Sleep and diabetes and the kidney

Krishna G. Seshadri¹

Published online: 12 December 2018

© Research Society for Study of Diabetes in India 2018

We spend a third of our lives sleeping. And forever we have been speculating why?. Sleep is universal in vertebrates and has been described in invertebrates. The unraveling of this mystery started with the the discovery of “glymphatic” channels carrying toxic wastes in the brain. Prior to this, the only known waste disposal recognized was a recycling process internal to the neuronal cells themselves. Glial cells control the transport of CSF through channels in cell membranes. Since the energy required to transport across membranes is considerable it was clear that membrane transport and sensory processing were probably not occurring at the same time. A “downtime” from sensory processing was required to divert energy to perform housekeeping. After training mice to sleep on a two photon microscope and using real time iontophoresis Xie et al. found out that larger amounts of CSF flowed into interstitial brain spaces during sleep and to a greater depth than when awake [1]. The interstitial volume expanded by 60% during sleep leading to clearance of accumulated toxins such as beta amyloid (which is implicated in Alzheimer’s) twice as fast as when awake. Thus sleep is a state that prepares the brain for waking through obligatory self regulating cycles of brain states.

Self reported sleep times have decreased by over 1.5 h in half a century in most developed and developing populations. This is in addition to circadian disruptions common in shift workers and increased exposure to light. Given its indispensable role, reduction and disruption of sleep has consequences. Significant among these are metabolic derangements including obesity and diabetes. Sleep restriction (5 h/d for 1 week) reduces insulin sensitivity [2]. An 18–24% reduction in insulin sensitivity with subsequent increase in risk for diabetes

has been shown [3]. Disorders of sleep have been demonstrated to increase insulin resistance. Various studies have demonstrated an association between inadequate, excess and disrupted sleep with T2DM after adjusting for variables. In addition there is evidence supporting the impact of circadian disruption on beta cell dysfunction and other parameters involved in glucose homeostasis. In addition, there is evidence linking duration and quality of sleep to worsening glycemic control.

That sleep would have on an impact on DKD and its progression is hardly surprising; sleep has effects on three risk factors that initiate promote and exacerbate CKD - obesity hypertension and diabetes [4]. Obstructive sleep apnea (OSA) is related to microvascular complications after adjusting for confounders. The Apnea Hypopnea index (AHI) is related to microvascular complications particularly retinopathy [5]. OSA and AHI were independent predictors of rate of GFR decline. The evidence points out to a higher prevalence of sleep disturbances in CKD. Reduced sympathetic activity and increased vagal tone are responsible for the nocturnal dipping of BP in sleep. Activation of the sympathetic nervous system (SNS) (both day and night) with attending attenuation of nocturnal BP reduction is seen in sleep disorders. Hyperactivation of SNS has been postulated to be a risk factor for progression of CKD due its effect on BP and renal hemodynamics [6]. It is possible that sleep disturbances further this effect. Further, homeostatic BP regulation is tightly linked to sleep. Normal plasma aldosterone and plasma Renin Activity increase during sleep with higher levels in the SWS. Disturbed sleep alters the RAAS system homeostasis by decreasing the nocturnal increase in PA and PRA possibly contributing to the attenuation of the nocturnal BP dip and progression of CKD. It is possible that kidney disease may also promote sleep disturbance. Excessive fluid volume with shift to the neck during recumbency may contribute to OSA. Depression which is a common companion of both T2DM CKD (and DKD) may also contribute. Indeed in the nurses health

✉ Krishna G. Seshadri
krishnagseshadri@gmail.com

¹ Chennai Diabetes and Endocrine Clinic, Chennai 60087, India

study when compared to 7–8 h fewer than 6 or 5 h of sleep was associated with an adjusted increase in 31% and 79% chance of rapid decline in GFR. However, in published meta-analysis the relation with short duration of sleep and CKD could not be clearly established (Pooled RR 1.54 (95% CI, 0.80–2.95, I² = 94%) [7].

That brings us to proteinuria. Short duration of sleep has been associated with proteinuria irrespective of the presence of CKD [8]. The pooled RR for an association was 1.47 (95% CI, 1.26–1.72) [7]. A U shaped relationship between short and long duration of sleep and UACR in patients with T2DM has also been demonstrated. Building on this Naseri et al. in this issue of the journal in a logistic regression model demonstrate an association between proteinuria and sleep duration in patients with diabetes and normal and near normal renal function (Naseri et al. 2018).

Sleep curtailment is associated with higher levels of proinflammatory cytokines and CRP indicating systemic inflammation. This in-turn can cause glomerular endothelial injury with consequent albuminuria. The Urine Albumin Creatinine Ratio (UACR) is directly related to insulin resistance both in diabetic and in non diabetic patients [9]. Insulin resistance is associated with CKD independent of T2DM. Insulin resistance conveys an increased risk for progression of CKD to ESRD [10]. DKD itself is associated with disturbed and altered sleep and disorders and its accompaniments such as the restless leg syndrome. Inflammation and insulin resistance in the neuronal cells have been shown to associated with conditions such as alzheimer's disease (dubbed T3DM). Is it possible that inflammation and insulin resistance worsen disordered sleep through a central mechanism? Is this a cycle that feeds on itself? We have much to learn.

India has a dynamic workforce. In addition to traditional shift workers in our factories and hospitals, a significant part of our young work-force wakes up and goes to bed corresponding to the working hours of a western time zone. The

risk of obesity diabetes proteinuria CVD and possibly CKD is high in this population. What are the health costs of our economic boom? What is the real cost of a few dollars more? We have much to introspect.

Compliance with ethical standards

Conflicts of interest The author has no conflicts of interest to report with reference to this editorial.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Xie L, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342:373–7.
2. Buxton OM, et al. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes*. 2010;59:2126–33.
3. Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. *Ann N Y Acad Sci*. 2014;1311:151–73.
4. 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;60:823–33.
5. Kosseifi S, et al. The association between obstructive sleep apnea syndrome and microvascular complications in well-controlled diabetic patients. *Mil Med*. 2010;175:913–6.
6. Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int*. 2004;65:1568–76.
7. Cheungpasitporn W, et al. The effects of short sleep duration on proteinuria and chronic kidney disease: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2017;32:991–6.
8. Yamamoto R, et al. Self-reported sleep duration and prediction of proteinuria: a retrospective cohort study. *Am J Kidney Dis*. 2012;59:343–55.
9. Pilz S, et al. Insulin sensitivity and albuminuria: the RISC study. *Diabetes Care*. 2014;37:1597–603.
10. Whaley-Connell A, Sowers JR. Insulin resistance in kidney disease: is there a distinct role separate from that of diabetes or obesity? *Cardiorenal Med*. 2017;8:41–9.