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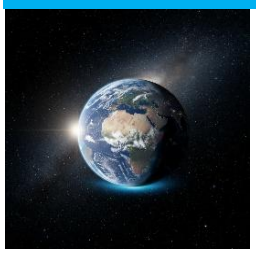

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Short Article

Sleep disturbances in inflammatory bowel disease: mechanisms, clinical consequences, and therapeutic implications

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Abstract

Background. Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is commonly associated with sleep disturbances and fatigue. Sleep disruption interacts bidirectionally with immune and neuroendocrine pathways, affecting disease activity, relapse risk, and long-term outcomes.

Aim. This review synthesizes current evidence on the relationship between sleep disturbances and IBD, focusing on pathophysiological mechanisms, clinical correlations, and prognostic and therapeutic implications. It evaluates whether sleep disorders are secondary to inflammation or independent contributors to disease progression, supporting the integration of sleep assessment into IBD care.

Material and methods. A narrative review of studies published between 2000 and 2025 was conducted using PubMed and Scopus. Search terms included "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "sleep", "circadian rhythm", "fatigue", and "cytokines". Included were clinical and preclinical studies, systematic reviews, and meta-analyses addressing sleep and inflammatory mechanisms in IBD. Selection was based on relevance and methodological quality.

Results. Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) regulate NREM sleep, while their chronic elevation in IBD contributes to sleep fragmentation and systemic inflammation. Sleep deprivation worsens intestinal barrier function via ER stress in goblet cells, increasing mucosal inflammation. Dysregulation of the HPA axis and leptin signaling further enhances immune activation. Poor sleep correlates with subclinical inflammation, higher relapse risk, fatigue, and long-term complications. Psychological comorbidities and pharmacotherapy additionally influence sleep quality.

Conclusions. Sleep disturbances are common in IBD, mechanistically linked to its pathophysiology, and impact disease course. Routine sleep assessment and targeted interventions may improve quality of life and potentially modify outcomes.

Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, sleep disturbances, fatigue, circadian rhythm, immune dysregulation

Content

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), comprises chronic, immune-mediated, relapsing inflammatory disorders of the gastrointestinal tract. Their etiology is multifactorial and involves a complex interaction between genetic predisposition, intestinal dysbiosis and environmental factors (Kucharzik et al., 2006; Khor et al., 2011). These diseases significantly reduce patients' quality of life, affecting not only physical health but also their psychosocial well-being (Alrubaiy et al., 2015).

Sleep is a fundamental physiological process essential for maintaining homeostasis, immune function, and overall quality of life. Its regulation relies on two interacting mechanisms, described in the dual-process model of sleep: the homeostatic process, which accumulates sleep pressure during wakefulness, and the circadian process, controlled by the suprachiasmatic nucleus (SCN), which synchronizes the sleep-wake rhythm with the light-dark cycle (Borbély et al., 2016; Bathory & Tomopoulos, 2017).

Normal sleep architecture is defined by a dynamic and cyclical progression between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. The NREM-REM cycle lasts approximately 90 minutes and repeats four to six times per night, providing both body regeneration and optimizing metabolic processes within the circadian rhythm (Carley & Farabi, 2016; Bathory & Tomopoulos, 2017).

IBD is associated with a high prevalence of sleep disturbances, affecting up to 56% of patients (Barnes et al., 2022). Routine assessment of sleep quality remains insufficient, partly due to organizational constraints and the lack of systematic incorporation of sleep evaluation tools into standard clinical care. Importantly, sleep disturbances may serve as a sensitive, non-invasive marker of subclinical inflammatory activity and a predictor of hospitalization, surgical intervention, and disease relapse (Ali et al., 2013). Systematic sleep evaluation and the implementation of behavioral or pharmacological interventions may improve health-related quality of life and potentially influence disease course through modulation of neuroimmune pathways (Qazi & Farraye, 2019a).

2.1. Pathophysiological mechanisms

The Immune-Inflammatory and Mediator Axis

Pro-inflammatory cytokines, specifically interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), serve as primary humoral regulators within the complex, bidirectional interplay between sleep physiology and the immune system. Under physiological conditions, systemic concentrations of TNF-α and IL-1 follow a distinct diurnal rhythm, accumulating progressively during wakefulness and declining during sleep. These mediators function as potent promoters of NREM sleep and enhancing both the intensity and duration of slow-wave sleep (SWS). The regulatory significance of these cytokines is underscored by experimental data showing that pharmacological inhibition of IL-1 or TNF-α reduces spontaneous sleep and attenuates the compensatory sleep "rebound" observed after deprivation. Other cytokines, including interleukin-2 (IL-2), interleukin-8 (IL-8), and interleukin-18 (IL-18), have also been implicated in promoting NREM sleep, potentially via direct neural pathways or secondary mechanisms such as nitric oxide production, which further supports SWS (Kapsimalis et al., 2005). Experimental endotoxin administration, producing dose-dependent increases in TNF-α and IL-6, has been shown to prolong NREM sleep duration in healthy adults (Mullington et al., 2000). Furthermore, genetic analyses reveal that multiple loci governing sleep regulation concurrently modulate inflammatory cytokine expression (Tafti et al., 1999).

In chronic inflammatory conditions such as IBD, sustained pathological elevation of these mediators disrupts sleep architecture, leading to fragmentation, increased nocturnal awakenings, and reduced overall sleep efficiency. This interaction forms a self-perpetuating feedback loop: inflammation alters sleep patterns, while sleep deprivation further amplifies IL-1, IL-6, and TNF-α release, potentiating systemic inflammatory cascades (Qazi & Farraye, 2019a, 2019b). Prolonged sleep restriction additionally shifts cellular immunity toward a Th2-dominant profile, which is particularly relevant to the pathogenesis and exacerbation of ulcerative colitis (Swanson et al., 2011; Axelsson et al., 2013).

Collectively, pro-inflammatory cytokines act as critical signaling molecules integrating central sleep-wake regulation with systemic immune homeostasis, linking disrupted sleep directly to disease activity in IBD.

Intestinal barrier integrity and cellular stress

Sleep disturbances directly impair intestinal mucosal barrier function, representing a critical intersection between disrupted sleep and the pathogenesis of IBD (Ananthakrishnan et al., 2014). Emerging evidence indicates that sleep deprivation and circadian misalignment act as potent triggers for mucosal barrier dysfunction, primarily through the induction of localized cellular stress and the disruption of epithelial homeostasis. Preclinical murine models consistently show that sleep deprivation aggravates chemically induced intestinal inflammation, compromises epithelial barrier integrity, and delays mucosal repair (Tang et al., 2009; Irwin et al., 2016; Li et al., 2024).

At the cellular level, insufficient or fragmented sleep induces endoplasmic reticulum (ER) stress in goblet cells, which are specialized epithelial cells responsible for the synthesis and secretion of the protective mucus layer. Activation of ER stress pathways in these cells diminishes their capacity to produce and secrete mucin, leading to thinning or depletion of the mucus layer. This breakdown of the physical barrier facilitates translocation of bacterial antigens and lipopolysaccharides from the intestinal lumen into the lamina propria, thereby amplifying the colonic inflammatory cascade (Li et al., 2024).

In patients with IBD, failure to achieve adequate and synchronized sleep may lead to persistent subclinical barrier dysfunction, increasing the risk of disease relapse and impairing the recovery of the mucosal lining.

Neuroendocrine and circadian regulation

The circadian system, orchestrated by the suprachiasmatic nucleus (SCN), serves as the central pacemaker coordinating sleep-wake cycles, gastrointestinal function, and immune responses (Plautz et al., 1997). The SCN synchronizes peripheral oscillators across organ systems - including the gut and immune tissues - with the external 24-hour light-dark cycle, primarily via light perception. In IBD, disruption of this temporal coordination reflects a state of molecular desynchronization extending beyond local inflammation (Rosselot et al., 2016; Liu et al., 2017).

The hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) exhibit pronounced circadian rhythms, reaching a nadir before sleep onset and a peak prior to awakening. Restorative NREM sleep actively inhibits HPA activity, reducing corticotropin and cortisol secretion, and thereby promoting tissue repair and immune homeostasis (Jawabri & Raja, 2025). Sleep deprivation disrupts this inhibitory control, resulting in HPA overactivity, elevated nocturnal cortisol, and a shift toward systemic pro-inflammatory states (Irwin, 2019).

Leptin, a metabolic hormone with a nocturnal peak, integrates energy metabolism with immune regulation. Sleep restriction perturbs leptin secretion, enhancing pro-inflammatory cytokine production - particularly IL-6 and TNF-α - by macrophages and other immune cells (Bruno et al., 2005; Park & Ahima, 2014). Dysregulated leptin also inhibits regulatory T cell proliferation and promotes natural killer (NK) cell activation, further driving gut immune activation (Zhao et al., 2003).

This neuroendocrine-cytokine imbalance highlights the need to restore circadian and hormonal rhythms as part of comprehensive IBD management. Targeting sleep and chronobiological regulation may therefore represent a complementary therapeutic strategy aimed at mitigating inflammatory activity and improving clinical outcomes.

2.2. Epidemiological and clinical data

Accumulating epidemiological and clinical evidence demonstrates a markedly elevated prevalence of sleep disturbances and fatigue among patients with IBD, substantially exceeding rates observed in the general population. These disturbances are not merely epiphenomena of active inflammation but appear to influence disease trajectory, relapse risk, and long-term systemic outcomes.

Sleep Duration and Risk of Disease Onset

Prospective cohort studies involving more than 150,000 participants have identified a non-linear association between habitual sleep duration and the risk of incident UC. Short sleep duration (≤6 hours/day) is associated with a significantly increased risk of UC, whereas prolonged sleep (>9 hours/day) confers an even greater risk . In contrast, similar associations have not been consistently demonstrated for CD, suggesting subtype-specific differences in the relationship between sleep patterns and disease susceptibility (Ananthakrishnan et al., 2014). These findings support the concept of sleep duration as a potentially modifiable epidemiological risk factor, particularly in UC.

Disease Activity and Sleep Parameters

Assessment using the Pittsburgh Sleep Quality Index (PSQI) consistently demonstrates significantly higher scores in patients with active IBD compared with patients in remission and healthy controls (Sobolewska-Wlodarczyk et al., 2018; Xu et al., 2021). Threshold values of an Inflammatory Bowel Disease Questionnaire (IBDQ) score <168 and a PSQI score >7,5 have been shown to distinguish patients with active IBD from those in remission (Xu et al., 2021).

Fatigue and Extraintestinal Consequences

Fatigue constitutes one of the most debilitating extraintestinal manifestations of IBD. It affects approximately 60% of patients overall and more than 86% of patients during active flares (Minderhoud, 2007; Hashash et al., 2018). Sleep disturbances are more prevalent in Crohn's disease (64,4%) than in ulcerative colitis (46,2%), with rates in both groups significantly exceeding those of healthy controls. Their severity correlates closely with inflammatory activity, depressive and anxiety symptoms, and impaired quality of life (Hashash et al., 2018).

Beyond its impact on daily functioning, chronic sleep disruption and persistent systemic inflammation may contribute to long-term cardiovascular complications. Large-scale epidemiological analyses demonstrate that patients with IBD carry a moderately increased risk of heart failure (HF) compared with the general population. In one population-based cohort, 5,582 incident HF cases were identified among individuals with IBD versus 20,343 cases in reference individuals over a median follow-up of 12,4 years. Notably, this elevated risk persisted for ≥20 years after IBD diagnosis, translating to approximately one additional HF case per 130 patients during that period. Increased risk was observed across IBD subtypes, including Crohn's disease, ulcerative colitis, and IBD-unclassified. Although sibling-controlled analyses modestly attenuated the association, the risk remained statistically significant, suggesting that shared familial factors do not fully explain the observed relationship (Sun et al., 2024).

Collectively, these data underscore the necessity of systematically evaluating sleep quality and fatigue as integral components of comprehensive IBD care. Sleep parameters not only reflect disease activity but also serve as valuable markers of subclinical inflammation and predictors of relapse.

2.3. Psychological and pharmacological factors

The interplay between psychological and pharmacological factors is a key determinant of sleep architecture and the chronic fatigue burden in patients with IBD.

Comorbid psychological conditions, particularly depression and anxiety, critically influence sleep quality in IBD. The prevalence of these disorders is notably high, with depressive symptoms reported in up to 80% and anxiety in 60% of patients during active disease phases. Clinical studies employing the Hospital Anxiety and Depression Scale (HADS) and the Pittsburgh Sleep Quality Index (PSQI) consistently demonstrate a strong positive correlation between psychological distress and sleep dysfunction. Depression has emerged as an independent predictor of poor sleep, exerting a significant effect even after controlling for nocturnal clinical symptoms such as pain or diarrhea.

This relationship is mediated by the bidirectional gut-brain axis. Intestinal inflammation and dysbiosis can alter central processes regulating mood and sleep, whereas psychological stress exacerbates intestinal permeability and may precipitate symptomatic flares. Perceived stress and psychological distress are directly associated with sleep fragmentation and prolonged sleep latency. Notably, pediatric patients with CD and depression exhibit significantly more disturbed sleep compared to healthy peers, underscoring the relevance of psychological factors across the lifespan.

Pharmacological therapies commonly used in IBD can exert profound effects on sleep homeostasis and the overall fatigue burden. Systemic corticosteroids, frequently administered to control acute disease flares, are well-established to induce insomnia, reduce slow-wave sleep, and fragment normal sleep architecture, often leading to clinically significant disturbances as reflected by elevated PSQI scores. In contrast, biologic therapies, including vedolizumab and anti-TNF agents, may have a beneficial impact on sleep quality by attenuating systemic inflammation, particularly the levels of proinflammatory cytokines such as TNF-α, which are known to disrupt normal sleep patterns. Evidence suggests that vedolizumab therapy is associated not only with improvements in sleep disturbance survey scores but also with concurrent enhancement of mood parameters, highlighting the interplay between inflammation control and neuropsychological well-being. Meanwhile, the use of psychotropic medications, such as antidepressants and benzodiazepines, as well as opioid analgesics for pain management, can paradoxically worsen sleep quality and exacerbate daytime fatigue. Opioid therapy, in particular, has been linked to decreased sleep efficiency, increased nocturnal arousals, and greater subjective reports of tiredness, illustrating the delicate balance between therapeutic benefit and side effect burden.

Collectively, these findings indicate that psychosocial and pharmacological factors often account for a larger proportion of variance in fatigue and sleep disruption than traditional inflammatory markers. This underscores the necessity for a multidisciplinary approach to patient care that integrates careful pharmacological management,

routine monitoring of sleep quality, and psychological support, ensuring optimal control of both physical and neurobehavioral dimensions of IBD.

3. Discussion

The growing body of evidence linking sleep disturbances with IBD pathophysiology has important clinical and therapeutic implications. Sleep dysfunction should no longer be considered merely a secondary consequence of active inflammation but rather a potentially modifiable factor influencing disease activity, relapse risk, and long-term outcomes.

From a clinical perspective, routine assessment of sleep quality should be incorporated into standard IBD care. Validated tools such as the PSQI may serve as practical screening instruments, while objective methods, including actigraphy or polysomnography, should be considered in selected patients with severe or refractory symptoms. Early identification of sleep disturbances may allow for timely intervention and improved overall disease management.

Behavioral interventions and structured sleep hygiene programs, represent first-line strategies with a favorable safety profile. In parallel, optimization of anti-inflammatory therapy remains essential, as effective control of systemic inflammation may directly improve sleep architecture. Careful consideration of pharmacological agents is also warranted, given the well-documented negative impact of corticosteroids and opioids on sleep quality.

Emerging therapeutic approaches targeting circadian regulation and the gut-brain axis offer promising avenues for future research. Chronotherapy, light-based interventions, and microbiota-modulating strategies may provide additional benefit by restoring physiological rhythmicity and reducing inflammatory burden.

Despite these advances, several important limitations persist in the current literature. Most studies rely on subjective sleep assessments, with limited use of objective methodologies. Heterogeneity in study design, patient populations, and outcome measures further complicates interpretation. Additionally, causality between sleep disturbances and IBD activity remains incompletely established.

Future research should prioritize well-designed longitudinal and interventional studies to determine whether targeted sleep optimization can modify disease course. Integration of objective sleep monitoring and personalized therapeutic approaches may ultimately lead to more comprehensive and effective management strategies in IBD.

4. Conclusions

Sleep disturbances are highly prevalent across all stages of IBD.

Experimental and clinical evidence supports a bidirectional interaction between sleep regulation and intestinal inflammation.

Impaired sleep is associated with subclinical inflammation, relapse risk, and adverse long-term outcomes.

Systematic sleep assessment should be incorporated into routine IBD management.

Future interventional studies are needed to determine whether sleep-targeted therapies modify disease course.

Disclosure

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of the use of generative AI and AI

In preparing this work, the authors used Google Gemini for the purpose of improving language and readability. After using this tool, the authors reviewed and edited the content as

necessary and accept full responsibility for the substantive content of the publication.

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