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Mini-Review

Sleep Disorders in Inflammatory Bowel Disease - A Mini-Review

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Abstract

Inflammatory bowel diseases, consisting of Crohn's Disease, Ulcerative Colitis, and IBD unclassified are chronic autoimmune conditions characterized by gastrointestinal inflammation that also can affect other organ systems. When evaluating patients with inflammatory bowel disease, screening for extra-intestinal manifestations is essential. An underappreciated extra-intestinal manifestation of inflammatory bowel disease is sleep disturbance. The purpose of this review is to summarize the existing and evolving literature linking inflammatory bowel disease with sleep disorders. Sleep Disorders in inflammatory bowel disease may stem from the disease process itself, the symptoms of the disease, or side effects of treatments. For example, disordered sleep may be secondary to pain, bowel changes, concomitant mood disorders, or to glucocorticoid use. We will also investigate how the disease process may affect sleep directly. When in the state of an active flare of inflammatory bowel disease, patients have increased difficulties with sleep, particularly in Crohn's disease. Further research may lead to advances in therapeutic options for sleep disorders in this patient population.

ABBREVIATIONS

IBD: Irritable Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; CCFA: Crohn's And Colitis Foundation Of America Partners Study; PROMIS: Patient Reported Outcomes Measurement Informations Systems; SCDAI: Short Crohn's Disease Activity Index; SCCAI: Simple Clinical Colitis Activity Index; PSQI: Pittsburgh Sleep Quality Index

INTRODUCTION

Inflammatory Bowel Disease (IBD), consisting of Crohn's Disease (CD), Ulcerative Colitis (UC), and IBD unclassified (IBDU), is a chronic autoimmune condition primarily affecting the gastrointestinal tract, but may also consist of Extra-Intestinal Manifestations (EIM). It is imperative that clinicians screen for EIMs of IBD such as sleep disorders. Sleep disorders can be a manifestation of IBD and have become a recent point of research interest. Sleep is a complex process by which environmental and biologic factors work together. It is known that active inflammation is associated with increased somnolence and sleep dysregulation [1]. The inflammatory state is a protective mechanism to aid in the body's defense against infection by upregulating various cytokines and immune cells. IBD is characterized by immune dysregulation leading to cytokine and immune cell activation, inflammation of the GI mucosa, and alteration of sleep patterns. Here we will review the available data linking IBD disease activity with fatigue and sleep disturbances.

Inflammatory State and Sleep

The vagus nerve serves as a connection between the CNS and the enteric nervous system. Gut bacteria have been found to send signals to the brain via the vagus nerve. Neurotransmitters and inflammatory signals from the gut are also transmitted to the brain via the vagus nerve which plays a role in sleep regulation [2]. During an active inflammatory state, there is an anti-infectious response initiated by antimicrobial peptides and cytokines when immune cells are activated. Pro-inflammatory cytokines orchestrate an immune response by increasing production of acute phase proteins, enhancing phagocytosis, and other mechanisms [3].

Acute phase reactions have been shown to cause changes to sleep. One study showed significant changes to rabbits' sleep patterns when injected with Staphylococcus to induce bacteremia. The results showed that there was an increase in the time spent in slow-wave sleep. This exemplifies a correlation between active infections and sleep disorders, a correlation thought to be from certain cytokines affecting sleep regulation directly [4]. IL-1β, a

pro-inflammatory cytokine, was shown to be a potent somnogen and a potent pyrogen. Other acute phase reactants that have been associated with sleepiness include TNF-alpha and IL-6 [1]. Elevated CRP and IL-6 levels have been found in those who are sleep deprived [5]. The above discussion shows a biological plausibility to the connection of IBD and sleep disorders. We will now summarize the existing clinical literature linking IBD with sleep disorders.

One study observed 131 subjects with IBD and evaluated the relationship between inflammatory marker elevation and disordered sleep. 19% of these subjects had elevated CRP levels, and this was associated with poor sleep [6]. Another study attempted to make a connection between cytokine levels and sleep quality. It measured patient's disease activity by using the Crohn's Disease Activity Index (CDAI) for CD and Partial Mayo Score for UC. For sleep quality, patients responded to a sleep questionnaire called the Pittsburgh Sleep Quality Index (PSQI). Labs were drawn on all patients to evaluate inflammatory cytokines. The study of 52 patients with IBD concluded that poor sleep was associated with active disease (Table 1). Patients with poor sleep had higher levels of IL-6, IL-17, and IL-23, all cytokines associated with active IBD [7].

In one review, chronic fatigue and risk of disease relapse were increased in patients with IBD who exhibited sleep disturbances. Depressive symptoms and active disease were the biggest risk factors for sleep disturbance in patients with IBD. Patients with active disease had longer sleep latency and more nighttime awakenings. They also had found from review of a cohort study, patients who had sleep disturbances were more likely to have disease flare than quiescent disease when it came to Crohn's disease, but not with UC [8]. One case control study not only found higher PSQI scores in patients with IBD (indicating poorer sleep quality), but also found statistically significant higher scores on the Hospital Anxiety and Depression Scale (HADS) questionnaires, indicating higher levels of depression and anxiety in patients with IBD when compared to control subjects [9]. A cohort analysis consisting of 489,050 participants revealed that an increased risk of IBD was associated with shorter sleep duration. They also concluded that there was a positive association between IBD and daytime napping [5]. Swanson, et al. used wrist actigraphy to evaluate rest-activity cycles in patients with IBD compared to control subjects. They found disruptions of rest-activity were associated with pro-inflammatory changes [10].

Another large cohort study evaluated 3173 patients with IBD, and 1798 of these patients were in clinical remission. The patients filled out a baseline survey regarding their IBD and demographics. After six months, they were able to complete another survey which questioned their disease activity, changes in treatment, and patient-reported outcomes. Sleep disturbance was measured using the National Institute of Health Patient Reported Outcomes Measurement Informations Systems (PROMIS). Patients were also asked 4 questions regarding their sleep quality which were scored on a 5-point Likert scale. Disease activity was measured using the Short Crohn's Disease Activity Index (SCDAI) or the Simple Clinical Colitis Activity Index (SCCAI). The study found that an increased risk of disease flare in CD was associated with sleep disturbances, however, there was no link in regard to UC [11]. One systematic review found that 72% of patients with active IBD experienced fatigue, while 47% of patients with disease in remission reported fatigue. These findings suggest that disease activity may not be the only factor in reporting fatigue [12]. There was a cohort study that evaluated patients with IBD (n = 133) and healthy controls (n = 57) and looked at what factors contribute to sleep derangements. They completed multiple sleep questionnaires (PSQI, AIS, and ESS).

Table 1: Key studies and findings that were referenced throughout this article.

Study	Sample Size	Key Finding(s)
Yuan et al.; 2023	N = 489,050	An increased risk of IBD is associated with short sleep duration and daytime napping
Wilson et al.; 2015	N = 131	Poor sleep quality is associated with elevated levels of CRP in patients with IBD
Sobolewska-Włodarczyk et al.; 2021	N = 52	Poor sleep is associated with active IBD. Increased serum levels of IL-6, IL-17, and IL-23 were noted in these patients
Gîlcă-Blanariu et al.; 2020	N = 176	Higher PSQI and HADS scores in patients with IBD when compared to controls
Swanson et al.; 2022	N = 52	Wrist actigraphy revealed disruptions in rest-activity cycles in patients whose IBD history was deemed more aggressive
Ananthakrishnan et al.; 2013	N = 3,173	An increased risk of disease flare was associated with sleep disturbances in CD, but not UC
Sochal et al.; 2020	N = 190	Patients with IBD when compared to healthy controls scored higher in three separate sleep questionnaires (PSQI, AIS, ESS) indicated poorer sleep quality in those with IBD
Wang et al.; 2022	N = 103	PSQI was administered to patients with IBD and the study revealed that there is a correlation with disease symptoms and sleep quality. CD recurrence was twice as high in those with disordered sleep than their counterparts with normal sleep
Bucci et al.; 2018	N = 94	Sleep bruxism was more common in patients with CD when compared to UC and controls
Hoffman et al.; 2022	N = 40,970,420	Obstructive sleep apnea is independently associated with IBD
Lee et al.; 2023	N = 147	Higher levels of fatigue are associated with greater disease activity while treatment with biologics result in decreased levels of fatigue
Borren et al.; 2020	N = 326	Biologic therapy and/or control of the patient's disease may improve symptoms of fatigue, however, many patients still report ongoing fatigue after one year of biologic therapy
Hashash et al.; 2022	N = 50	When patients with CD are treated with behavioral therapy, there are improvements in their sleep quality and fatigue
Marinelli et al.; 2020	N = 166	55.4% of patients with IBD who experience poor sleep quality also experienced poorer quality of life
Zhang et al.; 2022	N = 14,696	Individuals who have IBD were found to have shorter sleep duration

Higher scores were obtained in all three sleep questionnaires in people with IBD when compared to healthy control subjects [13]. Wang D, et al. administered the PSQI to patients with IBD and established that disease symptoms were correlated with sleep quality. Interestingly, they identified that CD recurrence was twice as high in those with disordered sleep than their counterparts with normal sleep [14]. A meta-analysis was conducted that revealed patients with inactive IBD still had poorer sleep quality when compared to healthy controls. There may be many reasons for this, however, underlying inflammation may play a role in the disordered sleep seen even in inactive IBD [15]. A smaller cohort study evaluated 47 patients with IBD compared with 47 control subjects and wished to evaluate the relationship of sleep bruxism in patients with IBD when compared to controls. Sleep bruxism was evaluated by administering a four question yes-or-no questionnaire to patients. Sleep bruxism was more common in patients with CD when compared to UC and controls [16]. Another disease that was independently associated with IBD was Obstructive Sleep Apnea (OSA). One potential reason for this association is increased levels of inflammatory cytokines that result in systemic inflammation [17]. Other factors that may contribute to poor sleep in patients with IBD include diarrhea, abdominal pain, joint disease, and psychiatric factors such as depression [18].

A study consisting of 147 patients with IBD evaluated the relationship between disease activity and fatigue. They found that higher levels of fatigue were associated with greater disease activity while treatment with biologics resulted in decreased levels of fatigue [19]. One study attempted to evaluate how treatment affected levels of fatigue. This study looked at 326 patients that were initiating biologic therapy for IBD and evaluated their level of fatigue at baseline versus at one year of being on biologic therapy. 61% of IBD patients reported fatigue at baseline when starting biologic therapy. As time progressed, fewer patients reported fatigue. However, 61% of the patients with baseline fatigue reported persistent fatigue at week 54. In the patients who achieved clinical remission, 28% of patients still reported fatigue at week 54. This suggests that biologic therapy and/or control of the patient's disease may improve symptoms of fatigue, but this symptom may persist in many patients despite adequate control of luminal inflammation [20]. To explore further therapeutic options, one study investigated the outcomes of patients with Crohn's disease who were treated with either behavioral interventions or behavioral interventions plus bupropion. The results revealed improvements in sleep quality and fatigue when patients were treated with behavioral therapy. Treatment with bupropion was found to further improveme fatigue but was not statistically significant when compared to behavioral therapy alone [21]. A cross-sectional study found that 55.4% of subjects with poor sleep quality also experienced poorer quality of life, leaving an opportunity open for gastroenterologists to work closely with mental health professionals to provide optimal care to this patient population [22].

CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

The existing literature demonstrates clearly that sleep disorders are related to inflammatory bowel diseases. Patients with IBD were found to have shorter sleep duration [23]. There is a complex relationship between inflammatory markers, cytokines, symptoms, and quality of sleep. Limitations include the subjective reporting of fatigue and many studies used questionnaires. Questionnaire answers depend on patients' memory and recall which may also affect results. Disordered sleep may be impacted by the disease process itself, the use of glucocorticoids or other medications, poor sleep hygiene, or a myriad of other factors. In patients with IBD, the most common reported risk factors for fatigue included sleep disturbance, anxiety, depression, and anemia [12]. Further studies are needed to directly observe sleep patterns in patients with inflammatory bowel disease. These studies may help guide treatment recommendations to improve both patients' quality of sleep and their IBD.

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