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INFLAMMATORY BOWEL DISEASE

Adjunctive Therapies for Inflammatory Bowel Disease: Beyond Prescriptions

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Abstract

Ulcerative Colitis (UC) and Crohn's Disease (CD) comprise the two major subtypes of Inflammatory Bowel Disease (IBD). IBD is a chronic relapsing-remitting disease with an underlying etiology that remains imperfectly understood. Complementary, or integrative, medicines are emerging therapies for patients with IBD. They provide a useful adjunct to conventional therapies, further augmenting clinical outcomes through quality-of-life measures and symptom management. However, research is limited in assessing how these alternative therapies modulate disease activity and the impact of these therapies on disease outcomes is not fully understood. As providers, we need to remain open-minded about integrating these therapies with good clinical judgement.

Introduction

The aims of this article are to summarize the application and discussion of adjunctive therapies for patients with Inflammatory Bowel Disease (IBD). In lieu of conventional therapies, alternative interventions include mind-body techniques, diet, supplements, vitamins, sleep management techniques, and acupuncture. Despite the promise of complementary medicine as an adjunctive treatment for IBD, few studies have been performed to demonstrate efficacy in modulating disease activity. However, gastroenterologists face an overwhelming need to engage with their patients on alternative therapies with increasing adaptation of these non-allopathic interventions.

Dietary interventions and herbal supplementation: The mediterranean diet

Diet is known to play a profound role in the pathogenesis, etiology, and treatment of IBD. Globally, the burden of IBD is on the rise, with its highest incidence in newly industrialized countries [1]. Emerging data shows a Western-style diet is associated with the rising prevalence of IBD [2]. Conversely, there is an inverse association of IBD rates with the consumption of certain food products characteristic of a Mediterranean-style diet [3]. A Western-style diet is a modern dietary pattern defined as high intake of refined sugar, omega-6 polyunsaturated fats, processed meats, and pre-packaged food items [4]. A Med-

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iterranean-style diet is characterized by a high intake of vegetables, fruits, whole grains, olive oil, fish, and nuts as well as low amounts of red meat and dairy [5]. Food components that are characteristic of the Mediterranean Diet (MD) have been associated with anti-inflammatory states and reduced risk factors for disease, with reductions in cardiovascular disease, cancer, and all-cause mortality [6-8]. The Dietary Guidelines for Americans recommends the MD to improve health and to prevent disease [6]. Consumption of vegetables, fruits, and whole grains is advised, along with avoidance of red meat, high fructose corn syrup, trans- and saturated fatty acids.

Many components of the Mediterranean-style diet have been shown to be beneficial in IBD. Vegetables and seeds contain a high amount of fiber. Additionally, extra virgin olive oil and nuts contain a high amount of polyunsaturated fatty acids, and vitamins, as well as a low amount of omega-6 and saturated fat. These dietary components suppress inflammation by influencing the composition and function of the commensal microbiome [7,8]. Adherence has also been correlated to a decrease in inflammatory markers and found to beneficially impact the metabolome [7,8]. Adherence has also been specifically associated with a lower risk of later-onset CD in a 20 year study of 83,147 individuals [9]. Non-adherence to the MD conferred an adjusted population attributable risk of 12% [9]. Several large clinical studies are underway for the Mediterranean diet, which will add greatly to our current understanding of the role of diet in IBD [10,11].

The Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission of Crohn's Disease (DINE-CD) study was presented at the 2021 Crohn's and Colitis Congress. The 12-week parallel-group randomized trial included 194 patients with mild-to-moderate CD; randomization was to the specific carbohydrate diet (SCD) or the MD [12]. The SCD is a dietary intervention focused on consumption of specific carbohydrates (monosaccharides such as glucose, fructose, and galactose). It excludes disaccharides (sucrose, lactose, and maltose) and most polysaccharides (starch, wheat, oats, barley, and rice) which are thought to be proinflammatory, as well as processed meat because it contains a variety of sugars including molasses and other sweeteners [13]. The SCD has been demonstrated to induce and maintain remission in patients with IBD [14]. The primary clinical end points of the trial were symptomatic remission, clinical remission, and inflammatory response (defined as a reduction in fecal calprotectin and C-reactive protein levels). At 6 weeks, symptomatic remission was observed by 44% in the MD cohort and 47% in the SCD cohort. Clinical remission was similar, with 48% for the MD cohort and 49% for the SCD cohort. At week 12, symptomatic remission rates were 40% and 42%, and clinical remission rates were 47% and 40%, respectively. Neither group demonstrated normalization of CRP or fecal calprotectin. DINE-CD showed no significant differences in the rate of symptomatic remission or clinical remission between diets, which demonstrates either diet as an effective supplement to current therapy in patients with CD.

Curcumin

Curcumin is a plant produced chemical, found in the spice turmeric, which is a member of the ginger family [15]. The purported medicinal properties of turmeric have received much interest as it has been shown to be an effective anti-inflammatory and antioxidant agent [16,17]. Curcumin targets multiple signaling molecules at the cellular level due to potent inhibition of NF-κB activation and inhibition of TNF-mediated actions [18-20]. In murine colitis models, curcumin inhibits NF-κB activation and CD4+ T cell infiltration [21]. Curcumin administration to mice has also been shown to improve gut barrier function and support a healthy microbiome [22]. Curcumin's effect on the microbiome has also been replicated in human studies, and showed an increase in species diversity [23]. Although curcumin's benefits in molecular studies and animal models has been well documented, its efficacy in randomized controlled studies (RCTs) and its side-effect profile are limited.

Curcumin has been shown to induce remission in patients with active mild-to-moderate UC [24]. Curcumin was given in combination with mesalamine to 50 patients with mild-to-moderate UC. Patients were randomly assigned to groups given mesalamine and curcumin capsules (3 g/day) or an identical placebo for 1 month. 53.8% of patients who had not responded to mesalamine treatment achieved clinical remission in the curcumin cohort. Improved clinical remission rates were evident with curcumin (53.8% *versus* 0%; P= 0.01), clinical response (65.3% *versus* 12.5%; P<.001), and endoscopic remission (38% *versus* 0%; P= 0.043). The study demonstrates the efficacy of curcumin as a synergistic supplement to standard therapy. These findings were strengthened by a 2020 meta-analysis of several RCTs [25]. The final analysis included seven studies for a total of 380 patients and demonstrated that adjunctive use of curcumin with mesalamine versus placebo increased the odds of clinical remission by threefold. The study concluded the use of curcumin as an adjunct to be superior to the use of mesalamine alone in the treatment of UC. These findings have not been demonstrated in CD patients. A recent investigation reported oral curcumin was no more effective than placebo in preventing post-operative recurrence of CD [26]. Overall, there is limited but promising evidence that curcumin as a dietary supplement, may yield favorable results as a naturopathic treatment option.

Cannabis sativa

Cannabis sativa, an annual dioecious plant, is indigenous to Eastern Asia. It has been cultivated throughout history as a therapeutic, medicinal, and recreational plant [27]. It is comprised of several key cannabinoid compounds, including cannabinol, cannabidiol, and δ-9-Tetrahydrocannabinol (THC) [28]. Cannabinoid compounds have been on sale in the USA since 1985, although restricted to medicinal use [28]. The therapeutic potential of cannabis and cannabinoid-based compounds has been demonstrated throughout history for multiple therapeutic benefits, such as relief of nausea and vomiting [29]. On the contrary, cannabinoid use has also been non-causally linked to mood and cognitive disorders, respiratory syndromes, and cardiovascular complications [30]. On the other hand, new research highlights potentially promising areas of therapeutic benefit of cannabis for neurological and psychiatric disorders [31-33]. This lends itself to the fact that state laws have allowed marijuana for recreational use (in 17 states, the District of Columbia, the Northern Mariana Islands, and Guam) and medical use (in 36 states, District of Columbia, Guam, Puerto Rico and U.S. Virgin Islands) as of 2021 [34].

Nearly 15% of patients with IBD report current active use of marijuana for relief of symptoms [35]. Despite its common use, objective data on marijuana use, the anti-inflammatory effects of cannabis, and its therapeutic potential IBD is limited. The limited literature does indicate cannabis use improves quality of life measures [36,37]. In one study, patients with active CD on various therapies were randomized to receive cannabidiol 20 mg/day or placebo [36]. Clinical Disease Activity Index (CDAI)

was measured between groups and no significant difference was noted by the end of the study. These findings were corroborated in a follow up study assessing the safety and tolerability of CBD-rich botanical extract in patients with UC [37]. However, the cannabidiol-rich botanical extract was superior to placebo in improving QOL outcomes, although remission rates at 10 weeks were similar between the 2 groups. Both studies reported cannabinoid use improved IBD symptoms, including pain, nausea, and appetite. It has been postulated that cannabis and its derivatives improve IBD symptoms *via* endocannabinoid receptors. These effects include lower esophageal sphincter relaxation, a decrease in gastric emptying, improvement in nausea and pain, a decrease in colonic motility, as well as secretions [38]. However, there is no clear evidence that cannabis and its derivatives improve biomarkers, reduce inflammation or improve disease activity. Ultimately, the effect of cannabis use in patients with IBD is inconsistent, with the outlined studies suggesting that cannabis may improve symptoms in patients with IBD, without biological remission or anti-inflammatory effect. Although there is potential for a positive impact on clinical symptoms, it remains challenging to counsel patients as there remains limited guidance on this topic.

Mindfulness Approaches

Mindfulness approaches and mind-body therapy incorporate cognitive therapy, mindfulness, yoga, and exercise. They can be utilized in a systematic approach to address the multifaceted aspects of IBD (psychological, cognitive, and psychodynamic factors). In fact, up to 21% of patients with IBD use mindfulness or mind-body therapy techniques such as massage therapy, meditation, yoga, and hypnosis [39].

Yoga

Yoga focuses on complex webs of associations between the mind, body, and behavior to promote optimal health. Although psychological therapies like meditation and yoga have shown limited effect on clinical and endoscopic disease markers, their effect on improvement in overall quality of life has been reliably reproduced [40]. Meta-analyses have suggested yoga improves QOL measures as well as pain control [41]. Additionally, the benefits of yoga include improving physical fitness, strength, flexibility, balance, and mobility [42].

Yoga has also been shown to have effects on other physiological systems of the body, including improving immune function [43,44]. In one meta-analysis investigating how yoga and similar practices reduce markers of inflammation, a conglomerate of 34 studies comprising over 2000 participants, reported improvement in inflammatory markers [44]. The study included 7 to 16 weeks of mind-body intervention and demonstrated that there was a moderate effect on reduction of C-reactive protein (effect size [ES], 0.58; 95% confidence interval [CI], 0.04 to 1.12) [44]. These immunomodulatory effects warrant further investigation as few prospective randomized controlled studies have evaluated the effect of yoga in biomarkers in IBD. However, QOL measures have been investigated. In a RCT investigating how yoga affected patients with UC currently in remission, patients were randomized to a supervised yoga session or self-directed reading over a period of 12 weeks [45]. In the patients practicing yoga, there was a significant increase in disease specific QOL. This finding has been replicated in subsequent studies [46].

Exercise

At present, it has been well established that exercise improves well-being, health and quality of life. Exercise is accessible, cost-effective, and a beneficial therapy for a multitude of diseases [47]. On the contrary, intensive training or extreme exercise has been associated with multiple gastrointestinal issues due to reduced blood flow to the gut [48]. Notwithstanding the gastrointestinal effects of extreme exercise, a sedentary lifestyle is an important risk factor for several disease states, including the development of IBD [49]. Further, exercise decreases all-cause mortality by augmenting cardiovascular disease risk [50].

In gastrointestinal disease states, exercise has been shown to decrease risk of constipation, diverticular disease, and cholelithiasis [51]. Further, moderate exercise may reduce risk of colorectal cancer [51]. Studies in murine models of chronic intestinal inflammation have demonstrated that exercise attenuates expression of pro-inflammatory cytokines [52]. The mucosal barrier integrity is challenged in stress-induced states, exacerbating dysfunction in the gut and mucosal biome. These findings have not been directly replicated in the IBD population as few studies have examined the effect of exercise on disease outcomes in human trials. Further, the studies that have been conducted vary greatly in their primary outcome but have included measures such as bone mineral density and oral-cecal transit time [52-55]. Given the large variability in the study outcomes, results have been mixed. For instance, a yearlong exercise intervention increased BMD [54], which is beneficial in IBD patients, whereas a subsequent study found that exercise worsened disease outcomes [55]. The study showed exercise had no significant effect on multiple parameters, including transit time, intestinal permeability and lipoperoxidation [55]. However, larger follow up studies have established that exercise has been shown to be an effective intervention when part of a multifaceted approach, even decreasing the risk of relapse for both CD and UC [56]. As part of a combined approach, stress management, exercise, and a Mediterranean diet was shown to have a significant increase in QOL scores [57].

Acupuncture

Acupuncture is a 3000-year-old therapy of traditional Chinese medicine. More Americans have adopted acupuncture with recent estimates approaching 14 million [58]. This recent trend can be observed in major hospital systems across the United States as now many offer and promote acupuncture services and recommend acupuncture therapy for treating pain. Another therapeutic modality of Chinese medicine is combining acupuncture with moxibustion, this involves burning dried mugwort (moxa) on acupoints [59]. These therapies offer an attractive option for IBD as a recent meta-analysis comparing the overall efficacy of acupuncture and acupuncture combined with moxibustion, concluded that either therapy was greater than the efficacy of oral sulfasalazine monotherapy for the treatment of UC [60]. The current literature to date suggests mindfulness approaches and mind-body therapies are safe complements to our conventional therapies. Regular participation in these techniques may help improve quality of life for people with IBD as well as immune function. Clearly more studies are needed to determine their clinical significance as objective data on disease markers is limited.

Sleep

Disruption of environmental factors, such as diet and sleep, is linked to impaired nutrient metabolism and systemic inflammatory response that is associated with IBD [61,62]. A large component of this effect is through alteration of the composi-

tion of the commensal microbiome [62-65]. Disordered sleep is common in modern society, and contributes to dysbiosis, gastrointestinal symptoms, and pathogenesis through inflammatory cascades [61,66,67]. Sleep deprivation, restriction, and fragmentation has been associated with cytokine expression [68-72]. The inflammatory cascade and impaired epithelial barrier function leads to bacterial translocation and further inflammation [73-76].

In addition to gut translocation, circadian dysrhythmia is associated with dysbiosis, changes in bacterial taxonomic composition that may promote progression to inflammatory disease, and this effect has been noted to be inducible in animal models [77,78]. Specific changes noted in disordered sleep include phylum-level changes, including increase in Firmicutes to Bacteroidetes ratio, and this effect has been noted to be inducible in animal models [68]. Changes in this composition can compromise the integrity of the intestinal epithelium barrier, immune response, as well as metabolic function [61].

While sleep dysfunction is associated with IBD pathogenesis, conversely, those affected by IBD also experience disordered sleep as a consequence of their disease. Over 50% of IBD patients experience abnormal sleep and this effect is associated with increasing severity of disease [79,80]. While there is some literature evaluating the effect of sleep interventions on fatigue and sleep quality in IBD patients, there is a paucity of literature on sleep interventions as a method to mitigate disease severity [81].

Melatonin

Melatonin is a neurohormone produced by the pineal gland that is responsible for regulating sleep-wake cycles. It is also produced by enterochromaffin cells in the gastrointestinal tract in approximately 400 times greater concentration than the pineal gland [82,83].

Precursors and biosynthesis

Biosynthesis of melatonin occurs through a pathway that starts with L-tryptophan (Trp) conversion to serotonin, and subsequent serotonin conversion to melatonin [84]. Intake of dietary Trp is associated with improved sleep, likely through this synthetic pathway [85]. Luminal Trp can be consumed by gut flora, directly affecting availability for melatonin synthesis, and in-turn affecting the sleep-wake cycle. Trp itself has also been implicated as a modulator of gut immune activity by inhibiting Angiotensin I Converting Enzyme 2 (ACE2)-dependent decreases in epithelial barrier function and progression to colitis, as well as through microbial metabolites [86,87]. This is demonstrated by literature suggesting that tryptophan deficiency is associated with IBD activity, though it is unclear if this is a precursor or consequence of IBD [88]. Serotonin is a neurohormonal intermediate in melatonin synthesis that has also been demonstrated to have anti-inflammatory and sleep effects. Medications affecting serotonin uptake including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have been demonstrated to decrease disease activity in CD and UC [89].

Gastrointestinal Effects

Melatonin acts as a modulator of several gut functions, including circadian fluctuation of microbial composition, direct antioxidant effects, and immunomodulatory effects [90,91]. Melatonin potentiates anti-inflammatory signaling cascades and oxidative stress [91]. The antioxidant effects of melatonin as a therapeutic intervention have been studied in several inflammatory disease states [92]. Melatonin improved disease severity in rat models with trinitrobenzenesulfonic acid (TNBS)-induced colitis [93]. The improvement in rat models was attributed to blocking transcription factors such as NF-κB and reducing free radical formation, which can cause intestinal mucosal barrier damage [94,95]. Melatonin has been demonstrated to decrease ulceration in animal models through decreased intestinal permeability and influx of bacterial toxins [93,96].

Therapeutic potential

Given the significant effects on gut-microbe interactions and anti-inflammatory effects, melatonin supplementation is a reasonable therapeutic target to optimize gastrointestinal physiological function and improve disease states such as IBD. In animal models, melatonin has been demonstrated to alleviate circadian dysrhythmia-related colitis, as well as sleep deprivation-related colitis through reduction in pro-inflammatory cytokines [97,98]. However, clinical trials investigating melatonin supplementation and their correlations with disease severity are lacking. Melatonin supplementation in combination with traditional therapy has been demonstrated to have both improved UC remission as well as decreased mucosal infiltrate when compared to traditional therapy alone in CD and UC [99,100]. A randomized, placebo-controlled clinical trial was designed but terminated prior to data analysis [101]. Controlled investigation of the therapeutic potential of melatonin on sleep and IBD disease activity is needed.

Conclusion

The treatment for IBD traditionally targets biologic or immunosuppressant medications. Recognizably however, there is increasing evidence that ancillary interventions through diet, sleep, exercise as well as some other homeopathic approaches may be beneficial and further enhance outcomes. Use of these approaches helps empower the patient to have a more active role in disease management and thereby transform approaches from global disease “en bloc” treatment to more patient specific targeted interventions. Recognizably a cardinal “rule of medicine” is to do no harm, but these adjunctive therapies beyond prescriptions seemingly offer translational opportunities to improve patient outcomes. Open minded care providers need to integrate these possibilities with good clinical judgement!

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