Acta Biomed 2023; Vol. 93, 4 e2023079 DOI: 10.23750/abm.v94i4.14142

Original article

Sleep duration and insulin resistance in obese adolescents with metabolic syndrome: is there a correlation?

Claudia Magdalena Felisia Kurube, Nur Aisiyah Widjaja, Eva Ardianah
Department of Child Health, Faculty of Medicine Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia

Abstract. *Background and aim:* Short sleep duration causes many changes in several hormones (leptin, ghrelin, insulin, cortisol, growth hormone) and increases sympathetic activity with elevated levels of catecholamines, which causes an energy imbalance and leads to overweight or obesity and insulin resistance. The present study aimed to analyze the relationship between sleep duration and insulin resistance in obese adolescents with metabolic syndrome. *Methods:* An observational cross-sectional research design concluded 124 obese adolescents with metabolic syndrome (MetS) aged 13-18 years. Anthropometry, blood pressure, and blood tests were conducted to determine obesity according to CDC 2000. MetS determination based on International Diabetes Federation 2007. Insulin resistance was assessed using HOMA-IR. Sleep duration was determined based on direct interviews with the research subjects. The obtained data were analyzed using the Spearman correlation test, Chi-Square, Mann-Whitney, and T-test (significant at P <0.05). *Results:* The subjects were dominated by male adolescents 67.5%. There was a strong relationship between age and sleep duration (p = 0.035). Subjects were divided into two age groups based on sleep duration: those with < 8 hours and > 8 hours of sleep. There was a significant difference in fasting insulin levels and HOMA IR value between the two groups, higher in the subjects with < 8 hours of sleep than the subjects with > 8 hours of sleep. Sleep duration and HOMA-IR values as a marker of insulin resistance had a significant negative correlation (r_s= -0.581; P <0.001) and insulin levels (r_s=-0.565, P <0.001). *Conclusions*: Sleep duration has a robust negative correlation with the HOMA-IR value, which is a parameter of insulin resistance. (www.actabiomedica.it)

Key words: insulin resistance, metabolic syndrome, obese adolescents, sleep duration

Introduction

The prevalence of obesity in children and adolescents has increased almost worldwide in the last three decades. Such a phenomenon is also followed by an increase in comorbidities especially the metabolic syndrome associated with insulin resistance. Insulin resistance is an independent risk factor for cardiovascular and metabolic diseases (1–3). Furthermore, short sleep duration is considered to engender insulin resistance either directly by changing glucose metabolism or indirectly by causing obesity (4).

Sleep determines the health status of children, adolescents, and adults through the control of diurnal rhythm that is associated with energy homeostasis (5). Short sleep duration causes changes in levels of several hormones including leptin, ghrelin, insulin, cortisol, and growth hormone, and increases sympathetic activity with elevated levels of catecholamines. These hormonal changes and sympathetic activity cause an energy imbalance and lead to overweight or obesity and insulin resistance (6,7).

Several studies have been conducted to assess the relationship between sleep duration and Insulin resistance with a contradictive results. Some researched a relationship between shorter sleep duration and the incidence of insulin resistance in children (8–10). Other studies also stated that there was no significant

relationship between shorter sleep duration and the incidence of insulin resistance in children (10,11) Therefore, this study was conducted to examine the relationship between short sleep duration and insulin resistance in obese adolescents with metabolic syndrome in Indonesia, especially in Surabaya and Sidoarjo.

Methods

Patient and methods

This study was a cross-sectional study taken from July to November 2020. The study was conducted in 12 junior and senior high schools in Sidoarjo and Surabaya, East Java Province, Indonesia. The subjects were determined by total sampling that met the inclusion and exclusion criteria. The inclusion criteria were obese adolescents aged 13-18 years who met the criteria for MetS. In addition, the subjects, along with their parents, volunteered to participate in this study by signing the informed consent. Children who had been diagnosed with diabetes mellitus or took anti-diabetes drugs were excluded.

Before the study was performed, the researchers visited the school to present obesity and its health problems to the subject's parents after the researchers got permission from the school's head. Other days after the presentation, the researchers screened the students who were suspected to be obese by measuring body weight and body height. Body weight was measured using the Seca Robusta 813 digital weighing scale, in which the subject was asked to step and stand up on the scales until the value was appear, and then recorded in a research datasheet. Height measurement was carried out using the Seca 213 stadiometer, in which the subjects were asked to stand up at the base of the stadiometer, shoulders, buttocks, and heels stick with the scale bar. The subject's chin was lifted with a straight gaze, and then the head slider was moved lower until it touches the skull, then the results were recorded in the research's data sheets. Waist circumference was measured using Seca measuring tape 201 by encircling the tape around the waist in a standing position at the top of the hip bone. Hip circumference was measured by keeping the feet together, and wrapping the tape around the widest part of the hip. The measurements were done when the subjects used a light cloth without a hat, footwear, or other accessories such as a belt, hair clip, etc. Obesity was determined based on the CDC 2000 criteria, which stated that the body mass index (BMI)/age was above the 95th percentile according to age and sex.

Sleep duration was obtained through direct interviews. Subjects were asked to report their sleep and wake times daily for the past three days. Sleep duration was considered insufficient if the duration was <8 hours a day (12). Insulin resistance was determined using the Homeostatic model assessment Insulin Resistance (HOMA-IR) value was calculated using the formula:

HOMA IR = Fasting insulin x fasting glucose/ 405 (13).

Blood samples were collected at 08.00-09.00 after the subject fasted for 12 hours through the median cubital vein. Ten ml of blood was taken. The blood sample collection was done by a laboratory's employers or a nurse who had been hired by the researchers. After the blood was taken, it was placed into a tube containing EDTA for further analysis of fasting blood glucose (FBG), total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, and fasting insulin (FI). After that, the tube containing blood samples was placed in a cooling box for transport to the lab.

Metabolic syndrome (MetS) was determined based on the criteria for metabolic syndrome from International Diabetic Federation (IDF) in 2007: Central obesity (waist circumference ≥ 90 percentile for age and sex) accompanied by at least two of the following criteria: (a) fasting triglyceride levels ≥150 mg/dL, (b) fasting HDL levels HDL <40 mg/dL, (c) fasting blood sugar levels ≥100 mg/dL, and (d) systolic blood pressure ≥130 or diastolic ≥85 mmHg (12,14). A blood pressure check was carried out using Omron Automatic Blood Pressure Monitor HEM-8712. Blood pressure measurements were performed in a sitting position after the subject had rested for 10 minutes.

Statistical analysis

The data were processed using SPSS version 21 (IBM, SPSS Inc). The normality test was conducted using the Kolmogorov-Smirnov test (normal distribution if $P > 0.05$), Test of homogeneity was also conducted using Levene's test (homogenous if $P > 0.05$). The measurement of sleep duration, HOMA-IR values, blood sugar levels, and lipid profiles used paired sample T-test or Mann-Whitney, Fischer's exact, and Chi-square. The relationship between sleep duration and insulin resistance in obese adolescents with metabolic syndrome was analyzed using Spearman's correlation and Scatter charts.

Results

Table 1 shows the primary characteristics of the subjects involved in this study. There were 120 obese adolescents with metabolic syndrome aged 13-18 years, consisting of 81 boys (67.5%) and 39 girls (32.5%). A total of 82 adolescents (68.33%) had short sleep duration (<8 hours) and were dominated by the 16-18 years age group (65.79%).

Anthropometric examination showed that the average body weight was 88.73 + 15.45 kg, height of 1.62 + 0.08 m, BMI 33.69 + 4.74, and waist circumference was 101.58 + 9.97 cm. Laboratory investigation showed that the mean fasting blood glucose (FBG) was 86.64 + 7.91 mg/dL, and 9 (7.5%) subjects had abnormal FBG. The mean values of HOMA-IR, fasting Insulin, cholesterol, and LDL-c were 5.59 + 3.24; 26.14 + 14.62; 172.37 + 32.99, and 114.72 + 27.75 mg/dL respectively. The mean HDL-c value was 38.47 + 6.23, which was dominated by 81.67% of subjects with abnormal HDL-c values. Moreover, the mean triglyceride value was 133.71 + 59.94 mg/dL, which was 42.74% of subjects had abnormal triglyceride values (more than 150 mg/dL) based on the metabolic syndrome criteria according to the IDF 2007. No significant difference was found in the calorie amount, percentage of carbohydrate, lipid, and protein (P<0.05).

In obese adolescents with metabolic syndrome, the mean HOMA-IR values and sleep duration were 5.59 ± 3.22 and 7.10 ± 1.51 respectively (Table 2). A Scatter chart was used to illustrate the direction of the relationship between sleep duration and insulin resistance. The scatter chart showed a negative linear relationship, which meant that the lesser the sleep duration, the greater the HOMA-IR value (Figure 1). The Spearman correlation test gave a value of r_s = -0.581 with a P <0.001, which meant that sleep duration and HOMA-IR value as a marker of insulin resistance had a strong correlation with a negative relationship. This negative relationship meant that the shorter the sleep duration, the higher the HOMA-IR value. A similar correlation was seen at fasting insulin levels with sleep duration (r_s=-0.565, P<0.0001).

Discussions

Sleep patterns in adolescents is an important issue to pay attention, to due to the direct impacts on academic performance, social behavior, and the cardiometabolic system (15), moreover, sleep pattern is a part of adolescents' development will change the sleep time, due to biological regulatory of the maturation on neuroendocrine rhythms such as melatonin, cortisol and pubertal hormones (16,17). The reduction of sleep time from late childhood through the second decade has been known, with the longer bedtime at middle school and high school (ages 11 through 17 years old) (16). This study found a significant difference between sleep duration and age group, in which short sleep duration (less than 7 hours) was more common in the 16-18 years of age group, which was in line with a finding that older adolescents go to bed later than younger adolescents, so they sleep less. The reduction of sleep duration in older adolescents due to external factors such as academic tasks, social and extracurricular activities (18), and also including physical activity and eating behaviors (17). Sleep disorders impacted adolescents by 72.7%, with less than 8-hour sleeps, with the most prevalent being in Senior High School adolescents (19). Older age was associated with more complex levels of education and was followed by more school assignments and activities, and more comprehensive social interactions, all of which would affect the sleep pattern by reducing sleep duration (20,21). Melatonin was decreased significantly along with age,

Table 1. Characteristics of subjects

Characteristics	All n=120 x ± SD	<8 hour n=82 (x ± SD)	≥8 hour n=38 (x ± SD)	*P* value
Demography				
Age, years-old	15.31 + 1.39	15.49 + 1.48	14.92 + 1.09	0.035[1*]
Age, n(%) 13-15 y.o (Junior High School) 16-18 y.o (Senior High School)	 61 (50.83) 59 (49.17)	 36 (43.90) 46 (56.10)	 25 (65.79) 13 (34.21)	0.031[1*]
Gender, n(%) Boys Girls	 81 (67.5) 39 (32.5)	 57 (69.51) 25 (30.49)	 24 (63.16) 14 (44.74)	0.533[1]
Number of Metabolic Syndrome • 3 signs of metabolic syndrome • > 3 signs of metabolic syndrome	 93 (77.5) 27 (22.7)	 62 (75.61) 20 (24.39)	 31 (81.58) 7 (18.42)	0.639[1]
Sleep duration, hours	7.07 + 1.51	6.22 + 0.86	8.89 + 0.76	<0.0001[2*]
Anthropometry				
Body weight (kg)	88.73 + 15.45	89.64 + 15.20	86.75 + 15.99	0.341[2]
Wight-for-age percentile based on CDC growth charts • Overweight (p90-p95) • Obesity (<p95)	 24 (19.35) 100 (80.65)	 12 (14.29) 72 (85.71)	 12 (30) 28 (70)	0.117[1]
Height (m)	1.61 + 0.08	1.61 + 0.08	1.62 + 0.07	0.741[3]
Stature-for-age percentile based on CDC growth charts • Very tall (>p95) • Tall (p75-p95) • Normal-stature (p25-p75) • Stunting (p10-025) • Severely stunting (<p10)	 3 (2.5) 9 (7.5) 49 (40.83) 24 (20) 35 (29.17)	 2 (2.44) 4 (4.88) 37 (44.05) 17 (20.73) 25 (30.49)	 1 (2.63) 5 (12.5) 15 (39.47) 7 (18.42) 10 (26.32)	0.656[3]
BMI (kg/m^2)	33.68 + 4.74	34.08 + 4.58	32.84 + 5.02	0.184[2]
BMI-for-age percentile based on CDC growth charts • Obesity (>p95)	 120 (100)	 82 (100)	 38 (100)	1.000[1]
Waist Circumference (cm)	101.58 + 9.98	101.93 + 10.33	100.82 + 9.25	0.578[2]
Blood Pressure (mmHg)				
Systolic blood pressure	126.84 + 12.59	126.77 + 11.24	127.00 + 15.27	0.926[3]
Diastolic blood pressure	83.16 + 10.70	83.15 + 9.88	83.18 + 12.43	0.986[2]
Blood Pressure Criteria, n(%) • Hypertension • Normotension	 108 (90) 12 (10)	 76 (92.68) 6 (7.32)	 32 (82.21) 6 (15.79)	0.192[1]
Laboratory Findings for Metabolic Syndromes (MetS)				
FBG (mg/dL)	86.64 + 7.91	87.04 + 8.21	85.79 + 7.23	0.424[3]
FBG Criteria, n(%) Hyperglycaemia Normal blood glucose	 9 (7.5) 111 (92.5)	 6 (7.32) 76 (82.68)	 3 (7.89) 35 (92.11)	1.000[1]
Triglycerides (mg/dL)	133.71 + 59.93	133.15 + 61.62	134.92 + 56.90	0.881[2]
Triglycerides Criteria, n(%) Hypertriglyceridemia Normal glyceride	 53 (42.74) 71 (57.26)	 34 (40.48) 50 (59.52)	 19 (47.5) 21 (52.5)	0.561[1]

Characteristics	All n=120 x ± SD	<8 hour n=82 (x ± SD)	≥8 hour n=38 (x ± SD)	*P* value
HDL-c (mg/dL)	38.47 + 6.23	38.20 + 6.14	39.05 + 6.46	0.485[3]
HDL-c Criteria, n(%) Low HDL-c level Normal HDL-c level	 98 (81.67) 22 (18.33)	 68 (82.93) 14 (17.07)	 30 (78.95) 8 (21.05)	0.618[1]
Other Laboratory Findings				
Fasting Insulin (µU/mL)	26.14 + 14.62	29.20 + 15.53	19.52 + 9.66	0.001[2*]
HOMA-IR	5.59 + 3.24	6.27 + 3.43	4.13 + 2.18	0.001[2*]
Cholesterol (mg/dL)	172.37 + 32.99	172.48 + 33.98	172.13 + 31.17	0.958[2]
LDL-c (mg/dL)	114.72 + 27.75	116.41 + 25.37	111.05 + 32.35	0.327[2]

[1]Fischer's Exact test, [2]Independent T-test, [3]Chi square test; [*]significant on $P<0.05$.

Table 2. Correlation between sleep duration with fasting insulin and HOMA IR

Variable	$\bar{x}$ ± SD	Min-Max	r	p
HOMA IR	5.59 + 3.24	1.16 - 18.93	-0.581	<0.0001[1]
Insulin	26.13	5.80 - 92.39	-0.565	<0.0001[1]

[1]Spearman Correlation

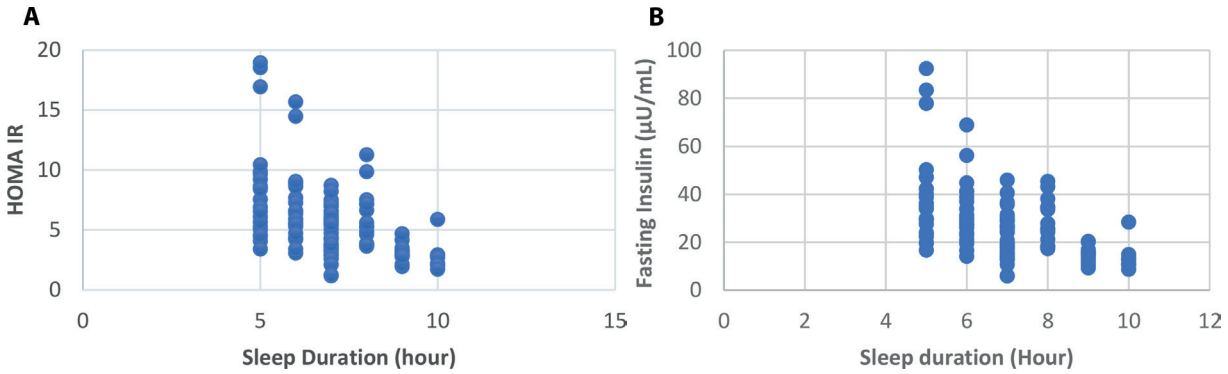

Figure 1. Distribution of the HOMA-IR (a) and fasting insulin (b) relationship scatter chart with sleep duration in obese adolescents with metabolic syndrome

with a greater decrease in night melatonin, and during Tanner stages, I and II, both day and night melatonin were reduced significantly (17). Melatonin is a neurohormone to maintain the circadian rhythm and regulates the sleep-wake cycle (22). Melatonin acts to stimulate the transcription of Pro-opiomelanocortin (POMC) mRNA in the hypothalamus and pituitary via its receptor MT1, to reduce food intake and regulate feeding behavior (23). With the reduction of melatonin, POMC synthesis will be reduced and stimulates more time for feeding. Moreover, anxiety in early adolescence is more common (generalized and social anxiety) than in younger children, which leads to the increment of cortisol (24). Long-term high levels of cortisol are strongly related to abdominal obesity by redistributing white adipose tissue to the abdominal region and increasing appetite with high energy food intake as the preferences (25).

The insulin levels were significantly higher in adolescents with sleep duration <8 hours per day than those who had sleep duration > 8 hours per day, which was in line with other studies conducted in the Elderly. Those with sleep duration of fewer than 5 hours per night had a risk for high levels of insulin by 1.29 times (risk for DM was 2.51 times), and those with 6-hour sleep had a 1.47 times risk for high levels of insulin (26). However, the study conducted in a white healthy population mentioned that sleep duration interacted with race, in which white race men with short sleep duration had lower insulin sensitivity (β=0.29, P=0.003) and insulin secretion (β=–0.28, P=0.004), but not in women (27). Sleep had modulatory effects on glucose metabolism. Sleep problems in adults not only alter glucose metabolism such as decreased glucose tolerance and insulin sensitivity, but also affect neuroendocrine regulation of appetite by decreasing leptin levels (anorexigenic hormone), while ghrelin (orexigenic factor) was increased. As a result, sleep problems increased hunger and appetite which leads to overeating and weight gain (28). It was stated that 5 hours of sleep per night and ad libitum of food intake will reduce insulin sensitivity by ~20% (oral or intravenous insulin) in both men and women due to an increment in insulin response towards glucose to maintain normal blood sugar. Insulin sensitivity will recover after 3 days of sleep for 9 hours/ night (29).

The mechanisms that caused insulin sensitivity impairment and glucose metabolism during short sleep duration were complex and challenging to explain. Short sleep duration or sleep deprivation would increase circulating cortisol and induce sympathetic activity and increase catecholamines. In addition, sleep restriction has been reported to reduce TSH and testosterone levels, disrupt growth hormone secretion patterns, and increase levels of proinflammatory cytokines. These complex endocrine changes were considered to contribute to the disruption of insulin signaling in peripheral tissues, leading to insulin resistance (19). Moreover, short sleep causes a reduction in daytime physical activity due to fatigue in young white men. The combination of short sleep, high-calorie intake, and lack of physical activity is related to insulin resistance (16). Another study also found a significant lower level of evening melatonin in obese than normal adolescents (0.54 ± 0.51 pg/ml vs 2.13 ± 1.88 pg/ml, p=0.023), and at night (4.3 ± 6.12 pg/ ml vs 13.79 ± 5.93 pg/ml, p=0.004). But melatonin was found to be higher in the morning and day even though there was no significant difference (30). The study in obese adolescents proved that those with insulin resistance had lower levels of melatonin at night than those without insulin resistance (P=0.0006) (31). Melatonin has been proven to increase insulin sensitivity and glucose tolerance via melatonin receptors (MT1 and MT2) by decreasing insulin secretion. Its action is mediated by cAMP and cGMP pathways (32). A longitudinal study found that melatonin production remains constant during childhood and adolescents, but a dramatic decrease was related to the increment in body size (33).

There was a strong correlation with a significant negative relationship between sleep duration and insulin resistance (HOMA-IR). Different results from the cross-sectional study undertaken by Thumann et al. (2020) stated that sleep duration was not related to HOMA-IR value, but it had a negative relationship with waist circumference (4). Some experimental studies conveyed that short sleep duration significantly affected the main components of energy homeostasis, including glucose tolerance, appetite for food, and a hormone that played a role in appetite regulation. Lack of sleep also increased the level of proinflammatory cytokines (e.g. TNF-α and IL-6) and this inflammatory process was part of insulin resistance (28,34). In addition, sleep restriction caused a decrease in leptin levels and an increase in ghrelin levels, which resulted in increased hunger and appetite (28,35). Several previous studies also supported the results of the present study (36,37). With special attention on melatonin, it has been identified as an important regulator for glucose metabolism, so the disruption of melatonin receptors signaling might contribute to the pathogenesis of type 2 diabetes. Animal studies have proved that abolishing melatonin synthesis produces glucose intolerance and insulin resistance. This effect will be restored when the animal receives exogenous melatonin, which showed that melatonin can alleviate several metabolic consequences of obesity. Daily intake of melatonin with sufficient amounts in rats can decrease the body weight gain due to a high-fat diet by 54% (23). In the obese mice model, melatonin was able to ameliorate the inflammatory infiltration and

adipokine alteration due to obesity (23,38) While the study in postmenopausal women, melatonin administration for 1 year was known to reduce fat mass so that increasing the lean mass by stimulating lipolysis by activating the sympathetic nervous system and intramuscular adipocyte lipolysis via activating extracellular signal-regulated kinase (ERK) 1/2 and protein kinase A (PKA) signaling (23,39).

The limitation of this study was that the researchers also did not check the genetic factors of each subject and did not take into account the physical activity of each subject, so this condition could be a research bias. We also did not measure the melatonin, cortisol, and leptin levels of the subjects.

Conclusion

Sleep duration has a robust negative correlation with the HOMA-IR value, which is a parameter of insulin resistance.

Acknowledgment: This study is part of a thesis conducted by Widjaja *et al.* (2020). The authors would like to thank the 12 high schools in Surabaya and Sidoarjo who volunteered to become the research respondents. We would thank all headmasters and counseling teachers who gathered our respondents along with their parents with us before and during the data collection.

Funding: The authors receive no funding from any other sources. The study was funded privately.

Ethical Clearance: The study was reviewed and approved by the Research and Ethics Scientific Committee at the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, number 141/EC/KEPK/FKUA/2020.

Conflict of Interest: The authors stated there was no conflict of interest on behalf of this study.

Authors Contribution: Conceptualization: Nur Aisiyah Widjaja; methodology: Claudia Felisia Kurube; data curation: Eva Ardianag; writing—original draft preparation: Nur Aisiyah Widjaja; writing—review and editing: Eva Ardianah. All authors have read and agreed to the published version of the manuscript.

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Correspondence:
Received: 23 December 2022
Accepted: 23 January 2023
Nur Aisiyah Widjaja
Nutrition and Metabolic Disease Division,
Department of Child Health, Faculty of Medicine Airlangga University, Dr. Soetomo General Hospital.
Surabaya, 60286, Indonesia
Phone: +62 812-3073-379
email: nuril08@yahoo.com