2019; Focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019;38:1015–1027.
16 Dalton HJ, Reeder R, Garcia-Filion P, Holubkov R, Berg RA, Zuppa A, *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med* 2017;196:762–771.

Give the Kidneys a Good Night of Sleep

Edward Suh M.D., and Ana C. Ricardo, M.D.

Department of Medicine, University of Illinois at Chicago, Chicago, Illinois

ORCID ID: 0000-0001-8670-3644 (A.C.R.).

Chronic kidney disease is a growing public health problem that affects 9.1% of the world population (1), including 37 million people in the United States (2). Chronic kidney disease is predominantly diagnosed and classified based on estimated glomerular filtration rate and urine albumin excretion (3). Albuminuria may be the first clinical manifestation of chronic kidney disease, and in glomerular diseases such as diabetic kidney disease, albuminuria usually presents before the reduction in glomerular filtration rate (4). Furthermore, albuminuria is associated with underlying hypertension and obesity and is a well-established risk factor for chronic kidney disease progression and cardiovascular events (3).

Over the past two decades, there have been significant advances in our understanding of mechanisms associated with the progression of chronic kidney disease, including genetic, behavioral, metabolic, and other novel risk factors (5). However, despite the high prevalence of sleep disorders among patients with chronic kidney disease, the association between sleep disorders and early markers of kidney disease such as albuminuria remains understudied. In the general population, the prevalence of sleep disordered breathing is estimated to be 10%. Among patients with chronic kidney disease, prevalence estimates are much higher, ranging from 25% in patients with early stages of kidney disease to 70% among patients with end-stage kidney disease. Of note, this finding does not seem to be explained by known factors such as age, body mass index (BMI), or other comorbidities (6). Therefore, there is a critical need to better understand the association between sleep disorders and chronic kidney disease.

Prior studies have reported significant associations between prevalent sleep disordered breathing and albuminuria in diverse community-based cohorts (7, 9, 10), as well as among patients with diabetes (6) and hypertension (7). In this issue of *AnnalsATS*, Murase and colleagues (pp. 451–461) report the results of a large community-based (8), cross-sectional study evaluating the association between sleep disordered breathing, blood pressure, and albuminuria. They evaluated more than 6,000 individuals enrolled in the Nagahama study who wore a wrist actigraph for at least 5 days and a pulse oximeter for at least 2 days and provided a spot urine sample for measurement of urine albumin to creatinine ratio. In addition, a subset of participants (5,313) underwent daytime and nighttime home blood pressure measurements to evaluate blood pressure as a potential mediator of the association between sleep disordered breathing and albuminuria. Patients with end-stage kidney disease, those with active malignancy, and those receiving treatment for sleep disordered breathing were excluded from the study. Sleep disordered breathing was defined using the actigraphy-modified 3% oxygen desaturation index (ODI) and the cumulative percentage of sleep time with oxygen saturation $<90\%$. At study entry, the mean age of participants was 58 years, 67% were women, 35% had hypertension, 6.5% had diabetes, and the mean BMI was 22 kg/m^2.

In this study, moderate to severe sleep disordered breathing (defined as ODI ≥ 15) was found in 12.4% of participants, and moderately increased albuminuria (defined as urine albumin to creatinine ratio 30–299 mg/g) in 7.0%. Albuminuria was higher among individuals with moderate to severe sleep disordered breathing compared with those with mild (ODI 5 to <15) or no sleep disordered breathing (ODI < 5). After adjusting for the presence of obesity, hypertension, and diabetes, individuals with moderate to severe sleep disordered breathing had higher odds of albuminuria (odds ratio, 1.90; 95% confidence interval [CI], 1.36–2.65). Furthermore, mediation analysis revealed that systolic blood pressure (measured in the morning and during sleep) explained 28.3% (95% CI, 14.9–41.7%) of the association between sleep disordered breathing and albuminuria, suggesting that other mechanistic pathways might be involved.

Interestingly, Murase and colleagues did not find a significant association between the cumulative percentage of sleep time with oxygen saturation less than 90% and

Supported by the National Institutes of Health grant R01DK118736 (A.C.R.).

DOI: 10.1513/AnnalsATS.202109-1096ED

prevalent albuminuria. This finding is in contrast with a prior study by Canales and colleagues, which reported that higher percentage total sleep time spent at <90% oxygen saturation was significantly associated with higher albuminuria among 5,995 community-dwelling men aged 65 years and older (9). These discordant findings could be due to differences in the study populations in terms of age, sex, racial and ethnic background, and comorbidity burden (in the study by Canales and colleagues, participants were male, were more likely to be older and White, and had higher prevalence of cardiovascular disease, hypertension, and diabetes compared with the current study). Moreover, sleep disordered breathing was defined using polysomnography in the study by Canales and colleagues compared with actigraphy-modified pulse oximetry in the present study.

There are multiple potential mechanisms by which sleep disordered breathing may be associated with albuminuria. In general populations, there is considerable evidence that sleep disordered breathing has a deleterious impact on hypertension, diabetes, and obesity (11–14) through activation of the sympathetic nervous system, insulin resistance, and appetite dysregulation, respectively (15). Therefore, exacerbation of these risk factors that are well known to be associated with incidence and progression of chronic kidney disease might lead to albuminuria. Furthermore, the intermittent episodes of hypoxia and reoxygenation experienced by patients with sleep disordered breathing might be directly associated with renal tubular damage by stimulating the formation of reactive oxygen species that promote inflammation and endothelial damage and by activating the sympathetic nervous system (15).

The results of the study by Murase and colleagues have to be interpreted in light of its strengths and limitations. This was one of the first studies to evaluate the association between sleep disordered breathing, blood pressure, and albuminuria using a large community-based cohort with more than 6,000 participants. However, given the cross-sectional nature of the study, causality or direction of the associations examined cannot be determined. Therefore, future longitudinal studies are needed to corroborate their finding of a significant association between sleep disordered breathing defined by an increased actigraphy-modified 3% ODI and albuminuria. This is an area of particular interest given that prior studies have shown a decrease in albuminuria among patients treated with continuous positive airway pressure (16, 17). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

References

1 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; 395:709–733.

2 Centers for Disease Control and Prevention. Chronic kidney disease in the United States, 2021. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2021 [accessed 2021 Sep 8]. Available from: https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.

3 Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco ALM, De Jong PE, *et al.* Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;3:1–150.

4 Tonneijck L, Muskiet MHA, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, *et al.* Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol* 2017;28:1023–1039.

5 Hannan M, Ansari S, Meza N, Anderson AH, Srivastava A, Waikar S, *et al.*; CRIC Study Investigators; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Risk factors for CKD progression: overview of findings from the CRIC study. *Clin J Am Soc Nephrol* 2021;16:648–659.

6 Lin C-H, Lurie RC, Lyons OD. Sleep apnea and chronic kidney disease: a state-of-the-art review. *Chest* 2020;157:673–685.

7 Faulx MD, Storfer-Isser A, Kirchner HL, Jenny NS, Tracy RP, Redline S. Obstructive sleep apnea is associated with increased urinary albumin excretion. *Sleep* 2007;30:923–929.

8 Murase K, Matsumoto T, Tabara Y, Ohler A, Gozal D, Minami T, *et al.*; Association of sleep-disordered breathing and blood pressure with albuminuria: The Nagahama Study. *Ann Am Thorac Soc* 2022;19: 451–461.

9 Canales MT, Paudel ML, Taylor BC, Ishani A, Mehra R, Steffes M, *et al.*; Osteoporotic Fractures in Men (MrOS) Study Group. Sleep-disordered breathing and urinary albumin excretion in older men. *Sleep Breath* 2011;15:137–144.

10 Ricardo AC, Chen J, Singh M, Heiss G, Raij L, Ramos A, *et al.* Sleep-disordered breathing and prevalent albuminuria in Hispanics/Latinos. *Kidney Int Rep* 2018;3:1276–1284.

11 Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378–1384.

12 Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. *Sleep Med Rev* 2016;30:11–24.

13 Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. *Chest* 2017;152:1070–1086.

14 Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol* 2009;5:253–261.

15 Turek NF, Ricardo AC, Lash JP. Sleep disturbances as nontraditional risk factors for development and progression of CKD: review of the evidence. *Am J Kidney Dis* 2012;60: 823–833.

16 Chen NH, Chou YT, Lee PH, Lin SW, Chuang LP, Lin YS, *et al.* Reversibility of albuminuria and continuous positive airway pressure compliance in patients of obstructive sleep apnea syndrome. *Medicine (Baltimore)* 2016;95:e4045.

17 Parmaksız E, Torun Parmaksız E. Reversibility of microalbuminuria with continuous positive airway pressure treatment in obstructive sleep apnea syndrome. *Int Urol Nephrol* 2020;52: 1719–1724.