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Review Article

The Mediterranean Diet, Optimizing Sleep Function and Melatonin Supplementation—Insights into Potential Therapeutic Interventions for Inflammatory Bowel Disease

*Lindsey B Cundra BS, Steve M D'Souza, Parth J Parekh and David A Johnson**

Department of Gastroenterology, Eastern VA Medical School, USA

Abstract

This review is intended to better define the evidence that diet modifications, sleep optimization, and melatonin supplementation could positively influence the gut microbiome and change Inflammatory Bowel Disease (IBD) disease mechanisms to improve clinical outcomes. With appropriate insight, therapeutic interventions are discussed directed to potentially alter the microbiome, as well as improve the immune response, to mitigate the disease mechanisms of IBD.

Keywords: Mediterranean diet; Sleep; Melatonin; Inflammatory bowel disease; Microbiome

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) comprise the main pathological manifestations of Inflammatory Bowel Disease (IBD). IBD is a severe disease of the gastrointestinal tract that results in a chronic mucosal inflammatory condition that undergoes a relapsing-remitting course. The overall etiology of IBD remains poorly understood and involves a complex web of environmental factors, genetic susceptibilities, and host dynamics. Underlying this disease state are maladaptive inflammatory responses in susceptible hosts. These aberrant immune responses are at least in part due to changes in the commensal microbiome [1]. The microbiome affects host immunity, maintains barrier integrity, and augments host metabolism [2-4]. The mechanism outlining this process remains incomplete however it has been postulated that microbial sensing of ligands (e.g. bacterial by-products, microbial proteins, and other intraluminal substrates) activate inflammatory cascades and induce changes in gene expression that in the long-term become maladaptive [1]. Subsequently, a key component of the microbe-host homeostatic axis is recognition of intraluminal substances at the intestine epithelium that influence its integrity [5]. Environmental factors that modulate these inflammatory responses, such as sleep [6], diet [2] and other lifestyle choices, provide potential goals for therapy [7].

Host Immunity: The Effects of Dysbiosis

The microbiome is a unique sum of microorganisms that function to support gut and host homeostasis. Since the microbiome supports host immunity, maintains barrier integrity and is key to host metabolism, any changes to its composition due to external factors can lead to dysbiosis [3,4]. Dysbiosis of the microflora has been linked to the pathogenesis of inflammatory disease states such as inflammatory bowel disease, metabolic syndrome, cardiovascular disease, and obesity [8]. Furthermore, diet is known to profoundly affect the composition, dynamics and function of the gut flora, precipitating dysbiosis [3,9-11]. Evidence of the intestinal microbiota's direct involvement in host biology changes comes from studies using germ-free mouse models colonized by microbiota transfers from dysbiotic microbiota. For instance, when microbiota from disease models of obese mice was transferred to germ-free mice, there was a notable increase in body fat [12,13] and induced insulin resistance [14] in the germ-free models. In mouse models of colitis, disease was evidenced to be transferred to naive hosts via fecal transplant [15,16]. This parallel has been replicated in human models as well in the form of transplanted fecal microbiota from obese humans to germ free mice, which resulted in an increase in body fat in the mice [17]. Additionally, the reverse has been demonstrated in which insulin resistance was induced in human models from murine fecal matter [14]. Mechanisms of how the microbiome can induce changes in host biology have been elucidated: alterations in energy extraction from the bacteria, changes in satiety via neurohormonal changes in the gut, changes in fatty acid oxidation, protein fermentation by-products, and production of secondary bile acids [3,18]. These mechanistic changes and by-products result in a pro-inflammatory state that can predispose a genetically susceptible host to adverse health effects and disease states such as weight gain, obesity, insulin resistance, diabetes, asthma and IBD [13,19,20]. Furthermore, there is evidence that this dysbiosis contributes to immune dysregulation in the host. The underlying mechanism is thought to be due to precipitating a pro-inflammatory state via inducing changes in molecular traffic, resulting in changes in transcription cascades and a shift toward a pro-inflammatory state [2,21,22]. Researchers have shown that the pro-inflammatory state is characterized by increases in inflammatory biomarkers such as: Interleukin (IL)-1β, IL-6, IL-12, lipopolysaccharide-binding protein, nuclear factor kappa beta, chemokines, tumor necrosis factor (TNF)-α, C-reactive protein and reactive oxygen species [2,3,23,24]. The pro-inflammatory cascade is initially induced via ligand binding to a receptor, known as Toll-Like-Receptors (TLR) [24]. These ligands

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***Corresponding author:** David A Johnson, Department of Gastroenterology, Eastern VA Medical School Norfolk Va, USA, E-mail: dajevms@aol.com

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include Pathogen-Associated Molecular Pattern Molecules (PAMPs) and Damage-Associated Molecular Pattern Molecules (DAMPs) [25]. An example of a PAMPs is Lipopolysaccride (LPS), a microbial ligand from Gram-negative bacteria that is recognized by TLR4 [26]. One pivotal player within this system is the inflammasome, a key mediator of the innate host immune response. The inflammasome serves as a gateway to the inflammatory response. It is activated by molecular signals such as bacterial by-products and microbial proteins which then activates inflammatory cascades via chemokines. It has been proposed that the inflammasome is a precipitation of the dysbiosis that contributes to immune dysregulation such as those with IBD [27,28]. As discussed previously, the etiology of IBD is complex and largely unknown; however in patients with IBD, there exists a dysfunctional microbiome [29,30]. This microbiome is characterized by low diversity, a decrease in *Firmicutes* and *Bacteroides*, loss of gut barrier integrity, high levels of pro-inflammatory cytokines and low production of short chain fatty acids (SCFAs) [31-33]. There is evidence that this dysbiosis contributes to the immune dysregulation present in the disease and acts as a role in its pathogenesis [33].

The Effect of Diet on the Microbiome

The gut microbiome taxonomy is mainly comprised of *Bacteroides* and *Firmicutes*, *Proteobacteria*, and *Actinobacteria* [34]. The composition of these phyla differ amongst individuals, especially when considering dietary habits [30]. Diet is known to directly influence this microbiota composition into distinct phenotypes [10,12,35]. The microbiota of obese individuals differs from that of lean individuals by the number of gut microbial genes [35]. Additionally a high fat diet induced changes in the microbiota irrespective of host phenotypes [36]. The microbiota biota changes were characterized by a decrease in *Bacteroides* and an increase in *Firmicutes*. Furthermore, a high-fat diet and Western diet induced a similar microbiota [37]. These changes in taxonomy resulted in changes of the metabolic function of the biome [38]. These changes in the gut microbiome can alter the host's own biology [17]. The Western diet is comprised of a high carbohydrate, high saturated fat, high protein, and low fiber diet [39]. It is typically characterized by high intakes of processed and pre-packaged food items, red meat, dairy and grains. It has been associated with a pro-inflammatory state contributing to increased disease states [39]. Epidemiologic data and studies in mice have shown that High-Fat (HF) and High-Sugar (HS) foods are associated risk factors with IBD whereby HF and HS diets exacerbated colitis severity in wild-type mice and CD models [40-42]. Food components that are characteristic of the Western diet have been shown to affect host immunity via microbiota dependent pathways shown to contribute to a pro-inflammatory intestinal environment [43,44]. For instance, a Western Diet has been associated with a decrease in microbial diversity, upregulation in pro-inflammatory markers, intestinal colonization with pathobionts, and disruption of intestinal barrier integrity [9,42,45,46]. On the contrary, a Mediterranean diet is comprised of a high fiber, low animal protein, and low saturated fat diet. It is characterized by a high intake of vegetables, fruits, and healthy fat and a low intake of red meat and dairy [47]. The Dietary Guidelines for Americans recommends the Mediterranean diet to improve health and to prevent disease [47]. Food components that are characteristic of the Mediterranean diet have been associated with an anti-inflammatory state and reduced risk factors for disease [8,9,48]. For example, soluble fiber found in the diet improves gut homeostasis via production of Short Chain Fatty Acids (SCFAs). SCFAs have anti-inflammatory effects that improve host immunity through various mechanisms: secretion of immunoglobulins, induction of regulatory T cells tissue repair, antimicrobial peptides, and mucus production [49,50]. These effects contribute to host cell immunity and optimal intestinal function and intestine barrier integrity [9,49]. These effects are possible via stimulation of G-protein-coupled receptors located in the intestine and elsewhere throughout the organism [49,51]. Consequently, a lack of fiber may compromise intestinal barrier function [52]. Murine models of colitis have demonstrated dietary fiber supplementation attenuated clinical and inflammatory parameters [53]. Fiber supplementation in clinical trials is lacking with further investigation warranted [54]. Other dietary components that have been shown to suppress inflammation via microbiota induced mechanisms which include omega-3 fatty acids, plant polyphenols, and tryptophan [29,55-57]. The discussed food components are found in high quantities in vegetables, nuts, seeds, and extra-virgin olive oil. However, it is difficult to isolate one dietary component as crucial in IBD severity, thus it is paramount to investigate dietary patterns. Clinical trials investigating dietary patterns, such as the Mediterranean diet, are lacking. A Mediterranean-inspired diet has been shown to reduce markers of inflammation and normalize the microbiota in a small cohort of Crohn's patients [58]. No studies have examined the effect of the Mediterranean diet on microbiome changes and disease severity in IBD patients. There is an apparent gap in the research and a need to test a mechanistic role of dietary intervention for a composite effect for inflammation biomarkers and clinical outcomes via manipulating gut dysbiosis and restoring a potentially better homeostatic microbiome. Dietary direction towards biomic balance, immunologic optimization, improvement of intestinal integrity hold significant potential towards new mechanistic approaches for IBD.

Sleep and Inflammatory Bowel Disease

Sleep is essential for optimal health and plays an important role in our metabolism, physiology and general behavior [59]. The National Sleep Foundation recently updated their guidelines on sleep recommendations for each age group: teenagers require 8 to 10 hours; young adults require 7 to 9 and older adults require 7 to 8 [60]. However, nearly a third of US adults report they do not get the recommended amount of sleep [61]. This equates to over 70 million Americans suffering from a chronic sleep disorder [60]. Sleep disorders disrupt hormonal balance and system physiology and negatively impact metabolism and immune function [22,62,63]. A fundamental to the host immune system is the gut microbiota balance which maintains barrier integrity. Changes to composition and function due to external factors such as sleep disturbance can lead to dysbiosis. Disruption of the circadian rhythm has been linked to the development of cardiovascular disease, obesity, insulin resistance, diabetes, and metabolic syndrome [59,61,64].

The Relationship Between Sleep Disturbances and Inflammation

The circadian clock is driven by internal molecular mechanism that organize sleep-wake cycles influencing autonomous pacemaker cells which drive this circadian rhythmicity via gene expression, known as "clock genes." [65] These genes are critical to systems physiology and metabolism and most evident in the gastrointestinal system. The Gastrointestinal (GI) system also displays circadian rhythmicity that is evident in its patterns of gastric acid secretion, enzyme production, colonic pressures, and colonic contractions [66]. These patterns contribute to the regulation of gut motility, nutrient absorption, and cell proliferation [65,67]. Chronic sleep

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disorders impair an organism's endogenous rhythmicity to alter the physiological synchrony between biological systems, especially the gastrointestinal system. Consequently, sleep dysfunction disruption has been linked to intestinal dysbiosis [6,68,69], gastrointestinal symptoms such as bloating, abdominal pain, diarrhea, or constipation and gastrointestinal disease [70]. Increases in inflammatory biomarkers have been demonstrated in partial sleep deprivation [71,72], continuous sleep deprivation [73], sleep restriction [74] and sleep fragmentation [75], although vary with sleep deprivation durations [76]. This systemic inflammation involves disruption of intestinal epithelial barrier integrity leading to bacterial translocation into the bloodstream and intestinal dysbiosis [21,65,77,78]. The intestinal epithelium acts as a barrier against pro-inflammatory intraluminal contents [79]. Disruption of the barrier's integrity allows translocation of harmful products that can result in local and systemic inflammation. This has been demonstrated in mouse models, where disruption of the circadian rhythm led to the loss of epithelial barrier integrity. A dysfunctional microbiome is characterized by loss of gut barrier integrity and high levels of pro-inflammatory cytokines. Furthermore, sleep disruption, similar to diet variance, has been linked to distinct changes in the taxonomy of the gut flora. One study observed distinct microbiota biota changes characterized by a decrease in *Bacteroides* and an increase in *Firmicutes* in response to sleep disruption. Changes in the microbiota composition directly compromised the integrity of the intestinal epithelium barrier. These findings were further supported by reproducing these outcomes using germ-free mouse models colonized by microbiota transfers from the dysbiotic microbiota [80,81]. This ratio of *Bacteroides* and *Firmicutes* has been associated in the pathogenesis of obesity and the metabolic syndrome. Additionally, microbiome changes induced by sleep dysfunction directly impair metabolic pathways and biological functions, resulting in detrimental changes to host immunity, metabolic function and health [82]. Intestinal dysbiosis can compromise the immune system of the host, leading to pathological consequences [83,84]. This dysbiosis has also been observed in patients with IBD and has been associated with the pathogenesis of the disease [29,85]. Sleep is reportedly disrupted in 60% of IBD patients [86,87]. Additionally, patients correlate poor sleep with their disease severity [87]. In IBD mice models, circadian rhythm disruption worsened intestinal inflammation, disease severity, inflammatory cytokines and mortality compared to IBD controls [88-90]. Disruption of circadian homeostasis is suggested to play a role in the pathogenesis of disease states such as IBD and to be a correlate in disease severity. However, clinical trials investigating the effect of sleep intervention on microbiome changes and disease severity in IBD patients are lacking. Therefore, circadian disorganization is a reasonable therapeutic target to optimize gastrointestinal physiological function and improve disease states such as that seen in IBD.

Melatonin

Notably, sleep dysfunction results in changes in molecular traffic, transcriptional cascades and biomarkers resulting in microbiome changes [91]. What is not clear is the signal of communication between the gut microbiome and the human host. One postulated signal is the hormone melatonin. An indication of this signal has been observed with the *Enterobacter aerogenes* species, a commensal organism of the human microbiome. One indication of which is the circadian swarming activity which has been induced in the *Enterobacter aerogenes* species with melatonin [92]. This indicates melatonin may be a link between host-commensal communication with the gut. Melatonin is a neurohormone produced by the pineal gland that is responsible for regulating sleep-wake cycles. Melatonin is also produced by the Enterochromaffin cells in the gastrointestinal tract which influence intestinal immune function [93]. Furthermore, melatonin has anti-inflammatory and antioxidant effects [94]. Specifically, melatonin can modulate immune function by potentiating signal cascades resulting in antioxidant and anti-inflammatory outcomes, thus regulating oxidative stress. The antioxidant effects of melatonin as a therapeutic intervention, have been studied in several inflammatory diseases [95]. Melatonin improved disease severity in rat models with trinitrobenzenesulfonic acid (TNBS)-induced colitis [96]. The improvement in rat models was attributed to blocking transcription factors such as NF-κB and reducing free radical formation [97]. Excessive free radical oxygen species can trigger oxidative stress, causing intestinal mucosal barrier damage [98]. This is associated with the initiation, progression, and inflammatory damage observed in IBD. It additionally enhances pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-8 [99].

Future Prospects

Optimized sleep effectiveness, as well as diet, are external factors that can act in concert to catalyze low grade inflammatory states which precipitate disease development such as metabolic syndrome, diabetes, cardiovascular disease and various gastrointestinal diseases [20,65,75,100,101]. There exists a gap in the research and a need to test how and if a directed sleep intervention (including counseling and melatonin) as well as directed dietary intervention, can improve disease and inflammation biomarkers by manipulating the dysbiosis and restoring a homeostatic microbiome. Optimization of sleep habits, dietary intake and supplemental melatonin supplementation have effects on the immune system by improving the composition of the microbiome and protecting the integrity of the intestinal mucosal barrier, which should improve the host immune response and improve the disease mechanisms in IBD. Clearly, further study is warranted for each as well as a composite approach to optimizing outcomes.

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