Chapter 5
Testosterone and Disordered Sleep

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5.1 Introduction

In the past few decades, our knowledge of the role that sleep exerts on many aspects of health has expanded significantly. Disordered sleep has been shown to negatively impact cardiometabolic health, diminish psychomotor performance, and affect multiple other physiological functions that are pertinent to men's health. Disordered sleep may be restricted or insufficient (decreased total sleep time), misaligned to the endogenous circadian rhythm (as may be seen in night shift workers), or disrupted (as occurs with nocturia or obstructive sleep apnea). Insufficient, misaligned, and disrupted sleep has distinct effects on sleep architecture. Since each sleep stage

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serves specific physiological functions, insufficient, misaligned, and disrupted sleep could differentially influence different aspects of andrological and metabolic health. Conceptualizing this requires an understanding of normal sleep architecture.

The adult human sleep cycle is 90–120 minutes in duration. Sleep cycles are divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Each stage of sleep can be recognized by characteristic electrophysiological features: specific waveforms and frequencies of brain activity on electroencephalogram (EEG), rolling or saccadic eye movements detected by electrooculogram, and skeletal muscle activity revealed by electromyography. NREM sleep contributes to 75–80% of total sleep time and is itself subdivided into three stages: N1, N2, and N3. N1 generally progresses to N3 as sleep deepens and waveform frequencies slow on the EEG. Stage 3 NREM sleep, also known as slow wave sleep (SWS), typically occurs during the first one-third of the night and is believed to be the most restorative type of sleep that underpins important metabolic processes, including restoring insulin sensitivity [1, 2]. During SWS, cerebral blood flow and metabolism are reduced. There is also increased secretion of growth hormone during SWS [1]. In contrast, REM sleep contributes to 20–25% of the total time spent in sleep, and REM cycles progressively lengthen as the night progresses [3]. REM sleep is required for memory consolidation and for sleep-related increase in systemic testosterone exposure [4].

Restricting sleep decreases total sleep time, but SWS tends to be maintained, so metabolic processes dependent on SWS such as insulin sensitivity may also be relatively preserved. Circadian misalignment of sleep may advance (initiating sleep earlier) or delay sleep (initiating sleep later). When sleep is advanced, SWS and REM are reduced. When sleep is delayed, N2 decreases, SWS is preserved, and REM sleep increases [5]. Disrupted sleep interrupts normal sleep architecture by interfering with the orderly progression of the sleep stages. Causes of disrupted sleep include environmental (e.g., light, noise, and bed partner movements) and pathologic (e.g., nocturia and OSA) factors. OSA may sometimes disrupt REM sleep in particular, when the collapsibility risk from reduced upper airway muscular tone is predominant. Accordingly, a reduction in systemic testosterone exposure with REM-associated OSA would be expected.

This chapter focuses on the effects of common causes of disordered sleep on andrological health, emphasizing well-established surrogates such as semen parameters for male fertility and circulating testosterone concentrations for hypogonadism.

5.2 Insufficient Sleep

It is recommended that adults aged 18–64 years sleep 8 hours per night on average, although the restorative amount of sleep ranges from 7 to 9 hours each night for any particular individual [6]. Despite these recommendations, over a third of American adults report insufficient sleep durations on a regular basis [7]. Some causes of

insufficient sleep include lifestyle and environmental factors, such as shift work, noise, prolonged working hours, and jet lag; other causes include sleep disorders such as insomnia and other medical conditions [3]. Insufficient sleep is linked to increased mortality, andrological and cardiovascular disease, and metabolic disorders including diabetes mellitus. Interventional studies investigating the effects of restricting sleep reveal worsened insulin resistance and increased blood pressure, especially nocturnal blood pressure [8].

5.2.1 Effect on Reproductive Health

Carefully conducted in-laboratory studies have shown that testosterone levels rise during sleep and disruption of the normal sleep architecture prevents this rise in testosterone [9]. Epidemiological studies have explored the relationship between sleep duration and testosterone. However, findings from epidemiological cohort studies have not been consistent. Some studies reveal lower testosterone levels with shorter durations of self-reported sleep, while other studies do not [8]. It may be that only sleep loss occurring during the second half of the night actually reduces testosterone levels [10]. This hypothesis, if correct, could explain the inconsistent findings from observational studies because the timing of sleep loss has not been considered. On the other hand, carefully controlled in-laboratory interventional studies have consistently shown that sleep restriction decreases testosterone [10–12], including a recent study showing for the first time that sleep restriction decreases testosterone levels in older men [13]. This novel finding raises the possibility that sleep loss accumulated over decades of life in older men may contribute to age-related hypoandrogenemia [14].

Epidemiological studies have also explored the relationship between sleep duration and male fertility. One study showed that in 1176 couples planning a pregnancy, male partners who self-reported sleeping <6 hour each night had lower conception rates [15]. However, it is difficult to know whether it was the male or the female partner's sleep that was actually responsible for reduced conception rates as bed partners may have similar sleeping patterns. Two studies of healthy young men found associations between sleep and semen parameters. One study of healthy, young Danish men showed that either low or high self-reported sleep quality was associated with lower sperm concentrations, lower total sperm count, and a decrease in the percent of sperm motility and morphologically normal spermatozoa, compared with those who reported mid-levels of sleep quality [16]. This study did not investigate sleep duration, and it is difficult to understand why both low- and high-quality sleep would be associated with poorer semen parameters. A second study in Chinese men, primarily military cadets, found that men who self-reported sleep durations of <6.5 hours or >9.0 hours had lower total sperm count and semen volume [17]. Sperm chromatin was less mature, but there was no significant effect on DNA fragmentation [18]. In a subset of these men who supplied semen samples 1 year later, a significant increase in total sperm count was observed in those who

shifted their sleep away from extreme durations toward a hypothesized ideal duration of 7–7.5 hours/night [17]. However, this study relied on self-reported sleep durations, the analysis appeared ad hoc, and the reasons for the improvement in sleep were not determined. In animal studies, male rats that underwent sleep deprivation for 96 continuous hours or partial sleep restriction (<6 hours/night) for 21 nights had lower sperm viability and elevated endothelial nitric oxide synthase expression compared to controls [19]. Another study also showed a decrease in sperm motility in rats that underwent 7 days of continuous sleep deprivation compared to controls [20]. A third study found a decrease in sperm count, motility and morphology, as well as decreased viability, in those rats that underwent 5 days of continuous sleep deprivation compared to controls [21]. The investigators also noted increased testicular gene expression of nuclear factor kappa beta (NF-κβ) and decreased nuclear factor-like 2 (Nrf2) expression. NF-κβ is involved in activating nitric oxide synthase, and Nrf2 is involved in regulating glutathione. Together, these findings suggest that sleep restriction affects semen quality, plausibly by increasing oxidative stress.

Two studies have also shown cross-sectional, inverse U-shaped relationships between sleep (quality or duration) and lower testicular volume in humans. In the aforementioned study of young Danish men, those who reported high (and low) levels of sleep quality had lower testicular size [16]. The other study using home actigraphy to objectively determine sleep onset and wake time, along with self-reported sleep duration and quality, showed an inverse U-shaped correlation only between sleep duration and testicular volume [22].

Longitudinal observational studies that examine the effects of sleep disturbances on changes in conception rates and testicular volumes have yet to be performed. To establish a direct relationship between sleep restriction and fertility rates, an interventional study might require sleep restriction for over 3 months, given that the spermatogenic cycle is 3 months in duration. Such an interventional study would be a major undertaking.

5.3 Misaligned Sleep

Every cell, tissue, and organ in the body contains a molecular clock. These peripheral clocks are synchronized by the master circadian pacemaker which lies in the suprachiasmatic nucleus (SCN) of the hypothalamus through hormonal (melatonin, and cortisol for metabolically active organs) and autonomic signals. The master circadian pacemaker is composed of specific neurons in the SCN that are coupled together through direct cell-to-cell connections. These neurons generate autonomous circadian rhythms which oscillate with a periodicity that is slightly greater than 24 hours. Accordingly, the master circadian pacemaker needs to be entrained to the environmental day/night cycle on a daily basis through external cues known as *zeitgebers* (“time-givers,” from German) to remain aligned with the environmental day. Unsurprisingly, the main *zeitgeber* is light, and SCN neurons receive direct

photic inputs from the retina for this purpose, which are distinct from the visual processing system [23, 24]. Other *zeitgebers* include personal and societal patterns of eating and physical activity.

Common causes of misaligned sleep include jetlag (fast trans-meridian travel) and certain work schedules (night and alternating shift work). Shift work in particular has been linked to multiple adverse health outcomes. Workers who sleep during the day are sleeping during the normal wake phase of their biological rhythms. They often also experience environmental factors such as light and noise at inappropriate times that further adversely impact the duration and quality of sleep and may also voluntarily wake up earlier to interact with family members, thus further curtailing the total sleep time. Shift work has been linked to lower performance and increased industrial incidents (e.g., Chernobyl nuclear disaster); cardiometabolic diseases such as diabetes mellitus, obesity, hypertension, and ischemic heart disease; as well as overall mortality [25]. These epidemiological studies cannot establish a definitive causal relationship between shift work and adverse health outcomes, however. On the other hand, interventional studies that misalign sleep under highly controlled laboratory conditions have demonstrated worsening of well-established markers of cardiometabolic health, such as insulin resistance and systemic blood pressure, thereby suggesting a causal link [8].

5.3.1 Effect on Reproductive Health

Epidemiological studies show that shift work in the male partner does not impair fertility if there is no actual sleep loss [26–28]. Several of these studies did find that male infertility was associated with higher levels of physical exertion and psychological stress but not with shift work [27]. Many of these studies were conducted in fertility clinics, and thus their participants may not be representative of the general population. Other epidemiological studies also did not find a significant difference in semen parameters with shift work [29, 30]. There are no randomized studies that investigate the relationship between misaligned sleep and semen parameters.

Epidemiological studies have also investigated the relationship between shift work and testosterone levels. However, these studies of clinic populations or of workplace employees may not be representative of the population as a whole. A study of men seen in an andrology clinic found that among men working nonstandard shifts, those who reported better sleep quality had fewer hypogonadal symptoms and superior sexual function. Blood testosterone levels were also measured in these men. However, over 40% of the men were receiving testosterone therapy or medications that alter systemic testosterone levels (such as clomiphene, anastrozole, or human chorionic gonadotropin) [31].

Other studies in the workplace investigated testosterone levels in the saliva or blood but did not measure samples over the entire day. One workplace study found no change in salivary testosterone levels in rotating shift workers examined during

a night shift schedule or during a recovery day shift schedule [32]. This study did not obtain salivary testosterone levels during sleep. A small study in junior physicians undergoing a rotating shift work schedule also found no change in testosterone levels when examined after a holiday, or after day shift and night shift conditions. Only one time point was assessed for each of the three conditions and the time of blood draw was not specified [33]. As testosterone levels vary widely during the day, a single time point will not provide a complete picture, especially if the time of awakening is unknown. Another small study found that the overall mean concentration of testosterone in shift workers was less than that of controls. However, blood draws occurred only during the night when the night shift workers were awake and the day shift worker controls were asleep [34]. Since testosterone rises during sleep, mean testosterone levels would be expected to be lower in the awake night shift workers compared with the asleep day shift workers, when only nighttime, not 24-hour, testosterone levels are assessed.

In fact, only one study has examined 24-hour testosterone exposure in the workplace. This study reported numerically higher 24-hour levels of urinary androgens and higher 24-hour levels of urinary testosterone in male night shift workers compared to male day shift workers. However, 24-hour urinary androgens and urinary testosterone were not statistically different between these day and night shift workers [35].

Whereas the prior studies were performed in a workplace setting, there is however one study that was conducted in a highly controlled laboratory environment. In this study, normal young men who were not selected on the basis of being habitual shift workers underwent a shift work schedule of nighttime wake or daytime wake in a balanced cross-over design in order to examine blood testosterone levels. No difference in 24-hour mean testosterone levels was observed, implying that the acute (1 day) shift in work schedule did not alter overall systemic testosterone concentrations. It did, however, find that testosterone levels rose with sleep and fell during wakefulness, irrespective of whether sleep occurred during the day or night [36].

In summary, there does not appear to be a significant change in mean testosterone levels with circadian misalignment due to shift work. However, this conclusion is based almost entirely on observational studies in actual shift workers. Most did not examine 24-hour testosterone exposure and were likely affected by sampling bias and other confounders. Furthermore, the single in-laboratory interventional study did not impose a realistic shift work schedule, nor was it designed to be able to fully separate changes in testosterone due to sleep from those due to circadian misalignment. Nevertheless, the diurnal rhythm of testosterone appears to be dependent upon sleep (regardless of whether it occurs during the day or night), and testosterone levels are therefore highest shortly after awakening. The Endocrine Society recommends measuring testosterone in the early morning on two separate occasions to assess for hypogonadism [37] and does not specify when testosterone should be measured in shift workers. Based on this review, testosterone should be measured soon after awakening, not necessarily in the early morning, in shift workers. This is to obtain blood levels that are most comparable with the standard testosterone reference range applied to non-shift workers.

5.4 Disrupted Sleep

Many medical conditions disrupt sleep. Perhaps the most common cause is obstructive sleep apnea (OSA). Nocturia, due to prostatic problems or diuretic use, is also a common cause. Other causes include poorly controlled asthma, heart failure, and gastroesophageal reflux disease. In OSA, recurring partial closure of the pharyngeal airway occurs during sleep leading to decreased airflow (hypopnea) or complete cessation of breath (apnea). This leads to hypercapnia and hypoxemia, causing the patient to arouse. OSA presents more commonly in men than in women and the prevalence of OSA increases with age. With the current obesity epidemic, it is estimated that 13% of men and 6% of women have moderate to severe sleep-disordered breathing [38]. OSA is treatable with the application of continuous positive airway pressure (CPAP) therapy. Epidemiological studies have shown that OSA increases the risk of all-cause mortality, type 2 diabetes mellitus, systemic hypertension, and coronary artery disease. Interventional trials have shown that effective CPAP improves cardiovascular parameters including blood pressure and ventricular ejection fraction and also decreases cardiac dysrhythmias. However, a clear decrease in cardiovascular mortality has not been evident [39]. Given the negative impact of sleep disruption on overall health, the underlying medical causes should be optimally treated.

5.4.1 Effects on Reproductive Health

There are no data from large-scale epidemiological studies linking OSA with male fertility. Interventional trials have demonstrated the relationship between OSA and erectile dysfunction, and most trials have shown improvement in erectile function and sexual satisfaction with treatment of OSA [8]. The only randomized sham-controlled trial reported that CPAP can improve erectile function but only if men are compliant with CPAP use [40]. No studies have been performed to examine the effects of OSA or reversal of CPAP on semen parameters or fertility in men. However, an animal study found that mice subjected to periodic hypoxia for 60 days had a decreased proportion of pregnant females per mating, decreased sperm motility, and increased markers of testicular oxidative stress [41].

Epidemiological studies link more severe OSA to lower testosterone levels, but it is not certain whether this relationship is or is not related to concomitant obesity [8]. Furthermore, many of the symptoms of OSA overlap with those of hypogonadism. The effects of OSA treatment on testosterone levels are also controversial. Although a recent meta-analysis concluded that CPAP does not increase systemic testosterone levels [42], this conclusion may not be warranted if only higher quality studies are examined. The authors recognized that only two of the studies included in the meta-analysis were randomized: one of these studies randomized between two different treatments of OSA and so was unable to capitalize on randomization to assess the effect of treatment of OSA alone [43]. Furthermore, combining studies that have

methodological or design flaws by meta-analysis does not overcome the original limitations. In contrast, when examining higher quality studies, the three most notable studies have each concluded that treatment of OSA increases testosterone. The first study is the only study utilizing a randomized sham-controlled design. It reported that those randomized to CPAP had greater increases in testosterone compared with those randomized to sham – but the difference between groups was due to a fall in testosterone in the sham group [44]. The second study is the only study that assessed testosterone exposure frequently over an extended period of time (every 20 minutes from 7 PM to 7 AM). A significant increase in testosterone after 9 months of CPAP was reported; however, only five highly CPAP-adherent men were studied [45]. Nevertheless, all other studies have assessed one or two time points, usually in the morning. The third study was the only study where near-complete reversal of sleep-disordered breathing was achieved [46]. This study reported an increase in morning testosterone levels after 3 months of therapy in 12 men, but the intervention was surgical uvulopalatopharyngoplasty, not CPAP. Accordingly, it may be that adherent CPAP therapy is needed to increase testosterone. However, large-scale studies are yet to be performed, and the overall data currently do not allow firm conclusions to be drawn.

5.4.2 Testosterone Replacement Therapy and Obstructive Sleep Apnea

Testosterone therapy is widely believed to induce or worsen sleep apnea, but the evidence that underpins this relationship is weak [37]. Nevertheless, two randomized controlled trials do show that testosterone therapy can acutely induce sleep-disordered breathing. One of the studies resulted in levels of testosterone that were definitely supraphysiological due to the dose administered [47] and the other likely induced supraphysiological peaks due to the drug pharmacokinetics of short ester-chain testosterone intramuscular injections [48]. Whether these adverse findings would occur with longer-term near-physiological testosterone replacement, as now occurs in clinical practice with modern testosterone formulations, is uncertain.

Two other randomized, placebo-controlled, parallel group studies have partly filled this gap in knowledge by investigating the effect of longer-term replacement dose and more steady-state testosterone therapy on sleep-disordered breathing [49, 50]. The first study administered a dose-titrated testosterone patch (n = 54) or a matching dose-titrated placebo patch (n = 54) to healthy men over the age of 65 for 3 years [49]. The initial dose was 6 mg/day, which was adjusted every 3 months to maintain blood testosterone levels below 1000 ng/dL. No significant difference between the two groups was detected after 6, 12, 24, or 36 months of therapy; however, sleep-disordered breathing was assessed at home with a relatively insensitive portable instrument which may not have detected the development of mild or moderate OSA. The second study is the only study to purposefully administer testosterone to men with known moderate to severe OSA. Obese men with OSA received three doses of testosterone undecanoate 1000 mg every 6 weeks (n = 33), or matching

placebo (n = 34), as well as a hypocaloric diet which caused weight loss that was comparable between the two groups [50]. The study reported that testosterone treatment significantly increased sleep-disordered breathing by a moderate amount (10 events/hour) at week 7 (1 week after the second injection of testosterone undecanoate), but not at week 18. Available studies suggest that sleep-disordered breathing occurs because testosterone affects ventilatory drive [51, 52]. A meta-analysis of 19 randomized controlled trials evaluating the effects of testosterone replacement therapy in hypogonadal men aged 45 and over on a range of outcomes did not find a significant difference in the incidence of OSA; however, only symptomatic severe OSA would have been reported since OSA was not systematically assessed by polysomnography so that effects on the apnea-hypopnea index (AHI) were not reported [53]. Overall, studies show some evidence that the initiation of testosterone therapy might induce or worsen OSA, but any effects are moderate in size and may not persist. Nevertheless, the Endocrine Society has made, for now, a prudent recommendation to avoid initiating testosterone therapy in those with untreated severe OSA [37].

5.5 Conclusion

Disordered sleep can be categorized as insufficient, misaligned, or disrupted. Epidemiological data have established a relationship between disordered sleep and increased mortality, cancer, cardiovascular disease, insulin resistance, and type 2 diabetes mellitus. This review shows that disordered sleep also affects andrological health: insufficient sleep decreases testosterone, whereas circadian misalignment due to shift work or simulated shift work schedule per se does not. Disrupted sleep due to obstructive sleep apnea is associated with lower systemic testosterone concentrations, although this may be due to concomitant adiposity. Preliminary data suggest the possibility that male fertility and semen parameters may also be impacted by sleep duration, but the impacts of circadian misalignment and/or disrupted sleep on fertility have not yet been studied comprehensively. In any case, sleep should be prioritized and valued to promote overall health, including andrological well-being. Methods to minimize deleterious effects of shift work and to promote CPAP adherence remain important research priorities.

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