)	61.4 ± 10.8	57	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

CSA central sleep apnea, *CKD* chronic kidney disease, *SDB* sleep disordered breathing, *SEM* standard error of mean, *ODI* oxygen desaturation index, *AHI* apnea-hypopnea index, *NM* not mentioned

[a] Quality assessment of the included studies checklist from questions from National Institute for Health and Clinical Excellence (NICE) 1–8: (1) Case series collected in more than one center? (2) Is the hypothesis/aim/objective of the study clearly described? (3) Are the inclusion and exclusion criteria clearly reported? (4) Is there a clear definition of the outcomes reported? (5) Were data collected prospectively? (6) Is there an explicit statement that patients were recruited consecutively? (7) Are the main findings of the study clearly described? (8) Are outcomes stratified?

Table 2 Polysomnographic parameters and dialysis status in CKD patients undergoing sleep studies

Study author	% of patients on dialysis	Type of dialysis	SDB definition	CSA definition	Inclusion of central hypopneas within CSA index	Type of sleep study
Fleischmann et al.	0	NA	AHI >5	Cheyne–Stokes breathing (CSB) with CSA was defined as periodic breathing in which apneas and hypopneas alternated with prolonged ventilatory periods of cyclic crescendo–decrescendo respiratory effort and airflow during wakefulness or sleep	No	In lab
Hanly et al.	100	HD	AHI >15	Cheyne–Stokes respiration was defined as an episode of central apnea (or hypopnea) alternating with breathing that had a pattern of crescendo and decrescendo.	Yes	In lab
Kimmel et al.	77	HD	AHI >30	Presence of more than half of the disordered breathing events as central apneas/hypopneas	Yes	In lab
Markou et al.	0	NA	AHI >5	–	No	In lab
Pressman et al.	88	HD (75 %) CAPD (13 %)	AHI >5	Presence of majority of scored events as central apneas, central hypopneas or mixed apneas	Yes	In lab
Roumelioti et al.	46	HD	AHI >30	–	No	Unattended Home
Stepanski et al.	100	CAPD	AHI >20	Presence of majority of scored events as central apneas	No	In lab
Tada et al.	100	HD	AHI >5	Central Apnea Index >5	No	In lab

CSA central sleep apnea, *AHI* apnea-hypopnea index, *CKD* chronic kidney disease, *SDB* sleep disordered breathing, *HD* hemodialysis, *CAPD* continuous ambulatory peritoneal dialysis, *NA* not applicable

prevalence of CSA as low as 0 % in patients with history of CKD. Although these two studies (Roumelioti et al. and Markou et al.) had the largest sample size amongst the eight studies reporting central apneas, both studies had certain limitations. Roumelioti et al. study based its results on findings from an unattended home study with limited EEG monitoring for sleep-stage recording. This study excluded all CKD patients already on CPAP prior to determining prevalence of SDB in patients with CKD. The study did not account for central hypopneas and had selectively excluded subjects with active medical and psychiatric comorbidities. Similarly, Markou et al. study preferentially excluded all patients with CHF or those on dialysis before selecting patients for the sleep study. Markou et al. study, similar to Roumelioti et al. study, did not record or report central hypopneas. Pressman et al. study reported the highest prevalence of CSA at 75 % in patients with CKD. This study used very liberal criteria to define hypopneas, including central hypopneas. Hypopneas were defined by at least a 20 % reduction in airflow and/or effort lasting for at least 10 s with a minimum 2 % oxygen desaturation. This is in contrast with other studies that define hypopneas only with greater flow decrements and concurrently requiring 3–4 % oxygen desaturation from baseline. They included mixed apneas under the reported central sleep apnea index. Also, Pressman et al. study had the smallest sample size of all the studies reviewed.

Second, the prevalence of CSA in CKD depends on cutoff criteria used to define CSA and the diligence to recognize and report central hypopneas. No correlation was found between the cutoff criteria to define SDB and the prevalence of CSA in patients with CKD (Fig. 2). Of the eight studies discussed, the established criteria used to define SDB varied between AHI >5 and AHI >30. AHI >5 was used by four studies (Tada et al., Pressman et al., Markou et al. and Fleischmann et al.), AHI >15 was used by one study (Hanly et al.), AHI >20 was used by one study (Stepanski et al.), and AHI >30 was used by two studies (Roumelioti et al. and Kimmel et al.). Similarly, criteria defining CSA varied widely across the studies. Two

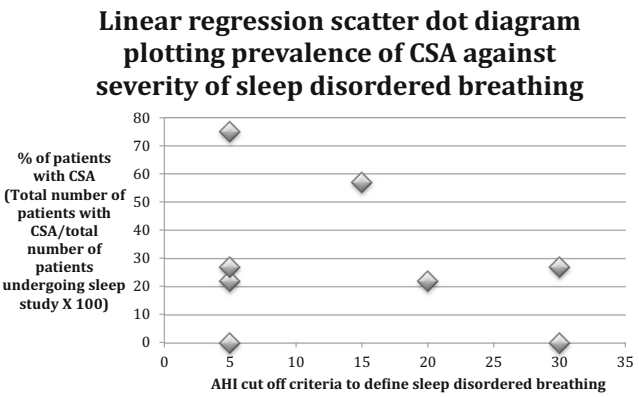

Fig. 2 Linear regression plot demonstrating prevalence of CSA against cutoff AHI used to define sleep disordered breathing

studies (Roumelioti et al. and Markou et al.) did not define what constituted CSA although they reported few central apneas in the subjects undergoing a sleep study. Hanly et al. used an uncommon definition, calling an apnea or hypopnea as central if the chest wall and abdomen moved synchronously. Tada et al. only used an absolute central apnea index >5 to define CSA, not concurrently requiring 50 % of total respiratory events to be of central origin. The remaining three studies utilized stringent criteria involving the presence of majority of scored events as central events to meet criteria to define CSA. All eight studies reported polysomnographically identified central apneas, with three (Hanly et al., Kimmel et al. and Pressman et al.) out of the eight studies doing meticulous work of reporting even central hypopneas. These studies reported CSA prevalence between 7 and 75 % indicating that central hypopneas could be a significant contributor to overall CSA index in patients with CKD. One study (Pressman et al.) included mixed apneas under central sleep apnea index. All studies except one (Roumelioti et al.) conducted full night in-lab attended sleep studies. Roumelioti et al. study conducted an unattended home sleep apnea study. Future studies should incorporate the latest AASM manual criteria for reporting central apneas and central hypopneas (2012) as well as the current recommended sensors as outlined by AASM scoring manual (version 2.2) to limit heterogeneity in the reported results.

Third, CKD independent of the coexisting CHF could be associated with development of CSA. Three studies (Tada et al., Kimmel et al., and Fleischmann et al.) included patients with coexisting CHF when calculating prevalence of CSA. Although it was not disclosed what percentage of patients had systolic and/or diastolic heart failure, all three studies reported prevalence of CSA in CKD within a narrow range. Two studies (Roumelioti et al. and Markou et al.) excluded patients with CHF before conducting sleep studies. Coincidentally, both these studies reported 0 % prevalence of CSA in CKD. It was not disclosed as to whether the remaining three studies had participants with heart failure. CSA with Cheyne-Stokes respiration was reported in two studies (Fleischmann et al. and Hanly et al.). In particular, Fleischmann et al. study calculated the prevalence of CSA with Cheyne-Stokes breathing in patients with CKD and coexisting heart failure. They found specific association of CSA with CKD even after statistical adjustment for heart failure.

Additionally, other putative associations for the emergence of CSA in CKD include NREM sleep (Kimmel et al. and Fleischmann et al.), especially increased stage N1 and sleep fragmentation (Stepanski et al.) and low arterial partial pressure of oxygen and carbon dioxide levels (Tada et al.). Stage REM sleep was found to be relatively protective against central apneas as compared to stage NREM in patients with chronic kidney disease. Given progression of CKD is associated with increased incidence of heart failure and possibly interstitial pulmonary edema, the presence of heart failure likely increases the risk of CSA in patients with pre-existing chronic kidney disease. It has been demonstrated that patients with end-stage renal disease on hemodialysis are extracellular fluid (ECF) volume overloaded. This can trigger the overstimulation of pulmonary mechanoreceptors in the interstitium leading to central apneas, and this ECF overload is potentiated by coexisting CHF [9]. Nevertheless, CSA in these patients might not be exclusively mediated by the coexistent heart failure. As demonstrated in Fleischmann et al. study, CKD has been specifically and strongly linked to CSA even after adjustment for medical comorbidities known to trigger CSA, including heart failure. Although some studies (Hanly et al.) claim nocturnal hemodialysis to be superior to other dialysis modalities in control of CSA, longitudinal studies with large sample size will be needed in the future to corroborate or refute these claims.

Our review has several limitations. Most of the limitations of the systematic review reflect the limitations of the constituent studies. There is considerable heterogeneity in the polysomnographic definition of SDB in the studies estimating prevalence of CSA. Similar heterogeneity pervades the definition of central apneas and central hypopneas. The review includes studies conducted over the last 30 years with majority of the included studies scored using Rechtschaffen and Kales manual for the scoring of sleep stages. Remaining few studies were scored based on the American Academy of Sleep Medicine scoring manual introduced in 2007. The rules for scoring respiratory disturbance events have undergone considerable changes over the last few decades, making it difficult to directly compare baseline AHIs and CAIs reported by different authors. Most studies did not disclose if they evaluated for or detected Cheyne-Stokes breathing. Most studies have not accounted for central hypopneas and hence only accounted for central apneas when calculating the overall index for CSA. This could lead to underestimation of overall prevalence of CSA. On the other hand, omission bias could have resulted in overestimation of the point prevalence of CSA. This could have resulted from search methodology-based marginalization of a large number of studies that discussed the prevalence of obstructive sleep apnea in CKD where CSA presumably did not occur or at least was not reported.

There were not many studies that directly reported prevalence of CSA in chronic kidney disease. Hence, authors individually looked for CSA reporting in studies that were conducted for evaluation of SDB in patients with kidney disease; therefore, reporting bias is also a concern. It is not inconceivable that some studies, to begin with, might have only evaluated for prevalence of OSA in patients with CKD but went ahead to briefly mention CSA as a secondary finding. Given our search was primarily focused to identify relevant articles for the occurrence of CSA in CKD, we may have failed to

capture these studies. Some of the non-English language articles were not readily available. These consisted of reviews and conference proceedings; hence, it is unlikely that these could have changed the major findings of our review. We could not conduct biostatical analysis to assess the risk of bias of individual studies given limited number of studies and high inconsistency amongst individual studies.

Other limitations included inability to conduct all sleep studies as attended in-lab studies, as home studies are not accurate for the detection of central apneas and periodic breathing. Studies that included patients with heart failure did not comment if the subjects had undergone prior sleep studies before onset of CKD, which would have helped compare the existence and severity of CSA over time. The studies including subjects with cardiac comorbidities did not entirely highlight the clinical volume status of subjects at the time of undergoing the sleep study, the ejection fraction on recent echocardiogram, or the type of heart failure (systolic versus diastolic) that the subjects had. The heterogeneity with regard to the use of dialysis and type of dialysis presented additional barriers to determining the precise prevalence of CSA in patients with CKD.

Conclusion

The aggregate point prevalence of CSA in adults with CKD is about 10 %. However, the range of overall prevalence of CSA in CKD varies widely between 0 and 75 %. This wide range is attributed to the use of varying and non-standardized polysomnographic criteria to diagnose SDB and CSA over the past few decades. Also, the inconsistencies around incorporating central hypopnea index in overall CSA index calculation and inclusion of varying proportion of patients with heart failure contribute to the marked heterogeneity in the estimation of CSA prevalence in patients with CKD. The association between CSA and CKD might remain to some extent even after adjusting for the cardiovascular risk factors such as heart failure, although more rigorous studies are needed to establish the strength of this association. Baseline severity of SDB by itself does not seem to affect the prevalence of CSA in CKD. In patients with end-stage renal disease, it is unknown if one particular mode of dialysis is relatively superior to other modalities in its ability to consistently abolish CSA. Utilization of uniform and standardized polysomnographic techniques and diagnostic criteria is of utmost importance when attempting to predict prevalence of CSA in CKD. Using attended in-laboratory sleep studies involving diligent detection and reporting of central hypopneas while computing overall central sleep apnea index will obviate underestimation of CSA prevalence in patients with chronic kidney disease.

Author contributions GN is the guarantor of the manuscript and takes full responsibility for the integrity of the presented data and the accuracy of the data analysis. GN is the principal investigator of the study. GN, CP, and MR contributed to the study concept and design, data acquisition and analysis, data interpretation, drafting of the manuscript, and approval of the final manuscript.

Compliance with ethical standards Not applicable as this is a systematic review.

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Informed consent Not applicable as this is a systematic review.

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Comments

The review is on an important clinical aspect in sleep medicine, which has not been well explored. The review demonstrates the limitations of the studies currently available on this subject.

The discussion is important since it concludes that, due to methodological limitations, final conclusions cannot be established yet.

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