COMISA, cardiometabolic risk, and other critical reasons for considering insomnia in OSA treatment with MAD.

Miguel Meira e Cruz1, Fausto Pinto1, João Winck2
1Centro Cardiovascular da Universidade de Lisboa (CCUL@RISE), Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal
2 Faculdade de Medicina da Universidade do Porto, Porto, Portugal
All the authors declare to have any conflict of interests regarding the current manuscript.

COMISA, cardiometabolic risk, and other critical reasons for considering insomnia when treating obstructive sleep apnea with mandibular advancement devices.

Cardiometabolic (CM) diseases contribute, in a large proportion, to cardiovascular diseases, a leading cause of death worldwide (1). Accepting the critical role of sleep for the cardiovascular (and related metabolic) health, the American Heart Association has recently updated the classic “Simple 7” to a contemporary form of the “Essential 8” supporting sleep duration as a mandatory aspect to be considered among other predictors of CM status (2). Insufficient sleep, sleep fragmentation, circadian misalignment and chronodisruption are typical features presented either by insomniacs or by sleep disordered breathing patients (SDB), with the later ones having more pronounced CM effects eventually related with nocturnal intermittent hypoxemic events due to the repetitive obstruction of the upper airway during sleep (3). All these features are commonly associated with a short sleep duration. Besides, overweight/obesity, which is likely to occur in OSA patients, independently affect CM risk, sleep duration (4) and daytime functioning. An interaction between circadian timing system, insomnia and obstructive sleep apnea through CM dysfunction has also been suggested (5).

Insomnia and obstructive sleep apnea (OSA) are indeed the most prevalent sleep disorders and the main reasons for patients to present with sleep-related complaints. Interestingly, while OSA is usually pointed out as the primary sleep-

related concern regarding CM risk, insomnia is also independently related to hypertension, diabetes and other CM risk factors (6). Still, as they are often concomitant, as in the case of COMISA (Comorbid Insomnia and Sleep Apnea), such interaction will further contribute to a higher CM compromise (7), and negatively influence other clinically relevant aspects of global health, like circadian balance, higher brain functioning, vigilance, ability to optimally perform during daytime and psychosocial stress. For instance, depressive patients may present with higher risk for CM disturbances even with distinct phenotypic traits, leading some authors to propose a “cardiometabolic subtype of depression” (8). Following this concept, is notable that some COMISA patients experiencing high levels of psychosocial stress were found to benefit from cognitive behavioral strategies directed to insomnia with impacting results not only on COMISA related outcomes but also on well established CM risk factors (9). Also of great interest is our preliminary finding that in OSA patients with sleep-onset insomnia as a common COMISA phenotype, respiratory status (assessed by the apnea-hypopnea index), insomnia (inferred by the polysomnographic based sleep latency $\geq$ 30 minutes) and autonomic balance as a surrogate of CM risk, all showed marked improvements after treatment with mandibular advancement devices (MAD) (9). However, insomnia may act sometimes as a significant challenge for OSA patients, either translated in difficulties with positive airway pressure, MAD or conservative/ hygienic measures compliance. The scope and relevance of those aspects concomitantly affect adults and a large pediatric range of ages where COMISA is still prevalent and have a putative prognostic value for future CM risk (10). Though MAD therapy became a landmark in the modern practice of respiratory sleep medicine field, an integrated approach for optimal management is very often required. Specialists interacting within OSA treatment should be aware of the risk factors, main clinical features, comorbid relationships and general therapeutic strategies related to insomnia as the most frequent and quite impacting OSA-comorbid sleep disorder. Yet, some constraints will be expected. For example, in some patients with low arousal threshold, insomnia may be exacerbated and thereby conflict with treatment success (11). Gender will eventually account for crucial clinical differences among symptoms and co-occurrences (12). On the other hand, insomnia with objective (but not subjective) short sleep duration (e.g. <6h) was shown to increase the risk of hypertension

(13). Given that major adverse cardiac events were observed to increase in older men with COMISA and excessive weight in controlled studies with younger patients (14), age will plausibly have a role on the way insomnia interact with OSA during lifetime. These findings subside relevant implications: 1) for instance, subjective measures of insomnia, valuable for other endeavors may be less useful for identifying risk of CM morbidity and mortality warranting medical attention in patients presenting with sleep difficulties suggesting insomnia, and thus limit otherwise preventive actions; 2) objective assessment of sleep duration by polysomnography is expensive and unpractical. Therefore, other easy-to-use objective sleep tools like wearable electronic records or sleep trackers may offer some benefit in this scope of practice, even though they should account with gender- and age-related specificities and clinical variability; 3) effective treatment for insomnia with short sleep duration rely on agents that are more likely to improve its pathophysiological mechanisms such as physiological hyperarousal. For clinicians treating OSA patients, particularly those managing with MAD, and whenever insomnia is present (either from the sleep-onset, maintenance or sleep-offset type), taking into account clinical and polysomnographic phenotypes (15) as well as environmental aspects and oriented behavioral strategies, together with adequate instrumental tools, should guide an efficient multicomponent treatment aiming to improve the general outcomes of this complex scenario.

Within the recent years, several dental sleep societal statements and guidelines have been published regarding the odontoestomatological practice in the Sleep Medicine field, especially focusing on the management of MAD directed to OSA patients. Therefore, recognizing the opportunity of statements and recomendations on a topic needing to flourish, and considering the great amount of evidence from the last decades, particularly on the relationship between sleep disordered breathing, CM risk and premature mortality, it seems acceptable to anticipate that the inclusion of insomnia will positively impact the standards of practice towards an optimal and personalized care, favoring clinical, social and financial outcomes. This also opens the door for further research in this important field while putting the dentist together with other specialties, in the front door of a gold standard primary care practice toward a better sleep.

Note – AI was not used in the writing process of this manuscript

References

1.Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Anderson, C. A. M., Arora, P., Avery, C. L., Baker-Smith, C. M., Beaton, A. Z., Boehme, A. K., Buxton, A. E., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Fugar, S., Generoso, G., Heard, D. G., Hiremath, S., Ho, J. E., Kalani, R., … American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee (2023). Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*, *147*(8), e93–e621. https://doi.org/10.1161/CIR.0000000000001123

2. Makarem, N., Castro-Diehl, C., St-Onge, M. P., Redline, S., Shea, S., Lloyd-Jones, D., Ning, H., & Aggarwal, B. (2022). Redefining Cardiovascular Health to Include Sleep: Prospective Associations With Cardiovascular Disease in the MESA Sleep Study. *Journal of the American Heart Association*, *11*(21), e025252. https://doi.org/10.1161/JAHA.122.025252

3. André S, Andreozzi F, Van Overstraeten C, Ben Youssef S, Bold I, Carlier S, Gruwez A, Bruyneel AV, Bruyneel M. Cardiometabolic comorbidities in obstructive sleep apnea patients are related to disease severity, nocturnal hypoxemia, and decreased sleep quality. Respir Res. 2020 Jan 29;21(1):35. doi: 10.1186/s12931-020-1284-7. PMID: 31996224; PMCID: PMC6990595.

4. Amiri S. Body mass index and sleep disturbances: a systematic review and meta-analysis. Postep Psychiatr Neurol. 2023 Jun;32(2):96-109. doi: 10.5114/ppn.2023.129067. Epub 2023 Jun 28. PMID: 37497197; PMCID: PMC10367528.

5. Meira E Cruz, M., & Gozal, D. (2019). Sleepiness and Cardiometabolic Impact of Short Sleep Duration and OSA: What About the Clock?. *Chest*, *156*(6), 1273–1274. https://doi.org/10.1016/j.chest.2019.07.029

6. Nobre B, Rocha I, Morin CM, Cruz MME. Insomnia and circadian misalignment: an underexplored interaction towards cardiometabolic risk. Sleep Sci. 2021 Jan-Mar;14(1):55-63. doi: 10.5935/1984-0063.20200025. PMID: 34104338; PMCID: PMC8157774.

7. Meira E Cruz, M., Salles, C., & Gozal, D. (2021). A Reappraisal on the Associations between Sleep-disordered Breathing, Insomnia, and Cardiometabolic Risk. *American journal of respiratory and critical care medicine*, *203*(12), 1583–1584. https://doi.org/10.1164/rccm.202102-0337LE

8. Geraets, A. F. J., Schram, M. T., Jansen, J. F. A., Backes, W. H., Schalkwijk, C. G., Stehouwer, C. D. A., van Boxtel, M. P. J., Eussen, S. J. P. M., Kooman, J. P., Verhey, F. R. J., & Köhler, S. (2022). The cardiometabolic depression subtype and its association with clinical characteristics: The Maastricht Study. *Journal of affective disorders*, *313*, 110–117. https://doi.org/10.1016/j.jad.2022.06.045

9. Meira e Cruz, M., Brito, R., Rocha, I., Salles, C., Kryger, M., Gozal, D., Sweetman, A. (2024). Clinically guided digital Cognitive Behavioural Therapy for insomnia (CBTi) in patients with COMISA: a case-control pilot study with focus on mental health and cardiometabolic risk factors. Sleep Medicine, 115(1), S165. https://doi.org/10.1016/j.sleep.2023.11.472.

10. Meira E Cruz M. (2024). Comorbid Insomnia and Sleep Apnea: COMISA. *Dental clinics of North America*, *68*(3), 455–466. https://doi.org/10.1016/j.cden.2024.03.002

11. Antonaglia, C., Vidoni, G., Contardo, L., Giudici, F., Salton, F., Ruaro, B., Confalonieri, M., & Caneva, M. (2022). Low Arousal Threshold Estimation Predicts Failure of Mandibular Advancement Devices in Obstructive Sleep Apnea

Syndrome. *Diagnostics (Basel, Switzerland)*, *12*(10), 2548. https://doi.org/10.3390/diagnostics12102548

12. Mysliwiec, V., Pruiksma, K. E., Matsangas, P., Powell, T., Straud, C. L., Taylor, D. J., Hansen, S., Foster, S. N., Mithani, S., Zwetzig, S., Martin, J., Gerwell, K., Young-McCaughan, S., Blue Star, J. A., Cassidy, D. G., Gomes, K. D., Moore, B. A., Peterson, A. L., Brock, M. S., & STRONG STAR Consortium (2024). Sex differences in US military personnel with insomnia, obstructive sleep apnea, or comorbid insomnia and obstructive sleep apnea. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *20*(1), 17–30. https://doi.org/10.5664/jcsm.10774

13. Dai Y, Chen B, Chen L, Vgontzas AN, Fernandez-Mendoza J, Karataraki M, Tang X, Li Y. Insomnia with objective, but not subjective, short sleep duration is associated with increased risk of incident hypertension: the Sleep Heart Health Study. J Clin Sleep Med. 2023 Aug 1;19(8):1421-1428. doi: 10.5664/jcsm.10570. PMID: 37078185; PMCID: PMC10394371.

14. Fang, F., Sun, Z., Gao, Y., Han, J., Zhao, L., Zhao, Z., He, Z., Zhang, Z., Bian, H., & Liu, L. (2024). Effects of combined morbid insomnia and sleep apnea on long-term cardiovascular risk and all-cause mortality in elderly patients: a prospective cohort study. *BMC geriatrics*, *24*(1), 622. https://doi.org/10.1186/s12877-024-05147-2

15. Manetta, I. P., Duarte, B. B., Nucci, L. B., & Enes, C. C. (2024). Relationship between OSA pathophysiological phenotypes and treatment response to mandibular advancement devices: a pilot study. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *20*(8), 1321–1330.