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The Relationship between Sleep Disorders and Inflammatory Bowel Disease Activity and the Progress in Treatment

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Abstract: *Inflammatory bowel disease (IBD) is a chronic, nonspecific inflammatory condition of the intestines. Its varying degrees of symptoms significantly impact patients' quality of life. Sleep disorders are prevalent among IBD patients. This review will explore the relationship between sleep disorders and inflammatory bowel disease by examining assessment tools for sleep disorders, mechanisms influencing disease activity, and current treatment advances.*

Keywords: *Inflammatory Bowel Disease, Sleep Disorders, Treatment*

1. Introduction

Inflammatory bowel disease (IBD) is a chronic and nonspecific intestinal inflammation encompassing two main forms: Crohn's disease and ulcerative colitis. Affected individuals commonly experience persistent or recurrent symptoms like abdominal pain, altered bowel habits with blood or mucus, and tenesmus. The variability and persistence of these symptoms markedly diminish patients' quality of life. Sleep disturbances are prevalent among IBD patients, with over half reporting poor sleep quality [1]. This review assesses how sleep disruptions correlate with IBD activity, with the goal of deepening clinical knowledge and fostering interventions that improve patient quality of life.

2. Sleep Disorders in IBD Patients

The causes of sleep disorders in patients with inflammatory bowel disease (IBD) remain poorly understood[2]. While IBD sleep research has examined individual-level factors affecting sleep health (e.g., age), information on social determinants contributing to sleep health is lacking[3]. Sleep apnea, insomnia, restless legs syndrome, and nightmares are among the sleep disorders frequently associated with IBD. Research evaluating these conditions, in conjunction with mood disturbances and health-related quality of life (HRQoL), indicates that interventions targeting sleep apnea and insomnia can lead to meaningful improvements in overall well-being[4].

Research has observed that in individuals with IBD, poorer sleep metrics, lower life quality, and higher levels of depression and anxiety correlate with disease flares, whereas these associations appear unrelated to dietary patterns[5,6]. Patients exhibiting active symptoms of inflammatory bowel disease (IBD) demonstrate a higher propensity for experiencing impaired sleep and clinical insomnia. Interestingly, while specific IBD-related nocturnal disturbances, such as awakenings caused by bowel urgency, do not show a strong link to overall sleep quality ratings, they are significantly associated with greater severity of insomnia symptoms[7]. IBD patients exhibit distinct sleep patterns compared to healthy individuals, characterized by increased sleep fragmentation[8]. Patients who have objective confirmation of active IBD exhibit alterations in sleep architecture, including a reduction in Stage 2 and overall NREM sleep duration, resulting in decreased total sleep time. They also demonstrate prolonged sleep onset latency, which contributes to lower sleep efficiency. Furthermore, higher depression scores in these individuals are correlated with both the extended latency and the shortened Stage 2 sleep, underscoring a link between mood, sleep disturbances, and objectively measured disease activity[9].

Currently, commonly used assessment tools for patients with inflammatory bowel disease (IBD) and sleep disorders are primarily questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), Athens

ISSN 2616-5791 Vol. 6, Issue 9: 34-41, DOI: 10.25236/AJMHS.2025.060906

Insomnia Scale (AIS), Epworth Sleepiness Scale (ESS), and Insomnia Severity Index (ISI).

3. Mechanisms of Sleep Disorders Contributing to Disease Activity

Circadian disruption in rest-activity patterns was linked to a more severe progression of inflammatory bowel disease (IBD), along with heightened gut permeability, raised fecal calprotectin levels, increased pro-inflammatory cytokine activity, and altered gut microbiota composition[10].

3.1 Circadian Rhythm Alterations

The suprachiasmatic nucleus (SCN) in the hypothalamus, together with peripheral clock genes present in somatic cells, serves as the central regulator of circadian rhythms. These rhythms are instrumental in modulating a wide array of physiological processes, including immune function, gut barrier integrity, microbial community structure in the intestine, and the translocation of bacterial components. Core circadian genes involved in this process include the circadian rhythm output genes CLOCK and BMAL1, as well as the transcription repressor genes PER1, PER2, CRY1, and CRY2. Research indicates that sleep disruption leads to weight loss and increased risk of inflammation. In active IBD patients, mRNA levels of circadian genes Bmal1, Cry1, Cry2, and Rev-erbα were significantly reduced in inflamed tissue compared to non-inflamed tissue[11]. A prospective cohort study demonstrated a positive correlation between short sleep duration and daytime napping with IBD risk[12]. Poor sleep quality increases abdominal pain and fatigue scores the following day[13]. The gut microbial metabolite urinary stonein A (UA) has been shown to counteract inflammation-induced dysregulation of circadian clock genes (BMAL1, PER2) and tight junction components (OCLN, TJP1, CLDN1). Specifically, UA modulates the rhythmicity of BMAL1 and PER2 in intestinal epithelial cells by engaging the Nrf2-SIRT1 signaling axis. Within the DSS-induced colitis model, the intervention yielded positive outcomes in key measures: fecal IgA levels were elevated; expression of tight junction genes (Clnd1 and Clnd4) was enhanced; and the circadian oscillations of Bmal1 and Per2 were ameliorated.Thus, UA has the potential to treat sleep-related disorders such as IBD by improving the intestinal barrier and restoring disrupted circadian rhythms in the SCN[14].

3.2 Gut Microbiota

Disruption of circadian genes affects the composition of the gut microbiota, potentially leading to dysbiosis. Gut biopsies and peripheral blood mononuclear cells (PBMCs) from IBD patients show reduced expression of nearly all circadian genes, including MAL1, CLOCK, CRY1, CRY2, PER1, and PER2, with this decline being more pronounced in UC than in CD. These genes exhibit bidirectional interactions with inflammation and dysbiosis, both of which play critical roles in the pathogenesis and progression of IBD. Patients with active ulcerative colitis exhibit a marked deficiency in fecal and colonic butyrate, a condition linked to the dysbiotic state characterized by the depletion of butyrate-producing bacterial populations such as Faecalibacterium prausnitziiand Ruminococcus longum. In a murine model, sleep fragmentation was found to worsen the severity of DSS-induced colitis relative to undisturbed sleep, as evidenced by increased weight loss, colon shortening, and disease activity indices. The pathological changes in SF mice were characterized by a collective deterioration across multiple systems: a drop in key tight junction proteins (claudin-1, occludin), upregulation of pro-inflammatory cytokines (CRP, IFN-γ, IL-6), reduced concentrations of melatonin and adiponectin, downregulated VPAC1/VPAC2 receptor expression, and a decline in the diversity of intestinal bacteria. While sleep disturbance was shown not to influence tight junction protein expression in the intestines of healthy mice, electroacupuncture (EA) application in a colitis model effectively reduced disease severity and provided protection against the loss of epithelial barrier proteins and VIP receptor function, particularly for the VPAC2 subtype. However, it did affect vasoactive intestinal peptide receptors and gut microbiota diversity—opposite to what was observed in inflamed mice[15]. A crossover randomized controlled trial evaluated the impact of a fortified dairy product on sleep, stress, and gut microbiota. The findings indicated that consumption of the product, which contained protein, galacto-oligosaccharides, vitamins, and minerals, did not yield a significant improvement in sleep quality among participants with sleep disturbances. However, it stimulated Bifidobacterium growth by reducing salivary cortisol levels, which may contribute to improved sleep[16]. A randomized controlled trial provided evidence that probiotics, which are known to act on the gut-brain axis, can induce significant changes in brain morphology and resting-state function, in addition to causing a minor increase in BDNF levels.[17]

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3.3 Brain-Derived Neurotrophic Factor (BDNF)

Studies point to a link between the gut microbiota and circadian biology, noting that germ-free conditions lead to suppressed rhythmic gene expression in the brain, liver, and gut. This connection highlights the functional significance of the gut-brain axis, through which signaling molecules like BDNF and proBDNF are known to govern brain-gut interactions and may thereby influence psychological health. A randomized controlled trial examining how anti-TNF therapy affects BDNF and the gut-brain axis in IBD stratified participants by disease activity and type (UC/CD). The evaluated metrics included questionnaire-derived data on sleep parameters and depression, as well as biomarkers measured from collected blood samples. Compared to healthy controls, patients with inflammatory bowel disease (IBD) demonstrated reduced BDNF mRNA expression alongside elevated levels of both proBDNF and mature BDNF protein. Notably, protein concentrations were higher in ulcerative colitis (UC) than in Crohn's disease (CD). Within the IBD cohort, BDNF protein levels showed a positive correlation with sleep efficiency. Furthermore, in patients achieving clinical remission, depression severity was positively associated with BDNF mRNA but inversely related to BDNF protein. Anti-TNF treatment was observed to upregulate BDNF mRNA, suggesting a potential disruption of the BDNF signaling pathway in IBD that may contribute to comorbid sleep and mood disturbances.[18]

Research indicates that individuals adhering to the Mediterranean or MIND dietary patterns experience significant enhancements in sleep quality and reductions in symptoms of depression and anxiety relative to control groups. This positive psychological and behavioral impact is further correlated with a substantial elevation in Brain-Derived Neurotrophic Factor (BDNF) levels.[19]. Clinical observations indicate that the therapeutic effect of serial ketamine infusions on sleep parameters in patients with sleep disorders is positively correlated with an increase in serum BDNF, suggesting BDNF may be a relevant biomarker for treatment response.[20]

3.4 Hypothalamic-Pituitary-Adrenal Axis, 5-HT, Serotonin Transporter (SERT)

Pro-inflammatory cytokines, notably TNF-α and IL-6, have been shown to suppress the expression of core circadian clock genes such as PER1, PER2, and CRY2. This mechanistic link is supported by clinical data: individuals with inflammatory bowel disease (IBD) who experience poor sleep present with significantly higher serum concentrations of IL-6, IL-17, and IL-23—a profile similarly observed during disease exacerbation. Consequently, the interplay between impaired sleep and a heightened pro-inflammatory state may indicate a greater vulnerability to severe intestinal inflammation in this patient population[21].

3.5 Pro-inflammatory Factors

Evidence suggests that inflammatory mediators like TNF-α and IL-6 contribute to the dysregulation of key clock genes (e.g., PER2, PER1, CRY2). Concurrently, clinical studies report that sleep disturbances in IBD are associated with elevated serum levels of IL-6, IL-17, and IL-23, which are notably upregulated during disease exacerbation. Assessing the connection between sleep quality and this specific inflammatory signature could provide insights into the susceptibility to aggressive inflammatory lesions among IBD patients with comorbid sleep disorders[22].

4. Pharmacological Management

4.1 Antidepressants

Benzodiazepine use is more prevalent among IBD patients than in population controls. Strategies are needed to reduce benzodiazepine reliance in IBD patients and provide alternative management approaches for sleep disturbances and other symptomatic concerns[23].

4.2 Sleep and Pain Medications

Melatonin exerts protective effects in inflammatory bowel disease through multiple mechanisms, including reinforcement of the gut mucosal barrier, modulation of the gut microbial community toward an anti-inflammatory profile, immune regulation, and attenuation of inflammatory and oxidative stress. Consistent with these actions, preclinical studies using animal models of IBD have demonstrated that melatonin administration can ameliorate intestinal inflammation and promote ulcer healing. Preliminary

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clinical investigations further indicate that, when used as an adjunctive treatment, melatonin may contribute to reduced disease activity in patients[24]. A clinical investigation found that administration of a melatonin-magnesium supplement delivered in a coffee pod format led to a modest yet significant enhancement in sleep quality among healthy participants experiencing sleep complaints. Despite this improvement, post-intervention scores on the Pittsburgh Sleep Quality Index (PSQI) remained within the range indicative of average overall sleep quality[25].

Proactive pain management protocols do not worsen pain but significantly reduce opioid use among hospitalized IBD patients[26]. Several drug classes, including opioids, anxiolytics, and biologics, are linked to poor sleep in patients, with opioids posing a distinct risk. These associations highlight the value of minimizing exposure to such medications in IBD care where feasible.

4.3 Butyrate

Experimental evidence indicates that butyrate, which may act as a probiotic, can counteract IBD aggravation linked to sleep deprivation. Administration of sodium butyrate led to a marked reduction in calmodulin and an upregulation of CRY1 gene expression. Consequently, butyrate supplementation holds promise as a complementary therapy for active UC, potentially alleviating inflammation, normalizing circadian rhythms, and improving sleep and quality of life[27].

5. Non-Pharmacological Treatments

5.1 Cognitive and Behavioral Therapies

The Brief Behavioral Therapy for Sleep (BBTS-I) applied to IBD patients improved sleep disturbances in CD patients[28]. A prospective, multicenter, randomized controlled trial was conducted to evaluate the clinical efficacy and cost-effectiveness of integrating mindfulness-based cognitive therapy into standard care for inflammatory bowel disease patients, with a focus on its impact on psychological distress, sleep quality, fatigue levels, and overall quality of life[29]. Concurrently, routine care supplemented with continuous care interventions, skin and inhaled aromatherapy, diaphragmatic breathing, and cognitive behavioral therapy also enhanced sleep quality in IBD patients[30–32].

Research indicates that cognitive behavioral therapy for insomnia (CBT-I), as the first-line recommended treatment for chronic insomnia disorder, may be particularly effective and important in managing insomnia and its associated pain and depression in individuals with inflammatory bowel disease[33]. A significant rise in serum BDNF was documented following acupuncture in insomnia-afflicted cancer survivors with low baseline BDNF, yet the therapeutic meaning of this effect remains to be fully elucidated. Clinical research indicates that integrating acupuncture with rTMS alongside standard escitalopram treatment produces greater improvements in cognitive function and sleep among individuals with depression than using the antidepressant alone or pairing it solely with rTMS. The underlying mechanism for this synergistic benefit could involve the upregulation of serum 5-HT and BDNF levels[34].

5.2 Exercise

Serum BDNF levels are diminished in patients with major depressive disorder (MDD). Healthy adults exhibit elevated BDNF following exercise. Thus, exercise therapy may help improve sleep disturbances and depression in IBD patients[35]. Significantly elevated serum resistin levels and lower serum adiponectin and leptin levels are observed in IBD patients with poor sleep. During IBD flare-ups, patients exhibit markedly elevated serum resistin levels, markedly reduced serum leptin levels, and a trend toward decreased serum adiponectin levels[36]. The interaction between disrupted circadian rhythms and particular adipokine patterns might help identify individuals with IBD who are at a heightened risk for developing inflammatory intestinal lesions.Treating sleep disorders, managing weight, and modifying dietary habits could emerge as novel therapeutic targets for IBD. Studies indicate that the prevalence of sleep quality impairment decreased after completing exercise programs[37]. A comprehensive study combining yoga with aromatherapy massage identified attitudes, subjective norms, and perceived behavioral control beliefs associated with yoga intervention and daily practice. Participants' depression and mental health scores improved[38]. Dance therapy demonstrates therapeutic potential for addressing the fatigue-sleep disturbance-depression symptom cluster and improving overall well-being in Chinese breast cancer patients receiving adjuvant chemotherapy[39]. For patients with post-stroke depression, a

ISSN 2616-5791 Vol. 6, Issue 9: 34-41, DOI: 10.25236/AJMHS.2025.060906

combined intervention of Ba Duan Jin and rational emotive behavior therapy improves mood, sleep, neurological function, and quality of life, potentially by modulating key serum biomarkers including 5-HT, BDNF, and IL-6[40].

5.3 Diet

Lifestyle interventions involving an anti-inflammatory diet and increased physical activity offer multifaceted benefits for UC patients, including relief from psychological distress and fatigue, better disease control, and improved sleep, social satisfaction, and overall quality of life[41]. Even at modest intake levels, alcohol consumption can have adverse effects on sleep health. Notably, it is associated with an elevated likelihood of snoring and can disrupt normal nocturnal sleep architecture[42].

5.4 Fecal Microbiota Transplantation

Studies indicate that among 52 patients receiving washed microbiota transplantation (WMT), all 47 patients demonstrated significantly reduced PSQI scores one month post-treatment compared to baseline. Furthermore, baseline PSQI scores correlated with the change in PSQI scores from baseline to after WMT[43].

5.5 Wearable Devices

Daily self-monitoring through wearable devices can track physical activity, heart rate, and sleep quality[44]. The well-established link between sleep problems and chronic pain, evident in disorders such as fibromyalgia, suggests that addressing symptoms prior to sleep could improve therapeutic outcomes. Home-based neuromodulation offers a promising strategy for controlling widespread chronic pain. One such method, alpha entrainment, utilizes 10 Hz stimulation administered via smartphone applications through visual flicker or auditory binaural beats to alleviate pain. Research in fibromyalgia patients indicates that pre-sleep alpha entrainment coupled with at-home EEG monitoring is a practicable approach, demonstrating preliminary benefits for both pain and sleep parameters with a favorable safety profile[45].

6. Conclusion

This review delve into the relationship between sleep disorders and inflammatory bowel disease by examining assessment tools for sleep disorders, mechanisms influencing disease activity, and current treatment advances. It offers new perspectives for research on inflammatory bowel disease complications, aiming to advance interventions that improve patients' quality of life.

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