Sleep and sleep medicine. From exotic research to a public health problem

**Abbreviations:** EEG, electroencephalography; REM, rapid eye movement; NREM, non-rapid eye movement; OSAS, obstructive sleep apnea syndrome

**Editorial**

For many years sleep research and sleep medicine have been restricted to a small number of scientists mainly active in the field of Neurology, Neuropsychology, and Psychiatry. Following the description of the electroencephalography (EEG) by Berger, the knowledge of sleep and sleep disturbances increased exponentially in the last six decades. The beginning of modern sleep medicine was developing the discovery of the typical EEG sleep pattern of both normal sleep or non-REM sleep (NREM) and paradoxical sleep or REM sleep.\(^1\) \(^2\) Sleep disorders appear early in human written history. Insomnia, for example, was described in the oldest human story “Gilgamesh” the king of Urak.\(^3\) There are a huge amount of nowadays celebrities who have declared problems of insomnia including George Clooney or Michael Jackson. Although insomnia clearly reduces the quality of life it has taken a long time until both health professionals and the general population accepted insomnia as a disease. Sleeplessness is a frequent disorder with about 10% of the population referring chronic insomnia.

A short-term or intermittent insomnia reaches values up to 35% of the population.\(^4\) It is now considered a fact, that insomnia and also sleep deprivation or sleep restriction may lead to a reduction in the physical capability and is an important risk factor for car accidents.\(^5\) \(^6\) Besides insomnia sleep related breathing disorders have been intensively investigated in the last decades. The most frequent one is the obstructive sleep apnea syndrome (OSAS). Also, here celebrities are not excluded with famous examples including Quincy Jones or Shaquille O’Neal. The most frequently cited prevalence of OSAS is 4% in men and 2% in women.\(^7\) However, due to the increased obesity in the industrialized countries the actual prevalence is possibly much higher. Recent studies indicate higher numbers with 15% of the US population and 30% of a São Paulo cohort fulfilling the criteria of sleep apnea.\(^8\) \(^9\)

Considering these numbers, it is highly probable that physicians not directly related to sleep medicine will encounter patients with relevant sleep disorders. Patients are frequently not aware that common health problems are influenced or even have their origin in the presence of sleep disorders. The relationship between OSA and cardiovascular diseases has been established for a long time with first descriptions in the 1980s just after the invention of positive pressure therapy.\(^10\) \(^11\) In several epidemiological studies, OSA was found to increase the risk of hypertension, especially nocturnal hypertension and coronary heart disease.\(^12\) \(^13\) Patients benefit of an adequate therapy of OSAS in the discussion if sleep fragmentation, restriction, and insomnia are also important risk factors. Both quality and quantity of sleep predict the risk of type 2 diabetes.\(^14\) \(^15\) Female shift workers with a rapid forward shift rotation are more prone to reach criteria of the metabolic syndrome when compared to colleagues working on a regular basis during the day.\(^16\) In an animal model, alteration of the circadian rhythm may cause hyperlipidaemia via clock gene regulations.\(^17\) The effect of sleepiness, fatigue and non-restoring sleep on cardiovascular and metabolic disorders is still unclear. At present it remains in the discussion if sleep apneas without sleepiness are in fact at an increased risk of cardiovascular diseases or metabolic disorders.\(^18\) \(^19\)

The interaction of sleep disorders with metabolic alterations is less clear but there is now ample evidence that sleep disturbances are associated with the metabolic syndrome.\(^20\) \(^21\) \(^22\) \(^23\) \(^24\) \(^25\) Positive pressure therapy abbreviates some of the altered parameters. OSAS is therefore in the interesting position that it helps to understand the pathogenesis leading to Type 2 diabetes but also, from the clinical point of view, that it is relevant for disease control.\(^26\) \(^27\) \(^28\) \(^29\) \(^30\) Similariy to the above stated association between OSAS and cardiovascular diseases, the intermittent hypoxia is considered one of the major risk factors to develop metabolic alterations.\(^31\) \(^32\) \(^33\) \(^34\) Both insulin resistance and lipid metabolism are connected to the liver function. In fact, the repetitive hypoxemia in OSAS patients has been recently linked to the development of non-alcoholic steatohepatitis and OSAS has been found associated with the prevalence of non-alcoholic fatty liver disease.\(^35\) \(^36\) \(^37\) \(^38\) This closes the circle of interacting metabolic diseases including obesity, OSAS, hypoxemia, liver dysfunction and altered glucose and insulin metabolism.\(^39\)

But once again, although well designed studies brought evidence that intermittent hypoxemia leads to metabolic alteration, it is yet in the discussion if sleep fragmentation, restriction, and insomnia are also important risk factors. Both quality and quantity of sleep predict the risk of type 2 diabetes.\(^40\) Female shift workers with a rapid forward shift rotation are more prone to reach criteria of the metabolic syndrome when compared to colleagues working on a regular basis during the day.\(^41\) In an animal model, alteration of the circadian rhythm may cause hyperlipidaemia via clock gene regulations.\(^42\) The effect of sleepiness, fatigue and non-restoring sleep on cardiovascular and metabolic disorders is still unclear. At present it remains in the discussion if sleep apneas without sleepiness are in fact at an increased risk of cardiovascular diseases or metabolic disorders.

**Conclusion**

We know that sleep effects various functions of the homeostasis. To address correctly the health problems of their patients any physician should be aware of this relationship. Although the impact of...
OSAS on cardiovascular and metabolic disorders is well established, there is still some uncertainty if sleep quality, sleep duration, and sleep fragmentation are not of relevance as well. To elucidate this complicated relationship between sleep, mental and physical health the publication of case reports will be of considerable importance.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

References

1. Berger H. Über das Elektroenzephalogramm des Menschen. Arch f Psychiat. 1929;87:527–570.
2. Davis H, Davis PA, Loomis AL, et al. Changes in Human Brain Potentials during the Onset of Sleep. Science. 1937;86(2237):448–450.
3. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Science. 1953;118(3062):273–274.
4. Aserinsky E, Kleitman N. Two types of ocular motility occurring in sleep. J Appl Physiol. 1955;8(1):1–10.
5. Kleitman N, Engelmann G. The development of the diurnal (24-hour) sleep-wakefulness rhythm in the infant. Acta med Scand. 1955;Suppl 307:106.
6. Summers-Brenner E. Insomnia: a cultural history. London, UK: Reaktion Books; 2008.
7. Medicine AAoS. International classification of sleep disorders. 3rd ed. In: Sateia M editor. American Academy of Sleep Medicine. USA; 2014. 389 p.
8. Williamson AM, Feyer AM. Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. Occup Environ Med. 2000;57(10):649–655.
9. Léger D, Bayon V, Ohayon MM, et al. Insomnia and accidents: cross-sectional study (EQUINOX) on sleep-related home, work and car accidents in 5293 subjects with insomnia from 10 countries. J Sleep Res. 2014;23(3):143–152.
10. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230–1235.
11. Young T, Palta M, Dempsey J, et al. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ. 2009;108(5):246–249.
12. Tufik S, Santos-Silva R, Taddei JA, et al. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441–446.
13. Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981;8(2225):862–865.
14. Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnoea in a hypertensive population. Lancet. 1984;2(8410):1005–1008.
15. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342(19):1378–1384.
16. Seif F, Patel SR, Walia HK, et al. Obstructive sleep apnoea and diurnal nondipping hemodynamic indices in patients at increased cardiovascular risk. J Hypertens. 2014;32(2):267–275.
17. Hla KM, Young T, Hagen EW, et al. Coronary heart disease incidence in sleep disordered breathing: the wisconsin sleep cohort study. Sleep. 2014;00357–14.
18. Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. Eur Respir J. 2009;33(6):1467–1484.
19. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J. 2009;33(5):1195–1205.
20. Bradley TD, Flores JA. Obstructive sleep apnoea and its cardiovascular consequences. Lancet. 2009;373(9657):82–93.
21. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009;32(5):589–597.
22. Vgontzas AN, Liao D, Bixler E, et al. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep. 2009;32(4):491–497.
23. Bruno RM, Palagini L, Gemignani A, et al. Poor sleep quality and resis-tant hypertension. Sleep Med. 2013;14(11):1157–1163.
24. Faraut B, Boudjeltia KZ, Vanhamme L, et al. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. Sleep Med Rev. 2012;16(2):137–149.
25. Palagini L, Bruno RM, Gemignani A, et al. Sleep loss and hypertension: a systematic review. Curr Pharm Des. 2013;19(13):2409–2419.
26. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354(9188):1435–1439.
27. Grandi AM, Laurita E, Marchesi C, et al. OSA, metabolic syndrome and CPAP: effect on cardiac remodeling in subjects with abdominal obesity. Respir Med. 2012;106(1):145–152.
28. Hall MH, Okun ML, Sowers M, et al. Sleep is associated with the metabolic syndrome in a multi-ethnic cohort of midlife women: the SWAN sleep study. Sleep. 2012;35(6):783–790.
29. Hung HC, Yang YC, Ou HY, et al. The association between self-reported sleep quality and metabolic syndrome. PLoS One. 2013;8(1):e54304.
30. Drager LF, Lopes HF, Maki–Nunes C, et al. The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. PLoS One. 2010;5(8):12065.
31. Reichmuth KJ, Austin D, Skatrud JB, et al. Association of sleep apnea and type II diabetes: a population–based study. Am J Respir Crit Care Med. 2005;172(12):1590–1595.
32. Lindberg F, Theorell–Haglow J, Svensson M, et al. Sleep apnea and glucose metabolism: a long–term follow–up in a community–based sample. Chest. 2012;142(4):935–942.
33. Kent BD, Grote L, Bonsignore MR, et al. Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: the ESADA study. Eur Respir J. 2014;44(1):130–139.
34. Coughlin SR, Mawdsley L, Mugarza JA, et al. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J. 2004;25(9):735–741.
35. Sharma SK, Agrawal S, Damodaran D, et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med. 2011;365(24):2277–2286.
36. Mota PC, Drummond M, Winck JC, et al. APAP impact on metabolic syndrome in obstructive sleep apnea patients. Sleep Breath. 2011;15(4):665–672.

37. West SD, Nicoll DJ, Wallace TM, et al. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax. 2007;62(11):969–974.

38. Weinstock TG, Wang X, Rueschman M, et al. A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. Sleep. 2012;35(5):617–625.

39. Olea E, Agapito MT, Gallego–Martin T, et al. Intermittent hypoxia and diet–induced obesity: effects on oxidative status, sympathetic tone, plasma glucose and insulin levels, and arterial pressure. J Appl Physiol. 2014;117(7):706–719.

40. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. Chest. 2015;147(1):266–274.

41. Lévy P, Pépin JL, Arnaud C, et al. Intermittent hypoxia and sleep–disordered breathing: current concepts and perspectives. Eur Respir J. 2008;32(4):1082–1095.

42. Corey KE, Misdradj J, Gelrud L, et al. Obstructive sleep apnea is associated with nonalcoholic steatohepatitis and advanced liver histology. Dig Dis Sci. 2015.

43. Minville C, Hilleret MN, Tamisier R, et al. Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea. Chest. 2014;145(3):525–533.

44. Sookooian S, Pirola CJ. Obstructive sleep apnea is associated with fatty liver and abnormal liver enzymes: a meta–analysis. Obes Surg. 2013;23(11):1815–1825.

45. Paschetta E, Belci P, Alisi A, et al. OSAS–related inflammatory mechanisms of liver injury in nonalcoholic fatty liver disease. Mediators Inflamm. 2015;2015:815721.

46. Cappuccio FP, D’Elia L, Strazzullo P, et al. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta–analysis. Diabetes Care. 2010;33(2):414–420.

47. Pan X, Zhang Y, Wang L, et al. Diurnal regulation of MTP and plasma triglyceride by CLOCK is mediated by SHP. Cell Metab. 2010;12(2):174–186.

48. Barbé F, Durán–Cantolla J, Capote F, et al. Long–term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. Am J Respir Crit Care Med. 2010;181(7):718–726.

49. Barbé F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. Ann Intern Med. 2001;134(11):1015–1023.

50. Robinson GV, Smith DM, Langford BA, et al. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. Eur Respir J. 2006;27(6):1229–1235.

51. Huang JF, Chen LD, Lin QC, et al. The relationship between excessive daytime sleepiness and metabolic syndrome in severe obstructive sleep apnea syndrome. Clinical Respir J. 2015.

52. Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. Thorax. 2009;64(10):834–839.

53. Pulixi EA, Tobaldini E, Battezzati PM, et al. Risk of obstructive sleep apnea with daytime sleepiness is associated with liver damage in nonmorbidly obese patients with nonalcoholic fatty liver disease. PLoS One. 2014;9(4):96349.