

# The Effects of Sleep and Sleep Deprivation on Metabolic, Endocrine and Immune Parameters

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**Abstract:** Sleep curtailment is becoming widespread in modern society. In parallel with this, more and more studies are dealing with the health consequences of sleep deprivation. This short review focuses on the main results of studies examining the effects of sleep and sleep deprivation on metabolism with extra emphasis on appetite regulation, and on the endocrine and immune system.

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## Introduction

A good sleep is one of the most satisfying human experiences with a role to play in maintaining a good mood and cognitive acuity as well as in promoting physiologic balance and resilience. Men spend about one-third of their lives asleep, sleep deprivation is a stressor affecting the brain as well as many body systems.

Sleep curtailment is becoming increasingly prevalent in modern society. According to self-reports, sleep duration in the United States has decreased by one to two hours during the second half of the 20<sup>th</sup> century [1]. Hence, poor sleep is one of the most common complaints in middle aged adults and over 55 years old, with between 9% and 12% reporting persistent sleep difficulties [2].

The first large-scale study to provide evidence that abnormal sleep duration is associated with health outcomes was the Cancer Prevention Study in 1964 [3]. Analyses of over 1 million participants showed that regular sleep of less than 7 hours or more than 7 hours is connected with increased mortality. Other smaller studies, similar to the previous one, show, that there is a U-shaped relationship between sleep duration and all causes of mortality (e.g.: diabetes, coronary artery disease, hypertension, etc.), suggesting that there may be an optimal sleep duration for healthy living [4, 5].

These data have served as a catalyst for studies of the health consequences of chronic partial sleep restriction.

## Sleep and metabolism

Recent data suggest that chronically short sleep time may cause obesity and increase the risk of diabetes through alterations in glucose metabolism and in neuroendocrine regulation of appetite. During sleep the body must maintain the circulating blood glucose levels so that the brain can continue to receive an adequate supply despite the absence of food intake.

A large number of studies have tested the levels of glucose and insulin in subjects who were examined in the sleep laboratory to find that despite prolonged fasting, the glucose levels remain stable or subside minimally throughout the night [6, 7].

Scheen A. J. et al. have found plasma glucose levels and insulin sensitivity rates markedly increased during early nocturnal sleep with returning to presleep values during the late sleep phase in subjects with administration of glucose infusion during the night without awakening the subject [8].

Decreased glucose uptake is probably partly caused by decreased muscle tone, partly by reduced glucose requirement by the brain during slow-wave-sleep (SWS) [9] and partly by release of the growth hormone during SWS [10].

In contrast, if the subjects are awake and fasting in a recumbent position, in the absence of any physical activity, the glucose level declines by an average of 0.5 to 1.0 mmol/l over a 12-hour period [11].

Major differences in glucose and insulin responses were observed during sleep deprivation. Spiegel et al. [12] studied metabolism of glucose in the group of healthy young men aged 18–27 years with sleep deprivation of 4 hours of sleep in 6 consecutive nights and compared the results with values of the same group while sleeping normally. The mean of blood glucose level was 15 mg/dl higher, their insulin response to glucose was 30% lower, and their glucose tolerance rates 40% slower. Sleep deprivation proved reversible prediabetic state in healthy young subjects.

Patel et al. in their review had analysed 36 studies examining sleep-weight association and found that short sleep duration might be a novel and independent risk factor for weight gain and obesity, particularly in younger population [13].

#### *Regulation of appetite*

Sleep loss and sleep disturbances might contribute to the development of insulin resistance and type 2 diabetes either directly by their deleterious effect on the components of glucose regulation, or indirectly through appetite dysregulation, leading to weight gain and obesity, a major risk factor for insulin resistance and diabetes [12, 14, 15].

#### *Ghrelin and leptin have major roles in the regulation of appetite*

Ghrelin is a predominantly stomach-derived peptide [16] with a central role in energy balance by increasing food intake and body weight, coupled with a reduction in fat utilisation [17]. Recent findings suggest that ghrelin is a sleep promoting factor promoting slow wave sleep and nocturnal release of the growth hormone (GH), adrenocorticotrophic hormone (ACTH) and cortisol in humans [18].

Through increased ghrelin activity sleep deprivation may exert a stimulating effect on ACTH, resulting in higher cortisol levels when compared with the baseline values [19]. Higher morning levels of ghrelin were found in subjects with short sleep duration [15].

Leptin is an adipocyte-derived hormone which reflects the amount of energy stored in adipose tissue. It has been implicated in the regulation of food intake and metabolism [20].

Furthermore, leptin levels appear to be markedly increased in sleep [21] but are also under circadian control reaching the lowest level in the morning and the peak in the evening [22], increasing the feeling of hunger in the morning and satiety in the evening. In contrast, ghrelin does not appear to be under endogenous circadian control and remains uninfluenced by sleep [23].

Short sleep duration is associated with decreased leptin and increased ghrelin levels. These changes have also been observed in reaction to food restriction, and weight loss and are typically associated with increased appetite [15].

Having examined 12 healthy men, first sleeping 4 hours for two nights and then sleeping 10 hours again for two nights, Spiegel K. et al. have found that the ghrelin-to-leptin ratio was 70% higher when the subjects slept less. There was also a strong relationship between increased hunger during sleep restriction and increased ghrelin: leptin ratio [24].

### *Orexin*

Orexin neurons, beside their crucial role as regulators of sleep and wakefulness, have been shown to play an important role in the regulation of energy homeostasis as well. Orexin-containing neurons in the lateral hypothalamus project directly to the locus coeruleus and other brainstem and hypothalamic arousal areas, where they interact with the leptin responsive neuronal network. Electrophysiological studies of orexin neurons show that the activity of isolated orexin neurons is inhibited by glucose and leptin and stimulated by ghrelin [25].

Orexin is also involved in autonomic function regulation. It stimulates sympathetic outflow and possibly accounts for the increased body mass index observed under conditions of low orexin levels. Orexin deficiency might decrease the sympathetic tone, and thus conceivably results in decreased energy expenditure [26].

In addition, orexin influences neuroendocrine function, thereby affects arousal and the stress response. For example, injection of orexin into cerebral ventricle stimulates the hypothalamic-pituitary-adrenal axis [27]. The link between this system and orexin neurons is reciprocal [28] and might maintain wakefulness during stressful events [26].

Narcolepsy patients have a decreased caloric intake but an increased body mass index, indicating that the abnormality that gives rise to narcolepsy has links to reduced energy expenditure or a low metabolic rate [29, 30].

### **Sleep and endocrine system**

It has been well known for decades that sleep exerts a profound modulatory effect not only on metabolism, but also on hormones. The secretion of the growth hormone (GH) and prolactin (PRL) is markedly increased during sleep, whereas the release of cortisol and thyrotropin (TSH) is inhibited.

The effect of sleep on the immune system is thought to be mediated in part through the neuroendocrine system.

### *Growth hormone (GH)*

Pituitary release of the GH is stimulated by the hypothalamic growth hormone releasing hormone (GHRH) and inhibited by somatostatin. GHRH promotes

slow-wave sleep (SWS). GHRH inhibition in rats attenuates both baseline sleep and IL-1 $\beta$ -induced sleep increases relative to the duration of SWS [31]. The release of GH depends, in particular, on the occurrence and quality of sleep.

In the late 1960s it was recognized that the most reproducible GH pulses occurred shortly after sleep onset [32]. Sleep onset elicits a pulse in GH secretion regardless of whether sleep is advanced, delayed or interrupted and reinitiated.

Spiegel et al. exhibited all subjects a GH pulse prior to sleep onset after chronic partial sleep restrictions [12]. There was negative correlation between presleep and postsleep onset GH secretion contrary to acute total sleep deprivation with minimal GH secretion during prolonged sleep [33].

#### *Corticotropin-releasing hormone (CRH) – Adrenocorticotrophic hormone (ACTH) – Cortisol*

The activity of the corticotropin axis, a neuroendocrine system associated with the stress response and behavioural activation, can be measured in peripheral blood with the plasma levels of the pituitary adrenocorticotrophic hormone and of the adrenal hormone directly controlled by ACTH stimulation. CRH is a potent inducer of waking. In animal models, it antagonizes the IL-1 $\beta$ -induced increase in SWS [34].

In a study by Spiegel and Leproult [12, 33, 35] the state of sleep debt was associated with alterations in the 24-hour profile of cortisol, including a shorter quiescent period and elevated levels in the afternoon and early morning.

#### *Thyrotropin (TSH)*

The daytime low and relative stable levels of plasma TSH are followed by rapid elevation starting in the early evening and culminating in nocturnal maximum at around the beginning of the sleep period [36].

The later part of sleep is marked by a progressive decline of TSH levels, the daytime values resume shortly after morning awakening.

The normal rise in thyrotropin at night was strikingly decreased in the state of sleep deprivation when compared with that of sleep recovery. The overall 24-hour mean thyrotropin concentration was significantly decreased [12]. The differences in thyrotropin profiles between the two states were probably related to changes in thyroid hormone concentrations, since the free thyroxin index was higher in the state of sleep debt than during sleep recovery [12].

### **Sleep and the immune system**

An independent body of evidence clearly indicates that sleep loss is associated with changes in parameters associated with the immune response. Exact mechanism of affecting systemic immunity by sleep or sleep deprivation is far from ascertained; however, the central feature of sleep, i.e., a change in brain function, is associated with both direct and indirect changes in other physiological systems. For example

sleep mechanisms directly initiate alterations in the respiratory control of respiratory system. By contrast, the effect of sleep on the heart rate is mainly indirect, being secondary to a fall in metabolism. In general, sleep and/or the concurrent changes in brain activity are believed to affect immune function mainly directly rather than indirectly [37]. There have been many experiments conducted in humans and animals, in which sleep is affected by infection [37, 38]. In general, animals show an increase in the duration of SWS and intensity of sleep in response to infection. This is usually followed by a period of less sleep, during which the sleep architecture is abnormal. Infection with influenza in humans leads to sleep reduction during the incubation period and to increased sleep during the symptomatic period, although the quality of sleep is unaffected [37].

A high dose of lipopolysaccharide increases the body temperature, the heart rate, the level of cortisol, and the level of the tumor necrosis factor (TNF) and its soluble receptors; it also disrupts sleep by causing a decrease and after that an increase in SWS duration with concomitant decrease in rapid eye movement (REM) sleep [39].

Although the exact mechanisms how acute infection is associated with sleep changes are yet to be identified, one persuasive hypothesis is that infection elicits immune responses that alter the expression of endogenous immunomodulatory substances, which in turn affect sleep [40].

Since cytokines are produced during infection concurrently with changes in the sleep pattern, they are good candidates for having a direct role in sleep regulation [39].

### **Cytokines**

#### *Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) and interleukin-1 $\beta$ (IL-1 $\beta$ )*

With respect to sleep, the most studied cytokines are TNF- $\alpha$  and IL-1 $\beta$ . Both pro-inflammatory cytokines fulfil the criteria of sleep regulatory substances as proposed by Kruger et al. [41]. TNF- $\alpha$  and IL-1 $\beta$  increase the duration of SWS [42], and by decreasing their intracerebral levels or antagonizing their effects an inhibition of SWS [43, 44]. Either of these cytokines influences the effect the other has on sleep. Pre-treatment with a fragment of the receptor for IL-1 $\beta$  attenuates TNF- $\alpha$ -induced SWS enhancement while the TNF- $\alpha$  antagonist inhibits IL-1 $\beta$ -induced increases in SWS duration [45]. TNF- $\alpha$  and IL-1 $\beta$  both stimulate the transcriptional activity of the nuclear factor- $\kappa$ B (NF- $\kappa$ B) which enhances sleep. The factors that inhibit NF- $\kappa$ B activation, such as IL-4, IL-10 and the inhibitor of NF- $\kappa$ B, inhibit sleep [46].

#### *Interleukin-6 (IL-6)*

Recent studies of human subjects suggest that IL-6 may be involved in sleep alterations during some pathological states. IL-6 mediates some aspects of sickness behaviour and responses to IL-1 and TNF- $\alpha$ . Plasma IL-6 exhibits a diurnal rhythm with peak values during sleep and nadirs during wakefulness.

Sleep deprivation increases IL-6 in the plasma of human volunteers. Subcutaneous injection of IL-6 increases slow wave sleep and reduces REM sleep in humans [47].

The role of other cytokines on sleep is more ambiguous. In summary, most pro-inflammatory cytokines seem to be somnogenic, whereas most anti-inflammatory cytokines are not.

#### *Sleep deprivation and cytokines*

The number of monocytes, a major source of cytokines, has been shown to increase during sleep deprivation of 39 hours [48] and 64 hours [49]. There are few studies, in which plasma cytokine levels were measured directly after sleep deprivation. For example, prolonged sleep deprivation of 5 days causes IL-6 levels to increase more than in control individuals, however, this effect can be negated by having a daily 2-hour nap [50].

The degree of sleep deprivation is important in determining its effect on immune function. The first study demonstrating the effects of sleep deprivation on immunisation in humans was written by Spiegel K. et al. [51]. They show that humans immunized against infection with the influenza A virus during a period of partial sleep deprivation had virus-specific antibody titres equal or less than half of those of non-sleep-deprived individuals at 10 days after sleep immunisation.

#### *Cellular immunity*

Only a few studies have directly measured host outcomes. Instead, the approach most often used is to choose a parameter associated with the immune system (e.g. NK activity) and determine whether it changes after sleep deprivation. In addition, it is very difficult in sleep deprivation studies to isolate sleep loss per se as an independent variable. Despite this limitation, there is a growing body of evidence suggesting that sleep loss does indeed influence the immune system. Paradoxically short-term sleep deprivation can enhance host defences, whereas long-term sleep loss is devastating.

Several studies have investigated the effect of sleep deprivation on the immune cell number, but the results are inconsistent, which might be partly explained by the different length of sleep deprivation used in those studies. A study by Dinges et al. was the first to find alterations in immune parameters with different lengths of sleep alteration [49]. By comparing 40 and 64 hours of sleep deprivation they showed that the count of T helper cells and NK cells decreased after one night of sleep deprivation, whereas the number of NK cells increased after two nights of sleep deprivation.

#### *B-cells immunity*

According to study of Boyum et al. [52], the level of human immunoglobulins decreases with sleep, however this finding has never been reproduced. Unlike

Ozurk, who found no statistically significant differences in IgG and IgM levels, L. Hui did find after one night of total sleep deprivation in 10 healthy adults statistically significant differences in serum levels of IgG, IgA, IgM, C3, C4 when compared to non-sleep-deprived groups [53]. All the immunoglobulin and complement parameters in the study were increased but remained within normal range, except for slightly elevated IgG. Therefore, no pathological changes were considered and a non-specific increase was suggested. The mechanism may operate through the production and release of cytokines such as IL-2, IL-6 in sleep deprivation [54, 55].

### Summary

The aim of this review was to present some of the accumulated evidence indicating that sleep deprivation can lead to changes in energy homeostasis, endocrine and immune parameters. Chronically short sleep time may cause obesity and increased risk of developing diabetes through alterations in glucose metabolism and in neuroendocrine regulation of appetite. Short sleep duration is associated with decreased leptin and increased ghrelin levels, changes also observed in reaction to food restriction and weight loss and typically associated with increased appetite.

The reported data show that sleep exerts profound modulatory effects on various hormones such as GH, TSH and cortisol.

The present studies show that sleep loss influences the measure of cellular immunity and B-cell immunity and alters the nocturnal secretion of the proinflammatory cytokines such as IL-6.

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