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CHRONIC SLEEP DEPRIVATION – ITS IMPACT AND RISK OF METABOLIC AND NEURODEGENERATIVE DISORDERS: A LITERATURE REVIEW

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ABSTRACT

Introduction and Purpose: Sleep plays a key role in maintaining physiological homeostasis, influencing not only cognitive functions but also the regulation of metabolic and immune processes. The modern lifestyle significantly contributes to reduced sleep duration and quality. Chronic sleep deprivation is becoming a widespread public health issue. The aim of this study is to review current scientific literature on the effects of chronic sleep deprivation on metabolism and to assess its role in the pathogenesis of metabolic and neurodegenerative diseases.
Brief Description of the State of Knowledge: A growing body of research indicates that chronic sleep deficits are associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, disturbances in glucose-insulin metabolism, and alterations in the secretion of appetite-regulating hormones. These consequences promote the development of insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. Moreover, increasing evidence links chronic sleep deprivation to heightened neuroinflammatory processes and the accumulation of pathological proteins in the central nervous system, raising the risk of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.
Conclusions: In recent decades, insufficient sleep has become a global issue affecting people of all age groups. There is growing evidence supporting the association between chronic sleep deprivation and the development of chronic diseases, as well as a shortened life expectancy. Enhancing transparency in reporting and improving public access to data on the consequences of sleep deprivation are essential for protecting public health.

KEYWORDS

Chronic Sleep Deprivation, Metabolism, Neurodegenerative Diseases, Insulin Resistance, Obesity, Type II Diabetes, Thermoregulation, Regeneration

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Introduction

Sleep and the accompanying regenerative processes are essential for the proper functioning of the human body. They improve not only regulation of metabolic processes but also nervous system performance. In recent decades, the overall sleep duration in the general population has declined, largely due to low socioeconomic status, occupational stress, modern lifestyle habits, and widespread exposure to electronic stimuli.

The multidimensional consequences of chronic sleep deprivation include not only cognitive impairments - such as reduced attention, memory, and learning ability - but also numerous somatic disorders. A strong association has been observed between chronic sleep deprivation and the risk of developing neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). These are progressive conditions that lead to irreversible neurological dysfunction and a significant deterioration in quality of life.

Given the increasing number of individuals affected by neurodegenerative diseases and the growing prevalence of sleep disorders, understanding the impact of chronic sleep deprivation on the development of these conditions is of critical importance for public health. There is an urgent need to further investigate the mechanisms linking these phenomena, which could lead to the development of new preventive and therapeutic strategies aimed at reducing the burden of these incapacitating diseases.

Prolonged sleep deficits may be associated with disturbances in carbohydrate, hormonal, and lipid metabolism, which in turn contribute to insulin resistance, overweight, obesity, type 2 diabetes, and metabolic syndrome. Inadequate sleep duration also affects regulation of the hypothalamic-pituitary-adrenal axis, resulting in elevated cortisol levels and chronic inflammation, thereby fostering the development of metabolic diseases.

Understanding the mechanisms underlying these associations is crucial for the prevention and treatment of civilization-related diseases.

Current State of Knowledge

Recommended Sleep Duration in Adults and Its Deficiency

For adults aged 18 to 64 years, the recommended sleep duration is between 7 and 9 hours per day; for individuals over 65, between 7 and 8 hours [1,2]. Sleep deficiency occurs when daily sleep duration falls below 6 hours. Short-term deficits result from one or a few nights of insufficient sleep, while chronic deficits persist for days, weeks, or even longer. Chronic sleep deprivation has particularly harmful health effects, contributing to metabolic disturbances and increased risk of cardiovascular and metabolic diseases [3,4].

The Whitehall II Study ($n > 10\,000$) showed that individuals sleeping <6 hours per day had ~20–30 % higher risk of premature death vs. those sleeping 7–8 hours [5].

Meta-analyses involving >1.3 million participants (Cappuccio et al.) indicate a U-shaped, nonlinear relationship—both short (<6 hours) and long (>9 hours) sleep durations are associated with increased mortality, with pooled risk ratios of 1.12 and 1.30, respectively [6].

Chronic sleep deprivation increases the risk of mortality by ~12–35 %, depending on the population studied, duration of observation, and adjustment for confounding variables [6].

The Physiological Role of Sleep in Human Metabolism

During sleep, the body's energy demands decrease, sympathetic nervous system activity is reduced, and catecholamine levels decline. Growth hormone (GH) secretion increases, stimulating lipolysis and protein synthesis, which positively impacts body composition and mass regulation [7].

Furthermore, sleep modulates tissue sensitivity to insulin - improving insulin responsiveness and glucose utilization by cells. It also enhances adiponectin expression, which boosts insulin sensitivity and has anti-inflammatory properties. Sleep increases leptin levels (which suppresses appetite and improves insulin sensitivity) and reduces ghrelin levels (which stimulates hunger and may contribute to insulin resistance) [8].

Another advantage of adequate physiological sleep duration is the improvement in immune system function and cytokine profiles, due to increased release of pro-inflammatory cytokines such as: interleukin-1β (IL-1β) - which promotes NREM sleep and enhances the inflammatory response; interleukin-6 (IL-6) - involved in the acute-phase response and activation of T and B lymphocytes; and tumor necrosis factor alpha (TNF-α) - which acts synergistically with IL-1β in the induction of deep sleep.

Simultaneously, during sleep, there is also increased activity of anti-inflammatory cytokines, including interleukin-10 (IL-10) - which inhibits excessive activation of monocytes and Th1 lymphocytes, and transforming growth factor beta (TGF-β) - which promotes immune tolerance and suppresses inflammatory cascades [10].

One of the key discoveries in recent years is the role of the so-called glymphatic system - a specialized brain waste clearance mechanism that is primarily active during deep sleep. This system is responsible for removing toxic proteins from the brain, including β-amyloid and tau proteins, whose accumulation is characteristic of Alzheimer's disease. Chronic sleep deprivation impairs the function of the glymphatic system, resulting in the buildup of these harmful substances and promoting neurodegeneration [9,11].

Metabolic Consequences of Chronic Sleep Deprivation

Chronic sleep deprivation is recognized as a significant risk factor for the development of overweight and obesity. It disrupts the function of the neuroendocrine system, increasing the risk of weight gain and metabolic diseases [12].

Epidemiological and experimental studies confirm that chronic sleep loss adversely affects glucose-insulin homeostasis, promotes insulin resistance, obesity, and metabolic syndrome. This occurs through a reduction in insulin sensitivity in peripheral tissues - mainly skeletal muscle and adipose tissue - contributing to the development of type 2 diabetes [13].

Individuals with insufficient sleep are more prone to daytime fatigue, which encourages a sedentary lifestyle [13].

Disturbances in the hypothalamic-pituitary-adrenal (HPA) axis, manifested as its hyperactivation due to chronic sleep deprivation, lead to persistent hypercortisolemia. This condition promotes increased gluconeogenesis, mobilization of fatty acids, and impaired pancreatic β-cell function. Consequently, HPA axis hyperreactivity contributes to sleep fragmentation, which may perpetuate chronic insomnia. Additionally, cortisol levels rise in individuals experiencing total sleep deprivation and prolonged wakefulness [14,15].

There is also a decrease in leptin - the satiety hormone - and an increase in ghrelin - the hunger-stimulating hormone - leading to increased appetite, especially for high-energy foods rich in saturated fats and simple sugars, thus contributing to excessive caloric intake [16,17]. Hypercortisolemia plays a pivotal role in the redistribution of adipose tissue toward central (visceral) obesity, ultimately leading to metabolic syndrome.

Chronic sleep deprivation also affects the sympathetic nervous system by activating it. As a result of sympathetic hyperactivity, levels of adrenaline and noradrenaline rise, enhancing lipolysis, glycogenolysis, and hepatic gluconeogenesis. It also reduces insulin-dependent glucose uptake in muscles and causes persistent adrenergic stimulation, which desensitizes tissues to insulin and further induces insulin resistance [14].

Clinical studies have shown that even short-term sleep restriction in adults significantly impairs insulin sensitivity and increases fasting glucose levels. In sleep-deprived individuals, phosphorylation of IRS-1 and AKT is diminished, GLUT4 expression is reduced, intracellular calcium homeostasis is disrupted, and endoplasmic reticulum stress occurs. Moreover, reactive oxygen species (ROS) levels increase, which damage components of the insulin signaling pathway [13].

Clinical trials have demonstrated that even a single night of partial sleep deprivation (e.g., <4–5 hours of sleep) may reduce insulin sensitivity by 20–30%. The rate of glucose uptake by skeletal muscle (the primary site of insulin-dependent glucose metabolism) declines, while hepatic glucose production rises due to impaired suppression of gluconeogenesis by insulin [18].

These changes result in compensatory hyperinsulinemia and progressive deterioration of glucose tolerance.

The Impact of Chronic Sleep Deprivation on Thermoregulation

Thermoregulation is a physiological process that allows the body to maintain a stable internal temperature regardless of external factors. Its disruption may lead to serious health complications. The primary neuroendocrine structure involved in this process is the hypothalamus. Body temperature follows a circadian rhythm regulated by the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. Under normal conditions, body temperature reaches its minimum during the deep sleep phase (around 2:00–4:00 a.m.) and peaks in the late afternoon (between 4:00–7:00 p.m.) [19].

Chronic sleep deprivation disrupts the synchronization between the SCN and peripheral biological clocks (including those in the liver, muscles, and brown adipose tissue – BAT). This results in a shallow and delayed circadian minimum of body temperature, destabilization of hormonal rhythms (e.g., cortisol, melatonin) which indirectly regulate heat balance, and disruption of the feedback loop between body temperature and sleep-regulating structures [19,20].

The autonomic nervous system, particularly the sympathetic nervous system (SNS), plays a crucial role in regulating peripheral vasoconstriction, activation of non-shivering thermogenesis in BAT, and sweating as a heat-dissipation mechanism. In a state of chronic sleep deprivation, excessive SNS activation is observed, leading to impaired skin perfusion and inefficient heat loss, disrupted thermal stimulus responses, and reduced capacity for adaptive BAT thermogenesis [19].

Thermoregulatory disturbances caused by chronic sleep deprivation may manifest clinically as fluctuations in body temperature throughout the day with abnormal spikes or drops, intolerance to cold or heat, excessive night sweating or a sensation of cold before sleep, reduced sleep quality secondary to thermal discomfort, and an increased risk of metabolic disorders such as metabolic syndrome or insulin resistance due to deregulated energy expenditure [19].

The Impact of Chronic Sleep Deprivation on Inflammation

Another consequence of chronic sleep deprivation is the potential exacerbation of inflammatory states within the body, which may contribute to the development of numerous

chronic diseases.

This involves an increase in inflammatory markers such as interleukin-1 (IL-1), interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and transforming growth factor beta (TGF-β). As a result, the balance between inflammation and tissue remodeling phases becomes disturbed [21,22]. Chronic low-grade inflammation and oxidative stress play a key role in the development of arterial hypertension, lipid disorders, cardiovascular diseases, as well as in the progression of type 2 diabetes through damage to pancreatic β-cells.

Furthermore, certain immune cell fractions - T lymphocytes, natural killer (NK) cells, and monocytes - are reduced. This gradually impairs the body's defensive response and increases susceptibility to infections and autoimmune diseases [21,23].

The Impact of Chronic Sleep Deprivation on the Risk of Developing Alzheimer's Disease

Growing empirical evidence indicates that chronic sleep deprivation (CSD) may be a significant, modifiable risk factor for the development of Alzheimer's disease (AD), acting through a range of interrelated pathophysiological mechanisms.

One of the most important mechanisms linking sleep deficiency with the pathogenesis of Alzheimer's disease is the impairment of the glymphatic system - a network responsible for the effective clearance of neurotoxic metabolites from the central nervous system (CNS). Studies have shown that glymphatic activity is most pronounced during the deep stages of slow-wave sleep (NREM stage 3), when intensive clearance of perivascular spaces occurs, facilitating the removal of β-amyloid (Aβ) and tau protein [9,24]. Chronic sleep deprivation reduces the activity of this system, resulting in the accumulation of β-amyloid in the cerebral cortex and hippocampus - regions particularly vulnerable to neurodegeneration in AD and among the first to be affected [24,25]. The hippocampus, a key structure for memory formation, is also highly susceptible to cortisol, whose chronically elevated levels are neurotoxic [26].

Prolonged sleep disturbances lead to chronic activation of microglia and astrocytes, promoting the increased production of pro-inflammatory cytokines. This environment contributes to the development of chronic neuroinflammation, which disrupts neuronal homeostasis, accelerates neurodegenerative processes, destabilizes synapses, and facilitates tau protein hyperphosphorylation. Moreover, activated microglia lose their ability to effectively phagocytose amyloid deposits, further exacerbating their accumulation.

Simultaneously, sleep deprivation induces oxidative stress and mitochondrial dysfunction, both of which play a critical role in neuronal energy metabolism and the maintenance of cellular integrity. Oxidative stress arises from excessive production of reactive oxygen species (ROS) combined with impaired antioxidant defense mechanisms. Consequently, oxidative damage to DNA, lipids, and proteins occurs, compromising cell membrane integrity and mitochondrial function. These phenomena significantly contribute to neuronal cell death (apoptosis) and the progression of AD [27].

The Impact of Chronic Sleep Deprivation on the Risk of Developing Parkinson's Disease

Parkinson's disease (PD) is another neurodegenerative disorder associated with chronic sleep deprivation, which may accelerate disease onset and progression.

Chronic sleep deprivation impairs autophagy, promoting the accumulation of misfolded α-synuclein. Under physiological conditions, this protein is highly soluble and involved in the regulation of neurotransmitter release, synaptic plasticity, and cellular homeostasis. Its aggregation in dopaminergic neurons of the substantia nigra, mesocorticolimbic system, hypothalamus, and locus coeruleus contributes to the formation of Lewy bodies and triggers neurotoxic responses, thereby accelerating neurodegeneration [28,29].

Sleep deprivation is also associated with mitochondrial dysfunction - particularly detrimental to high-energy-demanding dopaminergic neurons. This results in increased production of reactive oxygen species (ROS), intensifying oxidative stress. Excess ROS cause damage to mitochondrial DNA (mtDNA), membrane lipids, and enzymatic proteins, ultimately leading to neuronal apoptosis. In the context of PD, oxidative stress accelerates the loss of neurons in the substantia nigra and exacerbates disease progression [28,30].

Chronic sleep disturbances activate microglia, which shift toward a pro-inflammatory phenotype (M1), releasing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines. The resulting chronic neuroinflammation plays a critical role in PD pathogenesis, damaging dopaminergic neurons and disrupting neuroimmune balance. Notably, microglial activation is detectable in the early stages of the disease, even before the emergence of motor symptoms [28,29].

Sleep regulates numerous aspects of neurotransmission, including the homeostasis of the dopaminergic system. Chronic sleep deprivation disrupts circadian rhythms, partly through altered expression of core clock genes (CLOCK, BMAL1, PER, CRY), affecting dopamine metabolism and potentially accelerating the degeneration of dopamine-producing neurons. Sleep-wake rhythm disturbances often precede the onset of motor symptoms in PD and may serve as early biomarkers of the disease [9,29].

The Impact of Chronic Sleep Deprivation on the Risk of Developing Amyotrophic Lateral Sclerosis (ALS)

Sleep deprivation leads to the accumulation of reactive oxygen species (ROS) and impairs the function of antioxidant enzymes such as superoxide dismutase 1 (SOD1), mutations of which are among the primary genetic causes of ALS [31]. The mitochondria of motor neurons are particularly sensitive to oxidative stress, and their damage results in disrupted oxidative phosphorylation, mitochondrial membrane depolarization, and activation of apoptotic pathways. These processes accelerate motor neuron degeneration [31,32].

Chronic sleep deprivation impairs autophagy and proteasome-mediated protein degradation, which may promote the pathological aggregation of TAR DNA-binding protein 43 (TDP-43). TDP-43 is a neuropathological hallmark present in the majority of ALS cases. Its cytoplasmic inclusions exert neurotoxic effects, whereas sleep - particularly during the NREM phase - supports autophagy and interstitial space clearance, aiding in the removal of such pathological aggregates [32,33].

As in Parkinson's and Alzheimer's diseases, sleep deprivation intensifies microglial activation and increases levels of pro-inflammatory cytokines in the brain and spinal cord. These cytokines can exert cytotoxic effects on motor neurons and enhance their degeneration. Furthermore, sleep regulates the expression of receptors for glutathione and neuroprotective substances, which helps suppress inflammatory processes in the nervous system - a balance that is disrupted by sleep deficiency [33].

In recent years, the role of the so-called glymphatic system has been described - a network of perineuronal fluid channels and aquaporin pathways (especially AQP4) responsible for the clearance of brain metabolites, primarily during sleep. Chronic sleep deprivation impairs the drainage of toxic proteins, including excess TDP-43 and SOD1. Dysfunctional glymphatic outflow may therefore increase neurotoxic burden and exacerbate neurodegeneration [32].

Sleep deprivation also affects the epigenetic regulation of gene expression. Under conditions of deprivation, there is increased expression of pro-apoptotic genes (e.g., BAX, p53) and decreased expression of neuroprotective genes such as BDNF (brain-derived neurotrophic factor). A reduced level of BDNF is associated with increased susceptibility of neurons to cell death, which is particularly relevant in the context of ALS [31].

The Impact of Chronic Sleep Deprivation on Tissue Regenerative Capacity

During the slow-wave sleep phase (NREM stage 3), anabolic processes occur through the secretion of growth hormone and melatonin, both of which participate in the repair of damaged tissues by promoting the synthesis of structural proteins, stimulating fibroblast proliferation, angiogenesis, and activation of reparative pathways. Sleep deprivation lowers the levels of these hormones, as well as insulin-like growth factor 1 (IGF-1), thereby diminishing the body's regenerative capacity. Prolonged sleep deficiency increases the susceptibility of regenerating cells to apoptosis, especially in actively proliferating tissues such as epithelium, endothelium, and skeletal muscle [9].

Experimental studies have shown that sleep deprivation significantly delays wound healing, both in animal models and in humans. It impairs the migration of keratinocytes and fibroblasts to the site of injury and reduces the synthesis of type I and III collagen - both essential for extracellular matrix reconstruction. Additionally, sleep deprivation decreases the expression of vascular endothelial growth factor (VEGF) and inhibits the formation of new blood vessels (angiogenesis), resulting in hypoxia of regenerating tissue and delayed structural restoration [34,35].

Stem cells, including mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs), play a key role in tissue repair. Chronic sleep deprivation impairs their ability to differentiate, proliferate, and migrate, thereby limiting regenerative processes across multiple systems, including the skin, muscles, liver, and nervous system. A reduction in circulating EPCs has also been observed, along with decreased expression of genes involved in vascular repair and endothelial barrier restoration [34,36].

Conclusions

Chronic sleep deprivation poses a significant public health threat, exerting a multifaceted impact on the functioning of the human body. A multitude of studies clearly demonstrate that long-term sleep restriction leads to metabolic disturbances, including insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. At the same time, sleep deficiency contributes to the development of chronic inflammation, dysregulation of the neuroendocrine system, and impaired glymphatic system function, which may initiate and accelerate neurodegenerative processes such as Alzheimer's and Parkinson's disease.

Understanding the mechanisms underlying these associations is crucial for developing effective preventive and therapeutic strategies. Promoting sleep hygiene and educating the public about the consequences of chronic sleep deprivation should become an integral part of health promotion initiatives and public health policy.

Given the increasing prevalence of lifestyle-related and neurodegenerative diseases, incorporating sleep quality and duration as key risk factors in population health assessments and longevity strategies is not only justified - it is essential.

Disclosure

Author's contribution

- Conceptualization: Patryk Kondracki, Viktoria Kretschmer
- Methodology: Wiktor Daniszewski, Ewa Sobolewska
- Software: Patryk Kondracki, Daniel Markowski
- Check: Daniel Markowski, Jakub Rodziewicz
- Formal analysis: Viktoria Kretschmer, Ewa Sobolewska
- Investigation: Wiktor Daniszewski, Jakub Rodziewicz
- Data curation: Magdalena Baranowska, Daniel Markowski
- Writing - rough preparation: Patryk Kondracki, Ewa Sobolewska
- Writing - review and editing: Patryk Kondracki, Viktoria Kretschmer
- Visualization: Viktoria Kretschmer, Wiktor Daniszewski
- Supervision: Ewa Sobolewska, Jakub Rodziewicz
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