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The effect of sleep extension on metabolic and androgen parameters of healthy women with habitual short sleep duration: Pilot study

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ABSTRACT

Aims: Sleep curtailment, a common behavior in modern societies, is associated with significant alterations in metabolic and endocrine profiles. This pilot study aimed to investigate the potential benefits of sleep extension, under real-life conditions, on insulin sensitivity, androgens, and leptin, in women with habitual short sleep duration. Methods: In a single-arm study design, healthy pre-menopausal women with ≤ 6 hours of daily sleep (n=10) were instructed to increase their sleep duration by one hour daily for one month. Fasting blood samples were obtained on days 2-3 of the menstrual cycle, at baseline, and after the intervention. Samples were analyzed for glucose, insulin, leptin, total testosterone, sex hormone-binding globulin, and dehydroepiandrosterone-sulfate. Measurement of sleep duration was based on the participants' subjective reporting using sleep logs, and baseline data were compared to post-intervention. Results: Seven women completed the intervention and significantly increased their sleep duration by 40.7 ± 14 min (mean ± standard deviation). However, our pilot data did not indicate significant changes in any of the parameters assessed at the end of the intervention. Conclusion: The impact of sleep extension on various metabolic and androgen parameters in women requires further investigation with larger samples and more controlled designs.

Keywords: Sleep Curtailment; Insulin Resistance; Androgens, Leptin.

INTRODUCTION

One of the common characteristics of modern societies is sleep curtailment. Increased social and occupational demands and other major lifestyle changes resulted in an estimated shortage of 1.5 to 2 hours in sleep duration over the past century [1]. Research investigating the effects of partial sleep deprivation on human metabolic health reported an alteration in glucose tolerance and insulin sensitivity [2, 3] and an increased risk of developing obesity and type 2 diabetes [4]. Moreover, short sleep duration was found to up-regulate ghrelin and increase hunger while down-regulating leptin and curbing its satiety-stimulating effect [5]. Consequently, food intake is thought to increase [6], which could further impact insulin sensitivity. However, despite the extensive research in this field, little knowledge is available on the metabolic benefits of increased sleep duration of habitual short-time sleepers [5,7]. Most studies were cross-sectional observational studies or laboratory studies inducing partial sleep deprivation. Only a few studies investigated the effect of sleep extension under real-life conditions [8-10], as opposed to laboratory conditions, which we aimed to investigate in this study.

Furthermore, the extent to which sleep affects women's fertility and reproductive profile is still poorly understood. Androgens are the most abundant female sex hormones. They are precursors of estrogens and play an essential role in reproductive physiology. Hyperandrogenemia, or elevated blood levels of androgens, including testosterone and dehydroepiandrosterone-sulfate (DHEA-S), can clinically manifest in women with acne symptoms, hirsutism, androgenic alopecia, and menstrual disturbances [11]. Hyperandrogenemia, in particular, is a major feature of polycystic ovary syndrome (PCOS), a leading cause of infertility among women [12].

Furthermore, sleep quantity and quality can influence androgen levels in women, at least through the adverse effects of sleep restriction on insulin sensitivity [13, 14]. The latter is strongly associated with androgen levels in women during their reproductive years [15]. Insulin resistance and hyperandrogenemia

form a vicious cycle at the core of PCOS pathophysiology [12]. However, there is a scarcity of studies investigating the effect of sleep duration on androgen levels [16, 17], and research is still needed to elucidate this relationship. Therefore, this study aimed to investigate the effect of a one-hour sleep extension, as a home-based intervention, on insulin sensitivity, leptin, and androgen levels in a group of healthy women with habitual short duration of sleep. Extending sleep by one hour was made to increase the feasibility of the intervention while approaching the minimum recommended sleep duration for adults, which is 7 hours [26]. Sleep extension was also planned for one month to allow the evaluation of hormonal parameters, specifically androgens, at the same point in time, which is the early follicular phase of the menstrual cycle, before and after the intervention, given that the average cycle length is 28-29 days [27]. This will help eliminate the effect of hormonal physiological fluctuations during the cycle on the intervention results.

METHODS

In this pilot study, a group of healthy women who are habitual short-time sleepers was recruited in 2018; the inclusion criteria are provided in the following section. An initial interview was conducted to obtain the women's medical history and sleeping routine and arrange for baseline blood collection. To assess their sleep routine, women were asked to keep sleep logs for 3 days, excluding weekends since all participants had their sleep restricted only during the workdays—those with an average sleep duration of ≤ 6 hours/day were included in this study. After ensuring compliance with our inclusion/exclusion criteria (mentioned in the following section), participants were instructed to increase their sleep duration by one hour daily for one month, starting from the day the baseline hormonal assessment was performed. They were also provided individualized counseling to help them achieve this increase in sleep duration and improve their sleep quality. Baseline and final hormonal assessments, approximately one month apart, were performed on days 2-3 of the menstrual cycle (to represent hormonal levels at the early follicular phase) while fasting for at least 8 hours. During the study period, participants were also asked to keep sleep logs for their bed and wake-up times during the week (for four weeks), which were used to estimate their sleep duration. All participants provided written informed consent for their participation in this study. The Scientific Research Committee and the Institutional Review Board at the University of Jordan approved the study protocol.

Participants

Healthy women aged 20-30 years with a habitual short duration of sleep (≤ 6 hours daily) and a normal body mass index (BMI=18.5-24.9 kg/m^2) were included in this study. Age and BMI were limited to reduce confounders that affect metabolic and endocrine profiles. Our exclusion criteria included having any metabolic or endocrine conditions, insomnia, regular napping, sleep disorders, and the intake of drugs, including hormonal contraceptives, that may affect sleep, metabolic or endocrine profiles. In addition, shift workers, smokers, pregnant and lactating women, and women taking any nutritional supplements or herbal recipes were excluded.

Biochemical and Statistical Analysis

Serum was obtained from blood samples and stored at -20 °C until biochemical analysis. Samples were tested for glucose, insulin, sex hormone binding globulin (SHBG), total testosterone, and DHEA-S (primarily adrenal androgen) using COBAS Analyzer (Roche Diagnostics). Leptin was assayed using Leptin human ELISA kit (Thermo Fisher Scientific). The homeostasis model assessment for insulin resistance (HOMA-IR), as an index of insulin resistance, was calculated using the following formula: HOMA-IR = fasting insulin (µIU/ml) x fasting glucose (mmol/L)/22.5.

Statistical analysis was performed using IBM SPSS (version 26, IBM Corp.). Descriptive statistics are given as mean ± standard deviation (SD). The normality of the data was tested using the Shapiro-Wilk test. The paired t-test and Wilcoxon signed-ranks test were used for normally and non-normally distributed variables to assess the statistical difference between baseline and post-intervention. $P < 0.05$ was considered statistically significant. The target sample size for this single-arm study was 30 participants, and it was calculated based on an expected mean of 1.5

and a standard deviation of 2.5 for the paired differences (pre and post-intervention) in fasting insulin levels [18], in addition to an attrition rate of about 16%.

RESULTS

We could not attain our target sample size; only 10 women agreed to participate in this study. In addition, three women dropped out due to noncompliance with the intervention during the study. Participants mean age and BMI were 24 ± 4.8 years and 21.6 ± 1.9 kg/m^2 (mean ± SD). Based on the subjective reporting of sleep duration using sleep logs, the average sleep during workdays was significantly increased by 40.7 ± 14 min (mean ± SD). Baseline and post-intervention characteristics are listed in (Table 1). All participants had normal baseline levels of metabolic and androgen parameters. However, none of these parameters differed significantly at the end of the one-month sleep extension.

Table (1): Baseline and post-intervention parameters.

Variables	Baseline	Post-intervention	*P* value
Sleep duration (min)*	331.4 ±22.7	372.1 ±24.9	0.002[a]
Fasting glucose(mg/dl)	88.1± 7.4	94.0 ± 10.2	0.18[b]
Fasting insulin (µIU/ml)	4.8±3.0	4.5±3.0	0.35[b]
HOMA-IR	1.05 ± 0.61	1.07 ± 0.75	0.74[b]
Leptin (ng/ml)	1.08 ± 1.56	0.99 ± 1.28	0.5[b]
SHBG (nmol/L)	51.2 ± 12.5	53.8 ± 23.6	0.68[a]
Total Testosterone (ng/ml)	0.35 ± 0.24	0.48 ± 0.40	0.27[a]
DHEA-S (µg/dl)	274.8 ± 164.2	275.1 ±147.4	0.99[a]

Data are presented as mean ± SD.

*Only sleep duration was significantly different after the intervention.

[a]Using Paired t-test.

[b]Using Wilcoxon signed-ranks test.

Abbreviation: HOMA-IR; homeostasis model assessment for insulin resistance, SHBG; sex hormone binding globulin, DHEA-S; dehydroepiandrosterone-sulfate.

DISCUSSION

Insufficient sleep is a risk factor for several psychological, cardiovascular, and metabolic dysfunctions. Clinical evidence indicates that women with inadequate sleep are at a greater risk for these pathologies than men [17]. Regarding glucose homeostasis, most studies indicate that short sleep duration is associated with decreased insulin sensitivity and impaired glucose tolerance, as assessed by intravenous glucose tolerance tests and hyperinsulinemic-euglycemic clamp [2, 3, 5]. Similarly, studies investigating the metabolic benefits of sleep extension favor improving insulin sensitivity of habitual short-time sleepers [8, 19, 20]. Three nights of in-laboratory sleep extension (10 hours per night vs. 6 hours) after habitual sleep restriction was associated with reduced levels of fasting insulin and HOMA-IR [19]. Percent changes in total sleep duration correlated positively with fasting glucose and negatively with fasting insulin levels, according to Leproult *et al*. (2015), although no significant differences in glucose and insulin levels were reported after 6 weeks of one-hour sleep extension [20]. Two other studies did not report significant differences in glycemic parameters after sleep extension. However, on average, participants in both studies could not achieve more than 6 hours of sleep, which is still considered a short sleep duration [8, 21]. Interestingly, So-intern*et al*. (2019) found that improved glucose tolerance was only evident when evaluating data from participants who could achieve more than 6 hours of sleep during the extension [8].

In our study, we expected a positive effect of sleep extension on glucose homeostasis and insulin sensitivity. However, we found no significant changes in glucose, insulin, and HOMA-IR fasting levels. Although our results align with three previous studies reporting no significant effects of sleep extension on these

metabolic parameters [8, 20, 21], our small sample size may have made it difficult to observe significant changes after one month of sleep extension. Also, based on subjective reporting of sleep duration, participants could only extend their sleep by an average of 41 min, which may be considered rather insufficient. We also did not find significant changes in leptin levels, which contradicts the results of Killick *et al*. (2015), who reported a significant decrease in leptin levels after three nights of sleep extension (10 hours vs. 6 hours per night) [19]. However, the large difference in the duration of sleep extension (4 hr vs. 40 min) may explain the discrepancy in the results.

There is a paucity of knowledge about the impact of sleep disturbance on androgen levels in reproductive-age women [16, 17]. Sleep research mainly included men and male animals, which may indicate that the results can only be generalized to male rather than female physiology. In women, fluctuations in ovarian steroids during the menstrual cycle were found to be associated with sleep disturbances [17]. Sleep curtailment may augment androgen levels, not only because it adversely affects insulin sensitivity [12] but also because of a possible influence on LH secretion, which stimulates androgen production. However, evidence is still inconclusive on the effect of sleep duration on LH levels. A night of partial sleep deprivation was found to increase LH levels in 10 healthy women [22], and sleep was also found to have an inhibitory effect on the amplitude and frequency of LH pulsatile secretion in 11 healthy women during the early follicular phase of the menstrual cycle [23]. However, a larger cross-sectional study, including 106 healthy women, found no relationship between sleep duration and LH levels [24].

Furthermore, given the scarcity of evidence on a direct relation between sleep duration with androgen levels, it may be relevant to indicate that women with PCOS, who typically have hyperandrogenemia, were reported to have lower sleep duration and quality compared to healthy controls [25]. However, it remains to be further investigated whether this is a consequence or a contributor to the underlying hormonal dysregulation of PCOS. In our study, we hypothesized that sleep extension would result in lower levels of androgens, but we did not find significant differences in the levels of total testosterone, DHEA-S, or SHBG at the end of the intervention period. We speculate that the duration of sleep extension was insufficient to produce significant changes; therefore, this relationship requires further investigation. In any case, it may be valid to interpret the lack of changes observed in androgen and metabolic parameters because they were already in the normal range, which provides a small window for improvements to be observed.

Among the limitations of our study is its small sample size, as it was challenging to recruit participants. The argument of some women who met the inclusion criteria and refused to participate was that sleep extension is not a choice they can take due to their daily life obligations, which indicates the social and financial determinants leading to sleep curtailment. Therefore, this pilot study highlights the low feasibility of the intervention, i.e., long-term sleep extension under real-life conditions, which needs to be considered by researchers in any future studies. Furthermore, subjective measurement is not as accurate as using objective methods in assessing the actual duration of sleep, which can limit the validity of our results. At any rate, this is the first study to shed some light on the effects of sleep extension on androgen levels in young women under real-life conditions. More research with larger samples is warranted to elucidate the benefits of improving sleep quantity and quality on the sex-hormonal profile and metabolic parameters of reproductive-age women.

Ethics approval and consent to participate

All participants provided written informed consent for their participation in this study. The Scientific Research Committee and the Institutional Review Board at the University of Jordan approved the study protocol.

Consent for publication

The authors grant the Palestinian Medical and Pharmaceutical Journal permission to publish this work.

Availability of data and materials

The corresponding author, I H-H, can provide the data supporting the findings of this study upon reasonable request.

Author's contribution

Isra'a Haj-Husein: Conceptualization, data collection, analysis, and manuscript drafting. **Nour Hamdan:** Data collection and facilitation. **Hadeel Ghazzawi:** Funding acquisition, project administration, resources, and supervision.

Conflict of Interests

The authors declare that they have no conflict of interest.

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REFERENCES

1] Centers for Disease Control and Prevention (CDC). Short sleep duration among workers--United States. Morbidity and Mortality Weekly Report. 2012; 61(16): 281-285.

2] Donga E, van Dijk M, van Dijk JG, Biermasz NR, Lammers G, van Kralingen KW, et al. A Single Night of Partial Sleep Deprivation Induces Insulin Resistance in Multiple Metabolic Pathways in Healthy Subjects. The Journal of Clinical Endocrinology & Metabolism. 2010 Jun 1;95(6):2963-8.

3] Wong PM, Manuck SB, DiNardo MM, Korytkowski M, Muldoon MF. Shorter Sleep Duration is Associated with Decreased Insulin Sensitivity in Healthy White Men. Sleep. 2015 Feb 1;38(2):223-31.

4] Nielsen LS, Danielsen KV, Sørensen TIA. Short sleep duration as a possible cause of obesity: critical analysis of the epidemiological evidence. Obesity Reviews. 2011 Feb;12(2):78-92.

5] Morselli L, Leproult R, Balbo M, Spiegel K. Role of sleep duration in the regulation of glucose metabolism and appetite. Best Practice & Research Clinical Endocrinology & Metabolism. 2010 Oct; 24(5): 687-702.

6] St-Onge M. The Role of Sleep Duration in the Regulation of Energy Balance: Effects on Energy Intakes and Expenditure. Journal of Clinical Sleep Medicine. 2013 Jan 15;09(01):73-80.

7] St-Onge M. Sleep-obesity relation: underlying mechanisms and consequences for treatment. Obesity Reviews. 2017 Feb; 18: 34-9.

8] So-ngern A, Chirakalwasan N, Saetung S, Chanprasertyothin S, Thakkinstian A, Reutrakul S. Effects of Two-Week Sleep Extension on Glucose Metabolism in Chronically Sleep-Deprived Individuals. Journal of Clinical Sleep Medicine. 2019 May 15;15(05):711-8.

9] Stock AA, Lee S, Nahmod NG, Chang A. Effects of sleep extension on sleep duration, sleepiness, and blood pressure in college students. Sleep Health. 2020 Feb;6(1):32-9.

10] Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: A home-based intervention. Appetite. 2014 Sep;80:220-4.

11] Yildiz BO. Diagnosis of hyperandrogenism: clinical criteria. Best Practice & Research Clinical Endocrinology & Metabolism. 2006 Jun;20(2):167-76.

12] Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol. 2010 Oct;122(1-3):42-52.

13] Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired Insulin Signaling in Human Adipocytes After Experimental Sleep Restriction. Ann Intern Med. 2012 Oct 16;157(8):549.

14] Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, et al. Adverse Metabolic Consequences in Humans of Prolonged Sleep Restriction Combined with Circadian Disruption. Sci Transl Med. 2012 Apr 11;4(129).

15] Corbould A. Effects of androgens on insulin action in women: is androgen excess a component of female metabolic syndrome?. Diabetes Metab Res Rev. 2008 Oct;24(7):520-32.

16] Kloss JD, Perlis ML, Zamzow JA, Culnan EJ, Gracia CR. Sleep, sleep disturbance, and fertility in women. Sleep Medicine Reviews. 2015 Aug;22:78-87.

17] Mong JA, Cusmano DM. Sex differences in sleep: impact of biological sex and sex steroids. Phil Trans R Soc B. 2016 Feb 19;371(1688):20150110.

18] Singh, Navneet Dhand and Mehar. "Sample Size Calculator for Comparing Paired Differences." Statulator.com, statulator.com/SampleSize/ss2PM.html. Accessed 20 Aug. 2022.

19] Killick R, Hoyos CM, Melehan KL, Dungan GC, Poh J, Liu PY. Metabolic and hormonal effects of 'catch-up' sleep in men with chronic, repetitive, lifestyle-driven sleep restriction. Clin Endocrinol. 2015 Oct;83(4):498-507.

20] Leproult R, Deliens G, Gilson M, Peigneux P. Beneficial Impact of Sleep Extension on Fasting Insulin Sensitivity in Adults with Habitual Sleep Restriction. Sleep. 2015 May 1;38(5):707-15.

21] Al Khatib HK, Hall WL, Creedon A, Ooi E, Masri T, McGowan L, et al. Sleep extension is a feasible lifestyle intervention in free-living adults who are habitually short sleepers: a potential strategy for decreasing intake of free sugars? A randomized controlled pilot study. The American Journal of Clinical Nutrition. 2018 Jan 1;107(1):43-53.

22] Baumgartner A, Dietzel M, Saletu B, Wolf R, Campos-Barros A, Gräf K, et al. Influence of partial sleep deprivation on the secretion of thyrotropin, thyroid hormones, growth hormone, prolactin, luteinizing hormone, follicle stimulating hormone, and estradiol in healthy young women. Psychiatry Research. 1993 Aug;48(2):153-78.

23] Hall JE, Sullivan JP, Richardson GS. Brief Wake Episodes Modulate Sleep-Inhibited Luteinizing Hormone Secretion in the Early Follicular Phase. The Journal of Clinical Endocrinology & Metabolism. 2005 Apr;90(4):2050-5.

24] Touzet S, Rabilloud M, Boehringer H, Barranco E, Ecochard R. Relationship between sleep and secretion of gonadotropin and ovarian hormones in women with normal cycles. Fertility and Sterility. 2002 Apr;77(4):738-44.

25] Tasali E, Van Cauter E, Ehrmann DA. Relationships between Sleep Disordered Breathing and Glucose Metabolism in Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology & Metabolism. 2006 Jan;91(1):36-42.

26] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health. 2015 Dec;1(4):233-43.

27] Faust L, Bradley D, Landau E, Noddin K, Farland LV, Baron A, et al. Findings from a mobile application–based cohort are consistent with established knowledge of the menstrual cycle, fertile window, and conception. Fertility and Sterility. 2019 Sep;112(3):450-457.e3.