Obstructive sleep apnoea and the orexigenic pathway in type 2 diabetes

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Abbreviations

ODI Oxygen desaturation index
OSA Obstructive sleep apnoea

To the Editor: Strong epidemiological and recent pathophysiological evidence links sleep disorders and type 2 diabetes [1, 2]. Simultaneously, there is a growing global trend of obstructive sleep apnoea (OSA), paralleled by increases in diabetes [3]. In a recent interesting article, Muraki and colleagues elegantly illustrated in a large prospective multi-centre nationwide cohort study how nocturnal intermittent hypoxia as a surrogate of OSA was associated with an elevated risk of type 2 diabetes among middle-aged Japanese [4]. It is obviously imperative to analyse the magnitude of diabetes risk attributable to the nocturnal hypoxic spells per

se as opposed to that component due to sleep deprivation and fragmentation. Muraki et al. pointed out that their method of pulse-oximetry does not capture sleep stage, unlike polysomnography. Nevertheless, the authors demonstrated the existence of a dose–response relationship between diabetes and severity of the oxygen desaturation index (ODI), after having adjusted for sleep duration. While they conceded that sleep fragmentation activates the hypothalamic–pituitary–adrenal axis, with consequent elevated insulin resistance, and that sleep duration is a predictor of future diabetes, they made no reference to the fact that sleep interruptions and restriction can also adversely influence appetite regulation, which compounds the diabetes risk further.

The sleep–wake cycle is ‘hard-wired’ to the neuroendocrine orexin projections that govern mammalian energy balance [5]. As expected, OSA sufferers have a higher incidence of appetite disorders and nocturnal food binges when their sleep is interrupted [6]. Yet Muraki et al. did not report food intake prior to sleep or in between sleep periods in the instances of sleep fragmentation. Notably, there was no mention of whether any attempts were made to evaluate the ingestion of energy-dense foods among those whose sleep was fragmented by nocturnal apnoeic episodes. Furthermore, though the risk of type 2 diabetes varies in direct proportion to ODI after adjustment for BMI and abdominal adiposity, it is unclear from the information presented how the severity of ODI was correlated to the degree of obesity, an important consideration as obesity is a known predisposing factor for OSA. Conversely, those who ingest more energy may conceivably have higher ODI aggravated by the increasing fat burden, thereby setting up a feed-forward cascade. Published data on the association of hypoxia and ghrelin, uncited by the authors, lend credence to this conjecture [7].

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Despite the ambiguities addressed above, the provocative findings of Muraki et al. will undoubtedly pose major health and lifestyle implications. I concur largely with their views, but poignant questions remain. Do OSA sufferers with sleep fragmentation show greater orexin outflow associated with higher appetite and preference for energy-dense foods? After all, the shared hypothalamic neuronal circuitry, such as the sleep–wake and appetite centres governed by clock genes (e.g. *PER2*, *CLOCK*) interact with metabolic hormones including leptin, ghrelin and orexins [8]. Are differences in sleep quality among OSA patients clinically correlated to diabetes risks? Investigations to determine food preferences, appetite and actual energy intake among OSA patients would help dissect this conundrum. The results may translate into novel pharmacotherapeutics and public health priorities to address the burgeoning dual scourges of OSA and type 2 diabetes, fuelled by modern lifestyles with much curtailed sleep.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

References

1. Kolb H, Mandrup-Poulsen T (2010) The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation. *Diabetologia* 53:10–20
2. Nedeltcheva AV, Kessler L, Imperial J et al (2009) Exposure to recurrent sleep restriction in the setting of high calorie intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab* 94:3242–3250
3. Resnick HE, Redline S, Shahah E et al (2003) Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diab Care* 26:702–709
4. Muraki I, Tanigawa T, Yamagishi K et al (2010) Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). *Diabetologia* 53:481–488
5. Adamantidis AR, Zhang F, Aravanis AM et al (2007) Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature* 450:420–424
6. Olbrich K, Muhlhans B, Allison KC et al (2009) Night eating, binge eating and related features in patients with obstructive sleep apnea syndrome. *Eur Eat Disord Rev* 17:120–127
7. Harsch IA, Konturek PC, Koebnick C et al (2003) Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. *Eur Respir J* 22:251–257
8. Knutson KL, Van Cauter E (2008) Associations between sleep loss and increased risk of obesity and diabetes. *Ann NY Acad Sci* 1129:287–304