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1 Overview

Summary and Quick Facts for Inflammatory Bowel Disease (IBD)

- Inflammatory bowel disease (IBD) is a broad term describing a collection of conditions that affect the digestive tract, the most common being Crohn's disease and ulcerative colitis. The main goals of IBD treatment include managing inflammation and correcting vitamin deficiencies. Importantly, IBD can increase risk of colon cancer, so those diagnosed with IBD should have regular colon cancer screenings.
- In this protocol you will learn about blood tests that are used to detect nutritional deficiencies and monitor inflammation and disease progression. You will also learn about the positive and negative effects of conventional IBD treatment, along with several natural ingredients that can help regulate gut health and manage chronic inflammation.
- By combining conventional medical therapies with a healthy diet, regular exercise and the natural interventions discussed in the protocol, you can reduce chronic inflammation and improve outcomes associated with IBD.
- Probiotics and omega-3 fatty acids have immune enhancing and anti-inflammatory properties that can help manage symptoms associated with IBD.

What is Inflammatory Bowel Disease?

Inflammatory bowel disease (IBD) encompasses a collection of conditions that affect the digestive tract. The two most common types of IBD are Crohn's disease (usually affecting the lower small intestine) and ulcerative colitis

(affecting the large intestine). IBD results from immunologic imbalances in the gut that lead to chronic inflammation. Suppressing inflammation is the chief goal of IBD treatment.

IBD patients are at increased risk of colon cancer, cardiovascular disease, and other inflammatory conditions. Therefore, people diagnosed with IBD should have regular colon cancer screenings and monitor inflammatory markers.

Natural interventions such as **vitamin D** and **probiotics** may help reduce inflammation and modulate immune function for patients with IBD.

What are the Signs and Symptoms of Inflammatory Bowel Disease?

Note: Crohn's disease and ulcerative colitis can have similar symptoms and may include:

- Severe abdominal pain
- Diarrhea (often with blood, mucus, and/or pus)
- Painful bowel movements
- Fever
- Fatigue
- Loss of appetite and weight loss

What are Conventional Medical Treatments for Inflammatory Bowel Disease?

- Anti-inflammatory drugs (eg, 5-aminosalicylic acid and corticosteroids)
- Immunosuppressing drugs (eg, azathioprine, cyclosporine, and methotrexate)
- Other drugs (eg, cromolyn sodium and naltrexone)
- Surgery to remove severely damaged sections of the intestinal tract

What Dietary and Lifestyle Changes Can Be Beneficial for Inflammatory Bowel Disease?

- Crohn's disease patients should quit smoking
- Avoid foods that cause sensitivity. Bothersome foods vary between individuals, so get tested for IgG antibodies and eliminate any foods that cause symptoms.
- Supplement to correct potential nutrient deficiencies.
- Crohn's disease patients should consider avoiding the use of aspirin.
- Ulcerative colitis patients should consider avoiding foods high in sulfur-containing amino acids.

What Natural Interventions May Be Beneficial for Inflammatory Bowel Disease?

- **Probiotics**. Alterations in the gut microbiome can influence immune function. Multiple clinical trials have shown benefits of probiotic use in patients with IBD. **Bacteriophages**, viruses that target bacteria, have also gained interest for improving IBD by ridding the gut of harmful bacteria.
- **Omega-3 fatty acids**. Omega-3 fatty acids are powerful immunoregulatory agents that reduce circulating inflammatory cytokines. Clinical trials in patients with IBD have shown benefits of supplementation and correlation with disease remission.
- **Vitamin D**. Vitamin D is an immunomodulator that aids in suppressing inflammation in the gut. Patients with IBD often have low vitamin D levels. Taking vitamin D may lower the risk of relapse in IBD patients and improve bone health, which is important as bone loss is a major concern in patients with IBD.
- **Antioxidants**. Patients with IBD have high levels of reactive oxygen species in their intestines, which contributes to damage caused by the disease. An antioxidant combination of **vitamins A**, **C**, **E**, and **selenium** in combination with fish oil can reduce certain inflammatory markers in Crohn's disease.
- **Curcumin**. Curcumin inhibits the inflammatory signaling protein NF-κB, which is important in IBD. Curcumin reduced symptoms of IBD in a small clinical trial and improved the relapse rate when used as an adjuvant therapy in another.
- **Boswellia**. Resin from Boswellia trees, which contains a powerful anti-inflammatory compound, has been shown to be as effective at treating IBD as some conventional drugs.
- **Wormwood**. Wormwood blocks the proinflammatory cytokine TNF-α, which may account for its effectiveness at maintaining remission in Crohn's patients who tapered off their medications.

- **Aloe gel**. Gel from the inside of aloe leaves has immunomodulating, gut healing, and inflammation-quelling properties. Patients with ulcerative colitis saw acute flares improve with aloe gel.
- **Butyrate**. Butyrate, a short-chain fatty acid produced from the metabolism of intestinal fiber, has provided relief for both Crohn's and ulcerative colitis patients.
- Other natural interventions that may benefit patients with IBD include **L-carnitine**, **glutamine**, **melatonin**, **vitamin K**, and others.

2 Introduction

"Inflammatory bowel disease" describes a collection of conditions affecting the digestive tract. *Crohn's disease* and *ulcerative colitis* are by far the most prevalent and thus are the focus of this protocol.

Inflammatory bowel disease is a result of ***immunologic imbalances*** at the interface of the *intestinal lumen* (the "hollow" part of the digestive tract through which food passes) and the *intestinal epithelium* (the inward-facing surface of the intestinal wall). Suppressing inflammation is the chief goal of both conventional *and* integrative treatment. However, potent immunosuppressive medications employed in inflammatory bowel disease, such as *glucocorticoids*, are laden with side effects; which greatly limits their long-term efficacy (Bernstein 2011; Cosnes 2009; Rutgeerts 1994).

On the other hand, several natural interventions such as **omega-3 fatty acids**, **vitamin D**, and **probiotics** *modulate* immune cell function without impairing infection-fighting ability, which is one of the many side effects of *TNF-inhibitors*, another class of drugs used in inflammatory bowel disease (Cosnes 2009).

Patients with inflammatory bowel disease are predisposed to **colon cancer**. Even between disease flares, low-level inflammation irritates and damages intestinal tissue, which can lead to malignancy. This sub-clinical inflammation also propagates systemically, which can increase cardiovascular risk (Ruffolo 2010; Henriksen 2008). Therefore, not only is it imperative that patients with inflammatory bowel disease have regular colon cancer screenings, but also that they monitor inflammatory markers in their blood such as **C-reactive protein (CRP)** and **interleukin-6 (IL-6)**. In this protocol, you will learn how several natural ingredients powerfully regulate gut immunity and complement the action of conventional treatments to quench the fires of inflammatory bowel disease. You will also discover several convenient **blood tests** that can help identify nutritional deficiencies due to *malabsorption* – a common problem in inflammatory bowel disease. By integrating dietary strategies, evidence-based nutritional support, and pharmaceutical therapeutics one can develop a comprehensive program to help manage inflammatory bowel disease during both disease flares *and* periods of remission.

3 Anatomy of the Digestive Tract and Immunology of Inflammatory Bowel Disease

The digestive tract consists of a single long tube that has many folds and convolutions and extends from the mouth to the anus. The tube is divided into distinct parts (such as the esophagus, stomach, small intestine, and large intestine), each with a specific structure and function. Solid organs such as the liver and pancreas are also considered portions of the digestive system.

The hollow parts are responsible for breaking down large portions of food into small molecules that can be readily absorbed into the circulation. The sterile bloodstream is separated from the mass of nutrients, toxins, and organisms in various parts of the hollow digestive tract by only a very thin layer of cells, collectively called the ***intestinal mucosa***. This delicate and complex lining is responsible for secreting substances that aid in digestion and absorption of nutrients, and for defending the body against the toxins and other contaminants in the intestine itself.

The intestinal mucosa must selectively allow entry of beneficial molecules while excluding toxins and organisms that could be harmful. To do this, the mucosa is equipped with several kinds of cells including secretory cells that produce a layer of mucus to trap contaminants, immune cells that directly attack and destroy invading organisms (macrophages), and other inflammatory cells (neutrophils, killer T cells, and others) that respond to the presence of foreign molecules by producing proinflammatory *cytokines* (small cell-signaling protein molecules) (Abraham 2009).

During healthy conditions, the immune cells in the intestinal lining cope with invaders quickly and efficiently,

without producing excessive amounts of localized inflammation. However, in inflammatory bowel disease, inflammation becomes uncontrolled. Cytokines released by inflammatory cells in the intestine attract additional immune cells that produce destructive chemicals and propagate inflammation (Neuman 2004). In particular, a subset of inflammatory immune cells called **Th17 cells** are principally responsible for driving inflammation in Crohn's disease, while **Th2 cells** drive inflammation in ulcerative colitis. A number of factors cause Th17 and Th2 cells to produce excessive inflammation including penetration of the intestinal epithelium by gut microbes, composition of the intestinal microbiota, injury to the intestinal wall, insufficient mucus layer production, and allergies or sensitivities to foods. Genetics contribute to inflammatory bowel disease susceptibility, but the immune response as well as the intestinal microenvironment and diet can be modified to mitigate inflammatory propensity, even in genetically predisposed individuals.

Since the inflammatory reactions taking place in the gut can promote systemic inflammation people with IBD should monitor levels of inflammatory cytokines in their blood. Cytokine testing can be used as a measure of the effectiveness of anti-inflammatory therapies, and can also help determine risk for other conditions associated with inflammation, such as atherosclerosis. Cytokine blood profiles measure tumor necrosis factor-alpha (TNF-α), interleukin-1 (beta) (IL-1b), and interleukin-6 (IL-6).

4 Crohn's Disease: Background and Diagnosis

Crohn's disease can attack any portion of the digestive tract, although inflammation most commonly occurs in the lower portion of the small intestine, known as the *ileum*. The disease can cause ulcerations within the intestine that can erode into surrounding tissues such as the bladder (Sato 1999), vagina (Feller 2001), or even the surface of the skin (Tavarela 2004). Inflammation in Crohn's disease is not limited to the intestine—some people who have Crohn's disease have inflammation of the eyes and joints as well.

The most common symptoms of the disease include severe abdominal pain with or without diarrhea. Diarrheal stool may be mixed with blood, mucus and/or pus. Bowel movements are often painful. Cramping in the right lower side of the abdomen is common, especially after meals. People with Crohn's disease often have chronic low-grade fever, poor appetite, fatigue, and weight loss. Skin rashes may also occur. People who have Crohn's disease often have some degree of anemia, related to poor iron, folic acid, and/or vitamin B12 absorption and due to chronic blood loss. Those with mild Crohn's can eat and function reasonably normally, while those with severe disease often fail to respond to conventional treatment and have persistent gastrointestinal symptoms, as well as fevers, and infections. Blood tests for ferritin, which measures iron storage, and vitamin B^{12} and folate can help detect deficiencies due to malabsorption.

Diagnosis of Crohn's disease is usually based on a patient's medical history and symptoms. Diagnostic tests may be used to confirm the disease and to distinguish it from ulcerative colitis. Such tests include x-rays (with contrast material such as barium), colonoscopy, and endoscopy.

No blood test can diagnose Crohn's disease, but routine testing is usually done to detect anemia, infection, degree of inflammation, and determine liver function. Certain markers of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be used to follow a patient's course over time. The anti-*Saccharomyces cerevisiae* antibody (ASCA) blood test is sometimes used to help differentiate Crohn's disease from ulcerative colitis (Vermeire 2001).

There is a high prevalence of Celiac disease in people with Crohn's disease (Tursi 2005). Celiac disease blood testing such as tissue transglutaminase and anti-gliadin antibodies should be considered in Crohn's.

Ulcerative Colitis: Background and Diagnosis

Ulcerative colitis is characterized by inflammation of the large intestine (colon) that leads to episodes of bloody diarrhea, abdominal cramping, and even fever. Unlike Crohn's disease, ulcerative colitis usually does not affect the full thickness of the intestine and rarely affects the small intestine. The disease usually begins in the rectum or sigmoid colon and spreads partially or completely through the large intestine.

Ulcerative colitis typically begins gradually, with abdominal pain and diarrhea that is sometimes bloody. In more serious cases, diarrhea is severe and frequent. Fever, loss of appetite, and weight loss occur. The severity of the

disease depends on how much of the colon is involved. For many patients, there may be long periods with no symptoms at all, followed by flare-ups.

A definitive diagnosis can be made by direct examination of the colon by sigmoidoscopy (examination of the lower portion only) or colonoscopy (examination of the entire colon, the preferred approach). Both procedures can be used to take a biopsy of intestinal tissue, which can reveal important information about the degree and extent of inflammation and help rule out other causes of symptoms. A barium enema x-ray of the colon may also be required at some point in the course of colitis to determine the extent of involvement. Once diagnosed, ulcerative colitis can be categorized based on disease severity as follows:

- **Severe**. Severe ulcerative colitis, which involves the whole colon, is the least common form of the disease. Symptoms consist of profuse bloody diarrhea (occurring six or more times per day), often with a sustained fever and tachycardia (rapid heart rate). Severe anemia, increased white blood cell count, and decreased serum albumin levels are also characteristic symptoms.
- **Moderate**. Symptoms consist of recurrent diarrhea, small amounts of blood in the stool, possible low-grade fever, mild anemia, and minimal signs of inflammation. Moderate ulcerative colitis responds quickly to appropriate therapies. However, repeated attacks of equal or increased severity can occur, which can significantly increase the risk of developing colon cancer later.
- **Mild**. Mild ulcerative colitis is the most common form of the disorder, occurring in about 50 percent of patients. In most cases, ulcerative colitis will be limited to the lower portion of the colon and the rectum. Systemic complications are uncommon and the primary symptom is rectal bleeding.

5 Conventional Treatment Options

Conventional treatments for IBD depend on disease location and severity, complications, and response to prior treatments. The goals of therapy are to control inflammation, correct nutritional deficiencies, and relieve symptoms such as abdominal pain, diarrhea, and rectal bleeding. It is important to note that an early diagnosis is associated with greater efficacy of less-aggressive drug regimens and thus a less oppressive burden of side effects. Therefore, seeing a physician as soon as symptoms emerge is suggested. Therapy may include drugs, surgery, or a combination of approaches.

Drug Treatments

The following drugs can be used to treat IBD:

Anti-inflammatory drugs

- Aminosalicylates are drugs that contain 5-aminosalicyclic acid (5-ASA) and help control local inflammation of the gut. These drugs are primarily used to treat mild to moderate IBD and help with remission maintenance (Bebb 2004). Adverse effects include nausea, vomiting, heartburn, diarrhea, and headache. 5-ASA agents such as olsalazine, mesalamine, and balsalazide have fewer adverse effects and may be used by people who cannot take sulfasalazine. Balsalazide is converted in the colon to mesalamine, and has been shown to reduce bowel inflammation, diarrhea, rectal bleeding, and stomach pain (Muijsers 2002). 5-ASA agents are given orally or rectally (through an enema or in a suppository), depending on the location of the inflammation. Sulfasalazine interferes with folate absorption, so those taking this drug should also supplement with folate (Jansen 2004). Use of aminosalicylate drugs or antibiotics may deplete vitamin K in IBD patients, and oral supplementation of this vitamin relieves this problem (Krasinski 1985).
- **Glucocorticoids or cortiocosteroids** (such as prednisone and hydrocortisone) reduce inflammation. They are used to treat more severe cases of IBD and to end acute attacks. Glucocorticoids can be given orally, intravenously, or rectally (through an enema or in a suppository), depending on the location of the inflammation. These drugs can cause serious adverse effects, including increased risk of infection, diabetes, high blood pressure, bone loss, kidney suppression, and ulcers. Less serious adverse effects include weight gain, acne, facial hair, and mood swings. They are not recommended for long-term use and are typically replaced with 5-ASA drugs once remission has been induced. Calcium and vitamin D may help combat glucocorticoid-induced bone loss (Homik 2000).

Immune system suppressors

- Antimetabolites such as azathioprine and mercaptopurine prevent replication of inflammatory T cell lines. They are used to treat people with IBD who have not responded to 5-ASAs or glucocorticoids, or who are dependent on glucocorticoids. However, antimetabolites are slower acting than other types of drugs. Anyone taking these drugs should be monitored for complications such as pancreatitis, hepatotoxicity, reduced white blood cell count, and an increased risk of infection. A genetic test known as thiopurine methyltransferase (TMPT) genotyping can help predict who will have severe adverse effects from these drugs (Newman 2011).
- **Cyclosporine**. This drug inhibits T cell-mediated immune responses, thus reducing the immune reaction that underlies inflammation. It blocks a number of inflammatory cytokines, including TNF-α and various interleukins. Because cyclosporine is associated with significant risk of toxicity, its use is limited to severe ulcerative colitis or Crohn's disease.
- **Methotrexate**. The cancer chemotherapy drug methotrexate is used in Crohn's patients that are steroid dependent or have not responded to glucocorticoids (Preiss 2010). It can be given orally or by weekly injections under the skin or into the muscles (Xu 2004). Methotrexate is most effective for maintenance of remission when given as an injection (Patel 2009). This drug also interferes with folate metabolism. Folate should be supplemented with it, particularly to help prevent colorectal cancer, which this drug otherwise promotes (Patel 2009; Coogan 2007).
- **Biologics / TNF-inhibitors**. During flare-ups, levels of the inflammatory cytokine TNF-α become elevated. This has led to interest in antibodies such as infliximab, adalimumab, certolizumab pegol, and golimumab that block TNF-α. These have all been shown to induce and maintain remission including mucosal healing and restoration of gut barrier function (Malik 2012; Behm 2008; Gisbert 2006). However, these drugs are very expensive, have not been shown to prevent colectomy in severe ulcerative colitis (Aratari 2008), and may cause autoimmune diseases, cancer, infections, and viral reactivation syndromes including shingles (Colombel 2004).
- The following immunosuppressive agents may be considered as well: tacrolimus, mycophenolate mofetil and thalidomide.

Others

- **Cromolyn sodium**. This drug is modified from the natural compound known as khellin and works as a mast cell-stabilizing anti-inflammatory. One clinical trial found that daily administration of 200 mg cromolyn sodium rectally for 15 days induced remission in almost all patients with ulcerative colitis, and this was maintained in 93% of them when they took 240 mg daily for 2—3 years (Malolepszy 1977). In another trial, oral cromolyn sodium at a dose of 1,500 mg daily relieved diarrhea more effectively than an elimination diet (in which problematic foods are avoided) in patients with irritable bowel syndrome (Stefanini 1995). This indicates that cromolyn may ameliorate reactivity to some foods – a factor that possibly drives some inflammation in inflammatory bowel disease. As is so often the case with drugs that are off patent and thus not very profitable, no company or government has seen fit to fund further research on this safe and cheap drug for inflammatory bowel disease.
- **Naltrexone.** Originally developed to help treat heroin addiction, lower doses of naltrexone have shown a range of remarkable immunological activities. A placebo-controlled study on the use of low-dose naltrexone (4.5 mg per day at bedtime) suggested that the drug could resolve mucosal inflammation and induce clinical remission in patients with moderate-to-severe Crohn's disease (Smith 2011). This confirms one earlier uncontrolled study of low-dose naltrexone's efficacy for Crohn's disease (Smith 2007). Naltrexone appears to relieve inflammatory bowel disease in part by decreasing expression of proinflammatory cytokines and promoting tissue repair (Matters 2008). At low dosages, the drug may cause drowsiness, but other side effects are uncommon.

Surgery

In severe cases of Crohn's disease, abscesses can develop in chronically inflamed tissues. These abscesses can grow and tunnel through tissue barriers to produce *fistulas*, or channels between organs. Almost half of patients who have Crohn's disease develop perianal disease involving anal fissures, perianal abscesses, and fistulas.

These symptoms seldom respond well to conventional therapies (Braunwald 2001; McNamara 2004). Surgery may be required in a high percentage of these patients (Danelli 2003). Complications are frequent.

Surgery may also be recommended to remove severely inflamed portions of the intestinal tract. The goal of surgery is to preserve as much of the intestine as possible. Surgery commonly involves the colon or small intestine. Occasionally, the end of the intestine that has been left in place will need to be brought to the skin's surface to allow waste excretion. When this procedure involves the small intestine, it is called an ileostomy. If the procedure involves the colon, it is called a colostomy. Although Crohn's disease may recur after surgery, the symptoms are likely to be less severe and less debilitating than they were previously (Hwang 2008). Elemental diets (in which simple molecules like glucose and individual amino acids replace whole foods) have been shown to reduce recurrence of Crohn's disease when employed after surgery (Yamamoto 2007; Esaki 2005).

Newer surgeries, however, have been developed that can preserve fecal continence by using part of the ileum to create a pouch that is connected to the intact rectal sphincter (Hwang 2008). In a thorough review, the use of probiotic supplements was able to significantly reduce the occurrence of pouchitis, or inflammation of the reservoir formed upon surgical creation of an ilio-anal pouch, by 96% compared to placebo after surgery among ulcerative colitis patients (Elahi 2008).

6 Dietary and Lifestyle Considerations

Lifestyle changes and nutritional supplementation synergize to promote healthy digestion and absorption while simultaneously reducing the inflammation and damage associated with inflammatory bowel disease (IBD).

Crohn's disease

Since aspirin increases the risk of Crohn's disease (but not ulcerative colitis), people with Crohn's disease should consider avoiding the medication (Chan 2011).

The GI tract of individuals with Crohn's disease may also be exceptionally sensitive to the negative effects of smoking. Smoking among those diagnosed with Crohn's disease may increase the risk of flare ups, impede remission, and increase the overall severity of the condition necessitating more invasive treatments (Johnson 2005). The following steps may help patients with Crohn's disease first reduce their symptoms and then begin long-term repair of the damage caused by their disease:

Avoid troublesome foods. Remove all foods that precipitate symptoms. In one study of Crohn's disease patients, an elemental diet was followed by food reintroduction with one new food daily. If any food reintroductions led to symptoms such as diarrhea or pain, they were excluded. This approach was more effective than glucocorticoids in preventing relapse of Crohn's disease in this trial (Riordan 1993). A trial diet of just organic meat, spelt, butter, and organic tea was found to be superior to a low-fat, high-carbohydrate, low-fiber diet for people with Crohn's disease (Bartel 2008). Long-term remission was achieved in 31% of Crohn's patients in one study solely using an elimination diet (Giaffer 1991). Other evidence suggests Crohn's disease patients are more reactive to certain foods (Brown 2010; Van Den Bogaerde 2002). Some research suggests a reduced carbohydrate diet (84 g/day) may be associated with better outcomes in Crohn's disease (Lorenz-Meyer 1996). Also, elevated levels of trans-fats have been found in the adipose (fat) tissue of people with Crohn's disease (Heckers 1988; Lorenz-Meyer 1996). Baker's yeast should be avoided in those with elevated yeast antibodies, and has been shown to aggravate Crohn's disease in some research (Barclay 1992).

Following a diet based upon blood **IgG antibody testing** for food sensitivities has been shown to reduce stool frequency in Crohn's patients (Bentz 2010). In one trial, Crohn's disease symptoms were shown to be aggravated by diverse foods differing among study participants. Elimination of the problematic foods was helpful on an individual basis, but the bothersome foods were not the same for all subjects, underscoring the need to identify specific foods that cause symptoms (Triggs 2010). More information about testing for food allergies and sensitivities is available in the Allergies protocol.

Supplement to correct potential nutritional insufficiencies. The diets of most patients who have IBD are deficient in one or more vitamins or minerals (Tighe 2011). Vitamin D and vitamin K deficiencies are frequently found in those with Crohn's disease, as well as deficiencies in iron, vitamin B6, carotene, vitamin B12, and albumin (protein). (Nakajima 2011; Vagianos 2007; Siffledeen 2003). Patients with Crohn's disease are usually under

increased oxidative stress and have lower levels of antioxidant vitamins. Supplementation with vitamins C and E reduces oxidative stress (Aghdassi 2003).

Balance intestinal microbiota. A normal healthy intestine contains about 100 trillion microorganisms (Tsai 2009). In a diseased intestine, these bacteria are often not present in adequate amounts and/or have been replaced by pathogenic organisms. Balancing microbiota consists of taking mixtures of friendly bacteria (probiotics), which may include *Bifidobacteria* and *Lactobacilli* to promote continued repopulation with these beneficial bacteria (Zigra 2007). The probiotic yeast *Saccharomyces boulardii* may be considered as well. The role of probiotics in inflammatory bowel diseases is expounded upon below.

In children and adolescents who have Crohn's disease, a semi-elemental diet has been shown to be as effective as glucocorticoids in maintaining remissions (Scholz 2011). In one study of IBD, 44% of the study population went into remission by consuming an elemental diet (Axelsson 1977; Belli 1988). An elemental diet has also been shown to decrease inflammatory parameters in IBD intestinal tissue. The elemental diet also reduces intestinal permeability in those with Crohn's disease (Meister 2002; Teahon 1991). When coupled with individualized elimination of food triggers, elemental diets reduce the relapse rate of Crohn's disease (Jones 1987). In another trial involving 268 Crohn's disease patients, an elemental diet was associated with a reduced hospitalization rate (Watanabe 2010).

Those who use conventional elemental diets are sometimes noted to develop micronutrient deficiencies, such as of selenium (Kuroki 2003). Therefore supplementation with a high quality multivitamin/mineral, among other nutrients discussed below, may be pertinent.

Ulcerative colitis

Sulphate-reducing bacteria (SRB) have been implicated in the development of ulcerative colitis through the harmful effects of hydrogen sulphide, a waste product of their respiration (Rowan 2009; Pitcher 1996). Hydrogen sulfide is toxic to the colon lining cells, and is associated with ulcerative colitis. Hydrogen sulfide may, in particular, interfere with butyrate metabolism, a critical nutrient for colon cells produced by beneficial bacteria (Roediger 1997). Also, higher exposure to sulfur dioxide air pollution was associated with higher rates of ulcerative colitis in one study (Kaplan 2010).Ulcerative colitis has also been associated with a higher dietary intake of sulfur containing foods. Removing foods rich in sulfur-containing amino acids (such as milk, eggs, and cheese) is associated with benefits in ulcerative colitis (Jowett 2004; Roediger 1998; Wright 1965).

7 Nutrients

Inflamed intestines may not absorb nutrients properly. Therefore, people with IBD are prone to malnutrition and vitamin deficiencies (Alastair 2011; Mortimore 2010; Campos 2003; Goh 2003).

Probiotics. Variation in the population of microorganisms within the digestive tract is capable of altering immune cell function locally and systemically. One study describes a novel probiotic organism that can directly produce **interleukin-10 (IL-10)**, an anti-inflammatory cytokine that promotes immune tolerance (de Moreno de Leblanc 2011; Lavasani 2010; Chin 2004). Furthermore, ingestion of probiotic bacteria can blunt the effects of pathogenic bacteria via various mechanisms including, competing for epithelial receptor binding, and enhancing the barrier function of the gut (de Moreno de Leblanc 2011; Fedorak 2004; Furrie 2004). Some probiotics also produce *butyrate* – a short-chain fatty acid important for health of cells within the colon wall (see below) (Sartor 2011).

Clinical trials of probiotic use in IBD populations have indicated beneficial effects. Duration of trials and organisms employed has varied, but there have been several instances of positive results (Rogler 2011). A 2011 trial using a probiotic (*Bifidobacterium breve*) as well as a prebiotic (galacto-oligosaccharide) demonstrated a marked improvement in clinical status of people with ulcerative colitis (Ishikawa 2011). Clinical trials in Crohn's disease showed that supplements supplying 50 billion organisms per day or higher improved gut health (Fujimori 2007; Karimi, et al. 2005). In one trial relief was so great for two subjects they were able to discontinue glucocorticoid medication (Fujimori 2007). Other research suggests that probiotics may suppress the likelihood of colorectal cancer development, a major concern for patients with IBD (Azcarate-Peril 2011).

Another organism that has shown promise in IBD is *Saccharomyces boulardii* - a probiotic yeast. Several trials

have proven the efficacy of *S. boulardii* for ameliorating infectious diarrhea and other gastrointestinal problems (Dinleyici 2012). Moreover, specifically relevant to IBD, *S. boulardii* appears to modulate the inflammatory response in the intestinal epithelium, reducing TNF-α and IL-6 (Thomas 2011). This same study showed that *S. boulardii* promotes intestinal tissue repair and immune tolerance in cell samples from patients with IBD. In a randomized, placebo-controlled clinical trial, *S. boulardii* lessened intestinal permeability in Crohn's disease patients when it was added to conventional therapy (Garcia Vilela 2008). Supplementation with *S. boulardii* appears to generally be safe and effective in a variety of pathologic states (McFarland 2010).

Bacteriophages and IBD

Bacteriophages, or phages, are viruses that target bacteria. They are the most abundant organisms on the planet, and the human digestive tract is estimated to contain 1015 bacteriophages (Babickova 2015; McCarville 2016; Clokie 2011). Intestinal bacteriophages appear to play an important role in the ecology of the gut microbial community, including injecting viral genetic material into specific bacteria and, in some cases, causing their rapid death (McCarville 2016; Belizario 2015; Clokie 2011). Despite their abundance, until recently bacteriophages had received relatively little research attention (McCarville 2016; Clokie 2011). Emerging evidence suggest bacteriophages have therapeutic potential for the treatment of inflammatory bowel disease (McCarville 2016; Babickova 2015).

Bacteriophages appear to modulate immune activity and may impact inflammation in the intestinal lining. Disease-specific patterns of bacteriophage populations have been noted in individuals with inflammatory bowel disease and differ significantly from those seen in healthy individuals (Norman 2015; Wang 2015); in addition, the abundance of certain bacteriophages was found in one study to be related to reduced levels of some types of bacteria (Norman 2015).

Bacteriophage therapy may be safer than antibiotic therapy, in part because it causes minimal disruption to normal gut flora (Loc-Carrillo 2011). In a safety study, oral supplementation with a bacteriophage targeting the intestinal bacteria *E. coli* led to the detectable presence of these bacteriophages in the stools of healthy volunteers, but their presence was no longer detectable within one week after supplementation ended. Numbers of non-pathogenic *E. coli* bacteria remained unchanged, and no adverse side effects were noted (Bruttin 2005). Similarly, in a study in healthy adults given a cocktail of nine *E.coli*-targeting bacteriophages, no *E. coli* was detected in stool samples collected immediately after phage administration, and no adverse effects were reported or detected in blood, liver, and kidney tests (Sarker 2012).

Omega-3 fatty acids. The two most prominent omega-3's, *eicosapentaenoic acid* (EPA) and *docosahexaenoic acid* (DHA), are found in cold-water fish (Deckelbaum 2012). Omega-3 fatty acids are powerful immunoregulatory agents that reduce circulating inflammatory cytokines and decrease the cytotoxicity of natural killer cells (Iwami 2011; Almallah 1998; Hillier 1991; Ross 1993; Steinhart 1997). Additionally, in one animal study, α-linolenic acid (a plant-derived omega-3 fatty acid) suppressed expression of *adhesion molecules*, which are important in inflammation, immune responses and in intracellular signaling events (Golias 2011; Ibrahim 2012).

In clinical trials, fish oil supplementation improves the fatty acid profile in Crohn's disease and ulcerative colitis patients, and is associated with lower levels of inflammatory mediators (Uchiyama 2010; Stenson 1992; Aslan 1992). These changes have some correlation with remission from disease flares (Wiese 2011; Hawthorne 1992). Fish oil may also reduce the dosage of glucocorticoid drugs needed to cause a remission (Hawthorne 1992). *Enteric-coated* fish oil was found to be helpful in one study of Crohn's disease patients by reducing the rate of relapse (Belluzzi 1996).

The majority of Americans have unhealthy high ratios of omega-6's to omega-3's in their blood – an imbalance strongly associated with inflammatory diseases (Simopoulos 2011). Life Extension recommends that the omega-6 to omega-3 ratio be kept **below 4:1** for optimal health (Simopoulos 2002); this may be especially important for IBD patients. You can assess your omega-6 to omega-3 ratio using a convenient blood test called the **Omega Check™ test**.

Vitamin D is another powerful immunomodulator. Experimental models have shown that T-cells express a vitamin D receptor, and that lack of vitamin D signaling causes T-cells to produce higher levels of inflammatory cytokines.

Moreover, vitamin D is required for development of subsets of T^{reg} cells that are important in suppressing inflammation specifically in the gut (Chambers 2011; Ooi 2012). Patients with IBD often have low vitamin D levels, as revealed by low levels of serum 25-hydroxyvitamin D (Jahnsen 2002). Many other lines of evidence connect low vitamin D levels with IBD as well (Wang 2010; Lim 2005). Administration of 25-hydroxyvitamin D3 or calcitriol (fully activated vitamin D3, a very potent substance available only by prescription) lowered measures of inflammation and improved bone health in 37 patients with Crohn's disease in remission (Miheller 2009). Taking 1,200 IU of vitamin D3 per day showed a trend toward a lower relapse rate (from 29% to 13% [P = 0.06]) compared to placebo in one double-blind trial involving 94 Crohn's disease patients in remission (Jorgensen 2010). Moreover, bone loss is a major concern for IBD patients – both the disease and glucocorticoids used to treat it contribute to poor bone health. Supplementation with vitamin D has been shown to maintain bone density in Crohn's disease (Abitbol 2002).

Life Extension suggests maintenance of 25-hydroxyvitamin D levels within the range of **50 – 80 ng/mL**. Testing your vitamin D blood level is inexpensive and convenient. A 25-hydroxyvitamin D blood test should be performed regularly by those supplementing with vitamin D to ensure that they stay in the optimal range.

Antioxidants. Normal digestion produces a host of reactive oxygen and nitrogen species (also known as free radicals), against which the intestinal mucosa maintains an extensive defense system of antioxidants. When presented with excessive oxidant stress, however, the mucosal barrier can sustain damage and become leaky, setting the stage for inflammation (Almenier 2012; Koutroubakis 2004).

In addition, inflammation itself produces large quantities of reactive species, and a destructive cycle can be perpetuated. In patients who have IBD, there are high levels of reactive oxygen species in the intestines, which contributes to the damage caused by the disease (Almeiner 2012). In one study, the antioxidant capacity of individuals with IBD was found to be significantly lower than those without the disease (Kruidenier 2003). Some research has shown that an antioxidant combination of vitamin A, vitamin C, vitamin E, and selenium in combination with fish oil can reduce certain inflammatory markers in Crohn's disease (Trebble 2004, 2005). Moreover, IBD patients had significantly lower levels of carotenoids and vitamin C, in their blood (Hengstermann 2008).

Curcumin. The efficacy of the turmeric extract curcumin as an anti-inflammatory agent in a variety of settings is well-documented. Prominent among its multiple effects is the inhibition of ***nuclear factor kappa-B (NF-kB)*** signaling. NF-kB is a signaling protein that drives production of myriad inflammatory cytokines including interleukin-1b (IL-1b) and interleukin-6 (IL-6). Since NF-kB and related cytokines are central in IBD pathology, curcumin has been investigated as an intervention (Taylor 2011). In one study, curcumin helped reduce symptoms of Crohn's disease and ulcerative colitis in a small group of patients, many of whom were able to discontinue aminosalicyates and/or glucocorticoids (Holt 2005; Taylor 2011). Curcumin coupled with aminosalicylates reduced recurrence of acute flares and symptom severity compared to placebo plus aminosalicylates in a group of 82 ulcerative colitis patients. In the curcumin group, the relapse rate during 6 months of therapy was 4.6%, while in the control group it was over 20% (Hanai 2006).

Boswellia. Resin from the Boswellia genus of tree contains a powerful anti-inflammatory compound called *acetyl-11-keto-β-boswellic acid* (AKBA). One double-blind clinical trial found that boswellia was as effective as mesalamine at improving symptoms of Crohn's disease with far fewer side effects (Gerhardt 2001). One trial has also found boswellia as effective as sulfasalazine for inducing remission from ulcerative colitis in 30 patients (Gupta 2001). This confirmed an earlier report of efficacy of boswellia for ulcerative colitis patients (Gupta 1997). However, another double-blind trial involving 108 Crohn's disease patients did not find boswellia superior to placebo for maintaining remission (Holtmeier 2011). An improved extract called AprèsFlex™, or Aflapin®, which combines AKBA with other non-volatile boswellia oils, demonstrated improved anti-inflammatory activity at a lower concentration when compared to other preparations standardized to the same percentage of AKBA (Sengupta 2011).

Wormwood. A standardized extract of wormwood (*Artemisia absinthium*), a bitter herb native to the Mediterranean region, has been studied in patients with Crohn's disease. Compared to placebo it was much more effective at maintaining remission in patients who tapered off their medications (Omer 2007). The reason for this may be

because wormwood blocks TNF-α (Krebs 2010), a potent proinflammatory cytokine.

Aloe gel. The mucilaginous gel found in the interior of aloe leaves has been used traditionally for ulcerative colitis for many years. One double-blind, randomized trial found that aloe gel at a dose of 3 oz twice a day ended acute flares in ulcerative colitis patients better than placebo without adverse effects (Langmead 2004a). Aloe gel's immunomodulating, gut healing, and inflammation-quelling properties may all play a role in its efficacy (Langmead 2004b).

Selenium. Selenium is a trace element that is essential for the function of a number of selenium-dependent enzymes. Selenium deficiency is common in people who have IBD (Geerling 2000a; Hinks 1988; Ojuawo 2002). Supplementation helps alleviate this problem, based both on increases in serum selenium and improved glutathione peroxidase function (Geerling 2000b).

Butyrate. Butyrate (also known as butyric acid) is a short-chain fatty acid produced when intestinal fiber is metabolized by certain bacteria. Experimental models have shown that oral butyrate ameliorates inflammation in ulcerative colitis (Vieira 2011). One mechanism by which butyrate may function is to inhibit the activation of the proinflammatory cell–signaling component *nuclear factor kappa B* (NF-kB) (Segain 2000). In clinical trials, oral butyrate has provided relief in both Crohn's *and* ulcerative colitis (Assisi 2008; Di Sabatino 2005). In one trial, nearly 70% of subjects with Crohn's disease responded to a dose of 4 grams of enteric-coated butyrate tablets daily for 8 weeks. Of those responders, 53% achieved remission and their levels of NF-kB and another inflammatory factor – IL-1b – decreased significantly (Di Sabatino 2005).

L-Carnitine. The amino acid carnitine is necessary for proper cellular metabolism, and insufficient carnitine levels particularly affect cells that require a great deal of energy, such as those of the immune system. Several experiments have shown that carnitine modulates production of inflammatory mediators and that insufficient carnitine levels are associated with greater production of inflammatory cytokines (Abd-Allah 2009; Buyse 2007). Indeed, in a clinical trial involving 36 dialysis patients, 1 gram per day L-carnitine supplementation led to a 29% reduction in CRP levels and a 61% reduction in IL-6 levels (Shakeri 2010). With respect to the gut, L-carnitine significantly blunted the inflammatory response to oxygen deprivation and restoration in intestinal tissue in an animal model (Yuan 2011). In a randomized, placebo-controlled trial involving 121 subjects with ulcerative colitis, *propionyl-L-carnitine*, at 1 or 2 grams daily, led to greater remission rates than placebo when added to conventional therapy (Mikhailova 2011). In the group receiving 1 gram of carnitine daily, the rate of remission was 55%, while in the placebo group it was only 35%.

Glutamine is a conditionally essential amino acid and the major fuel for the enterocytes (intestinal absorptive cells). Oral glutamine supplementation can stabilize intestinal permeability and mucosal integrity (Den Hond 1999). A study demonstrated that glutamine can help improve capillary blood flow in inflamed segments of the colon in animals with colitis (Kruschewski 1998). Moreover, glutamine levels are low in people with moderate-to-severe Crohn's disease (Sido 2006). In a randomized clinical trial, a 0.5 g/kg body weight daily dose of glutamine for 2 months decreased intestinal permeability and improved morphology in patients with Crohn's disease (Benjamin 2011). However, the clinical benefit of glutamine supplementation may be limited to periods of remission, as another trial found that glutamine supplementation during a disease flare did not improve intestinal permeability (Ockenga 2005).

Melatonin. Though melatonin is known as a hormone that helps synchronize sleep-wake cycles, it has also been shown to be produced in the digestive tract in quantities far larger than in the brain (Bubenik 2002). Melatonin reduces TNF-α levels (Johe 2005). Numerous *in vitro* and animal studies have suggested that melatonin can reduce inflammation in IBD (Terry 2009). Melatonin synthesis increases in IBD patients and higher levels are associated with lower symptoms, suggesting it is part of the body's attempt to reduce excessive inflammation (Boznanska 2007). In a double-blind trial of 60 patients with ulcerative colitis being treated with mesalazine, half were randomized to take melatonin and half to take placebo for one year (Chojnacki 2011). Inflammation and clinical symptoms rose in the placebo group while the melatonin group remained in remission. This confirms an earlier, uncontrolled study showing that melatonin was helpful for patients with Crohn's disease and ulcerative colitis (Rakhimova 2010). Caution is warranted though - at least one case study has been published in which melatonin caused a flare of ulcerative colitis that did not respond to glucocorticoids (Maldonado 2008).

Dehydroepiandrosterone (DHEA) plays an important role in preventing chronic inflammation and to maintain healthy immune function. Published studies link low levels of DHEA to chronic inflammation, and DHEA has been shown to suppress levels of proinflammatory cytokines and protect against their toxic effects (Haden 2000; Head 2003). DHEA has been shown to suppress damaging IL-6 levels (Andus 2003).

The deficiency of DHEA in inflammatory diseases also implies a deficiency in peripheral tissue of various sex hormones for which DHEA serves as a precursor. These hormones, both estrogenic and androgenic, are known to have beneficial effects on muscle, bone, and blood vessels. However, mainstream therapy with glucocorticoids lowers androgen levels. Consequently, researchers argue that hormone replacement for patients who have chronic inflammatory diseases should include not only glucocorticoids but also DHEA (Andus 2003; Straub 2000).

Vitamin K. Vitamin K is used by the body to regulate blood clotting. A deficiency in vitamin K can result in bruising or bleeding. Patients with IBD are frequently deficient in vitamin K. One study showed that 31 percent of patients who had ulcerative colitis or Crohn's disease had a vitamin K deficiency (Krasinski 1985). Low vitamin K activity was linked with higher Crohn's disease activity in one study (Nakajima 2011). Vitamin K deficiency in IBD patients is associated with lower bone density as well (Nakajima 2011; Duggan 2004).

Fiber. Greater intake of dietary fiber is linked with lower incidence of Crohn's disease (Hou 2011), while higher sugar consumption is associated with increased risk (Sakamoto 2005). A diet low in refined sugar and high in dietary fiber has been shown to have a favorable effect on the course of Crohn's disease and does not lead to intestinal obstruction compared to a normal diet (Heaton 1979).

Fermentation of dietary fiber by intestinal bacteria is the major source of short-chain fatty acids, such as butyrate, and various studies have shown that vegetable fibers are helpful at preventing flares of ulcerative colitis (Hanai 2004).

Saffron. Saffron, a spice obtained from the flowers of *Crocus sativus*, has been used in traditional medicine for thousands of years, with recent studies demonstrating its anti-inflammatory and immune-modulating effects. Animal models of ulcerative colitis have shown saffron effectively improves colon histology, disease scores, and inflammatory factors, as well as positively modulates the gut microbiome and immune cell function (Singh 2022; Banskota 2021). One of the main bioactive compounds from saffron, crocin, has been shown to have positive effects in animal models of ulcerative colitis (Teng 2021; Kawabata 2012; Albalawi 2023), although a different bioactive compound, crocetin, has had inconsistent effects (Feng 2022; Kazi 2009).

Saffron has been studied in several small, preliminary clinical trials in patients with ulcerative colitis. In one placebo-controlled study with 75 ulcerative colitis patients, 100 mg saffron daily for eight weeks improved clinical activity index scores, total antioxidant capacity, and increased levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase compared with placebo (Tahvilian 2021). Further study showed the patients given saffron also had decreased levels of inflammatory TNF-α, increased levels of anti-inflammatory IL-10, and improved quality of life (Heydarian 2022). A placebo-controlled study conducted in Iran involved 30 ulcerative colitis patients who were given placebo, 25 mg, or 50 mg saffron twice daily for eight weeks. The study found that clinical activity index scores, depression scores, calprotectin (a marker of inflammation in the gut), and CRP levels all improved with high-dose treatment. Those given the lower dose had improved depression scores (Ashktorab 2022; Ashktorab 2024). As of March 2024, an ongoing study at Howard University in the United States plans to recruit 100 people with mild-to-moderate ulcerative colitis to further assess the efficacy of saffron supplementation in this context (Ashktorab 2021).

Glucosamine and N-acetyl glucosamine. Glucosamine is a glycosaminoglycan (GAG, a type of amino sugar) found in connective tissue throughout the body. It is best known as a component of joint fluid and cartilage, and its sulfated form is widely used to treat osteoarthritis (Vo 2023). Glucosamine is also found in the gut mucosa as N-acetyl glucosamine (NAG), where it has a structurally protective role and suppresses inflammation (Abo 2023).

Preclinical research has shown that a substantial portion of ingested glucosamine is not absorbed (Seto 2020). Moreover, research in human subjects shows that there is significant variability among healthy people in the amount of glucosamine absorbed (Asthana 2021). These findings, in conjunction with evidence of benefits for systemic health concerns like joint health, suggest that glucosamine may potentially exert some of its protective benefits via the gut, rather than only from systemic circulation. Indeed, NAG has demonstrated free radial

scavenging, anti-inflammatory, antimicrobial, anti-tumor, and prebiotic (promoting beneficial gut bacterial growth) properties in preclinical research (Liu 2023).

Low NAG levels and abnormalities in glycoprotein synthesis have been noted in the intestinal mucosa of IBD patients and may contribute to IBD pathology (Russell 1999; Winslet 1994; Burton 1983). Animal models of inflammatory bowel disease have reported glucosamine hydrochloride, NAG, and NAG oligomers (molecules made up of a few NAG units) increased beneficial gut bacteria, decreased harmful bacteria, reduced intestinal inflammation and blood levels of inflammatory cytokines, and improved gut barrier function (Choi 2023; Azuma 2015; Bak 2014; Yomogida 2008).

In a pilot trial, 12 children with severe IBD that had not responded to other therapies were given 3–6 grams of oral NAG daily. Clear improvement was seen in eight of the children, while four still required bowel surgery (Salvatore 2000). An observational study that followed 6,059 IBD patients for an average of 12.2 years found those who reported using a glucosamine-containing supplement regularly were 27% less likely overall to require surgery than those who did not. Dosages of glucosamine above about 600 mg daily were associated with lower risk of IBD-related surgery compared with lower dosages. When narrowed to include only those with Crohn's disease, the risk of surgery was 40% lower in those who used glucosamine; however, there was no significant effect in those with ulcerative colitis (Geng 2025). While this preliminary research is intriguing, randomized controlled trials are necessary to determine whether glucosamine supplementation can reliably improve outcomes for those with IBD.

Folate and Colon Cancer Risk in Ulcerative Colitis

People with ulcerative colitis are at increased risk of colon cancer (Mitamura 2002). It is assumed that chronic inflammation is what causes cancer in ulcerative colitis. This is supported by the fact that colon cancer risk increases with longer duration of colitis, greater anatomic extent of colitis, and the concomitant presence of other inflammatory manifestations (Itzkowitz 2004). Folate deficiency and an increased level of homocysteine have been linked to greater colon cancer risk in IBD (Phelip 2008).

In a comprehensive review involving data from 13 studies and over 725,000 subjects, each 100 mcg/day increase in folate intake was associated with a 2% decrease in colon cancer risk (Kim 2010). Other evidence highlights multiple ways that folate might protect against colon cancer in ulcerative colitis (Biasco 2005). However, data is conflicting as other studies have come to differing conclusions For example - another review found that long-term folic acid supplementation was associated with increased colon cancer risk (Fife 2011).

Deficiencies in folate and B12 are often observed in IBD (Yakut 2010). Supplementing the diet with vitamin B12 enables the body to metabolize folate better and avoids masking a vitamin B12 deficiency. Vitamin B12 supplementation is important, particularly for older people (when it is less effectively absorbed) and for vegetarians, especially vegans, who receive little B12 in their diet. More information is available in the Colorectal Cancer protocol.

Inflammatory Bowel Disease and Elevated Homocysteine Levels

A number of studies have shown that patients with IBD are more likely to have elevated homocysteine levels. A comprehensive review of published studies found that the risk of having high homocysteine levels was over **four times greater** in IBD patients compared to controls (Oussalah 2011). In one study, more than 55 percent of patients with IBD had elevated homocysteine levels (Roblin 2006). The greatest risk factor for elevated homocysteine in patients with IBD is reduced folate levels (Zezos 2005). Vitamin B12 deficiencies are also frequently encountered (Mahmood 2005).

The elevated homocysteine level that is typical in patients with IBD contributes to a 3-fold higher risk of blood clots and vascular disease (Fernandez-Miranda 2005; Srirajaskanthan 2005). It also helps explain why patients with IBD are more likely to have early atherosclerosis (Papa 2005).

Certain drugs used to treat IBD, such as methotrexate, are antimetabolites for folic acid, which may help explain why so many patients are deficient in folic acid. Supplementation of folic acid reduces adverse effects caused by methotrexate as well (Patel 2009).

Genetic studies have found that alterations in folate metabolism are associated with IBD (Zintzaras 2010). Therefore, IBD patients may benefit from supplementation with **5-methyltetrahydrofolate**, the active form of the

nutrient.

More information about managing homocysteine levels is available in the Homocysteine Reduction protocol.

Inflammatory Bowel Disease and Bone Loss

Osteoporosis is a serious complication of IBD that has not received adequate recognition despite its high prevalence and potentially devastating effects (Etzel 2011; Harpavat 2004). Osteoporosis can be caused by IBD itself, or it can be an adverse effect of glucocorticoid treatment. Data derived from a retrospective survey of 245 patients with IBD suggest that the prevalence of bone fractures in people with ulcerative colitis and Crohn's disease is unexpectedly high, particularly in patients who have a long duration of disease, frequent active phases, and high cumulative doses of glucocorticoid intake (Miheller 2010; Agrawal 2011). Low vitamin D and K levels have also been correlated to higher rates of osteoporosis in IBD patients (Kuwabara 2009). Bone-density measurements to predict fracture risk and define thresholds for prevention and treatment should be performed routinely in patients with IBD (Rogler 2004). Glucocorticoids can also contribute to the risk of osteoporosis because of their effects on calcium and bone metabolism. Glucocorticoids suppress calcium absorption in the small intestine, increase calcium excretion by the kidneys, and alter protein metabolism. Patients with Crohn's disease who take glucocorticoids have a higher risk of fractures compared to those who do not (Bernstein 2003). Nutrients that can help protect against bone loss include calcium, magnesium, vitamin D, and vitamin K. For more information, see the **Osteoporosis protocol**.

Inflammatory Bowel Disease and blood clot risk

Inflammatory bowel disease patients are at increased risk of forming blood clots - primarily venous thromboembolism (Kappelman 2011; Solem 2004; Sonoda 2004). These clots can break off and lodge in the blood vessels in the lungs, potentially causing death. Moreover, use of glucocorticoids by IBD patients potentiates clotting propensity (Kappelman 2011). Conventional medicine often relies on warfarin or heparin to mitigate thrombotic risk in IBD patients, but these drugs are prone to cause negative side effects and require clinical monitoring (Koutroubakis 2005). Vitamin E, vitamin D, and resveratrol, may all help offset the risk of clotting in IBD patients, though specific clinical trials are lacking (Phang 2011). IBD patients should review the **Blood Clot** Prevention protocol for further discussion of strategies to mitigate risk for blood clots.

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