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The relation between sleep deprivation and metabolic syndrome

Raghad A Tarawah
Medical Student, College of Medicine, Taibah University, Al-kaldiah- Medina, Saudi Arabia

Abstract
Sleep is a physiological mechanism that regulates some metabolic and endocrine functions. Therefore, disturbance in sleep quantity and quality precipitate in metabolic dysfunction. Chronic sleep deprivation, as well as metabolic syndrome, are conflicts that increasingly recognized in modern society, their prevalence is raised over the years. Several studies have suggested a correlation between sleep insufficiency and different aspects of metabolic syndrome namely obesity, hypertension, insulin resistance, and dyslipidemia. In contrast, others found the opposite that long sleep duration is correlated with metabolic syndrome factors. However, the exact pathophysiological pathway is still unknown. These factors can lead to serious health problems as cardiovascular disease and diabetes mellitus. This article reviews the current knowledge of the association between sleep deprivation and risk of metabolic syndrome development.

Keywords: sleep deprivation, metabolic syndrome, obesity, insulin resistance, hypertension, dyslipidemia

1. Introduction

Sleep is a complex physiological reversible event of decreased motor activity, responsiveness, and metabolism. Sleep consists of two stages, slow wave and rapid eye movement sleep. Slow wave sleep subdivided into four stages begins with N1 to N4 from the lightest stage a person can be easily aroused to the deepest stage respectively. The second stage is rapid eye movement, this one sub-segmented into phasic REM correlated with eye twitching, and tonic REM occurs during the phasic REM, it consists of low muscle tone [1].

Sleep is related to metabolism, it comprises of anabolism and catabolism processes. Although metabolism has a beneficial impact on the body, it linked with the liberation of free radical that results in cell injury. However, in non-REM stage, the metabolic rate decreases by around 15% allowing the body to manage with the damage occurred during the awake state. In addition, glucose utilization reduced to the minimum in non-REM, intermediate in REM stage and highest in the wakeful state.

Many hormones secreted at sleep time, these hormones regulate energy, affect growth, and control the endocrine and metabolic functions. Growth hormone is one of the hormones excretes during the early phase of sleep. As a result, it gives anti-insulin-like effect and decreases muscle tone, for that reason early phase of sleep associated with insulin resistance effect [2]. Meanwhile, stress hormone such as cortisol secretes at the end of the sleep cycle. Thus, growth hormone and cortisol contribute to glucose regulation. Moreover, secretion of hormones that control weight and appetite also affected by sleep cycle [3].

Sleep has two dimensions, quantity, and quality. The former means the duration of sleep, and the latter means the depth of sleep. Sleep insufficiency occurs when sleep is not enough to support daytime alertness, performance and health [1]. Inadequate sleep duration verify among studies, but typically defined as less than six or seven hours per night [4, 5].

Chronic sleep deprivation is considered prevalent in modern society, it can be caused by different influences such as medical condition, work demands and sleep disorders. This condition can affect the individual performance, physical and psychological health, and rises the risk of death [1].

Sleep insufficiency results when sleep is interrupted by five or more arousal per hour of sleep [6]. Population-based studies done in United States found that prevalence of short sleep duration grew up in the individual with rotating work, increase job stress or extended long hours [7].

Sleep is important in physiological and biological processes in human body. Therefore, insufficient sleep contributes to the progression of metabolic dysfunction and may lead to obesity and diabetes. Interaction between sleep dysregulation and metabolic derangement is being considerably recognized. [3]

Sleep deprivation gives rise to metabolic dysfunction. This can happen by multifactorial mechanisms. Firstly, increase sympathetic stimulation have been recorded in sleep deprivation [8]. Secondly, alteration of hormone secretion profile as cortisol and growth hormone [9]. Thirdly, by inflammation. Experimental studies have been found that insufficient sleep can change the immune response, thus it raises the proinflammatory cytokines namely TNF- α, IL-6, CRP [10].

Metabolic syndrome defines as inter-related metabolic origin risk factors associated with cardiovascular mortality since it establishes cardiovascular disease risk factors. These factors include insulin resistance, waist circumference, blood pressure level, cholesterol and triglyceride level. This condition becoming broadly common, [11] overall, the prevalence is 22 percent and it increases with age [12]. Although studies showed

strong association between metabolic syndrome and sleep deprivation, the results are controversial.

This review aims to determine the relationship between sleep insufficiency and metabolic syndrome.

2. Literature review

2.1 Sleep physiology

Sleep is a complex process constitutes of many stages. Brain potential can be recorded through electroencephalogram (EEG). This instrument uses electrodes placed either in the brain or in unopened skull. There is a variety of waves produced such as alpha, beta, and delta, each one with different frequency and amplitude. In addition, two types of sleep have been recognized, the first one is Non-Rapid Eye Movement (NREM) sleep and the second is Rapid eye movement (REM). NREM is subdivided into four stages N1, N2, N3, and N4. Along NREM sleep, no eye twitching occurs and skeletal muscle tone partially decreased. In REM sleep, EEG replaces delta wave by beta rhythm which characterized by high frequency, low voltage wave. REM sleep correlated with vivid dream, further decrease in muscle tone and eye movement [10, 13].

The sleep-wake cycle is affected by light and dark cycle. The suprachiasmatic nucleus (SCN) presents in hypothalamus receives light–dark information through retino-hypothalamic fiber, from here SCN can send hormonal and neural signals that play a role in sleep awake cycle and secretion of melatonin from the pineal gland. Melatonin is a hormone synthesized from serotonin, it is secreted during sleep from pineal gland, it requires nor-adrenalin to be released. Therefore, SCN descends fibers to preganglionic sympathetic neuron, this in turn, will transmit postganglionic fibers to the pineal gland [13].

Sleep affects some metabolic actions in the body. In the onset of sleep, metabolic rate decreased considerably followed by a reduction in energy expenditure. A study revealed carbohydrate oxidation as well as energy expenditure are reduced in the first half of sleep, and they increase significantly in the last hour. In contrast, fat oxidation raised in the first half and declined after midnight [14].

2.2. Sleep Deprivation

Sleep insufficiency has become a massive health care conflict in modern societies. Studies in US revealed that total sleep duration was less than in the past, the average amount of sleep in 1900 was nine hours, subsequent by seven hours in 1980, decreased to six and half hours in 2000. In 2014, it has been stated that among adult, one-third slept below six hours per night. However, the recommended sleep duration for adult is 7-8 h, for teenagers 9-10 h, and for children 10 h according to National Institute of Health [15].

In addition, an important aspect of sleep is sleep quality which is measured by the number of arousals in the sleep, duration, type of sleep stage and percentage. The arousal can be defined as shifting in frequency in EEG lasting for three second or more after at least ten seconds of continuous sleep then the subject return to the same stage that was interrupted, consequently the subject is unaware of them. Usually, it caused spontaneously or by sleep disorder e.g. periodic leg movements, obstructive sleep apnea.

Sleep insufficiency results when sleep is interrupted by five or more arousals per hour of sleep. Hence, Sleep duration is not enough indicator for adequate sleep to function properly and feels refreshed [4]. Several reasons should be considered for this problem. Firstly, it can be due to lifestyle, for example, using electronic devices precede sleeping which changes the physiological excretion of melatonin, or shift work and hard work schedule. Secondly, people are sleeping deprived because of aging, it is known that aging linked with the decrease of total sleep duration and perturbation of physiological sleep. Thirdly, sleep disorders as sleep disordered breathing [15].

Furthermore, there are two types of sleep deprivation, acute sleep deprivation and chronic sleep deprivation. The former, commonly lasts for one or two days when there is a reduction in the habitual total time of sleep or no sleep. While chronic sleep deprivation occurs when the subject sleeps less than the optimal amount of sleep routinely required for functioning [1].

2.3 Metabolic syndrome

Metabolic syndrome (MetS) also known as syndrome X described as a complex disturbance in metabolism recognized by constellation of factors that increase the risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease. Multiple definitions have been established for metabolic syndrome, the most popular criteria used was identified by National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III), World Health Organization (WHO), International Diabetes Federation (IDF), and the European Group for the Study of Insulin Resistance (EGIR) as shown in table (1).

There are core characteristics applied by these organizations related to MetS which are hypertension, obesity, dyslipidemia and insulin resistance. Each organization has different usage of criteria to identify the syndrome component [11]. Moreover, obesity associated with peripheral insulin resistance that ends by developing T2DM. Consequently, hyperinsulinemia, hyperglycemia and adipokine result in vascular endothelial dysfunction, beside hypertension, dyslipidemia and vascular inflammation that boost atherosclerotic cardiovascular disease development [16]. Study performed in 2005 assessed the prevalence of MetS over eight years, it showed an increased pattern along the period, from 26.8% to 56% for men and from 16.6% to 47% for women [17].

Table 1: different definition of metabolic syndrome

WHO (1999)[10]	EGIR (1999)[10]	NCEP ATP III (2001)[13]	IDF (2005)[10]
Diabetes or impaired glucose tolerance or insulin resistance, plus 2 or more of the following,	Insulin resistance or hyperinsulinaemia (only non-diabetic subjects), plus 2 or more of the following,	Three or more of the following,	Waist circumference – ethnicity specific, plus two or more of the following,
BMI > 30 kg/m² or waist to hip ratio > 0.9 in men, > 0.85 in women	Waist circumference: > 94 cm in men , ≥ 80 cm in women	Waist circumference: >102 cm in men, >88 cm in women	
Triglycerides: ≥ 1.7 mmol/l	Triglycerides: > 2 mmol/l	Triglycerides: > 1.7 mmol/l	Triglycerides: ≥ 1.7 mmol/l or medicaition
HDL–C: < 0.9 mmol/l in men < 1.0 mmol/l in women	HDL-C: < 1.0 mmol/l	HDL-C: < 1.03 mmol /l in men <1.29 mmol/l in women	HDL-C: <1.03 mmol/l in men <1.29 mmol/l in women or medication
Blood pressure: ≥140/90 mmHg or medication	Blood pressure: > 140/90 mm Hg or medication	Blood pressure: > 130/85 mmHg or medication	Blood pressure: > 130/85 mmHg or medication
Urine albumin excretion ≥ 20 µg/min or albumin:creatinine ratio > 30mg/g	Fasting plasma glucose: > 6.1 mmol/l	Fasting plasma glucose: > 6.1 mmol/l	Fasting plasma glucose: > 5.6 mmol/l or type II diabetes

WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; NCEP ATP III, National Cholesterol Education Program – Third Adult Treatment Panel; IDF, International Diabetes Federation; BMI, body mass index; HDL-C, high density lipoprotein cholesterol

Lam J, Ip M (2010) [11]

2.4 Sleep duration and metabolic syndrome

Several studies revealed an association between sleep duration and the development of MetS. However, the results are controversial. Most of the evidence have found that MetS was influenced from short sleep duration. In contrast, some studies suggested that long sleep duration also was a risk factor for impaired fasting glucose, diabetes, and cardiovascular disease, but still debatable if long sleep duration can lead to MetS or not [18].

Studies vary in determining the gender aspect. Cohort study performed on 7696 Chinese adults along 4 years follow-up concluded that short and long sleep duration were associated with MetS among males while no association was observed among females. Moreover, the study found an increase in the level of fasting blood glucose (FBG), total cholesterol (TC), systolic blood pressure (SBP), diastolic blood pressure (DBP), and insomnia in the participants who slept less than six hours [18]. Similarly, Korean study performed in 2008 showed a U-shaped pattern of MetS related to sleep duration which means that MetS risk raised as the sleep duration increased or decreased considerably than optimum hours. It deduced that individuals slept less than five hours per night have a high prevalence of hypertension and abdominal obesity. While in those who slept more than nine hours were related to high prevalence of triglyceridemia and hyperglycemia [19].

On the other hand, meta-analysis in 2014, revealed that short sleep duration alone correlated with MetS development, the effect in male and female were similar. Whereas non-significant relation between long sleep duration and MetS among both gender [20]. In addition, previous studies demonstrated raised level of evening cortisol, impaired glucose tolerance, increase sympathetic nervous system and down secretion of leptin hormone. However, the exact mechanism underlying this relation is still unclear [19].

2.5 Sleep deprivation and Obesity

Obesity has become a worldwide concern; its prevalence is increased in a plurality of developed countries. Obesity is a state in which adipose cells accumulate excess body fat that leads to health deterioration and decreased life expectancy. It can lead to the development of a variety of health concerning effects involve T2DM, hypertension, MetS, and coronary heart disease. These are correlated with mortality [21].

Recent studies suggested a strong association between sleep deprivation and development of obesity. In a study performed on 8860 subjects found that short duration sleepers were linked to increase obesity and body mass index (BMI), as well as the level of triglyceride (TG), cholesterol, DBP and SBP as suggested by Bjorvatn *et al.* [22]. Cross-sectional study among adult from various countries have reached a similar conclusion of this association [23]. Furthermore, Iranians youth female examined for dietary quality indices and relation to sleep insufficiency and deduced that individuals slept lower than six hours ate further dietary energy, and carbohydrate while less amount of fruit, whole grains, fibers, and beans, also to be obese and overweight [24]. On the other hand, Lin *et al.* [25] established a contrary finding and concluded that the correlation between sleep duration and overweight was not significant.

The exact mechanism underlying the correlation between obesity and sleep deprivation still unknown, but some explanation conducted by preceding studies can play a role. Firstly, sleep insufficiency induces daytime sleepiness and fatigue which lead to decreased activity during the day. For this reason, sedentary time increases without energy consumption, therefore weight stability will be affected.

Secondly, irregular eating habits corporate with sleep deprivation. As well as, elevates caloric intake specifically food constitute of high fat, carbohydrate, and energy dense content. Although caloric intake rises but energy consumption kept unchanged, hence weight will increase [25]. Thirdly, less amount of sleep leaves more time to eat and consume snacks since sleep restriction increases hunger and appetite [21].

Some physiological mechanisms have examined obesity and short sleep duration association, included leptin and ghrelin alterations. Ghrelin is a hormone associated with sleep cycle, it elevates NREM, slow wave activity and alleviate REM sleep in male but not in female. Ghrelin is responsible for metabolic homeostasis through sleep. Moreover, it has a function in energy expenditure and meal initiation. Sleep deprivation increases the level of ghrelin in early morning resulting in hunger and promoting food intake. On the other hand, leptin is a hormone secreted by adipose tissue and plays a role in satiety regulation, energy feeding behavior, and appetite suppression. Similar to ghrelin, leptin also takes part in sleep regulation, it minimizes REM and enhances NREM. It has been stated that leptin level increases during sleep more than wakefulness. Studies revealed that sleep insufficiency decreases the level of leptin serum concentration. Sleep deprivation alter level of these hormones, it increases level of ghrelin and decreases level of leptin, consequently, lead to higher BMI and obesity [21].

2.6 Sleep deprivation and hypertension

Hypertension is described as a chronic condition of elevated blood pressure, SBP reaches 140 mmHg or more and DBP equal 90 mmHg or more, or if an individual under antihypertensive medication, according to American Heart Association [26]. In addition, Chinese study pointed out to sleep duration that can decrease hypertension risk among male subject, which is 6 to 8 hours per day and napping for one hour [27].

Normally, blood pressure decreases during sleep by around 10% to 20% it is called dipping and rises just before waking and reaches its plateau after waking. This process underlying the clock genes (e.g. Per, BMAL1) they regulate BP along 24 hours, through sending signals from suprachiasmatic nucleus in hypothalamus to hypothalamic pituitary adrenal axis and sympathetic nervous system resulting in decline of circadian differences in blood pressure. Melatonin hormone that included in the sleep-wake cycle regulation has been revealed to decrease SBP and DBP, promotes nocturnal dipping of systolic and diastolic BP in the hypertensive patient [28].

Several studies suggested a relation between short sleep duration and hypertension, but the results were still inconsistent. In a study performed on 4810 to assessed the association between hypertension and short sleep duration over 8 to 10 years. Gangwisch *et al.* [29] deduced that individuals among age 32 and 59 years who slept less than five hours per night were correlated with hypertension significantly. Likewise, meta-analysis included 17 cross section studies and 6 prospective studies concluded by a positive association between short sleep duration and increased the risk of prevalent and incident hypertension in the subject under age 65. Similarly, Thomas *et al.* [28] reached the same conclusion. In contrast, participants over 60 years old who slept more than nine hours developed hypertension. Furthermore, significant association observed among long sleep duration and risk of hypertension development [28, 29, 30].

The biological mechanism that revealed how hypertension related to sleep deprivation is still unclear, but there were some possible explanations. In Wang *et al.* [30] view, sleep insufficiency increases sympathetic nervous system activity, heart rate and blood pressure, also promotes psychological and physical stressors. By these alterations, sustained hypertension can be developed. Moreover, changes in hypothalamic pituitary adrenal axis due to cortisol enhancement, pro-inflammatory responses, and endothelial dysfunction participate in hypertension development. Another demonstration to be assessed that individual deprived sleeping has emotional changes, namely, irritability, pessimism, feeling tired and stressed, and impatience. All these emotions can affect healthy lifestyle that in turn relinquish the protection against hypertension. There is insufficient evidence regarding long sleep duration and hypertension, it was hypothesized that confounding factors related to long sleep duration such as low educational level and depressive symptoms can play a role.

2.7 Sleep deprivation and insulin resistance

Insulin resistance develops before several years of T2DM diagnosis which considered multifactorial phenomena. Decline insulin formation and insulin resistance are the most prominent feature of T2DM. Furthermore, insulin resistance promoted by modern lifestyle, abdominal obesity, physical inactivity, and over abundant adipokine. Consequently, increased fatty acid, glucose level and insulin, drive to liberation of reactive oxygen species, and that in turn lead to oxidative stress accelerating T2DM onset. Many studies suggested a relationship between T2DM, insulin resistance, and short sleep duration [31].

Systematic review and meta-analysis of ten studies performed in 2010 estimated that sleep quality and quantity were risk factors for T2DM. Short sleep duration of less than five hours may contribute to T2DM. In contrast, long sleep duration also plays a role in the association as suggested by Cappuccio *et al.* [32]. In addition, another meta-analysis conducted in 2017 on patient with T2DM suggested that sleep quantity and quality were essential in controlling metabolic function of T2DM. The study confirmed that short sleep duration, as well as long sleep duration, elevated the level of hemoglobin A1C [33]. Similar result was gained from cross-sectional study from Fukuoka diabetes registry and nurses' health study [34]. Not only HbA1C increased by sleep deprivation, but also reduction in insulin sensitivity [35]. Experimental study on Wistar rats after exposure to paradoxical sleep deprivation resulted in reduction of leptin and insulin level while blood glucose level remained unchanged, increase leptin receptor occurred as a compensatory mechanism but insulin level left without upregulation insulin level left without compensatory mechanism as upregulation [36].

The underlying physiological mechanism of this relation is unclear but many studies may have some explanations. Leptin and ghrelin hormones play a role in appetite control. The decrease of leptin and increase of ghrelin levels associated with sleep deprivation will increase appetite, therefore causes elevation of BMI that lead to insulin resistance [33]. In addition,

insulin and leptin decrease as long as the paradoxical sleep deprivation increase in the rat. These hormones act on the central nervous system by binding to arcuate nucleus in hypothalamus, this in turn produces hormones that stimulate or inhibit feeding behavior. Therefore, adjusting energy homeostasis and food intake. Consequently, the compensatory mechanism for leptin lead to energy balance control while lack of insulin receptor upregulation causes food intake dysregulation. Therefore, binding to their hypothalamus receptors allow enhancement of energy consumption, reduction of food intake and loss of body weight. Disturbance of hormones that regulate food intake is the major pathway related to short sleep duration obesity and that in turn cause insulin resistance [36].

2.8 Sleep duration and dyslipidemia

Dyslipidemia is a serious problem and it is one of the components of metabolic syndrome, it considered a characteristic of cardiovascular disease. Dyslipidemia recognized as reduced level of high density lipoprotein-cholesterol (HDL-C), increase the level of TG, and an increase of low-density lipoprotein- cholesterol level (LDL-C) [8]. There were a number of studies correlate sleep duration to alteration of lipid profile. However, the findings are contentious. Some estimated that short sleep duration affects the lipid profile, while other suggested that long sleep duration is associated with lipid changes, and some found both can make an effect.

Recently, Shin *et al.* [37] found insignificant association appeared among short duration sleepers and dyslipidemia, while significant correlation between long sleep duration and decreased level of HDL-C. Likewise, Bojorvatn *et al.* [22] demonstrated an insignificant association between short sleep duration and TC level. on the other hand, Zhan *et al.* [38] showed increased level of TG, LDL-C, and TC, decreased level of HDL-C in both long and short sleep duration in women. Furthermore, increase serum TG and decrease HDL was reported in short and long duration sleepers women while, elevated LDL level among men [39] Ultimately, USA study among adults concluded that Hypercholesterolemia was correlated with short duration sleepers among females and long duration sleepers in males [40]. Further studies is needed to determine the association between lipid profile and sleep duration.

3. Conclusion

Sleep deprivation, as well as metabolic syndrome, are a conflict in modern society. Their prevalence is increasing among the population. The previous researches findings found that short sleep duration associated with metabolic syndrome, as well as long sleep duration. Particularly, a strong association has been confirmed between sleep insufficiency and obesity, hypertension. Insulin resistance is related to both short and long sleep duration, while dyslipidemia has an inconstant role in the correlation. Although, few studies have proposed possible explanation but still the precise mechanism inconsistent.

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