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REVIEW

Sleep, immunity and inflammation in gastrointestinal disorders

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Abstract

Sleep disorders have become a global issue, and discovering their causes and consequences are the focus of many research endeavors. An estimated 70 million Americans suffer from some form of sleep disorder. Certain sleep disorders have been shown to cause neurocognitive impairment such as decreased cognitive ability, slower response times and performance detriments. Recent research suggests that individuals with sleep abnormalities are also at greater risk of serious adverse health, economic consequences, and most importantly increased all-cause mortality. Several research studies support the associations among sleep, immune function and inflammation. Here, we review the current research linking sleep, immune function, and gastrointestinal diseases and discuss the interdependent relationship between sleep and these gastrointestinal disorders. Different physiologic processes including immune system and inflammatory cytokines help regulate the sleep. The inflammatory cytokines such as tumor necrosis factor, interleukin-1 (IL-1), and IL-6 have been shown to be a significant contributor of sleep disturbances. On the other hand, sleep disturbances such as sleep deprivation have been shown to up regulate these inflammatory cytokines. Alterations in these cytokine levels have been demonstrated in certain gastrointestinal diseases such as inflammatory bowel disease, gastro-esophageal reflux, liver disorders and colorectal cancer. In turn, abnormal sleep brought on by these diseases is shown to contribute to the severity of these same gastrointestinal diseases. Knowledge of these relationships will allow gastroenterologists a great opportunity to enhance the care of their patients.

Key words: Sleep; Immune function; Immunity; Irritable bowel syndrome; Inflammatory bowel disease; Gastro-esophageal reflux disease; Liver disorders; Colon cancer; Circadian rhythm

Core tip: Sleep disorders have become a global issue, and discovering their causes and consequences are the focus of many research endeavors. Recent research suggests that individuals with sleep abnormalities are at greater risk of all-cause mortality and serious adverse health and economic consequences. Several studies support the associations among sleep, immune function and inflammation. We review the current research linking sleep, immune function, and gastrointestinal diseases and discuss the interdependent relationship between sleep, overall immune function with emphasis on inflammatory bowel disease, irritable bowel syndrome, gastro-esophageal reflux and colorectal cancer.

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INTRODUCTION

Research into sleep and its associated health abnormalities has had a relatively recent surge, and sleep quality has been shown in many investigations to be an important, if not essential element of good health[1-3]. Sleep disorders can be primary, secondary or behavioral. Primary disorders are related to neurologic defects like narcolepsy and restless leg syndrome, breathing problems like obstructive sleep apnea and central sleep apnea, or circadian rhythm abnormalities like jet lag and delayed sleep phase syndrome. Secondary sleep disorders are secondary to primary diseases such as depression, chronic illness *etc*. Behavioral sleep problems such as insomnia or insufficient sleep are caused or perpetuated by poor sleep hygiene.

Sleep disorders have become a global issue. Sleep abnormalities occur in 17%-22% Japanese[4,5], while sleep disorders are estimated to range from 7% to 50% in people living in Portugal and Finland[6-8]. In the United States, more than 70 million people suffer from a sleep disorder, and modern lifestyles have led to Americans sleeping approximately 2 h less per night than 100 years ago[4,7,9]. Abnormalities in the sleep cycle are linked with neurocognitive consequences ranging from performance decrements, slower response times, and decreased cognitive ability[10].

Receiving fewer hours of sleep may also impact metabolism in a manner that contributes to obesity[10]. A strong association has been found between disruption in sleep and gastrointestinal disease. We will review the interdependent relationship of sleep dysfunction and gastrointestinal issues including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), gastro-esophageal reflux disease (GERD), liver disorders and colon cancer. Sleep abnormalities have been shown to worsen symptoms of IBS, IBD and GERD which, in turn, can worsen sleep abnormalities. Sleep disorders and circadian dysfunction have also been shown to increase the risk of colon cancer.

HUMAN SLEEP

Sleep is classified based on polysomnographic data into two main categories known as rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM sleep is further divided into three stages based on increasing depths of sleep and increasing arousal thresholds. These sleep stages cycle through REM and NREM approximately every 90 min[11]. More time is spent in slow-wave delta sleep each cycle during the first half of the night, with increasing time in REM sleep in the later portions of the night. Humans spend around 25% of total sleep time in REM sleep[12]. The exact biological purpose of sleep is unknown. However, slow-wave sleep is thought to be restorative, restful sleep, and REM sleep is associated with dream recall and memory consolidation[13]. Although the ideal quantity of sleep is different among individuals, most studies recommend seven to eight hours a night for adults as an optimal amount of sleep[14]. Alterations in normal sleep patterns are thought to be a significant contributor to a vast array of illness including depression, metabolic syndrome, inflammation, gastrointestinal diseases, and also cancer[15,16].

REGULATION OF SLEEP

Sleep regulation is often described by a two process model[17]. Process S, or the sleep homeostatic drive, linearly increases the longer an individual stays awake[18]. Process C, or the circadian alerting drive, oscillates with body temperature on an approximate 24-h cycle[15,18]. During the later hours of the day, Process C enters its decline in the circadian pattern, and Process S has accumulated approximately 16 h of continuous wakefulness. The combination of declining alertness and a sufficient amount of prior wakefulness facilitates the onset of sleep[18]. Biological clocks have evolved based on a 24-h cycle that allow organisms to anticipate and physiologically adjust to daily environmental changes and this circadian system provides a temporal organization of waking and sleep[15,19]. The circadian clock is entrained or synchronized to the specific day-night cycle (phase) of the environment through signals such as light, meals, and social interaction. These affect neuro hormonal pathways which influence the circadian clock. Light is the most important factor affecting the circadian rhythm. Light travels from the retina *via* the retinohypothalamic pathway to the suprachiasmatic nucleus (SCN), and then *via* a multisynaptic pathway to the pineal gland where it suppresses melatonin production. Melatonin is a neurohormone that serves to synchronize circadian rhythms both with the environment and the human body as melatonin receptors are found in nearly all human tissue. Furthermore, the 24-h circadian rhythm is governed by a main circadian clock and a system of peripheral clocks located in multiple tissues including the pancreas, liver, and adipose tissue[20]. The SCN also serves as a "standard time" which synchronizes peripheral tissue clocks[21]. A series of "clock genes" help regulate the timing through both positive and negative feedback loops. CLOCK and Brain and Muscle Arnt-like protein (BMAL-1) form heterodimers that accumulate throughout the day. These heterodimers then bind to the promoter regions of the genes Period (PER) and Cryptochrome (CRY) to activate their transcription. PER and CRY proteins then accumulate and form heterodimers that inhibit transcription of CLOCK and BMAL-1 proteins[22]. Point mutations in these clock genes have been linked to altered circadian function and sleep abnormalities in mammals including familiar ad-

vanced sleep phase syndrome and delayed sleep phase syndrome[23-25].

Research has also focused on determining whether similar feedback-loop clock genes are present within the gastrointestinal tract. PER2 expression has been identified in the myenteric plexus and affects the rhythmic releases of acetylcholine and nitric oxide, ultimately regulating peristalsis[26,27]. Hypotheses on circadian rhythms affecting nutrient transport in the small intestine, gastric acid secretion, gut motility, and production of digestive enzymes have also been proposed[27].

IMMUNE ACTIVATION AND CYTOKINE EFFECTS ON SLEEP

Many immune and endocrine pathways exhibit a diurnal profile including cortisol and growth hormone. The onset of sleep corresponds with an increase in the serum levels of some cytokines, peaking at 2.5 h after sleep onset[28]. This surge of cytokines and their pro-inflammatory effects are suggested to be linked with nocturnal exacerbations of diseases like asthma and rheumatoid arthritis[11]. Increasing evidence supports a reciprocal relationship between sleep and the immune system. An activated immune system alters sleep and sleep abnormalities affect immune function[29,30]. Studies have also shown that an immune response elicits a pro-inflammatory cytokine response that helps to modulate sleep[22]. This was first illustrated in the 1970s[31] after the identification of a sleep-inducing muramyl peptide known as factor S was found to have both immune and sleep regulatory properties[18,32]. Although the diverse range of cytokines released in early inflammation limits our ability to isolate individual contributions[33], tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), and IL-6 have shown the strongest potential[30]. However, numerous other cytokines with at least partial sleep regulatory properties have been identified. In animal models, IL-1 and TNF-α elevations have correlated with increased time in NREM sleep. Furthermore, an inhibitory effect on both spontaneous sleep and sleep rebound (increased REM sleep after sleep deprivation) was produced when IL-1 was inhibited by anti-IL-1 specific antibodies[34]. In addition, high serum levels of TNF-α has been linked to sleepiness in patients with obstructive sleep apnea and rheumatoid arthritis[35,36]. IL-6 also plays a role in sleep modulation. Sleep deprivation can increase IL-6 levels leading to daytime fatigue[37]. In a human study, subjects received an injection of IL-6 that simulated the levels found in infection, and they experienced marked subjective fatigue, inhibition of REM sleep, and elevated CRP in 6.5 h[33]. The inhibition of REM and the promotion of NREM sleep appear to play key roles in the immune response. IL-1, IL-6 and TNF-α are at high levels at time of infection and correlated with increased duration of NREM, changes in core body temperatures, more shivering, and an overall greater capacity to fight off illness[32]. This was confirmed in several studies evaluating the effect of infection with human immunodeficiency virus (HIV) on sleep. In early stages of HIV infection, polysomnographic data showed larger percentage of time spent in NREM than in REM and prolonged REM sleep latency[18,38]. Serotonin also is an integral component to IL-1 activity. Depletion of serotonin or inhibition of the serotonin receptor led to a reduction in the IL-1-induced increase in the amount of NREM sleep[39,40]. Thus, there appears to be an interaction of IL-1 and its ability to modulate sleep based on baseline levels of serotonin. Infection caused by viral, bacterial, fungal or even parasites was evidenced to increase the amount of time spent in NREMS and decrease the amount of time spent in REMS[41] based on severity of infection[12].

SLEEP EFFECTS ON THE IMMUNE RESPONSE

Both human and animal studies have shown that sleep has an overall protective role and that sleep deprivation is associated with an increased susceptibility to infection[18,22]. A study on infected rabbits showed that animals who had longer periods of sleep had less morbidity and mortality[42]. In humans, long-term sleep deprivation was shown to increase risk of septicemia[43,44]. Furthermore, decreased sleep has been linked to impaired antibody response to hepatitis A vaccine[29], influenza[45], and increased risk of getting a upper respiratory infection[46]. The timing of sleep is also important because most immune cells have their highest response to immune challenges during the night[12,18] and their lowest response in the morning[45]. This antibody impairment is very similar to the decrease in the immune response seen with human aging as both have a lowered T-cell response to antigens and impaired response to vaccinations[47].

GASTROESOPHAGEAL REFLUX DISEASE AND SLEEP

It is well established that gastroesophageal reflux and its most common symptoms, heartburn and regurgitation, is among the most frequently dealt with conditions encountered by gastroenterologists[48].

Approximately, 10%-20% of the people in the United States have GERD[49]. One study found that approximately 74% of patients with GERD had nocturnal symptoms[50]. A Gallup survey revealed that approximately 63% of the people with nocturnal GERD felt it impaired their ability to sleep and 40% felt it impaired their ability the following day[51]. Several factors likely contribute to nocturnal GERD. Numerous studies now have documented that reflux during sleep presents physiologic issues not encountered during the waking state. For example there is a notable prolongation of acid clearance due to the suppression of swallowing and salivation during sleep. This results in enhanced back diffusion of hydrogen ions and subsequent mucosal damage.

These issues are discussed in detail in a review by Orr *et al*[51] in which he presents an argument for considering nighttime reflux and its clinical manifestations as a distinct clinical entity[52]. However, sleep and GERD have been shown to have a more interdependent relationship. A study by Dickman *et al*[52] noted that poor quality of sleep led to exacerbations of reflux the following day. They also found that longer durations of reflux events correlated with reduced sleep quality. This was supported by the Gallup survey, a higher frequency of reflux was associated with higher frequency of sleep difficulties[51]. A likely contributing factor is the hyperalgesia due to sleep disturbances[54,55]. This was first reported by Onen *et al*[53] who found that sleep deprivation led to a somatic hyperalgesia. This hyperalgesia was evidenced after loss of REM sleep or cumulative 2 d loss of non-REM sleep[54]. Recently, Schey *et al*[54] have documented a visceral hyperalgesia and increased sensitivity to reflux in GERD patients with documented poor sleep prior to undergoing an acid perfusion test[55]. Further research in this area is needed, but current studies indicate that discussion and treatment of sleep abnormalities in patients with GERD may lead to improved management.

PEPTIC ULCER DISEASE

Patients with sleep apnea sustain cessation of breath during sleep, leading to intermittent hypoxia, systemic inflammation and sympathetic activation. These insults are not only be a threat to cardiovascular system but can also contribute to damage to the gastrointestinal mucosa and hence initiation or progression of peptic ulcers[56]. In a very large study of nearly 35000 patients from Taiwan, patients with sleep apnea experienced 2.4 fold higher risk for peptic ulcer bleeding[56]. This may warrant surveying for sleep apnea as a potential predisposing factor in patients with peptic ulcer bleeding and without any apparent risk factors.

INFLAMMATORY BOWEL DISEASE AND SLEEP

IBD is characterized by a chronic immune mediated inflammation of the gastrointestinal tract. It is estimated that approximately 400/100000 Americans suffer from IBD[57]. The relationship between sleep and IBD has been a topic of more recent consideration. Ranjbaran *et al*[57] used the Pittsburgh Sleep Quality Index (PSQI) to show a relationship with sleep abnormalities and the quality of life in patients with IBD. They noted several sleep-related issues: more sleep latency, less day time energy, and increased sleeping pill use[57].

Abnormal sleeping habits may also play a role on disease severity. One study noted both worsened severity of UC and higher mortality in phase-shifted mice than in unaltered circadian-phase mice[59]. They noted that chronic circadian phase shifts led to worsening mucosal inflammation and colitis likely secondary to altered inflammatory cascade regulation[59]. Another study found that occupations that have artificial working conditions (such as light) and irregular hours had higher odds ratio (1.6-1.7) for development for IBD[60,61].

Patients with Crohn's disease (CD) and sleep loss may also have a greater risk for disease relapse. These patients had twice the risk of active disease in 6 mo than patients who did not have sleep abnormalities[62]. In fact, Tang *et al*[62] performed a study examining sleep deprivation on mice with colitis and noted both acute and chronic sleep deprivation led to worsening colitis likely secondary to heightened sensitivity to pro-inflammatory cytokines such as IL-6 and TNF-α[9,30,61,63]. A large survey study looking at sleep disturbances in over 3100 participants found that CD patients in clinical remission and subjective sleep disturbances had a 2-fold increased risk of active disease at 6 mo. They discovered approximately 75% of patients with active disease have subjective sleep complaints compared to 48% inactive disease[62].

Recently, we performed a prospective observational cohort study looking at the sleep disturbances of IBD patients. We discovered that 100% of patients with active disease had poor sleep while only 72% of patients with clinically inactive disease had poor sleep. The difference between sleep disturbances became even higher when histology was used to define the disease activity. We found 100% of those in histologically active group had poor sleep while only 54% in the histologically inactive group had poor sleep (OR = 6.0, 95%CI: 2.9-12.5, $P < 0.0001$). An abnormal PSQI had a positive predictive value for histologic inflammatory activity of 83%[64]. These patients were prospectively followed for 6 mo, and the relapse rate in clinically inactive patients with poor sleep was found to be 67%. No patients with normal sleep patterns relapsed (RR = 3, 95%CI: 1.5-6.1, $P = 0.03$). We detected a significant correlation between the baseline PSQI and disease activity at the 6-mo follow up (CD: $r = 0.56$, $P = 0.0046$; UC: $r = 0.54$, $P = 0.024$)[65]. Although the study was limited by the small number of patients, the results are intriguing and hold very important therapeutic implication in the management of immune-mediated inflammatory diseases.

Melatonin has recently been investigated as a possible method of improving outcomes for patients with UC Data from several animal models indicate that melatonin administration increased serum levels of IL-10 (an anti-inflammatory cytokine) and decreased serum levels of pro-inflammatory cytokines such as IL-6 and TNF-α[66-69]. Patients with UC had abnormally high levels of pro-inflammatory cytokines, and melatonin may play a role in reducing the severity of UC by reducing these specific cytokines[69-73].

IRRITABLE BOWEL SYNDROME AND SLEEP

IBS is a chronic gastrointestinal syndrome that is associated with abdominal pain and distorted bowel behavior.

IBS is commonly diagnosed and there is an estimated 10%-15% of the North American population suffering from this syndrome[74]. IBS appears to have a significant association with anxiety, stress, and overall environment. Interestingly, sleep dysfunction also has similar associations. The study conducted by Kim *et al*[74] examined IBS occurrence among irregular-shift workers and traditional day-shift workers. They found that the prevalence of IBS in irregular-shift workers was significantly higher (32.7%) than in the day-shift workers (16.7%). They also found that many of the individuals that worked irregular shifts experienced less sleep quality, higher rates of daytime sleepiness, and higher levels of stress[75]. Chen *et al*[75] compared sleep patterns and rectal sensitivity using anorectal manometry among patients with IBS and healthy subjects. They noted that IBS patients with lower amounts of quality sleep were prone to lower thresholds for rectal sensitivity and altered anal sphincter function[76]. This rectal hyperalgesia in patients with sleep abnormalities and IBS is consistent with the visceral hyperalgesia noted in patients with sleep abnormalities and GERD[55].

COLON CANCER AND SLEEP

Colorectal cancer is the second most commonly diagnosed cancer in the world in women and the third most common in men[77]. Surgery is often the primary method of intervention while adjuvant chemotherapy and radiation therapy are often employed to improve survival or quality of life[78-80]. Several surveys noted that fatigue was one of the highest concerns for people with cancer[78,81,82].

Animal studies indicate that both circadian disruption by nocturnal light exposure or sleep deprivation accelerated tumor formation[83-85]. A recent study by Thompson and colleagues evaluated sleep and colon cancer and noted that shorter duration of sleep (< 6 h) led to an almost 50% increase in the risk for colorectal adenomas[86]. Shift work, abnormal clock gene expression, and other causes of disruption of circadian rhythms are emerging as cancer risk factors[83,87]. A study by Schernhammer *et al*[87] found an increased risk for colon cancer in women who worked night shifts[88]. Several theories have been proposed to explain the relationship between sleep and colon cancer. Increased obesity is a known risk factor for cancer[89]. Sleep disorders are also known to alter metabolism and contribute to obesity[10]. Sleep disturbance may play an indirect role in increasing the risk for cancer by increasing adiposity[90]. Another theory suggests melatonin and its anti-carcinogenic properties are a key factor. Nocturnal light exposure suppresses melatonin production, and the lack of melatonin and its anti-proliferative effects may contribute to intestinal cancer formation[88,91]. Open discussion, evaluation, and treatment of lower-than-normal duration of sleep may be an under-appreciated method of colorectal cancer risk modification.

SLEEP DYSFUNCTION AND THE LIVER

Sleep disturbances are seen in numerous types of liver diseases. One study found 47.7% of cirrhotic patients had unsatisfactory sleep when compared to 4.5% seen in controls[92]. Elevated levels of ammonia seen in hepatic encephalopathy is also evidenced to induce sleep wake cycle reversal and progressive electroencephalography changes with triphasic wave changes in Stage I hepatic encephalopathy and eventually delta waves and comatose state in Stage IV[93]. Another study found that women with primary biliary cirrhosis slept nearly twice as much during the day when compared to controls[94]. Although the exact mechanism behind this is known, it is thought that elevated IL-6 plays a role[95]. Patients with hepatitis C also are at higher risk for sleep abnormalities with 60%-65% reporting abnormal sleep complaints[96]. In addition, patients undergoing treatment with interferon-a are also at increased risk for sleep abnormalities as 22%-24% of patients experience sleep disturbance as a side effect[97].

Summa *et al*[97] study on mice found that circadian disorganization *via* Clock$^{\Delta 19/\Delta 19}$ mutation led to elevated liver/body weight ratios and advanced alcohol induced steatohepatitis[98]. The etiology behind this connection is thought to rely on abnormal intestinal epithelial permeability. Ideally, the intestinal epithelial barrier serves to protect the body from unwanted luminal contents while also allowing a fraction of permeability to allow immune surveillance and regulation[99]. Summa *et al*[97] followed the absorption of sugars in the gastrointestinal tract in phase shifted mice and found increased permeability in the colon when compared to control. This evidence indicates that circadian dysfunction may be a separate risk factor for alcohol induced liver damage[98].

Patients with sleep apnea sustain cessation of breath during sleep, leading to intermittent hypoxia, systemic inflammation, and sympathetic activation. These insults may contribute to initiation or progression of peptic ulcers[56]. In a very large study of nearly 35000 patients from Taiwan, patients with sleep apnea experienced 2.4 fold higher risk for peptic ulcer bleeding[56].

TREATMENT IMPLICATIONS

As the complexities regarding the association between sleep and gastrointestinal disorders continue to become better understood, it begs the question as to how the medical and psychiatric community should address comorbid sleep and gastrointestinal disorders. Though current clinical trials have not directly addressed this population, several small preliminary trials have investigated the efficacy of cognitive behavioral therapy for insomnia in patients with comorbid chronic pain[100-103]. Collectively, these studies suggest that insomnia can be effectively treated among patients with chronic pain and that improvement in sleep confers some clinical improvement in pain. Therefore, given the state of the current science, it seems prudent that medical providers would recommend the evaluation and treatment of sleep disorders in patients with gastrointestinal disorders. Treating both disorders in parallel may not only result in a better outcome

for the patient, but also allow the medical provider to use less invasive and expensive means to improve the patient's overall quality of life.

CONCLUSION

Sleep abnormalities are a global issue and its effects on well-known pathologies is both an interesting and relevant field of research. Sleep abnormalities contribute to many gastrointestinal diseases and conversely, gastrointestinal diseases often lead to sleep abnormalities. This interdependent relationship represents a novel approach to treating GERD, IBS, IBD, liver disorders and colon cancer. The evaluation, discussion, and treatment of sleep abnormalities may play a key role in further preventing and improving many gastrointestinal disorders.

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