COUNCIL ON
NUTRITION

Nutritional Foundations

Student Journal of the Council on Nutrition of the American Chiropractic Association

Volume 1 No. 1 **July 2021**

Council on Nutrition
American Chiropractic Association
1665 East 31st Street
Brooklyn, N 11234

Non-Profit Organization
U.S. Postage
PAID
Winchester, VA 22601
Permit #339

Volume 1 No. 1 July 2021

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NUTRITIONAL FOUNDATIONS
is published biannually by the ACA Council on Nutrition

ISSN: 2693-9703
eISSN: 2693-9711

Postmaster: Send Form 3579 to
1665 East 31st Street
Brooklyn, NY 11234

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Subscription rates: $50 per year USA, $65 outside the USA. Single copies $25 USA, $30 outside the USA.

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Small Intestinal Bacterial Overgrowth – Concepts and Considerations

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ABSTRACT

Background: Small Intestinal Bacterial Overgrowth (SIBO) is a condition characterized by a change in the number or quality of microorganisms present in the small intestine. It is associated with functional diseases of the gastrointestinal tract, such as irritable bowel syndrome.

Methods: Factors affecting the microbiota present as possible risk sources as well as potential treatment approaches. Nutritional intervention could be effectively employed as a treatment protocol for SIBO.

Results: A nutritional approach should include restoring the intestinal lining, enhancing nutritional status, and preventing recurrence. Use of the Bi-Phasic Diet Protocol, herbal therapy, and probiotic supplementation is suggested.

Conclusions: Nutritional therapy for SIBO should be complex and individualized. A functional approach may be a valid method to treat the condition.

Key Words: SIBO, bacterial overgrowth, nutrition, small intestine, microbiota

INTRODUCTION

The human gastrointestinal (GI) tract is a symbiotic home to a vast population of bacteria, viruses, and fungi. Commensal microbiota executes a variety of vital purposes from immune function to nutrient production and absorption, hence the GI tract is critical for maintaining overall homeostasis. There is a connection between several diseases and abnormal gut flora.[1] Bacteria predominantly inhabit the colon, whereas the small intestine harbors very little bacteria in comparison.[1] Small intestinal bacterial overgrowth (SIBO) is defined as an abnormally high number of bacteria or an alteration in the normal microbiome of the small intestine.[2] Research has identified that the GI dysfunction caused by SIBO is multifactorial.[1] While any inequality of the intestinal microbiome can potentially lead to SIBO it is the failure of endogenous mechanisms to prevent overgrowth that ultimately contribute to the pathogenesis.[3] Processes that naturally inhibit bacterial overgrowth include gastric acid secretion, the mucosal layer, intestinal motility, an intact ileo-cecal valve, immunoglobulins, and bacteriostatic pancreatic and biliary secretions are likely contributors.[4]

Research has shown that people with SIBO have an increase in colonic bacterium. These bacteria ferment carbohydrates into gas, which causes abdominal discomfort and pain via bloating and distension.[1] SIBO is associated with an extensive assortment of diseases such as achlorhydria, pancreatic exocrine insufficiency, immunodeficiency syndromes, small intestinal obstruction and stagnation, irritable bowel syndrome, Chron's disease, celiac disease, scleroderma, autonomic neuropathy in diabetes mellitus, post-radiation enteropathy, small intestinal pseudo-obstruction, liver cirrhosis, and fibromyalgia.[5] Additionally, imbalances in the gut microbiome have been correlated to the development of mood and behavior disorders, Alzheimer's disease, and several chronic systemic disorders including diabetes, obesity, and cardiovascular disease.[5]

Not only is SIBO an under-recognized source of a variety of nonspecific GI symptoms, it is also an identified cause of malabsorption.[3] Chronic inflammation induced by bacterial dysbiosis in SIBO facilitates harmful effects on the epithelium involving the blunting of the villi, damage to the brush border, and damage to tight epithelial junctions.[3] Inflammation-induced destruction increases the permeability of the small intestine leading to the escape of endotoxins and the release of proinflammatory cytokines.[5] These events can produce numerous extra-intestinal symptoms such as rosacea, restless legs syndrome, arthralgias, anemia, and interstitial cystitis.[6] Furthermore, fat malabsorption caused by deconjugation of bile acids can lead to fat-soluble vitamin deficiency, oxalate kidney-stones, and steatorrhea. Vitamin B12 deficiency can be triggered by pathogenic or non-resident bacteria consuming the supply before it reaches the ileum.[7]

Diagnosis SIBO can be challenging for clinical practitioners. Quantitative jejunal aspirate culture is currently the diagnostic gold standard; however, there are limitations to this test including the necessity of a minimally invasive endoscopy.[1] Endoscopy is typically

outside chiropractic scope of practice which requires chiropractors to use other methods of diagnosing SIBO such as noninvasive breath tests. The accuracy of these assessments, however, remains controversial.[8]

Research on small intestinal bacterial overgrowth suggests that factors affecting the microbiota are coming into focus as possible risk sources as well as potential treatment approaches.[7] Special nutrition may be successfully utilized to re-establish a healthy microbiota, decrease bacterial gas creation, and prevent relapse.[7]

METHODS

Healthy people have few bacteria in the stomach and upper small intestine due to the innate acid barrier.[2] There is a transient microbiota chiefly composed of aerobic and gram-positive bacteria. More numerous or changes in commensal microbiota in the small intestines generates competition in the processing and uptake of nutrients and produces excessive gas. Distally, the microbiota alters in numbers and composition. The ileum operates as a transitional region. The ileocecal valve remains contracted and aids in the prevention of the influx of the anaerobic microbiota from the colon.[2] Any disruption in the local balances or alteration in the dispersion of the gastrointestinal microbiome can theoretically influence the incidence of bacterial overgrowth.[2]

Colonization of the intestines with commensal microorganisms commences in the womb, intensifies through vaginal birth, and continues with breastfeeding and throughout early childhood.[1] Nutrition plays a significant role in the intestinal microbiota as bacteria depend on substrates from the diet for energy and necessary cellular growth. All non-digestible and non-absorbed dietary components serve as substrates for the resident microbes in the colon.[2] Indigestible polysaccharides are the most important substrates because they cannot be broken down before reaching the colon. Metabolism of colonic substrates requires fermentation due to low levels of oxygen. Substrates are converted into short-chain fatty acids and intestinal gases.[2] Therefore it can be proposed that diet regulates which substrates are accessible, subsequently determining the intestinal environment.

Research has not been able to verify whether changes to gut microbiota is the cause or the result of diseases like SIBO. Researchers have discovered that fermenting bacteria respond rapidly to short chain-carbohydrates.[2] With a continuous source of nutrients from food, non-resident bacteria colonizing the small intestine can multiply locally and permanently inhabit the small intestine where they compete for nutrients. Since the bacteria of the small intestine can adapt to nutrient availability very quickly, the ratios of various microbial species can modify over time.[2]

SIBO interventions are often based on experimental procedures rather than established recommendations. Therapy must be individually tailored to the patient. Treatments conventionally cited for SIBO are directed towards resolution of underlying causes, administration of antibiotics, and correction of nutritional deficiencies. Approaches that use special diets to treat or alleviate symptoms of SIBO are currently under investigation.[7]

Elimination of the underlying cause(s) of SIBO is the foundation of treatment and relapse prevention.[7] Structural defects should receive surgical correction, and medications that inhibit motility, or gastric acid secretion, should be substituted, ceased, or restricted.[1] Rifaximin is a locally acting antibiotic currently prescribed for SIBO because it cannot be absorbed through the intestinal lumen; however, it is not yet approved for the treatment of SIBO, and patients often incur a high cost.[6] A one month supply is approximately $1200, and comes with the known effect of potentially inducing Clostridium difficile colitis. Furthermore, nine months following antibiotic therapy, 44% of patients experience relapses with increased symptomatology.[6] Considering adverse effects associated with antibiotic treatment, such as the threat of resistance and the possibly harmful consequence on the microbiome and the protective biofilm of the intestinal epithelium, it is not surprising that other remedies have been tested for effectiveness.[7]

Prebiotics and probiotics have shown efficacy in the treatment of intestinal dysbiosis but show conflicting results in the treatment of SIBO.[7] Herbal remedies for SIBO indicate the same effectiveness as rifaximin without the negative side effects.[6] Interestingly, some patients who did not respond to rifaximin as an initial treatment achieved treatment success using herbal therapies. In the event of steatorrhea, blood work is necessary to evaluate the levels of the fat-soluble vitamins A, D, and E. In the case of severe weight loss, supplementation of medium-chain triglycerides or digestive enzymes should be considered.[7]

In a study by Saffouri et al., researchers found that patients with irritable bowel syndrome (IBS) who followed a hydrolyzed formula diet with maltodextrin as the main component showed a reduction of symptoms following two weeks of treatment.[9] Although the exact mechanisms of the diet have not yet been clarified, there are three potential postulates for this formulated diet that could demonstrate equal success in the management of SIBO. First, maltodextrin is readily absorbed early in the GI tract; therefore, the bacteria could be eliminated or reduced through the removal

<table>
<tr><th colspan="3">PHASE 1 – Restrict & Repair</th></tr>
<tr><th>RESTRICT</th><th>SEMI-RESTRICT</th><th>AVOID</th></tr>
<tr><td>Protein
Meat, fish, poultry, eggs</td><td>Protein
Meat, fish, poultry, eggs</td><td>Protein
All legumes, lentils, beans</td></tr>
<tr><td rowspan="2">Vegetables (unlimited)
Bamboo shoots, bok choy, carrot, chives, cucumber, eggplant, witlof, ginger, kale, lettuce, olives, capsicum, radicchio, radish, spring onion (only green part), tomatoes, sunflower, and alfalfa sprouts</td><td>Vegetables
Parsnip</td><td>All Dairy</td></tr>
<tr><td>Vegetables (1 per meal)
Asparagus – 2-3 spears
Brussel sprouts – ½ c
Pumpkin – ½ c
Leeks – ½ c
Spinach >15 leaves/150g
Zucchini – 1 c</td><td>Vegetables
All potatoes & starch powder Arrowroot, corn, rice, tapioca, canned vegetables, onions, garlic, mushrooms</td></tr>
<tr><td>Vegetables (1 per meal)
Asparagus – 1 spear
Artichoke hearts – 1/8 c
Beet root – 2 slices
Broccoli – ½ c
Brussel sprouts – 2 ea
Butternut or kabocha – ¼ c
Cabbage – ½ c
Celery – 1 stick
Celery root – ½ c
Chili – 28g
Fennel bulb – ½ c
Green beans – 10 ea
Peas – ¼ c
Snow peas – 5 pods
Spinach – 15 leaves
Zucchini – ¾ c</td><td>Fruit (2 servings/day)
Banana – ½
Berries, any – ½ c
Citrus – 1 piece
Kiwi – 1 piece
Honeydew – ¼ c
Pineapple – ¼ c
Passion fruit – 1 piece
Rhubarb – 1 stalk
Avocado – ¼
Cherries – 3
Grapes – 10
Lychee – 5
Pomegranate – ½ small or ¼ c seeds</td><td>Fruit
Canned fruit in fruit juice Apples, apricots, blackberries, custard apple, fig, jam, mango, nashi, nectarine, peach, pear, persimmon, plum, watermelon

Grains
All grains, breads, cereals, cakes, biscuits

Soups
Canned soups & bouillons, broths made from chicken frames</td></tr>
<tr><td>Fruits (2 servings/day)
Lemon, lime</td><td>Grains
Quinoa, white rice: basmati or jasmine only – ½ c</td><td>Beverages
Soft drinks, fruit juices, wine, beer, dark liqueurs, spirits, energy drinks</td></tr>
<tr><td>Soups
Homemade broths: beef, lamb, or chicken</td><td>Sweeteners
Dextrose, Glucose, Organic honey – 2 tbsp/daily</td><td>Sweeteners
Xylitol, artificial sweeteners, agave nectar, maple syrup</td></tr>
<tr><td>Beverages
Water, herbal teas, black coffee (1 c/daily), black tea</td><td rowspan="2">Nuts/Seeds
Unsweetened almond milk (w/out added thickeners) – 1 c
Hazelnuts – 20 ea
Pecans – 40 ea
Walnuts – 100g</td><td>Nuts/Seeds
Peanuts, chia, or flax seeds</td></tr>
<tr><td>Sweeteners
Stevia (non-inulin containing)</td><td></td></tr>
</table>

Nuts/Seeds Almonds – 10 ea Coconut – ¼ c Coconut milk no thickeners – ¼ c Hazelnuts/Pecans/Walnuts – 10 ea Macadamia – 20 ea	**Condiments** Coconut amino Fish sauce – 2 tbsp	**Condiments** Spice sachets or premixes No maltodextrin, starches, sugar added asafetida, chicory root, gums/carrageenan/ thickeners, soy sauce/tamari, balsamic vinegar, onions, garlic
Condiments Sugarless mayonnaise, tabasco, wasabi, mustard (no garlic), vinegar, all fresh/dried herbs, turmeric, ginger	**Fats/Oils** Butter, infused oils (ie garlic or chili)	**Fats/Oils** Palm oil, soybean oil
Fats/Oils Coconut, olive, ghee, MCT, vegetable, grape seed, pumpkin seed, sesame, sunflower, walnut	**Data Source:** Jacobi, N. SIBO, Food Intolerance, and the Bi-phasic Diet Protocol. Naturalhealthresearch.org http://www.natu-ralhealthresearch.org/wp-content/uploads/2017/04/SIBO-Food-Intolerance-and-the-Bi-phasic-Diet-Protocol-Jacobi-HANDOUT.pdf	

of the substrates they require. Next, the researchers hypothesized that bacteria are transported away from the vulnerable area by the action of increased secretion of cholecystokinin, which in turn intensifies motility. Additionally, increased secretion of immunoglobulins may help eliminate non-resident bacteria from the small bowel. Finally, researchers suggested the diet itself helps modulate the composition of the microbiome.[9] The natural management approach to SIBO seems to be multifaceted and research conclusions suggest that nutrition therapy could be effectively utilized to help restore harmony to the microbiota in the future.[7]

RESULTS

Gewecke and Nannen-Ottens concluded that the objective of nutritional therapy should include restoring the intestinal lining, enhancing nutritional status, and preventing recurrence.[7] Incorporation of a hydrolyzed formula diet for treatment of SIBO in clinical practice is impractical as most Americans will likely struggle with compliance on a liquid nutrition diet that lasts for an extended period, unless their case is severe enough to warrant hospital admission. Although research on nutritional interventions remains unfinished, based on the principle that bacteria from the large intestine inadvertently populate the small intestine, and are fermenters of short-chain carbohydrates, it can be hypothesized that a diet restrictive in fermentable short-chained carbohydrates may be an effective way to manage symptoms of SIBO. Jacobi proposed combining the low FODMAP and Specific Carbohydrate Diet into a Bi-Phasic Diet Protocol with the goal of helping eliminate bacterial overgrowth from the small intestine.[10] This approach could result in better patient compliance and be easier to implement in clinical practice.

The Bi-Phasic Diet Protocol employs a method of treatment that restricts the side effects of rapid bacterial and fungal death. The elimination of microbes quickly creates a release of endotoxins, which the body absorbs causing adverse side effects. These side effects can be overly intense for some people. Phasing nutritional intervention via stages leaves time for the body to repair damage to the intestines caused by the non-resident microbes, in turn restoring disturbed digestion to a healthy state.[10] Although this diet plan contains a re-challenging period, it is best to personalize a patient's diet according to individual tolerance. This can produce the best results for digestive symptom management.[10]

The first phase of the diet is the elimination phase. This phase is designed to starve the bacteria of necessary substrates for their continued existence by eliminating all grains and fermentable fiber such as legumes, dairy, sugar, and certain vegetables, as well as canned, processed, and fermented foods. This phase of the diet is accomplished in two successive stages comprised of restrictive and semi-restrictive. It is difficult to give a standard time-length recommendation as there are other factors involved in the treatment of SIBO. The length of time spent in each stage of phase one depends on the severity of symptoms and how quickly they resolve. Typically, phase one is accomplished in 4-6 weeks but can last longer in severe cases.[10]

During the next phase of the diet, restoration of the normal motility of the small intestines is desired. Foods from phase one plus new foods are slowly

PHASE 2 – Restore	
ADD	AVOID
Protein Meat, fish, poultry, eggs	
Dairy (organic only) Homemade yogurt, butter, cheese (aged 1+ month, ie parmesan, pecorino)	**All other dairy**
Vegetables (1-2 servings per meal) Brussel sprouts – ½ c Cauliflower – ½ c Cabbage – ½ c	**Vegetables** All potatoes & starch powder Arrowroot, corn, rice, tapioca, canned vegetables, onions, garlic, mushrooms
Fruit (use discretion) Apples, apricots, blackberries, custard apple, fig, jam, mango, nashi, nectarine, peach, pear, persimmon, plum, watermelon	**Fruit** Canned fruit in fruit juice
Grains Plain rice cakes – 2 Rice noodles – 1/3 c cooked	**Grains** All grains, breads, cereals, cakes, biscuits
Legumes (cooked) Lentils: - Brown – ½ c - Green/Red ¼ c Lima Beans – ¼ c	**Legumes** All others
Beverages Clear spirits – no more than 30ml every other day	**Beverages** Soft drinks, fruit juices, wine, beer, dark liqueurs, sprits, energy drinks
Sweeteners Raw cocao – 1 tsp/daily	**Sweeteners** Xylitol, artificial sweeteners, agave nectar, maple syrup
	Soups Canned soups & bouillons, broths made from chicken frames
	Nuts/Seeds Peanuts, chia, or flax seeds
Data Source: Jacobi, N. SIBO, Food Intolerance, and the Bi-phasic Diet Protocol. Naturalhealthresearch.org http://www.naturalhealthresearch.org/wp-content/uploads/2017/04/SIBO-Food-Intolerance-and-the-Bi-phasic-Diet-Protocol-Jacobi-HANDOUT.pdf	**Condiments** Spice sachets or premixes No maltodextrin, starches, sugar added asafetida, chicory root, gums/carrageenan/ thickeners, soy sauce/tamari, balsamic vinegar, onions, garlic

challenged and reintroduced. Fermentable fibers are important prebiotics and necessary to feed the microbiome, which performs many vital functions. The goal of reintroducing these foods is to eventually reinstate those fibers.[10] Fermented foods should be reintroduced as well to help repopulate the bowel with beneficial microbes. Food sensitivities must be taken into consideration while administering the Bi-Phasic Diet. Histamines, oxalates, and salicylates located within specific foods can cause adverse reactions in those with a severely disrupted mucosal lining of the small intestines.[10] As the mucosal lining repairs, food reactions ought to clear up, but patients should be closely monitored while re-challenging foods that cause known consequences. Most forms of alcohol can result in intestinal inflammation, hyperpermeability, and reduced microbial diversity. Thus, as a general recommendation, alcohol should be avoided while attempting to treat SIBO. However, emerging observational research suggests the polyphenols in red wine may create a more hospitable environment that favors diverse gut micro-organisms.[11]

DISCUSSION

The concept that structure governs function is well known in the physiology realm; therefore, optimal structure favors the best function. This poses the question: how are healthcare providers ensuring the most favorable health of vital structures? If fundamental structures are made of cells, and all cells are made of essential compounds that require other specific compounds to continue to work efficiently, how is an optimal function at a physiological level guaranteed? Defects reveal irregularities when functionality is compromised. Since the GI tract is ultimately required

as a medium of adsorption of essential nutrients, protecting its health is of utmost importance.

SIBO can negatively alter absorption in the digestive system.[5] In the absence of proper nutrients, structures of the body can undergo adverse changes leading to a failure of the physiology.[12] A functional approach can be utilized to help restore balance to the intestinal flora without the side effects of antibiotics. Herbal supplements, in combination with dietary and lifestyle changes, create a platform of success in the fight against bacterial overgrowth. One retrospective study demonstrated that herbal therapy has the potential to be as effective as antibiotic therapy for the treatment of SIBO.[6] The herbs utilized in this study were proposed to be antibacterial, anti-anxiety, anti-depressant, anti-diarrheal, and growth-inhibitory agents, some have anti-inflammatory properties which can be important for intestinal repair.[6] It is important to appreciate that data regarding herbal supplements for SIBO is limited and that products available may differ considerably in both composition and quality.

There have been significant changes in our understanding of SIBO and how to approach treatment. In clinical practice, a functional approach to SIBO could include combination therapy of diet and supplementation. Alternative therapy can represent a reasonable option for those that are unresponsive to traditional conservative treatment methods. This is relevant as approximately 40% of patients with SIBO symptomatology may not experience resolution of symptoms with antibiotic therapy.[13] The patient could be placed on the Bi-Phasic Diet until symptom resolution began, at which point herbal therapy as described above could be introduced. Herbal therapy would proceed for four weeks while continuing strict adherence to the diet plan. If the patient presented with steatorrhea, they could be given bile salts to take with meals.[5] After completion of dietary phase one and herbal therapy combination, a further goal becomes restoring the normal microbiome with probiotic supplementation.[14]

Bifidobacterium longum supplementation was found to drastically improve emotional function scores in a randomized controlled trial involving 120 patients with GI conditions, and several other studies have referenced the benefits of probiotic therapy as well.[14] The patient could be placed on a probiotic combination to provide 1–5 billion CFU: *Lactobacilli: L. acidophilus, L. rhamnosus Bifidobacteria: B. bifidum, B. lactis, B. longum, B. breve.*[14] Equal importance is given to nutritional supplementation to help prevent a reoccurrence of SIBO symptoms by supplying essential nutrients that can be deficient in a diseased state, such as zinc (75 mg), glutamine (750–1,500 mg), and antioxidants such as quercetin (400–800 mg), Vitamin C (1,000–2,000 mg), and Vitamin E (200–400 mg).11 Furthermore, supplementation with digestive plant enzymes can help regulate impaired digestion caused by GI pH imbalances following a bout with SIBO.[14]

CONCLUSIONS

A functional approach to SIBO may be a valid method to treat the condition. The process focuses on identifying and removing the root causes of the disease, then utilizes a comprehensive approach to restore normal digestive function and health. Although time consuming, it can produce lasting results and is less costly. With a myriad of disease processes associated with SIBO, proper diagnosis is vital. Breath tests can be a safe option utilized in the office or via a take-home kit. Patient education is the cornerstone to the effectiveness of treatment. It is imperative that patients understand functional treatment is a lengthy process, but compliance is necessary to recover a higher quality of life. A healthy diet, appropriate supplementation, adequate water intake, daily exercise, and proper sleep are key components of overall health. The use of a functional approach in the treatment of SIBO may have a significant impact on the health and wellbeing of patients.

Competing Interests: The authors declare they have no competing interests.

Funding: Not applicable.

Acknowledgments: Not applicable.

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Evidence-based Recommendations for the Treatment and Management of Ulcerative Colitis

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ABSTRACT

Background: Ulcerative Colitis (UC) is a chronic inflammatory bowel disease involving the mucosa of the rectum that commonly affects those between the ages of 15 and 30 years and is characterized by exacerbations and remissions.

Methods: A literature review was performed relevant to the clinical practice of UC utilizing a functional approach to treatment. Nutritional interventions with evidence were analyzed and reviewed.

Results: Treatment goals should focus on a combination of symptomatic remission and mucosal healing through correction of nutritional inadequacies and targeted supplementation with sufficient evidence. Support for interventions including a low FODMAP diet, restoration of gut microbiota through probiotic supplementation, and mind-body therapies were discussed.

Conclusions: A functional management strategy for UC is suggested that is guided by nutritional interventions that are evidence-based.

Key Words: ulcerative colitis, dietary management, microbiota, nutritional adequacy

INTRODUCTION

An emerging trend in patient care illuminates an important point about what happens when conventional treatments fail. Patients are likely to search for alternative care. Research indicates this is often the case when patients are suffering from functional gastrointestinal disorders.[1] Current thinking recognizes the independence of a traditional allopathic approach while also acknowledging and respecting the contributions from alternative medicine. They are viewed as more complimentary to each other than competitive. As one alternative approach, functional medicine is a complex, patient-centric interpretation of health care that looks to address disease through multilayered, biochemical individuality.[2] It operates through a series of integrated principles that offer an all-encompassing, biochemical approach to pathology. Functional medicine examines the root causes of disease on a cytological and splanchnological level, recognizing how environmental factors, i.e. diet, lifestyle, and stress, can affect physiology and, in turn, genetic predisposition.[3] In all, it offers a comprehensive and detailed understanding of a patient's functional requirements. Much of scientific literature aims to evaluate isolated treatment protocols for the management of Ulcerative Colitis (UC). The objective is to present a comprehensive perspective of the underlying pathophysiology of the condition through complementary, evidence-based methodologies. Ultimately, this functional approach will focus on various forms of dietary augmentation and psychological considerations.

Ulcerative Colitis (UC) is a non-specific, non-transmural inflammatory disease of the gastrointestinal (GI) tract that commonly affects the mucosal lining of the large intestine and leads to endoscopic corrosion and/or ulceration.[4] While the etiology is unknown its pathogenesis is considered multifactorial including intestinal microbiota and composition, genetic susceptibility, environmental factors (diet, drugs, injection, geographical location, and stress).[5,6] The expression and severity of UC can be markedly variable, ranging from mild to severe in classification and affecting different parts of the colonic mucosa. Location-based cataloguing includes proctitis, distal colitis (up to the sigmoid colon), left-sided colitis (up to the splenic flexure), and pancolitis.[7] UC is also characterized by cyclical episodes of relapse and remission in which there can be resolution of symptoms and pathogenic activity along the colonic lining. In severe cases, characteristic UC symptomatology includes persistent or recurrent hematochezia and/or mucous stools, elevated frequency of bowel movement, diarrhea, weight loss, abdominal pain, fever, and anemia.[7]

The large intestine plays a critical role in metabolism and the proper function of internal systems. Basic physiology of the large intestine is centered around absorption and production of vitamins, i.e. Biotin

and Vitamin K, and further absorption of water and electrolytes. Due to the detrimental, inflammatory nature UC has on the colonic mucosa, nutritional complications are common during both relapse and remission. Examples of nutritional impairment include nutrient malabsorption and macro- and/or micronutrient deficiencies due to reduced dietary intake.[8]

METHODS

There is a growing interest in research examining the efficacy of dietary intervention as a therapeutic approach to induce and maintain remission of UC flare-ups. Rationale for this interest is driven by patient preference and the failure of traditional pharmacological treatments like 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, and biologics to provide adequate symptom relief without accompanying adverse side effects.[8] Due to the known physiological interplay of nutrition, metabolism, and gut microbiota, engineered dietary intake modification should theoretically have a tremendous impact on patient symptomatology. Research conducted using diet to address UC has shown some promise.[9-11]

Food Group	High FODMAP Food	Low FODMAP Food
Fruit	Apples, Apricots, Cherries, Blackberries, Most dried fruit, Peaches, Pears, Plums, Watermelon, Mango, Nectarines	Banana, Blueberry, Cantaloupe, Grapefruit, Grapes, Kiwi, Lemon, Line, Orange, Passionfruit, Pineapple, Raspberry, Strawberry
Vegetables	Artichokes, Asparagus, Cauliflower, Garlic, Sweet Potato, Mushrooms, Onion, Peas, Spring Onion	Carrot, Celery, Chives, Corn, Cucumber, Eggplant, Ginger, Green beans, Lettuce, Olives, Peppers, Potato, Spinach, Tomato, Yams, Zucchini
Protein Sources	Cashews, Baked beans, Red kidney beans, Pistachio nuts	Beef, Chicken, Eggs, Lamb, Macadamia nut, Peanut, Pork, Tofu, Veal, Walnut
Grains	Barley, Rye, Wheat	Buckwheat, Corn, Gluten-free bread, Oats, Quinoa, Rice, Spelt
Dairy	Lactose, Cow / Goat milk, Custard, Ice cream, Yogurt	Almond milk, Butter, Feta cheese, Hard cheeses, Rice milk
Other	Honey, Sorbitol or mannitol, High fructose corn syrup	Maple syrup, Regular syrup (sucrose), Glucose

Nanayakkara WS, Skidmore PM, O'Brien L, Wilkinson TJ, Gearry RB. Efficacy of the low FODMAP diet for treating irritable bowel syndrome: the evidence to date. *Clin Exp Gastroenterol*. 2016;9:131–142. Published 2016 Jun 17. doi:10.2147/CEG.S86798
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RESULTS

Low-FODMAP Diet

It is believed that certain foods can act as etiopathogenetic and/or exacerbating factors of UC due to their molecular composition.6 One such catalogue of antagonistic bioactive ingredients is indicated by the collective term FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyol. These substances include fermentable short-chain carbohydrates such as fructose, lactose, fructans, galacto-oligosaccharides, and polyalcohols.7 The disposition of these osmotically active carbohydrates leads to poor absorption in the small intestine, which can result in an increased passage of water to the large intestine and/or diminished enzymatic activity.[6] Once FODMAPs are passed to the colon, they are rapidly fermented by colonic microbiota and produce excess gas. Consequently, GI complications arise like abdominal pain, bloating and diarrhea.[9] In addition, FODMAPs have been clinically linked to alterations in intestinal motility and volume.[6]

Select restriction of dietary intake has been shown to be an effective method in the reduction of UC symptomatology.[9-11] Numerous randomized controlled trials (RCTs) have demonstrated statistical and clinically significant improvements in overall quality of life.[13] General dietary recommendations include cutting the daily intake of FODMAPs from 15–30 g/day (commonly found in the usual diet of patients), to 5–18 g/day.[19] Patients are then instructed to maintain this restriction for 4-8 weeks before FODMAPs are slowly reintroduced to patient tolerance.[6]

Gut Microbiota

The Low FODMAP Diet is meant to serve as a temporary solution for those suffering from UC and Irritable Bowel Syndrome (IBS) symptoms. This is due to the detrimental effect dietary restriction of FODMAPs can have on gut microbiota. Fructans and galacto-oligosaccharides provide a meaningful prebiotic function within the gut mucosa and thus their restriction may lead to reduction of beneficial bacteria.[14] RCTs have demonstrated that reduction of carbohydrates resulted in a notable decrease in concentration and proportion of luminal Bifidobacteria after only several weeks.[6] Furthermore, metagenomic studies have established that UC is described by dysbiotic microbiota in the gut with hampered microbial diversity and stability[15] Concern has been raised that further alteration of this microbiota could provoke additional pathological side-effects.[6]

The Efficacy of Probiotics, Prebiotics, & Synbiotics

The International Scientific Association for probiotics and prebiotics has provided a consensus statement on both the scope and appropriate use of the term probiotic. Important highlights of that document for both the patient and the physician include a clear distinction in the claims of what constitutes a probiotic. For example, if the label claim states "Contains live and active cultures" that is not considered a probiotic by the expert panel as those label claims to do not imply probiotic activity.[16] This would also include fermented foods. What is considered a probiotic includes specific foods or supplements with claims such as "contains probiotics", "helps to reinforce the body's natural defenses in children", "helps to reduce the risk of antibiotic-associated diarrhea", or as a drug "useful for the prevention of relapse of ulcerative colitis".[16] This is an important consideration when making recommendations for probiotics.

The use of probiotics can serve as an aid to restrictive diets in the treatment of UC by supplementing subsequent microbiota deficiencies. Probiotics contain many of the beneficial microorganisms lost throughout the course of UC in sufficient amounts to exert positive health effects.[14] Probiotics mostly contain bacteria like Bifidobacteria and Lactobacilli, which were shown to be the most negatively affected microorganisms of the low FODMAP diet. Replenishment of these bacteria along with the added supplementation of other organisms found in probiotics, such as Escherichia coli and the yeast Saccharomyces boulardii, have been found to prolong remission of symptoms.[15] These organisms are thought to reduce symptomatology by modulating membrane permeability and the colonic immune system.15 Probiotic bacteria also release bioactive substances like short-chain fatty acids (SCFAs) that have potent immunomodulatory effects, are influential factors in anti-inflammatory gene regulation processes, and are key players in the maintenance of intestinal lining function.[15]

The most well-researched probiotic for use in achieving remission of UC is VSL#3. It is a highly concentrated mixture of 8 live bacterial strains, including *Streptococcus thermophilus,* 4 strains of *Lactobacilli (L. paracasei, L. plantarum, L. acidophilus,* and *L. delbrueckii),* and 3 strains of *Bifidobacteria (B. longum, B. breve,* and *B. infantis).*[17] Appraisal of peer-reviewed literature has yet to yield an established dietary recommendation concerning the bacterial concentration and frequency of VSL#3 supplementation, but RCTs have consistently reported successful outcomes in achieving remission of UC. One such RCT found that patients given VSL#3 at 900 billion bacteria/day for 6 weeks experienced 50% improvement in UC activity and at 12 weeks, 42.9% of patients achieved remission.[17]

Prebiotics and synbiotics are other substances that can be utilized to supplement probiotics in the treatment of UC. Prebiotics are defined as materials applied by microorganisms, i.e., probiotics, that confer a health benefit to its host organism.[15] Synbiotics are a comprehensive collection of prebiotics and complementary probiotic bacteria. Research conducted on the efficacy of synbiotics found that patients with UC experienced significant improvements in colonic integrity and reduced inflammation.[15] While effective, prebiotics can normally be obtained in adequate amounts through dietary intake, so utilization of prebiotic and symbiotic supplementation may be best warranted in severe cases.

Curcumin

The anti-inflammatory and antioxidative properties of curcumin have led medical professionals to consider it as an adjunct treatment option for UC. While its application is sensical in theory, current research has offered conflicting and often inconsistent evidence of its effectiveness. A RCT found that an intake of 3g/day was moderately beneficial when paired with traditional corticosteroid therapy at inducing the remission of UC.17 Similarly, another RCT found that curcumin taken in 2-3g daily increments was moderately effective at maintaining remission when paired with the same traditional therapy.[17] However, a recent systematic review and meta-analysis concluded that adjunct curcumin does not appear to contribute to either attaining or maintaining remission of UC symptoms.[18] The meta-analysis cited the quality and unreliability of several other RCTs as justification for this conclusion, but with the caveat that the lack of substantiated

evidence in its review did not discredit curcumin as a therapeutic agent.

Enzymatic Supplementation

Although UC is normally isolated to the colon, the corrosive, inflammatory nature of the condition can negatively affect the entire digestive system. It can alter the physiology of the small intestine, e.g. the ileum, and directly affect basic enzymatic activity. To combat this potential progression, enzymatic supplementation has been speculated as a potential, compensatory treatment. Anecdotal evidence suggests that bromelain, a protein-digesting enzyme with anti-inflammatory properties, can decrease inflammation in UC.[20] This has been demonstrated in vitro, where it was found to reduce levels of pro-inflammatory cytokines and chemokines in inflamed tissue.[20] It was also found to significantly reduce UC symptoms in two women who were adjunctively taking medication.[20] Despite the limited quality and quantity of current evidence supporting the use of enzymatic supplementation, the approach may warrant additional examination due to its known physiologic associations.

Amino Acids: Glutamine

Amino acids are notoriously known as the building blocks of nearly all biological processes. They are essential for intestinal development and the preservation of the mucosal barrier function.[21] Glutamine is among the most important and the most utilized amino acid in the intestine. Studies have shown that about 30% of the total glutamine content in the body is absorbed and metabolized by intestinal cells.[23] It is known to have a direct impact on gut physiology by influencing various processes, including stimulation of enterocyte proliferation, regulation of tight junction proteins, modulation of pro-inflammatory pathways, and

Step	Recommended Treatment	Rationale
Step 1a	Mind-Body Therapies • 16-20 weeks	Psychological stress is a major factor in the severity and duration of UC. Mind-body therapies should be utilized throughout the duration of treatment to help mitigate its detrimental effects and speed the time of recovery. Patients should be given the freedom to select whatever mind-body therapy is most comfortable and viable to them with the stipulation that they try other recommended therapies if marked improvement is not observed.
Step 1b	Low – FODMAP Diet • 5-18 g/day for 4-8 weeks	The primary goal in acute flare-ups of UC should be symptom management. Restriction of antagonistic foods will help to calm the GI system and reduce adverse symptomatology. Strict adherence to this diet will also help to reset the colon and create a bare environment where positive reconstruction can occur.
Step 1c (Optional)	Curcumin Supplementation • 3g/day for 4-8 weeks	Curcumin supplementation should be considered as an adjunct to the low-FODMAP diet. The goal of curcumin ingestion is to reduce intestinal inflammation, so it is perfectly suited to act as a complementary measure.
Step 2a	VSL#3 Supplementation • 900 billion bacteria/day for 12 weeks	Beneficial gut microbiota now needs to be reintroduced into the colon following the cleansing of the low-FODMAP diet. The proliferation of new, healthy gut microbiota will support the restoration of normal intestinal function and promote colonic healing.
Step 2b	Glutamine Supplementation • 21 g/day for 12 weeks *(28 days minimum)*	The body should be well primed to begin repairing damaged tissue. Glutamine should be ingested to facilitate the reconstruction of the intestinal lining. Coupled with healthy gut microbiota, the two agents will work in tandem in the restoration process.

shielding from necrosis induced by stressful pathologic conditions.[23] Consequently, glutamine supplementation is an active focus of study in the healing and repair of damaged intestinal tissue.

Most of our current understanding of how the therapeutic effects of glutamine could be used to augment the treatment of chronic inflammatory conditions like UC is based upon experimental animal studies. Despite ranging wildly in methodology, criteria, and focus, a plethora of research exists supporting the efficacy of glutamine supplementation for the suppression of immunological response and colitis-based symptomatology in rats and mice.[23] However, less convincing evidence exists for its effectiveness in treating humans; only a limited number of studies have reported favorable outcomes. Included in that minority is a systematic review that found that 21g of glutamine/day for 28 days was effective in improving the intestinal permeability and cellular morphology in patients with Crohn's disease.[23] While no directly comparable study currently exists for UC, the similar pathophysiology of both diseases provides circumstantial evidence that glutamine could be a viable treatment. In addition, most of the current research on the therapeutic effects of glutamine are observational in nature, so future research must focus on understanding the underlying mechanisms behind its physiological effects.

The Mind-Body Connection

It is well documented that UC and psychological stress are interconnected in pathogenesis and expression. While UC's etiology is thought to be multifactorial, it is understood to be the byproduct of complex genetic and environmental interactions. Stress, an environmental factor, has been proven to have a direct effect on the Central Nervous System (CNS) through its complex interaction and integration with the hypothalamus, amygdala, and hippocampus of the brain.[24] This connection, in turn, also has a direct effect on the immune system and gastrointestinal function. It is through this relationship that stress can act as a pro-inflammatory agent and detrimentally affect gastrointestinal motility and water and ion secretion.[23]

Mind-body therapies have been shown to adequately address psychological stressors and improve the quality of life in patients with UC.[17] These therapies include an array of cognitive, relaxation, yoga, hypnotherapy, and/or exercise-based approaches that help reduce stress perceptions and improve patient symptomatology.[17] This has been repeatedly demonstrated in various RCTs focused on these distinct therapeutic approaches. For example, patients with UC in remission were found to have a higher probability of maintaining remission after undergoing 7 sessions of gut-directed hypnotherapy over the course of a year.[14] Collectively, mind-body therapies offer an alternative, complimentary tactic to treat UC.

DISCUSSION

Incorporation into Practice

The complex pathogenesis and diverse presentation of UC does not lend itself to a simple, singular treatment plan. Cases will need to be examined on an individual basis and with consideration of the patient's overall constitution, lifestyle habits, psychological status, and environmental exposures. Patient progress should be monitored regularly, and treatment amended accordingly.

A colonoscopy may be warranted to assess the severity and status of patients' UC condition. The primary, non-intrusive indicators of UC are all linked to patient symptomology; this should be monitored regularly using objective measures like the Crohn's and Ulcerative Colitis questionnaire (CUCQ).[25] The duration of recommended treatments may vary depending on clinical case. Specific recommendations regarding enzymatic supplementation are not justified at this time due to insufficient evidence supporting its efficacy in treating UC. However, patients should not be discouraged from utilizing moderate supplementation of enzymes like bromelain or lactase to serve as a digestive aid.

CONCLUSIONS

UC is a chronic, auto-immune disease that can drastically affect the lives of those who are diagnosed with it. It is important to make patients aware of the fact that there is no cure for the condition, but remission is possible if proper steps are taken. Patients should never be allowed to feel a sense of hopelessness or despair about the state of their health and should instead feel empowered by the evidence supporting the methodologies presented in this approach. Wellness is achievable through diligence, persistence, and a positive attitude.

Competing Interests: The authors declare they have no competing interests.

Funding: Not applicable.

Acknowledgments: Not applicable.

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