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# The Role of Sleep Curtailment on Leptin Levels in Obesity and Diabetes Mellitus

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## Keywords

Short sleep duration · Leptin · Obesity · Diabetes

## Abstract

Emerging evidence has identified sleep as a significant, but modifiable, risk factor for metabolic syndrome, diabetes, and obesity. Leptin, an adipocyte-derived peptide and a regulator of food intake and energy expenditure, has been shown to be associated with a short sleep duration in the pathophysiology of obesity and consequently type 2 diabetes. This review focuses on the current evidence indicating the effects of a short sleep duration on the regulation of leptin concentration in association with obesity and diabetes mellitus. In summary, the evidence suggests that sleep deprivation, by affecting leptin regulation, may lead to obesity and consequently development of type 2 diabetes through increased appetite and food intake. However, findings on the role of leptin in diabetes due to sleep deprivation are contradictory, and further studies with larger sample sizes are needed to confirm previous findings.

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## Introduction

Sleep is a biological and behavioral process that is fundamental for life and optimum health. Sleep is controlled by diurnal, homeostatic, and neurohormonal mechanisms [1]. Existing research acknowledges that sleep is an essential modulator of cardiovascular function, glucose regulation, and hormonal release [2]. Sleep duration has also been shown to have a pivotal function in metabolic hormones and body weight and it has been linked to other biological mechanisms including inflammation, the autonomic nervous system, the coagulation system, endothelial function, and metabolic regulation [3, 4]. Sleep quality varies in individuals according to factors such as age, gender, occupation, educational level, socioeconomic status, race, family relationships, and pathological conditions including insomnia, depression level, and sleep-disordered breathing [5–7]. According to the US National Sleep Foundation, adequate sleep duration requirements vary across lifespans and from person to person, with 7–9 h recommended for adults [8, 9]. In recent decades, the average sleep duration has decreased worldwide, and this is widely attributed to a modern lifestyle [10]. Based on National Sleep Foundation criteria, 75% of preadoles-

cents and 45% of late adolescents experience sleep deficiency [11].

Insufficient sleep is characterized by either a considerable reduction in sleep time during a certain period due to 24-h wakefulness or a reduction in sleep time less than the optimal level for individual needs. Sleep loss, related to a decreased total sleep time, can be a result of habitual behavior or the presence of a pathological condition including addiction (medications or alcohol), anxiety, depression, idiopathic, somatic and painful diseases, and subjective and psychophysiological insomnia [12].

The reports from recent epidemiological studies, meta-analyses, and systematic reviews have indicated that sleep duration is significantly correlated with several adverse health outcomes including diabetes mellitus, cardiovascular diseases, coronary heart diseases and stroke, dyslipidemia, hypertension, metabolic disease, obesity, and mortality [1, 13–20]. Recent evidence proposes that that relationship between a short sleep duration, obesity, and diabetes risk may include at least 3 pathways, i.e., (1) an altered glucose metabolism, (2) up-regulation of hunger and appetite or dysregulation of appetite/satiety hormones, and (3) down-regulation of energy expenditure [21].

Leptin, a metabolic hormone, has a pivotal function in balancing appetite and satiety via food intake regulation and energy homeostasis [22]. Leptin works in synergy with another metabolic hormone, i.e., ghrelin. Whereas leptin suppresses food intake and induces weight loss, ghrelin increasing hunger and food intake [22]. Leptin is the product of the *ob* gene, which has an impact on growth, metabolism, and reproduction [23, 24]. Leptin has several other biological roles in the body [24], including functions in glucose homeostasis via suppression of insulin production in pancreatic  $\beta$  cells [25]. The regulation of diurnal blood leptin is controlled by multiple factors such as gender, age, feeding, fasting, sleep, obesity, and endocrine disorders [26]. The concentration of serum leptin is directly related to fat mass, where increased circulating leptin, termed leptin resistance, is related to obesity [27]. The proposed mechanisms involved in leptin resistance are comprised of a reduction in the number of leptin receptors, impairment of receptor function, a reduction in transport across the blood-brain barrier, and a circulating suppressor of leptin function [28]. Since a leptin deficit in lipodystrophy is accompanied by dysglycemia and insulin resistance, it is expected that glucose metabolism is affected by leptin resistance [28]. Defects or dysfunction in the leptin signaling pathway plays a role in the pathophysiology of obesity, diabetes mellitus, and

cardiovascular disease, and downstream targets of leptin may have a therapeutic potential role in the management of diabetes [29, 30]. Furthermore, the adiponectin-leptin ratio has been found to be significantly correlated with the insulin resistance index in diabetes mellitus [31–33]. Leptin stimulates cytokine activation and immune-cell proliferation, which predisposes to inflammatory conditions [34].

The evidence suggests a bidirectional relationship between sleep duration and leptin. Leptin has central neural specific effects beyond modulation of appetite alone [35]. Leptin concentrations display a circadian pattern, with its levels increasing during the first part of the night and then decreasing during the latter part of the night [36]. Furthermore, leptin has a function in preserving deep sleep by antagonizing the orexin neuron function in the hypothalamus [37]. The findings of animal studies presented that the orexin (hypocretin) system monitors sleep and wakefulness through interactions with the system that regulates energy homeostasis and facilitates adaptive intensification of arousal in response to fasting. The orexin neuron actions are inhibited by leptin, blood glucose, and food intake [37–39]. An animal study in leptin-resistant (db/db) genetically obese and diabetic mice showed that impaired leptin signaling had deleterious impacts on the regulation of sleep duration [40]. This study proposed that leptin signaling plays an important role in coordination of sleep-wake states and metabolism. It appears that sleep-related changes in leptin level promote progression of metabolic and immune disorders. Leptin's proinflammatory role [24, 41, 42] proposes that increased serum leptin levels in metabolic syndrome and obesity in a sleep deprivation status may be associated with low-grade systemic inflammatory diseases, characterized by increased proinflammatory cytokine levels including interleukin-6 and tumor necrosis factor (TNF)- $\alpha$ . Leptin regulates the brain appetite-regulating center with information about energy balance [43]. It has been believed that there is an interaction between leptin and insulin in peripheral tissues [44, 45]. Leptin inhibits energy storage mechanisms, whereas insulin enhances leptin production [46]. Evidence also indicates that leptin promotes insulin sensitivity through enhancement of fatty acid oxidation and declined fat accumulation in non-adipose tissues. Leptin induces fatty acid oxidation in muscle via AMP-activated protein kinase (AMPK) [47]. Moreover, leptin has a significant role in increasing the glucose uptake in skeletal muscle through a  $\beta$ -adrenergic mechanism and the hypothalamic-sympathetic nervous system axis [47].

As one of the factors affecting leptin level regulation, the effect of sleep has been investigated in several experimental studies. Sleep loss with an effect on appetite hormone (leptin) and energy expenditure has been linked to an increased risk of obesity and diabetes. This review aims to provide an update on the influence of short sleep duration on leptin levels in association with obesity and diabetes mellitus.

### Data Sources and Searches

PubMed, Google Scholar, and Science Direct were searched using the following terms: “leptin,” “sleep duration,” “sleep length,” “sleep period,” “sleep deprivation,” “sleep deficiency,” “sleep curtailment,” “sleep loss,” “short sleep duration,” “diabetes,” “weight gain,” and “obesity.” Original articles, reviews, and conference abstracts were included. Hand searching of reference lists was undertaken to identify any additional eligible studies. Publication dates were limited to 2000–2020, and papers written in English were included.

### Sleep Duration, Leptin, and Obesity

Obesity, the result of a modern lifestyle, has progressively increased globally over the past century. The obesity epidemic and its consequent metabolic dysfunctions have been paralleled by the reduction in sleep duration [48, 49]. It has been suggested by recent studies that sleep restriction adversely affects metabolic homeostasis, leading to increased hunger and appetite, and food intake, which consequently leads to insulin resistance [49, 50]. The appetite hormones ghrelin and leptin work in synergy to manage hunger and satiety. Ghrelin, a stomach-derived peptide, increases appetite [51], while leptin sends a message to the brain and suppresses appetite [52]. Appetite hormones rise throughout the day to a peak at 1:00 p.m. and then decrease overnight to a nadir at 9:00 p.m., which might be the cause of low leptin levels in short sleepers [53]. It has been proposed that dysregulated leptin and ghrelin play a key role in the increased BMI in short sleepers [4]. In an early study by Spiegel et al. [54], 2 days of sleep restriction (4 h) reduced leptin (18%) and elevated ghrelin levels (28%), indicative of an enhanced drive to eat (hunger, 24%; appetite, 23%) in young, healthy men. A study by Taheri et al. [4] showed that sleep duration below 7.7 h was associated with decreased leptin and increased ghrelin concentrations and consequently an in-

creased body mass. These researchers suggested that a leptin deficiency increases appetite and consequently may cause obesity. The Child and Adolescent Metabolic Syndrome cohort studies [55, 56] suggested that a short sleep duration (<8 h/day), compared to a long ( $\geq 10$  h/day) sleep duration, affects the association of polygenic risk for obesity and the leptin pathway explains a key mechanism through a modification effect.

Thus far, there are conflicting results regarding leptin circulation in sleep curtailment, with its level being shown to be reduced [4, 57–59], unchanged [60–62], or elevated [63–67]. Chaput et al. [57], in their study in adults, reported that a sleep duration of 5–6 h/day was associated with a reduction in leptin levels and an increased risk of obesity and overweight compared to 7–8 and 9–10 h/day. A study in postmenopausal women showed that a sleep duration of less than 6 h per night was associated with lower serum leptin level compared to a sleep duration of more than 8 h [59]. In a study in healthy men, Mullington et al. [58] reported a rapid reduction in leptin amplitude in that sleep deprivation period, which returned toward normal during the period of recovery sleep. Spiegel et al. [68] evaluated associations between leptin and sympathovagal balance, cortisol, thyroid-stimulating hormone (thyrotropin or TSH), glucose, and insulin under different bedtime conditions. They reported that sleep restriction (4 h for 6 nights) was associated with a decrease in the mean and maximal levels and rhythm amplitude of leptin (–19, –26, and –20%, respectively) compared to an extended sleep time (12 h for 7 nights). The effects of a short sleep duration on leptin level have also been shown to be associated with an elevation of sympathovagal balance and alterations in the cortisol and TSH profiles [68]. The thyroid gland regulates thermogenesis (body temperature) and appetite, and its dysfunction (hypothyroidism or hyperthyroidism) results in alterations in body mass [69]. Furthermore, higher TSH levels are associated with obesity and a higher body mass [70–72]. The exact mechanism underlying the influence of TSH on obesity is still unclear, but increases in energy expenditure and hyperleptinemia have been proposed to be influenced in this relationship [69].

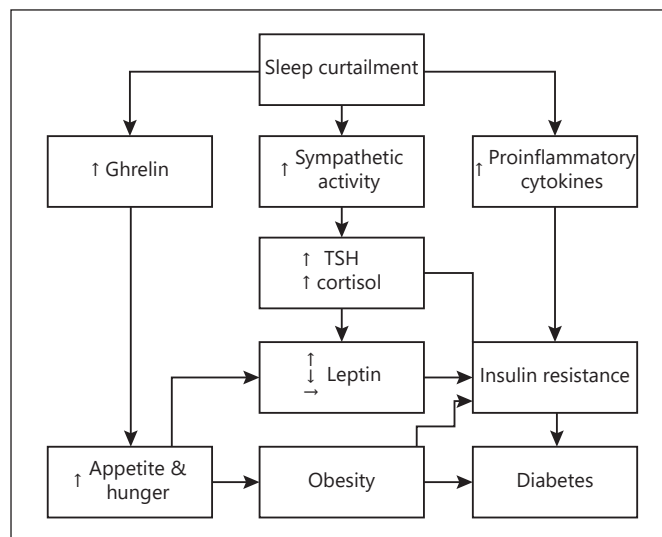
Although short-term sleep curtailment has been shown to be associated with activation of the stress system, which leads to decreased leptin levels and increased hunger and appetite, acute loss of sleep in a less stressful environment has been shown to increase leptin levels in the body [66]. Therefore, it seems that a combination of sleep curtailment and activation of the stress system but not sleep loss itself may lead to decreased leptin levels and

increased hunger [66]. Hayes et al. [65] have examined the level of leptin in association with a reduced sleep time among adults. They reported that a 1-h decrease in total sleep duration was associated with a 10% increase in leptin levels [65]. A study on salivary cortisol and leptin in young healthy women showed that a single night of restricted sleep (3 h) altered the diurnal pattern of cortisol rhythms (the level of morning cortisol was reduced, and afternoon/evening cortisol levels were elevated) and increased morning leptin levels in subjects but it did not have an effect on hunger and craving scores [67]. Bosy-Westphal et al. [73] found that consecutive nightly decreases in sleep duration significantly increased body weight, energy intake, glucose-induced thermogenesis, leptin/fat mass, free triiodothyronine, and free thyroxine [73]. Charles et al. [74] showed that both short (<5 h) and long (>8 h) sleep durations were associated with increased leptin levels related to obesity.

However, unaffected leptin levels have been reported in patients with a sleep deficiency [61]. In a study in men with and without insomnia, circulating levels of leptin and ghrelin were measured across the night. Serial measurement of appetite hormones showed that ghrelin levels were significantly lower in insomnia patients, whereas leptin did not differ between the groups. Furthermore, the findings of this study concluded that dysregulation in energy balance in patients with insomnia results in weight gain in this population [61]. A Circadian Locomotor Output Cycles Kaput (CLOCK) gene study showed that a shorter sleep duration increased ghrelin levels with no effects on leptin values [60]. This study suggested that sleep reduction with alterations in ghrelin levels and changes in eating behaviors may affect weight and weight loss. Schmid et al. [62], in a study in healthy normal-weight men, reported that feelings of hunger and ghrelin levels were elevated after 1 night of total sleep deprivation, whereas morning serum leptin concentrations was unaffected. A large multiethnic study also found no association between sleep duration and leptin levels [75].

### Sleep Duration, Leptin, and Diabetes

Sleep plays a critical role in glucose regulation, and sleep duration has been shown to have an inverse effect on endocrine function and carbohydrate metabolism [2, 76]. The link between sleep and glucose metabolism has been explored in several studies, where it has been proposed that both short [13, 77–80] and long sleep durations [81–83] may increase the risk of developing obesity and con-



**Fig. 1.** Role of sleep restriction on leptin regulation in obesity and diabetes.

sequently diabetes mellitus. It was shown by a systematic and meta-analysis study that both short and long sleep durations in type 2 diabetes patients is significantly associated with an increase in hemoglobin A1c (HbA1c) levels, suggesting poorer glycemic control compared to that with a normal sleep duration, with the relationship being U-shaped [84]. In another study both a short sleep duration (>5.5 and 5.5–6.4 h) and a long sleep duration (7.5–8.4 h) were associated with an increase in the risk of metabolic syndrome, insulin resistance, and high-sensitivity C-reactive protein in diabetic patients compared to those with 6.5–7.4 h of sleep [85]. These findings also concluded that sleep duration has a U-shaped relationship with metabolic syndrome and insulin resistance. A recent meta-analysis confirmed that short sleep (> 6 compared to 7 h) may increase the risk of type 2 diabetes by approximately 30% [86]. It has been proposed that sleep deprivation impairs insulin sensitivity and pancreatic  $\beta$ -cell function and glucose uptake by target cells, increasing insulin resistance and leading to type 2 diabetes [87–94]. Recent evidence suggests that the metabolic hormones leptin and ghrelin are involved in the relationship between sleep and dysregulation of insulin and glucose and increase the risk of diabetes [63, 68, 94–97]. Given the effects of sleep deficiency on leptin levels and metabolism, a short sleep duration may mediate its effects on incident diabetes through weight gain [98, 99] (Fig. 1).

The reviews on the role of sleep restriction in the metabolic and endocrine alterations propose that a decreased



sleep duration impairs glucose tolerance and insulin sensitivity, increases evening concentrations of cortisol and levels of ghrelin, decreases levels of leptin, and increases appetite and hunger [100, 101].

In contrast, a multiethnic study in a population at high risk for diabetes showed that a short sleep duration ( $\leq 5.5$  h) was associated with an increase in leptin levels [75]. A study in diabetic patients showed that an insufficient sleep duration increased the level of leptin and insulin resistance compared to those with an appropriate sleep duration [102]. A laboratory-based sleep study showed that sleep restriction (5 nights of 4 h in bed) impaired glucose homeostasis and increased fasting and insulin levels [63]. Sleep restriction was associated with an increase in afternoon cortisol and leptin levels compatible with an increased insulin resistance [63]. It has been reported that a 1-h reduction in sleep duration was associated with a 7% elevation in leptin levels [65]. Furthermore, a study in rotating-shift-work women reported an inverse association between leptin levels and the risk of type 2 diabetes. However, there was no association between sleep duration, leptin levels, and diabetes [103].

Considering the role of leptin in regulation of energy consumption, a decrease in the production of leptin due to a lack of sleep may explain the contribution of adjustment of this hormone to obesity, decreased insulin sensitivity, and increased insulin resistance. It is noteworthy that elevation of serum leptin levels results in decreased leptin transport across the blood-brain barrier [104]. It has been indicated that when leptin reaches its threshold the blood-brain barrier limits the leptin transport from peripheral blood to the central nervous system, inhibiting its activity [105]. This condition may explain the elevation of leptin levels due to sleep restriction, where the effectiveness of it is attenuated. In this way, leptin resistance, characterized by a decreased response to leptin due to a reduced receptor expression, is another possible mechanism that explains elevated leptin levels in the blood but decreased leptin effects [28]. Thus, in the case of elevated plasma leptin levels it does not consistently reflect increased leptin efficacy and function in glucose homeostasis [28].

In summary, recent evidence indicates that an insufficient sleep duration, with an effect on leptin metabolism, may promote the development of type 2 diabetes through increased hunger/food intake and weight gain. Furthermore, leptin dysregulation contributes to decreased insulin secretion and sensitivity, increased insulin resistance and inflammation, and consequently an increased risk of diabetes mellitus. Several studies have in-

vestigated the role of a short sleep duration on leptin regulation; however, the findings regarding the role of leptin in diabetes as a consequence of sleep curtailment are conflicting and more studies with a larger sample size are required to confirm the previous findings.

## Strengths and Limitations

We reviewed and discussed the probable mechanism underlying the effect of sleep duration on leptin regulation as the potential physiological mechanism underlying obesity and type 2 diabetes. Potential limitations of this work include the conflation of sleep quality and sleep duration where these were not always reported separately in the studies included in this review. Furthermore, this review was conducted as a narrative review and as such a quality appraisal of the included papers was not undertaken. Further work is required to compare the findings of both sleep quality and duration on leptin circulation related to obesity and diabetes.

## Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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## Author Contributions

Maryam Mosavat drafted this paper. Mitra Mirsanjari, Diana Arabiat, Aisling Smyth, and Lisa Whitehead reviewed and revised this work. All authors read and approved the final version of this article.

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