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Editorial

Do Sleep Disorders Predispose to the Development of Type 2 Diabetes Mellitus?

The technological marvels in recent times has globalised the world in a true sense. The perks of this can just be judged while 'googling' the entire universe at our fingertips. One would believe life has gone simple from banking with a card swipe to foods being delivered at your doorstep. However, the story is not that rosy, is it? The ever increasing competition, never-ending deadlines, sedentary lifestyle and unhealthy food have resulted in what we call the modern day epidemic. Obesity, metabolic syndrome, diabetes and the consequent cardiovascular morbidity and mortality are ever increasing. Developed nations which *hitherto* were the major contributors of this epidemic have been surpassed by developing nations. If the current trend continues then more than half of the world's population will be under the umbrella of this epidemic.[1] Despite several technological advances in medicine, surgery and lifestyle practices the situation continues to be beyond control. The sense of panic among the health professionals have resulted in desperate search for alternate measures. This is where sleep medicine steps in!

Sleep — The golden chain linking health and body has been aptly described by the English dramatist Thomas Dekker. The disruption of this golden chain was demonstrated by Rechtschaffen *et al*[2] in his classical experiments where, sleep deprivation resulted in death of rats. This was the beckoning of clinical sleep medicine. A considerable amount of work has been done over the past few decades. Quality and quantity of sleep, chronobiology and physiology of sleep all have been probed for their role in human health and disease. Change from normal sleep to a sleep disorder can be catastrophic; mood and behaviour changes, cognitive impairment, impaired concentration and indecisiveness as a consequences of inadequate or irregular sleep have been well studied.[3] Besides, increased predisposition to occupational hazards, road traffic accidents, anxiety and depression. Ample evidence exists to demonstrate various metabolic abnormalities (obesity, dyslipidaemia, type 2 diabetes mellitus [T2DM] and cardiovascular disease) leading to increased morbidity and mortality.[4]

The recent surge in understanding the pathobiology of sleep in hyperglycaemia and insulin resistance has left us asking one question. What is the link between various sleep disorders and T2DM? If there is a link then how strong is the evidence to support it? The pathogenesis begins with compromise in any aspect of sleep, be it a brief sleep deprivation, circadian mis-alignment or fragmented sleep due to sleep apnoea. The mechanistic part of this has been well researched and includes excessive release of cortisol and catecholamine, occurring due to altered hypothalamic-pituitary-adrenal (HPA) axis and sympathetic over-activation. There is overproduction of reactive oxygen species (ROS) and inflammatory markers (interleukin [IL]-6, tumour necrosis factor [TNF] -α) along with alternation of the adipokines. Furthermore, there is also a change in appetite ($\downarrow$leptin,$\uparrow$ghrelin). All these lead to increased insulin resistance as well as pancreatic β cell dysfunction, thus, resulting in hyperglycaemia and T2DM.[5] Exploring the link between T2DM and various aspects of sleep disorders raises a variety of questions.

Does habitual snoring produce T2DM? Habitual snoring is a marker of obstructive sleep apnoea (OSA) and has been defined as snoring for $\geq$3 or in some studies as $\geq$4 nights per week. Epidemiological study during the mid-1980s explored the link between snoring and T2DM. Though, higher prevalence of T2DM in habitual snorers was observed in a study, but confounding factors, like body mass index (BMI), waist-hip ratio (WHR) were not carefully adjusted.[6] Similarly, a cross-sectional study[7], showed independent relationship of snoring in women with T2DM after adjustment for BMI. These and other confounding factors were further adjusted in Nurses' Health Study (NHS) which, was a 10-year prospective cohort (non-diabetic) study on 69,852 nurses. It proposed snoring to be independently associated with increased risk of T2DM.[8] However, long-term prospective study[9] carried out during 1984 to 1994 in 2668 male population showed increased incidence of T2DM in obese habitual snorers in comparison to obese non-snorers. An independent association with snoring could not be established as obesity was a confounder in this study.[9] There are other population-based studies[10,11] which show association between snoring and insulin resistance/T2DM. Majority of these studies have used questionnaire based, self-reported snoring, which might obscure the true picture. However, evidence of snoring and T2DM is stronger for female population. Despite availability of studies in both male and female populations, the causality evidence is far from convincing. This requires confirmation in well-designed long-term, future prospective studies.

Recently, a joint consensus statement of the AASM (American Academy of Sleep Medicine) and SRS (Sleep Research Society) has recommended that an adult should sleep for 7 or more hours per night on regular basis to promote optimal health.[12] Consequence of increasing modernisation has led to curtailment of sleep in the last 2 to 3 decades. The average duration of sleep

has decreased from 8.5 to less than 6 hours. Chronic effect of sleep deprivation (sleep debt) on carbohydrate metabolism, thyroid function, HPA axis, and sympathetic system has been studied.[13] Several cross-sectional studies[14-17] have explored association between quantity of sleep and T2DM. An increased prevalence of impaired glucose tolerance and T2DM was observed among both short and long sleepers after adjusting for confounding factors.[18] Similar results were reported in a meta-analysis of 10 prospective cohort studies involving 107,756 participants from US, Europe and Japan.[19] Included studies had used varied definitions of short (<4, <5, <6) and long (>8, >9) hours of sleep. Besides, the dose-response relationship was not reported. This dose-response relationship was addressed by another meta-analysis of prospective cohort studies where authors, showed a U-shaped dose-response relationship.[20] Both, long and short sleep durations are associated with increased risk, while 7 to 8 hours of sleep per day had lowest risk of developing T2DM. In comparison with 7 hours sleep duration, the pooled relative risks for T2DM were 1.09 (95% confidence interval [CI] 1.04-1.15) for each 1-hour loss of sleep among individuals who slept <7 hours per day and 1.14 (95% CI 1.03-1.26) for each 1-hour increase in sleep among individuals with long hours of sleep (>7 hours).[20] While use of actigraphy and polysomnography would have been more objective, most of the studies included used self-reported sleep duration, because of cost implication. The reported sleep duration was a one-time observation. Change in sleep pattern and its long-term effect still needs to be explored. Further, the studies included were from one part of the globe and extrapolation of results particularly, in context of India, where the disease is assuming epidemic proportion is not known. Thus, application of these findings in Indian context requires further research.

The urban life style and resulting change in the chronobiology has been a subject of interest for a long time. Circadian rhythm 'internal clock' of human body is a regulator of many physiological processes. 'Circadian misalignment' brought about by shift work, nocturnal lifestyle, professional demand has a major risk on human metabolic profile. Several cohort studies from Japanese population reported increased risk of impaired glucose tolerance and T2DM with shift working.[21] These studies, however, lacked information on shift duration and the magnitude of risk incurred. These queries were further addressed by a study in two large cohorts from US, NHS I (1988 – 2008) and NHS II (1989 – 2007). Over 177,000 nurses were prospectively followed-up for 20 years with surveys repeated every 2 to 4 years. Findings showed that working ≥13 night shifts per month for extended period was associated with increased risk of T2DM.[22] Similarly, a meta-analysis of 12 observational studies[23], which examined the strength of association between shift work and T2DM, concluded that there is 9% increased risk of T2DM in shift workers. Subgroup analysis further indicated that the risk is significantly higher in males and rotating shift workers (shifts rotation or change according to a set schedule).[23] Despite, the confusion among definition of various shift works, the available evidence is strong enough to probe future research in understanding the underlying mechanisms, explore gender differences and establish causality.

Obstructive sleep apnoea (OSA) is an evolving health problem and India matches the global prevalence of OSA, 4% and 2% in males and females, respectively.[24] OSA is associated with increased risk of cardiovascular disease, hypertension and metabolic syndrome.[25] Additionally, because of excessive day-time sleepiness, OSA results in vehicular and occupational accidents and impairs neurocognitive function and quality of life.[26] On exploring the relationship between T2DM and OSA, cross-sectional and longitudinal studies were able to hypothesise the link. OSA was proposed as an independent risk factor for T2DM. It was also seen that about 15% to 20% of patients with OSA have T2DM.[27] Though weak, still cross-sectional studies have explored the relationship between OSA and micro- and macro-vascular complications of T2DM. Despite several pieces of evidence, the association was not clear-cut. This was further addressed in a meta-analysis of six prospective cohort studies.[28] A statistically significant association between T2DM and OSA was observed. Further, the result was more in favour of moderate-severe OSA (AHI >15), thus implying increased risk of T2DM with increasing severity of OSA.[28] Intermittent hypoxia and sleep fragmentation were proposed as the inciting events linking OSA with insulin resistance. Although the causality between OSA and T2DM is still unanswered, however, considerable interest has been garnered to ask the next big question. Will the treatment of OSA reverse the metabolic complications? Continuous positive airway pressure (CPAP) is the first-line treatment of OSA. Several randomised controlled trials and meta-analysis have concluded that short-term use of CPAP though, improves insulin sensitivity, however, causes no change in HbA_{1c}.[29-31] Subsequently, another systematic review showed improvement in both HbA_{1c} and/or insulin sensitivity but with long-term CPAP therapy of ≥13 months.[32] Despite, the available evidences, further carefully conceived large-scale randomised controlled studies are required to confirm these findings.

In conclusion, evidence base showing effect of habitual snoring in development of T2DM is far from convincing. On the other hand, strong evidences are present demonstrating role of sleep debt, circadian misalignment and OSA in development of T2DM.

Despite all limitations of the published literature, the evidence is strong enough to underscore the importance of quality and quantity of sleep in human health and its association with several metabolic disorders. Besides, with the growing knowledge on sleep disorders, their available treatment and practice of sleep hygiene would certainly give us a foot ahead in limiting this metabolic epidemic.

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References

1. Kelly T, Yang W, Chen C-S, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes* 2008;32:1431–7.
2. Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep* 1989;12:68–87.
3. Walker MP. The role of sleep in cognition and emotion. *Ann N Y Acad Sci* 2009;1156:168–97.
4. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep* 2010;33:585–92.
5. Briançon-Marjollet A, Weiszenstein M, Henri M, Thomas A, Godin-Ribuot D, Polak J. The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms. *Diabetol Metab Syndr* 2015;7:25.
6. Norton PG, Dunn EV. Snoring as a risk factor for disease: an epidemiological survey. *Br Med J Clin Res Ed* 1985;291(6496):630–2.
7. Enright PL, Newman AB, Wahl PW, Manolio TA, Haponik EF, Boyle PJ. Prevalence and correlates of snoring and observed apneas in 5,201 older adults. *Sleep* 1996;19:531–8.
8. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. Snoring as a risk factor for type II diabetes mellitus: a prospective study. - PubMed - NCBI [Internet]. *Available from*: http://hinarilogin.research4life.org/uniquesig www.ncbi.nlm.nih.gov/uniquesig0/pubmed/11867347. Accessed on May 29, 2015.
9. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G. The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. *J Intern Med* 2000;248:13–20.
10. Shin C, Kim J, Kim J, Lee S, Shim J, In K, *et al.* Association of habitual snoring with glucose and insulin metabolism in nonobese Korean adult men. *Am J RespirCrit Care Med* 2005;171:287–91.
11. Lindberg E, Berne C, Franklin KA, Svensson M, Janson C. Snoring and daytime sleepiness as risk factors for hypertension and diabetes in women: a population-based study. *Respir Med* 2007;101:1283–90.
12. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, *et al*. Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015;38:843–4.
13. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354(9188): 1435–9.
14. Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, *et al*. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med* 2005;165:863–7.
15. Chaput J-P, Després J-P, Bouchard C, Tremblay A. Association of sleep duration with type 2 diabetes and impaired glucose tolerance. *Diabetologia* 2007;50:2298–304.
16. Tuomilehto H, Peltonen M, Partinen M, Seppä J, Saaristo T, Korpi-Hyövälti E, *et al*. Sleep duration is associated with an increased risk for the prevalence of type 2 diabetes in middle-aged women: The FIN-D2D survey. *Sleep Med* 2008;9:221–7.
17. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med* 1982. 2010;71:1027–36.
18. Ferrie JE, Kivimäki M, Akbaraly TN, Tabak A, Abell J, Davey Smith G, *et al.* Change in sleep duration and type 2 diabetes: the Whitehall II study. *Diabetes Care* 2015;38:1467–72.
19. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and auality of sleep and incidence of type 2 diabetes. *Diabetes Care* 2010;33:414–20.
20. Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, *et al*. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care* 2015;38:529–37.
21. Suwazono Y, Dochi M, Oishi M, Tanaka K, Kobayashi E, Sakata K. Shiftwork and impaired glucose metabolism: a 14-year cohort study on 7104 male workers. *Chronobiol Int* 2009;26:926–41.
22. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med* 2011;8:e1001141.
23. Gan Y, Yang C, Tong X, Sun H, Cong Y, Yin X, *et al*. Shift work and diabetes mellitus: a meta-analysis of observational studies. *Occup Environ Med* 2015;72:72–8.
24. Sharma SK, Katoch VM, Mohan A, Kadhiravan T, Elavarasi A, Ragesh R, *et al*. Consensus and evidence-based INOSA guidelines 2014 (first edition). *Indian J Med Res* 2014;140:451–68.
25. Robinson GV, Pepperell JCT, Segal HC, Davies RJO, Stradling JR. Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials. *Thorax* 2004;59:777–82.
26. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirol Carlton Vic* 2013;18:61–70.
27. Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? *Front Neurol* 2012;3:126.
28. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirol Carlton Vic* 2013;18:140–6.
29. Iftikhar IH, Khan MF, Das A, Magalang UJ. Meta-analysis: continuous positive airway pressure improves insulin resistance in patients with sleep apnea without diabetes. *Ann Am Thorac Soc* 2013;10:115–20.
30. Yang D, Liu Z, Yang H, Luo Q. Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. *Sleep Breath* 2013;17:33–8.
31. Feng Y, Zhang Z, Dong Z. Effects of continuous positive airway pressure therapy on glycaemic control, insulin sensitivity and body mass index in patients with obstructive sleep apnoea and type 2 diabetes: a systematic review and meta-analysis. *NPJ Prim Care Respir Med* 2015;25:15005.
32. Gallegos L, Dharia T, Gadegbeku AB. Effect of continuous positive airway pressure on type 2 diabetes mellitus and glucose metabolism. *Hosp Pract* 1995 2014;42:31–7.