EBioMedicine 33 (2018) 20–21

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Metabolic Syndrome, Adiponectin, Sleep, and the Circadian System

Germaine Cornelissen

Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA

Keywords:
Metabolic syndrome
Adiponectin
Sleep
Circadian system

A recent meta-analysis concluded that metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality [1]. While many studies investigate adult populations, the cohort investigated by Li et al. consisted of younger subjects aged 15–28 years recruited from the Beijing Child and Adolescent Metabolic Syndrome study and aimed to identify cardiovascular risk factors from childhood to adulthood [2]. Assessing the association of several GWAS–identified adiponectin-related genetic variants with left ventricular mass index (LVMI), used as a gauge of cardiovascular disease risk, these authors report (a) that CDH13 rs4783244 is positively correlated with adiponectin concentrations; (b) that this locus is also significantly associated with decreased LVMI independent of adiponectin concentrations and other conventional cardiovascular risk factors; and (c) that the cardio-protective effects at this locus are lost in subjects with short sleep duration.

In a single study, Li et al. linked several important factors affecting cardiovascular risk in the presence of metabolic syndrome, namely genetics, metabolism, and sleep. They deserve special credit for their assessment of the role of sleep duration on cardio-protection gained from an adiponectin-related genetic variant in a young population diagnosed with the metabolic syndrome. Indeed, sleep duration is both predictive of the metabolic syndrome [3] and directly affects adiponectin [4], a protein hormone involved in regulating glucose concentrations and fatty acid breakdown. Adiponectin, in turn, has been associated with both the metabolic syndrome [5] and cardiovascular health status gauged by LVMI [6].

Specifically, a dose-response relationship exists between short sleep duration and the presence of metabolic syndrome, as shown by a meta-analysis of 75,657 participants in 18 studies [3]. Conversely, an increase in objective sleep duration is reportedly associated with a significantly increased serum adiponectin concentration, independent of the change in body fat during a 7-month weight loss intervention in overweight or obese women [4]. Low adiponectin concentrations at the outset and decreasing adiponectin concentrations over a 10-year follow-up are predictive of the metabolic syndrome [5]. Plasma adiponectin is also inversely correlated with LVMI and pulse wave velocity, the corresponding multiple regression model accounting for 73.3% of LVMI variability, results suggesting a direct influence of adiponectin on LVMI [6].

Not mentioned in the paper by Li et al. and worth further investigation is the existence of a bidirectional relationship between adiponectin and the circadian system. Adiponectin expression is circadian periodic. It is mediated by the helix-loop-helix transcription factor sterol regulatory element binding protein (SREBP)-1c. In murine white adipose tissue and differentiated adipocytes, adiponectin expression is reportedly coordinated by the circadian system through the circadian expression of its transcription factor PPARγ and its co-activator PGC1α [7]. Conversely, circadian clock rhythmicity is modulated by adiponectin in a metabolic syndrome mouse model that expresses the human adiponectin transgene in the liver [8]. As compared to control mice, transgenic mice exhibit a blunted and phase-shifted circadian variation of locomotor activity. Transgenic mice also show phase-advanced circadian rhythms of the clock genes Arntl, Dbp, Cry2 and Per2 in both liver and skeletal muscles. Adiponectin may thus be a peripheral coordinator of the circadian clock in the brain and peripheral organs [8].

Numerous studies have documented associations between circadian rhythmicity, sleep duration, and metabolism. Circadian disruption and disturbed sleep patterns can alter metabolism in a manner that predisposes to weight gain [9]. Alterations in the circadian clock machinery have also been linked to a host of disease conditions, including cardiovascular disease. The role of clock genes in relation to components of the metabolic syndrome (obesity and diabetes) is noteworthy since circadian clocks are tightly coupled to cellular metabolism as they share a number of nutrient-sensing pathways. Disease risk elevation and the presence of overt disease are also often associated with a weakened circadian system, with reduced circadian amplitude and a less tightly synchronized circadian system [10].

A robust circadian system thus presents itself as a strategy for health maintenance and disease risk avoidance. Since environmental synchronizers such as the rest-activity schedule and meal timing are effective ways to strengthen the circadian system, it is not surprising that sleep and nutrition play such important roles in the presence of metabolic syndrome, as illustrated herein by the study of Li et al.

Disclosure

The author declares no conflicts of interest.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.05.033.
E-mail address: corne001@umn.edu.

https://doi.org/10.1016/j.ebiom.2018.06.013

References

[1] Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk. A systematic review and meta-analysis. J Am Coll Cardiol 2010;56(14):1113–32.

[2] Li G, Feng D, Wang Y, Fu J, Han L, Li L, et al. Loss of cardio-protective effects at the CDH13 locus due to gene-sleep interaction: the BCMAS study. EBioMedicine. In Press, https://doi.org/10.1016/j.ebiom.2018.05.033.

[3] Iftikhar IH, Donley MA, Mindel J, Pleister A, Soriano S, Magalang UJ. Sleep duration and metabolic syndrome. An updated dose–risk metaanalysis. Ann Am Thorac Soc 2015;12(9):1364–72.

[4] Sawamoto R, Nozaki T, Furukawa T, Tanahashi T, Morita C, Hata T, et al. A change in objective sleep duration is associated with a change in the serum adiponectin level of women with overweight or obesity undergoing weight loss intervention. Obes Sci Pract 2016;2(2):180–8.

[5] Lindberg S, Jensen JS, Bjerre M, Frystyk J, Flyvbjerg A, Jeppesen J, et al. Low adiponectin levels at baseline and decreasing adiponectin levels over 10 years of follow-up predict risk of the metabolic syndrome. Diabetes Metab 2017;43(2):134–9.

[6] Hong SJ, Park CG, Seo HS, Oh DJ, Ro YM. Associations among plasma adiponectin, hypertension, left ventricular diastolic function and left ventricular mass index. Blood Press 2004;13(4):236–42.

[7] Barnea M, Chapnik N, Genzer Y, Froy O. The circadian clock machinery controls adiponectin expression. Mol Cell Endocrinol 2015;399:284–7.

[8] Hashinaga T, Wada N, Otabe S, Yuan X, Kurita Y, Kakino S, et al. Modulation by adiponectin of circadian clock rhythmicity in model mice for metabolic syndrome. Endocr J 2013;60(4):483–92.

[9] Huang W, Ramsey KM, Marcheva B, Bass J. Circadian rhythms, sleep, and metabolism. J Clin Invest 2011;121(6):2133–41.

[10] Cornelissen G. Altered circadian energy metabolism and chronobiological risk factors of chronic diseases. In: Watson RR, Singh RB, Takahashi T (Eds.) The role of functional food security in global health. Elsevier, [in press].