

Inflammatory Bowel Disease

Inflammatory bowel disease is a common cause of discomfort and misery for tens of thousands of people in the United States. The two major types of inflammatory bowel disease are Crohn's disease and ulcerative colitis. Because Crohn's disease and ulcerative colitis are comparable and treated similarly, they have been combined in this chapter.

As the name implies, inflammatory bowel disease is characterized by inflammation within the gastrointestinal tract. In Crohn's disease, the inflammation can extend to any part of the gastrointestinal tract, from the mouth to the anus. Up to 55 percent of people have Crohn's disease that affects both the small and large intestines. In Crohn's disease, diseased portions of the intestine often alternate with healthy intestinal areas. By contrast, ulcerative colitis is limited to the colon.

Both Crohn's disease and ulcerative colitis typically have active periods followed by periods of remission. Conventional medical therapy relies on anti-inflammatories to provoke a remission and for remission maintenance. In serious cases, surgery may be necessary.

Fortunately, both diseases offer excellent opportunities for nutritional therapy. It is important that patients with these diseases pay careful attention to their nutritional intake, making sure to maintain healthy levels of nutrients. Many people with inflammatory bowel disease almost completely stop eating during flare-ups. Also, malabsorption of nutrients is a significant problem (especially in Crohn's disease), making it doubly important to use supplements. Finally, a number of nutrients have been shown to reduce inflammation and possibly reduce symptoms associated with these difficult conditions.

No definitive cause has been uncovered for inflammatory bowel disease, although there is clearly an interaction among genetic, environmental, nutritional, and inflammatory factors (Marteau P et al 2004; Prehn JL et al 2004; Soderholm JD et al 2004).

CROHN'S DISEASE: BACKGROUND AND DIAGNOSIS

Because of the nature of Crohn's disease, nutritional supplementation is extremely important. The Life Extension Foundation advocates the 4-R Program (described later in this chapter) for people who have Crohn's disease. This program of lifestyle changes and nutritional supplementation works to provide healthy digestion and absorption, while simultaneously reducing the inflammation and damage associated with Crohn's disease.

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 S et al 1999), vagina (Feller ER et al 2001), or even the surface of the skin (Tavarella VF 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 and often with mucus 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. Symptoms outside the gastrointestinal tract include joint pain and swelling, and occasionally eye pain and vision disturbances. Skin rashes may also occur. People who have Crohn's disease almost always have some degree of anemia, related both to poor iron absorption and to chronic blood loss from inflamed tissue.

Guidelines produced by the American Society of Gastroenterology classify patients into mild-moderate, moderate-severe, or severe-fulminant disease categories. Those at the milder end of the spectrum can eat and function reasonably normally, while those at the severe end fail to respond to treatment and have persistent symptoms, fevers, and infections.

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) and endoscopy, in which a fiber-optic telescope is passed into the intestines. Endoscopy allows specimens to be taken for culture and microscopic examination.

No blood test can diagnose Crohn's disease, but routine testing is usually done to detect anemia, infection, and degree of inflammation, and to determine liver function. Certain markers of inflammation, such as erythrocyte sedimentation rate and C-reactive protein, may be used to follow a patient's course over time.

Depending on the severity of the symptoms, medical treatment of Crohn's disease involves a three-pronged approach: first, drug therapy and a restricted diet; second (if necessary), hospital treatment; and third, the last resort of surgery to remove the affected sections of the intestine. Some patients with Crohn's disease may be prescribed high-protein, high-calorie liquid supplements. Children may require these supplements to maintain growth and development (Gupta SK et al 2004).

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 doesn't affect the full thickness of the intestine and never 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. In about half of patients, the disease is limited to the rectum and rectosigmoid. In about 30 percent of patients, the disease extends beyond the sigmoid but does not involve the whole colon. In about 20 percent of people, the disease involves the entire colon (Kasper DL et al 2005).

The symptoms caused by ulcerative colitis tend to come and go. There may be long periods with no symptoms at all, followed by flare-ups. Approximately 70 percent of patients will have complete remissions between attacks. Ten percent of patients will have an initial attack and experience no subsequent attacks, and 15 percent to 20 percent will be troubled by continuous symptoms that occur without remission.

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. Small, painless biopsies that reveal certain features of ulcerative colitis are sometimes taken. A barium enema x-ray of the colon will also be required at some point in the course of colitis. Once diagnosed, ulcerative colitis can be categorized based on the following disease severity:

- **Severe.** Severe ulcerative colitis, which involves the whole colon, is the least common form of the disease. Symptoms consist of profuse diarrhea (occurring six or more times per day), with constant and severe rectal bleeding. There is a sustained fever (up to 104°) and tachycardia greater than 90 beats per minute. Severe anemia, increased white blood cell count, and decreased serum albumin levels are also characteristic symptoms.
- **Moderate.** Symptoms consist of diarrhea that occurs less than five times a day, small amounts of blood in the stool, no fever or tachycardia, 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. Most often the disease will remain in this area, although in 10 percent of patients it will eventually involve the whole colon (Paterson WG et al 2000).

People who have colitis should consider having cytokine blood tests to measure autoimmune cytokine activity. These tests are simple and effective ways of monitoring cytokine levels and can be used as a measure of the effectiveness of any other therapies. Cytokine blood profiles measure tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (beta) (IL-1b), interleukin-6 (IL-6), leukotriene-B4 (LTB4), and leukotriene-C4 (LTC4).

Anatomy of the Digestive Tract

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 organs (such as the 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 tract.

The hollow organs 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 organs 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, for absorbing the resulting nutrient molecules, 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 mucus to trap

contaminants, immune system cells that directly attack and destroy invading organisms, and inflammatory cells that respond to the presence of foreign molecules by producing cytokines and other inflammatory molecules (Braunwald E 2001).

Under normal circumstances, the immune and inflammatory cells in the intestinal lining cope with invaders quickly and efficiently, without producing large amounts of local inflammation. However, in inflammatory bowel disease, inflammation becomes uncontrolled. Cytokines released by inflammatory cells in the intestine attract additional cells that produce destructive chemicals and cause further inflammation (McNamara DA et al 2004; Neuman MG 2004).

Because intestinal mucosa is so delicate, it cannot function properly when inflamed. Inflamed intestines may not absorb nutrients properly, and simultaneously allow the absorption of toxins and bacteria into the bloodstream. As a result, people with inflammatory bowel disease disproportionately have malnutrition, vitamin deficiencies, and infection (Campos FG et al 2003; Goh J et al 2003). Furthermore, undigested nutrients in the colon ferment, which draws fluid into the colon and produces gas. The result is diarrhea, pain, cramping, and bloating.

Over the long term, inflammation can damage nerve endings in the intestine, leading to disturbances in movement of the intestinal muscles (Hanani M et al 2004), while poor absorption of bile acids exacerbates malnutrition and diarrhea (Kwon RS et al 2004).

DRUG TREATMENTS

Traditional treatments for inflammatory bowel disease depend on the disease's 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. Therapy may include drugs, nutritional supplementation, surgery, or a combination of approaches.

The following drugs are used to treat inflammatory bowel disease:

- **Aminosalicylates.** Aminosalicylates are drugs that contain 5-aminosalicylic acid (5-ASA) and help control inflammation. These drugs are primarily used to treat mild to moderate inflammatory bowel disease, as well as to help with remission maintenance (Bebb JR et al 2004). Adverse effects include nausea, vomiting, heartburn, diarrhea, and headache. 5-ASA agents such as olsalazine, mesalamine, and balsalazide have a different carrier and fewer adverse effects and may be used by people who cannot take sulfasalazine. Balsalazide is one of the newest drug therapies and has the advantage of slow release. It is converted in the body to mesalamine and has been shown to reduce bowel inflammation, diarrhea, rectal bleeding, and stomach pain (Muijsers RB et al 2002). 5-ASA agents are given orally or rectally (through an enema or in a suppository), depending on the location of the inflammation.
- **Corticosteroids.** Corticosteroids (such as prednisone and hydrocortisone) reduce inflammation. They are used to treat more severe cases of inflammatory bowel disease and to induce remission. Corticosteroids 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, 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.
- **Antimetabolites.** Antimetabolites (such as azathioprine and mercaptopurine) reduce inflammation by preventing replication of inflammatory cell lines. They are used to treat people with inflammatory bowel disease who have not responded to 5-ASAs or corticosteroids or who are dependent on corticosteroids. However, antimetabolites are slow acting; it may take up to 6 months before their full benefit is seen. Anyone taking these drugs should be monitored for complications such as pancreatitis, hepatitis, a reduced white blood cell count, and an increased risk of infection.
- **Methotrexate.** The cancer chemotherapy drug methotrexate can promote remission in approximately 50 percent of patients with inflammatory bowel disease but it is less effective in maintaining remission (Harrell LE et al 2004, Xu CT et al 2004). Methotrexate has been effective in treating patients who have moderate to severe ulcerative colitis and in patients with Crohn's disease who are not responding to corticosteroids, mercaptopurine, or azathioprine. It can be given orally or by weekly injections under the skin or into the muscles (Xu CT et al 2004). Methotrexate is most reliably absorbed by injection.
- **Infliximab.** During flare-ups, levels of the inflammatory cytokine TNF-alpha become elevated. This has led to interest in drugs such as infliximab that suppress TNF-alpha. In early experiments, infliximab has shown clinical promise in treating inflammatory bowel disease and offers a good, although very expensive, therapy option. Its use is generally limited to severe cases of Crohn's disease.
- **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-alpha and various interleukins. Because cyclosporine is associated with significant risk of toxicity, its use is limited to severe ulcerative colitis or Crohn's disease.
- **Pentoxifylline.** Pentoxifylline is an inexpensive prescription drug that has been shown to lower TNF-alpha. This drug was approved to reduce blood viscosity and treat occlusive arterial disease, but a beneficial side effect is its ability to down-regulate the release of TNF-alpha, IL-1b, and IL-6. Pentoxifylline is well tolerated. It has very low toxicity and minimal adverse effects associated with chronic use. This makes it a very desirable drug for treatment of chronic conditions. The suggested dose of pentoxifylline to reduce these inflammatory cytokines is 400 milligrams (mg) twice a day.

Other drugs that may be considered include immunosuppressive agents such as tacrolimus, mycophenolate mofetil and thalidomide. Each of these drugs acts to reduce the immune response.

NUTRIENT AND SUPPLEMENT THERAPY

Because most medications for inflammatory bowel disease have substantial adverse effects, people who have inflammatory bowel disease may want to seek additional or alternative treatments. Attention to nutrition and diet can reduce dependence on medications to stave off active disease or induce remission. Intolerance to certain foods and other nutritional factors can be causes of exacerbations, so elimination of these is important to avoid flare-ups.

In people who have Crohn's disease, elemental diets (in which nutrients have been reduced to simple molecules) have been shown to be as effective as corticosteroids at inducing remission (Ogata H et al 2003; O'Keefe SJ 1996). In patients already taking prednisone, the drug could be reduced or eliminated in 50 percent of patients who follow an elemental diet. While on an elemental diet, inflammatory parameters and intestinal permeability decrease (Meister D et al 2002; Teahon K et al 1991). This diet does not work for ulcerative colitis.

The 4-R Program for Crohn's Disease

The following steps are recommended to help patients with Crohn's disease first reduce their symptoms and then begin long-term repair of the damage caused by their disease:

- **Remove.** Remove all suspicious foods from the patient's diet that precipitate inflammation. The following are the most likely to be troublesome: dairy, eggs, nuts, fruit, tomatoes, corn, wheat (or gluten), and red meat. All refined carbohydrates should be removed. All fats except for essential fatty acids should be eliminated, because hard or trans fats are detrimental to people with Crohn's disease (Heckers H et al 1988; Lorenz-Meyer H et al 1996). Products such as Vivonex®, UltraMaintain®, or UltraClear® can be used at the outset. UltraClear® is preferable because it contains sufficient fiber to maintain regular bowel evacuation. Removal of gastrointestinal parasites, undesirable bacteria, or fungal elements is important.
- **Replace.** The diets of most patients who have inflammatory bowel disease are nutritionally imbalanced. Replacement of vital nutrients consists of a good multivitamin, together with minerals that are lacking. The vitamins that most patients with inflammatory bowel disease lack are the B-complex vitamins such as folic acid and vitamin B6, and particularly vitamin B12 (Rogler G et al 2004). Iron and calcium deficiencies are frequently found in patients with Crohn's disease (Capurso G et al 2002; Lomer MC et al 2004; Siffledeen JS et al 2003), as well as deficiencies in zinc, protein, vitamin D, and folic acid (Rath HC et al 1998; Siffledeen JS et al 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 E et al 2003). Long-term use of corticosteroids warrants the inclusion of supplemental calcium and vitamin D to prevent corticosteroid-induced osteoporosis.
- **Reinoculate.** A normal healthy intestine contains 5 to 7 pounds of friendly bacteria, the good bacteria that are responsible for manufacturing some vitamins and cell food in the intestine. In a diseased intestine, these bacteria are not present in adequate amounts or are absent, having been replaced by pathogenic organisms or yeast overgrowth. Reinoculation consists of taking mixtures of the friendly bacteria *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* along with fructose oligosaccharides to promote continued repopulation with these beneficial bacteria (Fedorak RN et al 2004). Inhibition of pathogens by lactobacilli follows the lowering of pH through liberation of acids, resulting in an antimicrobial action. Stool samples provide information regarding these overgrowth factors, pH, and the balance of fatty acids.
- **Repair.** Frequently the lining of the small intestine becomes permeable, allowing antigens and other incompletely digested products to pass through the bowel wall. Repair of the protective layer consists of adding nutrients such as pantothenic acid (vitamin B5), zinc (Cario E et al 2000; Kapp A et al 1991; Weimann BI et al 1999), fructose oligosaccharides, and vitamin C to build up the integrity of the intestinal wall itself.

In a study of patients who had Crohn's disease with "leaky gut" (increased intestinal permeability as measured by a lactose/mannitol challenge), patients who did not have their small bowel mucosal integrity restored (those who still had a leaky gut), relapsed within 1 year (76 percent to 81 percent of the patients). Patients with normal intestinal mucosal integrity and healing had less than a 5 percent probability of relapse (Wyatt J et al 1993).

Supplements for Healthy Digestion

The following supplements can promote a healthy digestive system:

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 system of antioxidants. When presented with excessive oxidant stress, however, the mucosal barrier can sustain damage and become leaky, setting the stage for inflammation.

Inflammation itself produces large quantities of reactive species, and a destructive cycle can be perpetuated. In patients who have inflammatory bowel disease, there are high levels of reactive oxygen species in the intestines, which contributes to the damage caused by the disease. Oxidative damage is emerging as a key factor in the disease process (Koutroubakis IE et al 2004). The levels and the balance of important antioxidants are impaired within intestinal mucosa in inflammatory bowel disease (Kruidenier L et al 2003). Studies have shown that antioxidant combinations, including vitamin A, vitamin C, vitamin E, and selenium, can reduce the symptoms associated with inflammatory bowel disease (Trebble TM et al 2004, 2005).

Butyrate. Butyrate (also known as butyric acid) is a short-chain fatty acid produced when intestinal fiber is metabolized by bacteria. Butyrate ameliorates inflammation in ulcerative colitis and Crohn's disease, but the mechanism is not known. One mechanism by which butyrate may function is to inhibit the activation of a proinflammatory cell–signaling component called nuclear factor kappa B (NF-kappa B). This inhibition makes cells less responsive to proinflammatory cytokines (Segain JP et al 2000). Butyrate is often administered as an enema twice daily. The turmeric extract known as curcumin also inhibits NF-kappa B and can be taken orally.

Selenium. Selenium is a potent antioxidant necessary for metabolism of calcium and vitamin C, conversion of blood sugar into energy, reduction of platelet aggregation, and promotion of cardiovascular health. Selenium deficiency is common in people who have inflammatory bowel disease (Ishida T et al 2003; Kuroki F et al 2003). Supplementation may alleviate this problem.

Omega-3 fatty acids. Omega-3 fatty acids are well-known anti-inflammatories. They can be found in cold-water fish such as salmon, halibut, sardines, trout, or herring. Precursors to the most active omega-3s (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) can be obtained in walnut oil, flaxseed oil, perilla oil, and canola oil. Omega-3 fatty acids have been shown to reduce inflammation in inflammatory bowel disease by reducing the production of inflammatory cytokines (Almallah YZ 1998; Hillier K 1991; Ross E 1993; Steinhart AH 1997). They may also reduce the dosage of corticosteroid drugs needed to cause a remission (Grimminger F 1993; Hawthorne AB et al 1992). Gamma linolenic acid (GLA), an omega-6 fatty acid found in evening primrose oil, borage seed oil, and blackcurrant oil, is also showing promise in ulcerative colitis (Burke A et al 1997).

Similarly, a ginger extract called zerumbone has been shown to reduce inflammatory biomarkers in animals that have inflammatory bowel disease (Murakami A et al 2003).

Glutamine. Glutamine is an amino acid that is frequently used as a sports and fitness supplement. It has been found to help modulate the immune system and protect the mucosal protective layer in the intestine. Studies have demonstrated that glutamine can help improve blood flow in inflamed segments of the colon in patients who have ulcerative colitis, although its benefits did not extend to the most seriously affected portion of the colon (Kruschewski M et al 1998). Glutamine is also able to reduce leakiness of the intestine, which may help to reduce symptoms of inflammatory bowel disease.

Arginine. Research has suggested that arginine suppresses the growth of some strains of unfavorable bacteria and inhibits bacterial toxin release, a common problem in people who have chronic intestinal inflammation (Karasawa T 1997). Dietary supplementation of RNA and arginine promote healing of small-bowel ulcers in experimental ulcerative ileitis. Rats with experimental ileitis that received yeast RNA and/or arginine showed a significant decrease in the number of their ulcers compared to control rats. Scientists concluded that diets that were supplemented with yeast RNA, alone or in combination with arginine, accelerated ulcer healing by promoting increased cell proliferation (Sukumar P 1997; Vardareli E et al 2003).

Other studies, however, raise questions about the use of arginine for some models of colitis. Arginine promotes nitric oxide synthesis, and excess nitric oxide production may be detrimental to patients with colitis. Although many people benefit from the healthy effects of arginine-induced nitric oxide synthesis, some patients with colitis may not.

Dehydroepiandrosterone (DHEA). DHEA plays an important role in preventing chronic inflammation and provides signals needed to maintain healthy immune function. DHEA is a vitally important hormone. In fact, published studies link low levels of DHEA to aging and diseased states. Specifically, a deficiency of DHEA has been found to correlate with chronic inflammation. Excess levels of one or more of the inflammatory cytokines (TNF-alpha, IL-6, IL-1b, or LTB4) are usually found when a cytokine blood profile is conducted. DHEA has been shown to lower these proinflammatory cytokines and protect against their toxic effects (Haden ST et al 2000; Kipper-Galperin M et al 1999; Straub RH et al 1998). These proinflammatory cytokines rise with age and are especially high in patients who have inflammatory diseases. DHEA has consistently been shown to boost beneficial interleukin-2 (IL-2) and

suppress damaging IL-6 levels.

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. Mainstream therapy with corticosteroids is also known to lower androgen levels. Consequently, researchers argue that hormone replacement for patients who have chronic inflammatory diseases should include not only corticosteroids but also DHEA (Andus T et al 2003; Straub RH et al 2000).

Probiotics. With more than 400 microorganism species in the human gastrointestinal tract, the overall balance can profoundly influence intestinal health. Intestinal bacteria produce toxins and antitoxins, alter chemical composition of foods and drugs, produce and degrade vitamins, degrade dietary toxins, and inhibit the growth of certain pathogens. Intestine-derived bacterial products play a role in the systemic immune inflammatory response (Chin J 2004). Several probiotic mechanisms of action have been elucidated. Probiotics compete with microbial pathogens for a limited number of receptors present on the surface epithelium, have antimicrobial activity, suppress pathogen growth, and enhance barrier function (Fedorak RN et al 2004; Furrie E et al 2004).

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 ulcerative colitis are frequently deficient in vitamin K. One study showed that 31 percent of patients who had chronic gastrointestinal disease had a vitamin K deficiency, and all of them had either ulcerative colitis or Crohn's disease (Krasinski SD et al 1985).

Fiber

Dietary fiber is essential to good health and is found in many plant foods, such as fruits, vegetables, beans, nuts, and whole grains. Insoluble fiber found in such foods as fruit pulp, vegetable peels and skins, and grain brans adds bulk to stool and hastens the movement of food through the digestive tract, helping to prevent constipation and diarrhea. Soluble fiber found in fruits, vegetables, grains, oatmeal, and dried beans helps to lower cholesterol and prevent such diseases as colon cancer and diabetes.

A high-fiber diet may be helpful in reducing flare-ups of colitis. However, during active cases of colitis, fiber should be avoided because of its harshness to the walls of the intestinal tract. Juice from green leafy vegetables is a better alternative. After healing occurs, soluble fibers can be reintroduced into the diet.

SURGERY: A LAST RESORT

In severe or advanced 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. More than one third of patients who have Crohn's disease develop perianal disease involving anal fissures and perianal abscesses and fistulas. These symptoms seldom respond well to conventional therapies (Braunwald E 2001; McNamara DA et al 2004). Surgery may be required to drain abscesses or remove and close fistulas (Danelli P et al 2003). Surgery on inflamed tissue is itself potentially dangerous, and 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. 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. However, when the disease does recur, it usually does so at the site of the last surgery.

In patients with ulcerative colitis, surgery is indicated for up to half of patients in the first decade of their illness. At one time, the surgery of choice was removal of the anus and a portion of the lower colon, which resulted in lifelong incontinence and an ileostomy. 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.

THE PROTECTIVE EFFECT OF FOLATE ON COLON CANCER IN ULCERATIVE COLITIS

Evidence suggests that people with ulcerative colitis are at increased risk of colon cancer (Mitamura T et al 2002). About 5 percent of people with ulcerative colitis develop colon cancer. The risk of cancer increases with the duration and the extent of involvement of the colon. For people with ulcerative colitis, there are two factors affecting the risk of developing colon cancer. The first factor is that risk increases after 8 to 10 years of having ulcerative colitis. The second is the extent of the disease in the colon. Patients who have ulcerative colitis only in the rectum have the lowest risk. Having the disease in only part of the colon carries an intermediate risk. The greatest risk is for people whose entire colon is diseased (called pancolitis) (Itzkowitz SH et al 2004). 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

Two case-control studies have shown that folate may protect against the development of colon cancer caused by ulcerative colitis. The most recent study showed that folate use for at least 6 months reduced the risk of colon cancer by 28 percent in 98 patients who had ulcerative colitis for at least 8 years. Of the patients with ulcerative colitis, 29.6 percent developed cancerous lesions. The greater the dose of supplemental folate consumed, the lower the rate of colon cancer. Scientists concluded that "daily folate supplementation may protect against the development of neoplasia in ulcerative colitis" (Lashner BA et al 1997). 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 (because vitamin B12 is found only in red meat).

INFLAMMATORY BOWEL DISEASE RAISES HOMOCYSTEINE LEVELS

A number of studies have shown that patients with inflammatory bowel disease are more likely to have elevated homocysteine levels. In one study, more than 55 percent of patients with inflammatory bowel disease had elevated homocysteine levels (Roblin X et al 2006). The greatest risk factor for elevated homocysteine in patients with inflammatory bowel disease is reduced folate levels (Zezos P et al 2005). Vitamin B12 deficiencies are also frequently encountered (Mahmood A et al 2005). Certain drugs used to treat inflammatory bowel disease, such as methotextrate, are antimetabolites for folic acid, which may help explain why so many patients are deficient in this vital nutrient.

The elevated homocysteine level that is typical in patients with inflammatory bowel disease accounts for a 3-fold higher risk of blood clots and vascular disease (Fernandez-Miranda C et al 2005; Srirajaskanthan R et al 2005). It also helps explain why patients with inflammatory bowel disease are more likely to have early atherosclerosis (Papa A et al 2005). Based on these findings, it is logical that patients with inflammatory bowel disease should take a prophylactic B complex vitamin, with adequate folic acid and vitamin B12.

INFLAMMATORY BOWEL DISEASE AND BONE LOSS

Osteoporosis is a serious complication of inflammatory bowel disease that has not received adequate recognition despite its high prevalence and potentially devastating clinical effects (Compston JE 1995; Harpavat M et al 2004; Scharla SH et al 1994). Osteoporosis can be caused by inflammatory bowel disease itself or it can be an adverse effect of corticosteroid treatment. Data derived from a retrospective survey of 245 patients with inflammatory bowel disease 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 corticosteroid intake (Bischoff SC et al 1997; Gassull MA 2003; Vanis N et al 2003). Recent advances in the diagnosis and management of osteoporosis have facilitated early detection of bone loss and identified means by which it may be prevented. Bone-density measurements to predict fracture risk and define thresholds for prevention and treatment should be performed routinely in patients with inflammatory bowel disease (Rogler G et al 2004). For more information, see the chapter Osteoporosis.

Corticosteroids can also contribute to the risk of osteoporosis because of their effects on calcium and bone metabolism. Corticosteroids suppress calcium absorption in the small intestine, increase calcium excretion by the kidneys, and alter protein metabolism. Patients with inflammatory bowel disease who are taking corticosteroids experience a 6.2 percent annual loss of total bone mass compared with only a 0.9 percent annual loss of total bone mass in patients who are not taking corticosteroids. Nutrients that can help protect bone loss include calcium, vitamin D, and vitamin K.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

First-line therapy for inflammatory bowel disease involves lifestyle changes and supplementation with valuable nutrients. A strong multivitamin is recommended to provide the basic nutrition needed. It is important to reinoculate the intestine with beneficial bacteria. Also, patients should be aware that many people with inflammatory bowel disease are anemic to some degree and should carefully monitor their iron levels. If iron levels are low, supplementation with iron is recommended. A standard dose is 15 mg/day of elemental iron. Inflammatory bowel disease is also strongly associated with elevated homocysteine levels. Blood testing is recommended to make sure homocysteine levels remain in safe ranges. For more information, see the chapter Homocysteine.

People who have Crohn's disease may respond to the 4-R Program:

1. Remove all suspicious and proinflammatory foods, including processed foods and refined sugar. Also, foods high in saturated fat and trans fat should be removed. Instead, focus on intake of healthier fats, such as olive oil.
2. Replace any missing nutrients with a high-potency multivitamin (and other nutrients as needed).
3. Reinoculate the intestine with beneficial bacteria by taking *L acidophilus* and *L bulgaricus* with fructose oligosaccharides.
4. Repair the inner wall of the damaged intestine with supplements that have been shown to support the integrity of the intestinal wall itself, including glutamine, zinc, vitamin C, and fructose oligosaccharides.

Specific supplements that have been shown to help reduce the symptoms associated with inflammatory bowel disease include:

- **Glutamine**—1000 to 3000 milligrams (mg)/day
- **Probiotics**—300 mg, three times daily, of Life Flora, or 900 mg, three times daily, of Primal Defense. Both products contain beneficial bacteria. It's suggested to start with a single dose and gradually add more.
- **Zinc**—30 mg/day
- **Vitamin C**—1000 to 3000 mg/day
- **Vitamin E**—400 International Units (IU)/day with at least 200 mg of gamma-tocopherol
- **Vitamin K**—10 mg/day
- **Vitamin B complex**—A complete B-complex vitamin that includes high potencies of all the essential B vitamins including B1, B3, B6, and B12
- **Selenium**—200 micrograms (mcg)/day
- **Arginine**—1800 to 5400 mg/day
- **Butyrate enemas**—Two enemas a day are suggested for patients who have ulcerative colitis or Crohn's disease that affects their lower colon.
- **EPA/DHA**—At least 1400 mg/day of EPA and 1000 mg/day of DHA
- **Gamma Linolenic acid (GLA)**—900 to 1800 mg/day
- **Ginger extract**—250 mg/day
- **Soluble fiber**—5 to 15 grams (g)/day during remission periods
- **DHEA**—Start with 15 to 75 mg (in 3 to 6 weeks have blood tested to make sure optimal blood levels are maintained)
- **Folic acid**—800 micrograms (mcg)/day (in addition to the folic acid that is in the B-complex vitamin)

Because of the association between inflammatory bowel disease and osteoporosis, people with inflammatory bowel disease are encouraged to carefully monitor their bone density. For more information on supplements that can help prevent osteoporosis, see the chapter Osteoporosis.

Also, based on the association between colitis and colon cancer, patients are encouraged to closely monitor their colon health through regular screening. For more information on colon cancer screening and prevention, see the chapter Colon Cancer. Supplementation with folic acid and vitamin B12 (800 mcg of folic acid and 300 mcg of vitamin B12) has been shown to reduce the risk of colon cancer.

INFLAMMATORY BOWEL DISEASE SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure

Fiber

- Take fiber supplements with a full 8-ounce glass of water.
- Drink eight 8-ounce glasses of water daily while taking fiber.

Folic Acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

Ginger

- Do not take ginger if you have a bile duct obstruction or gallstones. Ginger may stimulate bile production.
- High doses of ginger (6 grams or more) can cause damage to the stomach lining and ulcers.
- Ginger can cause allergic skin reactions.
- Consult your doctor before taking ginger if you take blood thinners such as warfarin (Coumadin). Ginger can increase the risk of bleeding.

GLA

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

L-Arginine

- Do not take L-arginine if you have the rare genetic disorder argininemia.
- Consult your doctor before taking L-arginine if you have cancer. L-arginine can stimulate growth hormone.
- Consult your doctor before taking L-arginine if you have kidney failure or liver failure.
- Consult your doctor before taking L-arginine if you have herpes simplex. L-arginine may increase the possibility of recurrence.

L-Glutamine

- Consult your doctor before taking L-glutamine if you have kidney failure or liver failure.
- L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix

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