Review

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Sleep Deprivation: A Modifiable Cause for Male Infertility

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Abstract: Male infertility is a growing global concern with increasing prevalence in both developing and developed nations. While many associations between environmental factors and male infertility have been explored, the relationship between sleep deprivation and male infertility remains underexplored. This narrative review examines the reported effects of sleep deprivation on the Hypothalamic-Pituitary-Gonadal (HPG) axis, Hypothalamic-Pituitary-Adrenal (HPA) axis, oxidative stress, and testicular function, and their consequential effects on male infertility. Disruption of the HPG axis results in altered FSH and LH levels, leading to fluctuation in testosterone levels, negatively affecting spermatogenesis and other critical reproductive processes. Activation of the HPA axis, often due to stress, elevates cortisol levels, which, in turn, suppresses gonadotropin-releasing hormone (GnRH), impairing reproductive function. Reactive oxidative species accumulate in periods of oxidative stress and have been shown to damage sperm and reduce their quality. The blood-testis-barrier (BTB) is disrupted in states of sleep deprivation, leading to decreased sperm quality. A literature review was conducted using PubMed and Google Scholar to assess peer-reviewed studies from 1990 to 2024, revealing a complex interplay between sleep deprivation and male reproductive dysfunction. While existing studies support a link between sleep disturbances and hormonal dysregulation, further research is needed to establish causal relationships and identify potential therapeutic interventions. Addressing sleep deprivation may represent a modifiable factor in improving male fertility outcomes.

Keywords: male infertility; sleep deprivation; oxidative stress; HPA axis; HPG axis

1. Introduction

Clinical infertility is defined as the inability of a couple to conceive after at least 12 months of trying [1]. Male factors are estimated to contribute to about 30-50% of infertility cases [1]. The global trends of infertility have been very concerning. Developed countries have seen rates rise from 3.5% to 16.7%, while the rates increased from 6.9% to 9.3% in underdeveloped countries [2]. With increasing trends in infertility, the potential links between sleep deprivation as a modifiable cause and infertility have received increasing attention.

Medical residents have been notably affected by chronic sleep deprivation [3]. Abnormal work hours, night shifts, and quick turnovers are all factors that disrupt the circadian rhythm, contributing to decreased sleep in medical residents and health care providers [4]. Additionally, studies have shown an increasing infertility rate among physicians compared to the general population, suggesting a possible relationship between sleep loss and impaired reproductive health [5]. Further investigation is needed to explore the relationship between long-term sleep deprivation and infertility in this unique population.

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The circadian rhythm, the body's internal clock, regulates sleep, metabolism, and hormone secretion, particularly the release of gonadotropin-releasing hormone (GnRH). GnRH controls reproductive function by modulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The circadian rhythm promotes wakefulness during daylight and sleep at night by regulating melatonin and cortisol levels. Disruptions, such as shift work or irregular sleep patterns, can lead to insomnia, hormonal imbalances, metabolic disorders, and cognitive impairments. To maintain a healthy circadian rhythm, it's essential to establish a consistent sleep pattern and exposure to natural light.

This article delves into the connection between sleep deprivation and male infertility, specifically examining its effects on crucial physiological systems. Sleep deprivation disrupts the hypothalamic-pituitary-gonadal (HPG) axis, resulting in hormonal imbalances, including fluctuations in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, as well as reduced testosterone production. These hormonal changes can lead to hypogonadism and hinder spermatogenesis. Chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis due to sleep deprivation results in chronically elevated cortisol levels, decreasing gonadotropin-releasing hormone (GnRH) secretion. Increased production of reactive oxygen species (ROS) negatively affects sperm quality and increases the permeability of the blood-testis-barrier (BTB).

The Hypothalamic-Pituitary-Gonad (HPG) Axis is the hormonal connection between the hypothalamus, pituitary gland, and gonads that regulates reproductive function [6]. The hypothalamus releases Gonadotropin-Releasing Hormone (GnRH), causing the pituitary gland to release Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH). LH signaling results in the production of testosterone, and FSH signaling leads to spermatogenesis.

Sleep deprivation has been shown to increase or decrease FSH/LH levels, contributing to reproductive dysfunction [6]. FSH stimulates Sertoli cells to produce Androgen-binding protein (ABP) and Inhibin. ABP maintains testosterone levels for sperm production, while Inhibin provides negative feedback for FSH. LH acts on Leydig cells to produce testosterone. Both elevated and decreased FSH/LH levels can cause infertility. Elevated FSH/LH with reduced testosterone indicates testicular insensitivity to hormonal signals, while decreased FSH/LH leads to hypogonadism, insufficient testosterone production, and impaired spermatogenesis. Testosterone is essential for male overall and sexual health, initiating and maintaining spermatogenesis and regulating LH, FSH, and GnRH release through negative feedback. Decreased testosterone reduces sperm quality and causes infertility. Sleep deprivation has been associated with decreased testosterone levels, leading to infertility [7].

Sleep deprivation activates the Hypothalamic-Pituitary-Adrenal (HPA) Axis, leading to an increase in cortisol production [8]. As a physiological stressor, sleep deprivation triggers the hypothalamus to release Corticotropin-Releasing Hormone (CRH). CRH stimulates the pituitary gland to release Adrenocorticotropic Hormone (ACTH), which prompts the adrenal glands to produce cortisol [8]. Normally, cortisol levels peak in the morning and decline throughout the day. However, sleep deprivation results in chronically elevated cortisol levels. Elevated cortisol decreases Gonadotropin-Releasing Hormone (GnRH) production, negatively impacting Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and testosterone, which are essential for reproductive function.

Reactive Oxygen Species (ROS), byproducts of normal cellular metabolism, serve a beneficial role at low to moderate levels. However, high ROS levels lead to oxidative stress, causing damage to proteins, lipids, and DNA [9]. Oxidative stress has been linked to male infertility through lipid peroxidation and damage to spermatozoa, negatively impacting sperm quality and morphology [10]. A study showed that patients with Obstructive Sleep Apnea (OSA), which affects around 50% of the population, had elevated ROS biomarkers, supporting a relationship between and OSA and ROS levels [11].

The hypothalamic-pituitary-gonadal (HPG) axis regulates the testes, which are the primary male reproductive organs, involved in both spermatogenesis and testosterone production. Sertoli cells and

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Leydig cells are located within the testes and serve critical roles in the production of sperm and testosterone, respectively. Sleep deprivation has known effects on increasing the permeability of the blood-brain barrier, but it has also been found to increase the permeability of the blood-testis and blood-epididymis barriers [12]. The blood-testis-barrier (BTB) serves various functions, including as an immunological barrier. Injury to the BTB leading to increased permeability has been shown to lead to the production of anti-sperm antibodies and autoimmune disease, which lead to male infertility [13,14]. Increasing age is linked with gradual dysfunction in the BTB, leading to male infertility. Disruption of the BTB due to sleep deprivation can accelerate this process, resulting in an increase in male infertility at an earlier age.

2. Materials and Methods

A literature search was conducted to identify peer-reviewed studies examining the effects of sleep deprivation on male infertility. The databases PubMed and Google Scholar were used to gather relevant literature published between January 1990- December 2024. The following keywords were combined in different configurations: “sleep cycle,” “sleep deprivation,” “sleep disturbance,” and “sleep apnea,” in combination with “male infertility,” “hormone dysregulation,” “sperm morphology,” “sperm count,’’ “sperm motility”, “testosterone,” “luteinizing hormone,” “Follicle stimulating hormone,” “cortisol,” “ROS,” “oxidative stress,” “blood-testis barrier (BTB),” “HPA”. Boolean operators (AND, OR) were used to optimize the search. References from selected studies were also screened to ensure the comprehensiveness of the literature gathered.

3. Results

3.1. Hypothalamic-Pituitary-Gonadal Axis

3.1.1. FSH/LH

FSH/LH secretion typically exhibits a circadian rhythm pattern, characterized by pulsatile secretions throughout the day, with the most pronounced secretion occurring during sleep. Consequently, testosterone levels tend to be elevated in the morning [15]. Sleep deprivation results in disruption of the circadian rhythm, negative effects on the secretion of FSH/LH, and abnormal melatonin secretion. Melatonin is secreted by the pineal gland and regulated by the suprachiasmatic nucleus (SCN). Light is an inhibitor of the secretion of melatonin. Melatonin secretion typically occurs early in the evening, with levels reaching their peak during the night. Dysregulated melatonin secretion disrupts the circadian rhythm, which, in turn, alters the secretion of FSH/LH. Melatonin also exerts effects on oxidative stress and the hypothalamic-pituitary-adrenal (HPA) axis, particularly with cortisol, which will be further elucidated below.

Karasek et al. examined the circadian variations in plasma melatonin, FSH, LH, prolactin, and testosterone levels in infertile men. The study found that FSH and LH levels exhibited a circadian rhythm, with peak levels occurring during the night [15]. Additionally, the study also found that the circadian rhythm of FSH and LH levels was disrupted in infertile men, with peak levels occurring at different times of the day compared to fertile men [15]. This disruption in the circadian rhythm of FSH/LH levels may be related to sleep deprivation, as sleep deprivation can disrupt the body's natural circadian rhythms.

Zheng et al. investigated the impact of chronic sleep deprivation on male reproductive health in mice. The study found that chronic sleep deprivation led to decreased testosterone levels and increased FSH/LH levels [16]. Zheng et al. also found that chronic sleep deprivation led to increased expression of the FSHβ gene, which is involved in the regulation of FSH levels [16]. Overall, the findings of these studies suggest a complex relationship between sleep deprivation and FSH/LH levels, with sleep deprivation potentially leading to increased FSH/LH levels through various mechanisms [16].

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Studies have consistently found that sleep disturbances are associated with increased levels of FSH and LH, which may be indicative of impaired spermatogenesis [17]. A cross-sectional study conducted in Zhejiang, China found that men with poor sleep quality had lower levels of testosterone and higher levels of FSH and LH [18]. Similarly, a study conducted among men attending infertility clinics found correlations between poor self-reported sleep quality and conditions like oligozoospermia and asthenozoospermia, which are often associated with abnormal FSH and LH levels [19].

The correlation between FSH/LH levels and sleep deprivation has important implications for global infertility, which affects approximately 15% of couples worldwide [18]. As sleep disturbances are increasingly prevalent in modern society, it is essential to investigate the impact of sleep on reproductive health. Future studies should focus on exploring the underlying mechanisms by which sleep deprivation affects FSH and LH levels, as well as the potential therapeutic benefits of addressing sleep disorders in infertile individuals. By further elucidating the relationship between sleep and reproductive hormones, researchers may uncover novel strategies for improving fertility outcomes and addressing the growing global burden of infertility.

3.1.2. Testosterone

Hypogonadism is defined as a testosterone level <300 ng/dl by the American Urological Association (AUA). An estimated four to five million men in the United States have hypogonadism, with increased prevalence occurring in older males (Boston University School of Medicine). Reports by the Institute of Medicine estimate that about 50-70 million Americans have a chronic sleep disorder, with suggested sleep being 7-9 hours a night [20]. A 2012 National Health and Nutrition Examination Survey was conducted among 9756 individuals to further explore the relationship between sleep duration and total testosterone level [7]. A linear relationship was found between sleep duration and testosterone levels, with a measured decrease of 5.9 ng/dL for every hour less of sleep. This finding was noted to be statistically significant [7].

In a study by Schmid et al, 15 young men underwent sleep time restriction to 4 hours (02:45 - 07:00) for two consecutive nights, followed by a control of 8 hours (22:45 - 07:00) of normal sleep conditions. Following the second night, testosterone concentrations were monitored over 15 hours. No differences in testosterone were noted between the two sleep settings [21]. Another experiment was performed where 8 healthy young men underwent one night of sleep deprivation of 4-5 hours (22:30 - 03:30) and a control night of 7 hours (22:30 - 06:00). Different time intervals were used to see if restricted sleep in terms of when the men are waking up would affect testosterone. The 4-5 hours of sleep deprivation, with waking the subjects up at 3:30 AM, had a markedly decreased morning testosterone and prolactin concentration compared to the control of 7 hours of sleep [21]. Data suggest that the effect of sleep on testosterone levels may be more associated with the timing of the sleep rather than the duration, suggesting that early awakening is more strongly related to decreased morning testosterone and prolactin compared to sleep loss [21].

In a study conducted between January 2003 and September 2009, Leproult and Cauter examined the effects of light exposure on the sleep patterns of ten men. Subjects had a week of 8-hour bedtimes (23:00 - 07:00) followed by 3 nights of 10-hour bedtimes (22:00 - 08:00) followed by 8 days of 5-hour bedtimes (00:30 - 05:30). The 3 nights of 10-hour bedtimes and 8 days of 5-hour bedtimes were held in a laboratory. Blood samples were collected every 15-30 minutes for 24 hours following the second 10-hour night and the seventh 5-hour night. Daytime testosterone levels decreased by 10-15% in the group of young healthy men who underwent sleep restriction of 5 hours per night [22].

Alvarenga et al explored the effect of sleep deprivation and OSA (obstructive sleep apnea) on male reproductive function levels. Two groups, a defined OSA group and a group of healthy volunteers, were used for this study. The group of healthy volunteers was either subjected to total sleep deprivation or REM sleep deprivation for 48 hours [23]. Results showed that the OSA group had decreased total and free testosterone compared to both sleep deprivation groups, even after

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controlling for BMI, which was increased in the OSA group [23]. Decreased total testosterone was found in the total sleep deprivation group, but not the REM sleep deprivation group.

Additionally, in animal studies such as Choi et al. (2016), paradoxical sleep deprivation (PSD) in rats and its relationship with hormone levels were explored [24]**.** Significant reductions in testosterone levels were found (45% decrease, from 6.5 ng/mL to 3.6 ng/mL, $p < 0.001$) [24]. The relationship between sleep deprivation and testosterone levels in rats was also explored by Oh et al. A younger group of rats (12 weeks old) and an older group of rats (20 weeks old) were split into four different groups: control group, PSD 3 days, PSD 5 days, and PSD 7 days [25]. For the young group, the control testosterone was 6.16 +/- 2.49, and for the old group, it was 4.37 +/- 1.66. Following sleep deprivation of 3, 5, and 7 days, the measurements of testosterone were 5.10 +/- 2.05, 3.02 +/- 1.85, and 1.31 +/- 0.29, respectively, for the younger group [25]. For the older group the testosterone measurements after PSD were 2.29 +/- 0.98, 0.74 +/- 0.28, and 0.14 +/- 0.06, respectively [25]. A clear decrease in testosterone was shown in association with increasing PSD [25].

Despite studies demonstrating a correlation between reduced sleep duration and decreased testosterone levels, some studies have failed to establish this relationship. In a cross-sectional study among 970 outpatients in Zhenjiang, China, over 2 years from October 2017 to July 2019, a possible association between sleep quality and reproductive hormones was explored [15]. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), where <5 is good sleep and > or equal to 5 is poor sleep. These participants delivered a semen sample, underwent a physical examination, and answered the PSQI. No evidence was found to correlate poor sleep quality with a decrease in reproductive hormone levels [15].

However, symptoms of hypogonadism can be present despite normal testosterone levels. Symptoms of hypogonadism seem to be exacerbated by decreased sleep duration despite the actual measurement of hypogonadism. Using the Androgen Deficiency in Aging Males questionnaire (ADAM: a survey designed to screen for symptoms of low testosterone), 144 out of 409 college-aged men indicated a positive ADAM [26]. Despite the absence of significant differences in average height, weight, and BMI between the positive and negative ADAM scores, it is noteworthy that out of the 144 students with a positive ADAM score, 107 (75.35%) reported poor sleep quality. This is markedly higher than the 57.73% of ADAM negatives (people who did not exhibit symptoms of low testosterone) that reported poor sleep quality [26]. These findings indicate that sleep deprivation is associated with hypogonadism symptoms despite unchanged testosterone levels, suggesting that the effects of sleep deprivation on male infertility may be due to mechanisms other than direct hypogonadism.

The relationship between testosterone and sleep deprivation has been extensively studied. Numerous studies have demonstrated an association between prolonged sleep deprivation and a reduction in total testosterone levels. However, it is important to note that additional factors, such as sleep disruptions associated with obstructive sleep apnea (OSA), have also been shown to be correlated with decreased testosterone levels. Furthermore, early awakening is associated with reduced testosterone levels, rather than overall sleep deprivation. Despite these findings, there remains much to explore in the complex relationship between sleep and testosterone levels. Nevertheless, sleep deprivation or loss is associated with decreased testosterone levels, which have been shown to have a detrimental impact on male fertility.

3.2. Hypothalamus-Pituitary-Adrenal Axis

The Hypothalamus-Pituitary-Adrenal (HPA) Axis, as its name suggests, is a neuroendocrine system that involves interactions between the Hypothalamus, Pituitary Gland, and Adrenal Glands. This pathway is primarily activated by stress, leading to the release of cortisol [27]. While cortisol is essential for maintaining homeostasis, overactivation of the HPA Axis in times of acute and chronic stress leads to elevation of cortisol levels, inhibiting reproductive function [27].

3.2.1. Cortisol

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The secretion of cortisol follows a 24-hour circadian rhythm [28]. Cortisol levels peak in the early morning, followed by a gradual decline throughout the day before reaching their lowest point at night [28]. Low levels of cortisol at night are associated with increased melatonin secretion, allowing for more effective sleep. Cortisol, a well-established stress hormone, is synthesized in direct proportion to the level of stress an individual encounters. Sleep deprivation or sleep loss leads to heightened stress levels in an individual, resulting in elevated cortisol production via the hypothalamic-pituitary-adrenal (HPA) axis [29].

In Wright et al., cortisol levels were measured after acute sleep deprivation and after chronic circadian rhythm misalignment. Participants maintained a 3-week consistent sleep schedule preceding the experiment to establish their base cortisol levels. 8 participants at random were subjected to either acute sleep deprivation or circadian rhythm misalignment. Those who underwent acute sleep deprivation saw a significant increase in their cortisol levels ($p<0.0001$), and those who had circadian rhythm misalignment saw a reduction in their cortisol levels ($p<0.05$) [27]. Additionally, stress levels were significantly increased ($p<0.0001$) in acute sleep deprivation, but stayed low for the sleep misalignment group [30].

Despite these results from Wright et al., questions about whether sleep deprivation itself is responsible for stress persist. Some people hypothesize that the results of sleep deprivation studies are results of increased stress that happens due to the methods of sleep deprivation, instead of the sleep deprivation (lack of sleep) itself being responsible for causing the stress [29]. In studies where humans underwent moderate sleep loss, the cortisol release pattern was minimally affected; however, in studies where humans underwent greater sleep loss, there was a noticeable decrease in morning cortisol levels, followed by an increase in evening levels [29]. Elevated cortisol is associated with the decreased nocturnal secretion of 6-sulfatoxymelatonin, which is the chief metabolite of melatonin [31]. This supports that elevated cortisol is associated with decreased melatonin which leads to sleep deprivation.

Castro-Diehl et al. explored the relationship between sleep quality and cortisol levels to ascertain if a relationship existed. Using actigraphy-based measures, sleep duration was measured over 7 days, along with 2 days of salivary cortisol levels. A relationship was confirmed: Shorter sleep duration (<6 hours a night) was associated with a less pronounced late decline in cortisol and a less pronounced wake-to-bed slope [32]. No association was found between shorter sleep duration and awakening cortisol levels, implying that elevated cortisol at night can be attributed to shortened sleep duration [32].

Given the positive relationship between sleep deprivation and elevated evening cortisol levels, we asked whether elevated cortisol levels were associated with infertility. Rehman et al. performed a cross-sectional study with infertile males (subjects) and fertile males(controls). Of the 376 subjects, 64% were infertile and 36% were fertile. Median cortisol levels, along with FSH, reactive oxidative species, and LH, were elevated in the infertile men, while testosterone levels were elevated in the fertile men [33]. These findings suggested a positive correlation between elevated cortisol levels and infertility.

In a study by Shukla et al (2010), the effect of Mucuna pruriens, known for its L-dopa content, on improving male fertility was measured. Sixty infertile subjects were selected for the study, all of whom had elevated cortisol levels. After 3 months of treatment with M. pruriens seed powder (5 g daily), cortisol levels were remeasured. There was a significant decrease in cortisol levels after treatment, suggesting a possible treatment for stress-related infertility [34].

3.3. Oxidative Stress

Male infertility is a known health issue, but in 30-50% of infertile men, there is no identifiable cause (idiopathic) [35]. In recent years, among many other causes, oxidative stress has been linked to male infertility [35]. It disrupts the normal homeostatic levels of reactive oxygen species (ROS) and antioxidants within the body. ROS are necessary for many physiological functions, including the normal functioning of sperm, particularly capacitation, hyperactivation, and acrosomal reaction [36].

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Recent studies suggest that a large proportion of infertile men (possibly as high as 80%) exhibit elevated ROS in semen, highlighting oxidative stress as a prevalent and potentially treatable factor in idiopathic male infertility [35].

Various intrinsic and extrinsic factors can induce oxidative stress in the male reproductive tract. These factors either increase ROS production or weaken antioxidant defenses, tipping the cellular redox balance toward a pro-oxidant state. Causes of oxidative stress relevant to male fertility include but are not limited to: varicocele, infection, metabolic conditions, aging, lifestyle factors (smoking, alcoholism, illicit drugs, poor diet), pollutants, radiation, stress, and sleep quality. [35, 36].

3.3.1. Stress and Sleep

Psychological stress elevates cortisol and catecholamine levels, which may reduce antioxidant defenses, leading to increased oxidative stress and potential sperm damage [37]. Chronic stress has been linked to impaired sperm parameters, including reduced concentration, motility, and morphology, likely due to oxidative stress and hormonal disruptions [37, 38]. Sleep quality is an emerging factor related to both oxidative stress and male infertility. Individuals with higher oxidative balance scores (pro-antioxidant) were observed to have significantly better sleep quality and duration [37]. This could suggest that poor sleep quality and duration can impair men's fertility via oxidative stress.

3.3.2. Risk Facvtors for Oxidative Stress

Many common factors can increase oxidative stress in the body. Identifying risk factors and taking steps to reduce exposure and improve sleep quality and duration could be used to treat idiopathic male infertility. Varicoceles are a prevalent cause of male infertility, increasing scrotal temperature and ROS levels, though varicocelectomies have been shown to reduce ROS [39]. Infections (epididymitis and prostatitis among others) trigger leukocyte infiltration and elevate ROS production [39]. Metabolic conditions, including diabetes, contribute to increasing oxidative stress levels [39]. Aging is a large risk factor in increasing oxidative stress, leading to a decline in semen quality [39]. Lifestyle factors including alcohol use, obesity, and smoking induce inflammation and the formation of toxic byproducts, promoting increased ROS levels [39.40]. Environmental exposures including ionizing radiation, heavy metals, air pollutants, and pesticides all stimulate ROS production, leading to fertility problems [39,41,42].

3.4. Testes

The testes, primary male reproductive organs, are under precise hormonal control via the hypothalamic-pituitary-gonadal (HPG) axis. Within the testes reside Leydig cells, responsible for testosterone synthesis when stimulated by luteinizing hormone (LH), and Sertoli cells, essential for nurturing germ cells and maintaining spermatogenesis. These cells function in concert to ensure proper sperm development and hormone balance, both vital for male fertility. As such, external stressors such as sleep deprivation have far-reaching consequences via disturbance of the HPG axis.

3.4.1. Disruption of Blood-Testis Barrier

Recent studies have indicated that chronic sleep loss disrupts the blood-testis and blood-epididymis barriers, critical components of the male reproductive system [12]. As was the case with E2F1 within different cancers, it appears that the degree to which the barrier is affected varies greatly depending on the cohort [12]. The blood-testis barrier (BTB), formed by tight junctions between Sertoli cells, creates an immune-privileged microenvironment essential for meiosis completion. It is apparent, though, that a disruption to the BTB has significant ramifications. This barrier selectively restricts the passage of substances, protecting developing germ cells from harmful agents while facilitating the exchange of essential nutrients. The BTB acts as the "gatekeeper," regulating which molecules enter the seminiferous tubules, and disruption of this barrier will allow toxic agents to

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enter. This is why toxic agents, such as cadmium, directly cause defragmentation of Sertoli cells [40]. The ensuing effects of toxicants within the cell result in immune responses that are not normally supposed to occur within the testes. The importance of a functioning BTB is also emphasized by the findings that abnormalities in BTB proteins, tight junctions, and adhesion molecules can compromise the BTB, leading to immune responses against meiotic and postmeiotic cells, ultimately resulting in spermatogenic failure and male infertility [12]. Thus, the preservation of the BTB architecture and function should be of utmost importance.

3.4.2. Mechanisms of BTB Disruption

Multiple factors can compromise BTB integrity. A high-cholesterol diet, chronic stress, and insufficient sleep all negatively affect sperm quality by damaging the BTB [12]. Sleep deprivation is closely linked to the disruption of BTB with decreased expression of tight junction proteins, actin, and androgen receptors, leading to reduced sperm viability and motility due to alterations in the blood-testis environment. This effect is further underscored by findings that elevated temperatures in the scrotal region can also lead to germ cell apoptosis, resulting in oligospermia or azoospermia across various species [12]. As such, it is important to both regulate what enters and what is released from the testes. The underlying mechanisms of BTB breakdown have also been found. For example, fine particulate matter exposure is linked to male reproductive toxicity through the degradation of blood-testis barrier proteins [12]. Furthermore, toxicants may provoke hormonal imbalances, initiate apoptosis, and impede the proliferation of spermatogenic cells by adversely affecting the structure and functionality of Sertoli cells, leading to the impairment of the BTB, and an increase in reactive oxygen species (ROS) production. The effect is a testicle under siege by both external and internal sources [12]. The influx of damaging agents combined with the body's self-destruction results in a diminished ability to reproduce. The connection between sleep disturbance, oxidative stress, and BTB integrity highlights the importance of sleep for male fertility.

3.4.3. L-cysteine

Interestingly, research has focused on therapies to mitigate BTB damage. L-cysteine, a precursor to glutathione, a crucial antioxidant, has shown promise in protecting against testicular injury and promoting the expression of BTB genes [43]. L-cysteine derivatives function as antioxidants, preserving redox balance and protecting against oxidative stress. Supplementation with L-cysteine may reinstate glutathione synthesis, enhance redox equilibrium, and mitigate oxidative stress, thereby supporting testicular function. The protective effects of N-acetyl-L-cysteine (NAC) are also seen in various animal models, as NAC has the capability of mitigating damage caused by chemicals, radiation, and other toxicants. While NAC may have been initially designed for prognostic information, it is also capable of being used to evaluate therapeutics and their effectiveness [43].

3.4.4. Aging

The functionality of tight junctions in Sertoli cells declines with age, closely correlating with age-related testicular dysfunction. The aging process involves both degradation and renewal of inter-testicular cell junctions, but at some point, this is no longer sustainable [43]. External factors such as diet and sleep affect long-term sperm function. Disruption of the BTB due to sleep deprivation can accelerate BTB's natural deterioration due to aging, resulting in an increase in male infertility at an earlier age. Therefore, further studies should focus on what the early predictive markers are in young men in hopes of detecting early BTB damage. Given the reliance on the HPG axis for proper testicular function, perhaps an investigation into the HPG hormone levels should be considered a first step [12]. More research still needs to be done to help develop treatment for these men.

4. Discussion

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This narrative review explores the relationship between sleep deprivation and male infertility, focusing on its effects on the hypothalamic-pituitary-gonadal (HPG) axis, hypothalamic-pituitary-adrenal (HPA) axis, oxidative stress, and testicular function. Sleep deprivation is known to disrupt hormonal balance, elevate cortisol levels, increase reactive oxygen species (ROS), and compromise the blood-testis barrier (BTB), all of which contribute to reduced sperm quality and fertility. While existing studies have identified correlations between sleep disturbances and reproductive dysfunction, establishing causal relationships remains a challenge. Further research is needed to elucidate the underlying mechanisms and explore potential therapeutic interventions, such as antioxidants and lifestyle modifications.

Recent findings highlight that sleep deprivation can precede male infertility by adversely affecting key physiological systems. Disruptions in the HPG axis lead to fluctuations in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, as well as decreased testosterone production, contributing to hypogonadism, a significant factor in male infertility, with approximately 40% of males experiencing low testosterone levels when presenting with couple infertility. Chronic sleep deprivation also activates the HPA axis, increasing cortisol levels, which suppresses gonadotropin-releasing hormone (GnRH) secretion and further reduces testosterone production.

Oxidative stress plays a critical role in male infertility, with up to 80% of infertile men exhibiting elevated ROS levels. Environmental and lifestyle factors, including smoking, exposure to heavy metals, and excessive alcohol consumption, are well-documented contributors to increased ROS. Recent research suggests that sleep deprivation may also elevate ROS levels by diminishing antioxidant defenses, thereby compromising sperm quality. Additionally, sleep deprivation affects the BTB by reducing the expression of tight junction proteins, leading to increased permeability and impaired sperm viability and motility.

Despite these insights, the direct relationship between sleep deprivation and male infertility requires further investigation. Gaps remain in the exact mechanisms between the relationship of sleep deprivation and infertility. Longitudinal studies are necessary to establish causal links and understand whether sleep deprivation causes stress, which then leads to infertility, or if stress-induced sleep deprivation contributes to reproductive dysfunction. Developing a clearer understanding of this interplay could pave the way for strategies aimed at preserving male fertility rather than treating infertility.

In this article, the effect of sleep deprivation (shortened sleep duration) on infertility was explored, but the effects of sleep quality have been understudied. Performing studies where subjects undergo sleep fragmentation, decreasing their sleep quality, can be used to ascertain if an association with male infertility exists. This is prevalent in people who work night shifts, as they often have circadian misalignment and irregular sleep schedules. Studies focusing specifically on those who work atypical hours can see if other factors around sleep (sleep quality, irregular sleep schedules, time of sleep) have detrimental relationships with fertility. Research exploring the relationships of acute sleep loss, followed by acute sleep recovery, has shown to fluctuate and then recover reproductive hormone levels, but studies encompassing a longer time frame need to be performed to see if improved sleep can help recover reproductive hormone levels after chronic sleep deprivation. These studies can explore if recovering sleep patterns can reverse reproductive dysfunction or if there is a threshold where damage becomes permanent. By addressing modifiable factors like sleep quality, researchers and clinicians may identify effective interventions to mitigate the adverse effects of sleep deprivation on male reproductive health.

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