

# Inflammatory Bowel Disease Part I: Ulcerative Colitis – Pathophysiology and Conventional and Alternative Treatment Options

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## Abstract

Ulcerative colitis (UC), a subcategory of inflammatory bowel disease, afflicts 1-2 million people in the United States, and many more worldwide. Although the exact cause of ulcerative colitis remains undetermined, the condition appears to be related to a combination of genetic and environmental factors. While conventional treatments can be effective in maintaining remission and decreasing the length of active disease periods, the treatments are not without side effects, and a significant number of people suffering from UC fail to respond to even the strongest drugs. This article reviews potential unconventional treatments – transdermal nicotine, heparin, melatonin, DHEA, probiotics, fiber, dietary changes, botanicals, essential fatty acids, and other nutrients – that may be considered in conjunction with conventional approaches or as part of a comprehensive alternative treatment protocol. In addition this review addresses risk factors, pathogenesis, nutrient deficiencies, conventional treatment approaches, and extra-intestinal manifestations of the disease.

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## Introduction

Inflammatory bowel disease (IBD) encompasses several chronic inflammatory conditions, most significantly ulcerative colitis (UC) and Crohn's disease (CD). While these two conditions share many common features – diarrhea, bloody

stools, weight loss, abdominal pain, fever, and fatigue – each has unique features (Table 1). A complete discussion of Crohn's disease will be addressed in a future article. This review focuses on ulcerative colitis and associated risk factors, pathogenesis, nutrient deficiencies, conventional treatment approaches, natural treatment approaches, and extra-intestinal manifestations of the disease.

## Description and Symptomology

Ulcerative colitis affects the colon and rectum and typically involves only the innermost lining or mucosa, manifesting as continuous areas of inflammation and ulceration, with no segments of normal tissue. The Crohn's and Colitis Foundation of America defines several varieties of UC. Disease involving only the most distal part of the colon and the rectum is termed ulcerative proctitis; disease from the descending colon down is referred to as limited or distal colitis; and disease involving the entire colon is called pancolitis.<sup>1</sup>

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*Table 1. Comparison between Symptoms of Ulcerative Colitis and Crohn's Disease*

Sign/Symptom	Ulcerative Colitis	Crohn's Disease
Area of intestinal tract affected	Any part of inner most lining of colon, continuous with no "patches" of normal tissue	Lower ileum most common but can flare up anywhere, including the colon; "patches" of normal tissue between affected areas; can affect entire intestinal wall
Diarrhea	Typically four episodes per day	Typically four episodes per day
Abdominal pain/cramping	Mild tenderness, lower abdominal cramping	Moderate to severe abdominal tenderness in right lower quadrant
Blood in stool	Present; amount depends on disease severity	Present; amount depends on disease severity
Fatigue	Result of excessive blood loss and anemia	Result of excessive blood loss, anemia, and poor nutrient absorption
Fever	Low-grade in severe cases	Low-grade in severe cases
Physical examination	Rectal exam may show peri-anal irritation, fissures, hemorrhoids, fistulas, and abscesses	Peritoneal irritation, abdominal or pelvic mass
Weight loss/anorexia	Weight loss in more severe cases	Weight loss and anorexia common due to poor digestion and intestinal absorption
Appetite	Often decreased during periods of disease exacerbation	Often decreased during periods of disease exacerbation
Risk of colon cancer	Increased	Increased

UC may be insidious, with gradual onset of symptoms, or the first attack may be acute and fulminate. More mild symptoms include a progressive loosening of the stool, abdominal cramping, and diarrhea. As the disease progresses from mild to more severe, the patient may also experience weight loss, fatigue, loss of appetite that may result in nutrient deficiencies, mucus in the stool, severe rectal bleeding, fever, and anemia.<sup>1,2</sup>

### ***Epidemiology and Risk Factors***

It is estimated that 1-2 million Americans suffer from IBD; approximately half of these have ulcerative colitis. UC can occur anytime in life, but is usually diagnosed prior to age 30. The disease appears to affect men and women equally. Approximately 20 percent of people with UC have a close relative with IBD.<sup>1</sup> Caucasians have a higher incidence of UC, with Jewish people of European descent 3-6 times more likely to develop the disease.<sup>3</sup> Regions with a low incidence of UC include Asia, Japan, Africa, and South America.<sup>4</sup>

Breast feeding,<sup>5,6</sup> appendectomy,<sup>7,8</sup> and smoking,<sup>8,9</sup> are associated with reduced risk of UC. Consumption of a "Western diet,"<sup>10-12</sup> left-handedness,<sup>13,14</sup> and depression<sup>15,16</sup> may increase risk for ulcerative colitis.

### ***Diagnosis of Ulcerative Colitis***

Since the early symptoms of UC are similar to irritable bowel syndrome (IBS), Crohn's disease, diverticulitis, and colorectal cancer, a complete patient history is essential. In addition, it is initially necessary to rule out infectious causes of diarrhea and cramping with stool cultures and ova and parasite analysis. Other tests that may be performed early in the diagnostic process are fecal occult blood and a complete blood count (CBC) to check for intestinal blood loss and anemia. If UC is not ruled out, confirmation is usually via either flexible sigmoidoscopy or colonoscopy.<sup>1,3</sup>

### **Factors in the Etiopathogenesis of Ulcerative Colitis**

Although the exact cause of ulcerative colitis remains undetermined, the condition appears to be related to a combination of genetic and environmental factors. Whole genome scans have found susceptibility genes for UC on chromosomes 1 and 4, although these loci have not been uniformly confirmed.<sup>17</sup>

Among the pathological findings associated with UC are an increase in certain inflammatory mediators, signs of oxidative stress, a deranged colonic milieu, abnormal glycosaminoglycan (GAG) content of the mucosa, decreased oxidation of short chain fatty acids (SCFAs), increased intestinal permeability, increased sulfide production, and decreased methylation. While no one factor has been identified as the initial trigger for ulcerative colitis, pieces of the puzzle have been elucidated; fitting them together to create a complete picture remains to be accomplished.

### ***Inflammatory Mediators***

Differing cytokine and other inflammatory-mediator profiles have been identified for UC and CD. The classic lesions of UC, involving the mucosal layer with extensive epithelial damage, abundant neutrophils, and crypt abscesses have led to a search for an immune mechanism to explain the epithelial damage.<sup>18</sup>

While it has been hypothesized that CD is a T-helper 1 (Th1) dominated (cell-mediated) immune reaction, there is evidence UC is characterized by T-helper 2 (Th2) (humoral) domination.<sup>17</sup> The picture is far from clear, however (see Kidd P. *Altern Med Rev* 2003;8(3)) Enhanced humoral immunity in UC is evidenced by high levels of immune globulins and autoantibodies. Mucosal plasma cells from patients with UC have demonstrated high levels of immune globulins, especially IgG1.<sup>19</sup> Autoantibodies, including anticolon and antineutrophil antibodies, have been detected in the serum of UC patients.<sup>20,21</sup> Das et al have identified protein on colonic epithelium (40 kDa) that elicits an IgG antibody response.<sup>22</sup> Halstensen et al found evidence of immune globulins and

complement on the apical surface of colonic enterocytes – more evidence of a potential auto-immune response.<sup>23</sup>

The cytokine profile in UC patients provides more evidence of an exaggerated Th2 response – elevated interleukin-5 (IL-5) but no significant elevation of interferon-gamma (IFN- $\gamma$ ) and other cytokines associated with an overactive Th1 response.<sup>24</sup> Other researchers have reported elevated IL-8 in the mucosa of UC patients compared to controls or patients with CD.<sup>25</sup> Other cytokines associated with generalized inflammation – IL-1, IL-6, and tumor necrosis factor-alpha (TNF- $\alpha$ ) – are found elevated in both inflammatory bowel conditions.<sup>18</sup> Table 2 compares cytokine profiles typically seen in UC and CD.

Animal models of colitis have yielded evidence of both Th1- and Th2-mediated conditions. In a mouse model, Th1 cytokine responses yielded acute transmural and focal lesions, whereas Th2 cytokine responses resulted in diffuse atrophic changes in crypts and the mucosal layer. The authors conclude that in the animal model Th1 responses more closely resemble inflammation associated with CD, while Th2 responses induced lesions resembling UC.<sup>26</sup>

**Table 2. Cytokine Profiles: Comparison between Ulcerative Colitis and Crohn’s Disease**

Cytokine	Ulcerative Colitis	Crohn’s Disease
IL-1	Normal in serum; raised in mucosa	Normal in serum; raised in mucosa
IL-2	Normal in serum and mucosa	Raised in serum and mucosa
IL-6	Normal in serum; raised in mucosa	Raised in serum and mucosa
IL-8	Undetectable in serum; high in mucosa	Undetectable in serum; mucosa levels not reported
Interferon-gamma	Serum levels not known; normal in mucosa	Serum levels not known; high in mucosa
Tumor necrosis factor-alpha	Serum levels high; mucosa levels high	Serum levels high; mucosa levels high

Adapted from: MacDonald TT, Murch SH. Aetiology and pathogenesis of chronic inflammatory bowel disease. *Balliere’s Clin Gastroenterol* 1994;1:1-34.

While antibodies and complement may be associated with lesions of UC, the colon damage may also be the direct result of an exaggerated T-cell response. In another mouse model of colitis, it was established that a bacterially associated antigen could stimulate pre-committed Th1 or Th2 cells to mount an inflammatory reaction in the colon. Lamina propria cells recovered from Th2-stimulated mice produced IL-4 and -10, but no detectable IFN- $\gamma$ .<sup>27</sup>

TNF- $\alpha$ , although not specific to UC, may be a means of monitoring disease activity. Compared to healthy controls (n=10) or children with diarrhea (n=14) (mean TNF- $\alpha$  58- and 45 pg/g, respectively), children with active UC or CD had

**Table 3. Plasma Antioxidant Levels in Inflammatory Bowel Disease**

Antioxidant	Ulcerative Colitis (n=43)	Controls
Retinol	1.8 ± 0.1 (p<0.0001)	2.7 ± 0.07
Alpha tocopherol	18.3 ± 1.0 (p<0.0001)	26.8 ± 0.7
Lutein	0.42 ± 0.03	0.38 ± 0.01
Zeaxanthin	0.11 ± 0.01	0.10 ± 0.003
Lycopene	0.37 ± 0.03 (p<0.0001)	0.68 ± 0.02
Beta cryptoxanthin	0.25 ± 0.03 (p<0.01)	0.31 ± 0.01
Alpha carotene	0.13 ± 0.02	0.15 ± 0.01
Beta carotene	0.40 ± 0.05 (p<0.0001)	0.83 ± 0.03

p values are in relation to control

Adapted from: D'Odorico A, Bortolan S, Cardin R, et al. Reduced plasma antioxidant concentrations and increased oxidative DNA damage in inflammatory bowel disease. *Scand J Gastroenterol* 2001;36:1289-1294.

### ***Oxidative Stress in Ulcerative Colitis***

Signs of increased oxidative stress are in evidence in the intestinal mucosa of patients with ulcerative colitis and may be secondary to inflammation. One study examined signs of oxidative stress and plasma antioxidant levels in controls compared to patients with UC and CD. Oxidative DNA damage was noted in both IBD groups compared to controls, measured by production of 8-hydroxy-deoxyguanosine (8-OHdG). UC patients were found to have significantly lower plasma levels of vitamins A and E and several carotenoids compared to controls (Table 3); there were no differences between UC and CD groups.<sup>30</sup>

Other researchers have also found increased oxidative stress in ulcerative colitis patients. Mucosal biopsies of UC patients were

analyzed and shown to have increased reactive oxygen intermediates, DNA oxidation products (8-OHdG), and iron in inflamed tissue compared to controls. Decreased levels of copper and zinc, cofactors for the endogenous antioxidant superoxide dismutase, were also observed.<sup>31</sup> In addition, increased protein carbonyls in inflamed mucosa were noted. The authors speculate this supports the theory that free radicals can produce damage to mucosal proteins in IBD.

A theory proposed by several researchers involves TNF- $\alpha$  production of reactive oxygen species (ROS); ROS in turn activate nuclear factor-kappa B (NF-kB), which then enhances further TNF- $\alpha$  production, propagating a vicious cycle (Figure 1).

significantly higher levels of stool TNF- $\alpha$ . This study looked at only four children with UC and found levels of this cytokine ranged from 276-5,982 pg/g. In patients with inactive disease, levels fell to those of controls.<sup>28</sup>

In another study, frequency of TNF- $\alpha$ -secreting cells from intestinal mucosal biopsy specimens was analyzed. Although levels were higher in children with UC than normal subjects, they were not higher than in children with non-specific intestinal inflammation.<sup>29</sup>

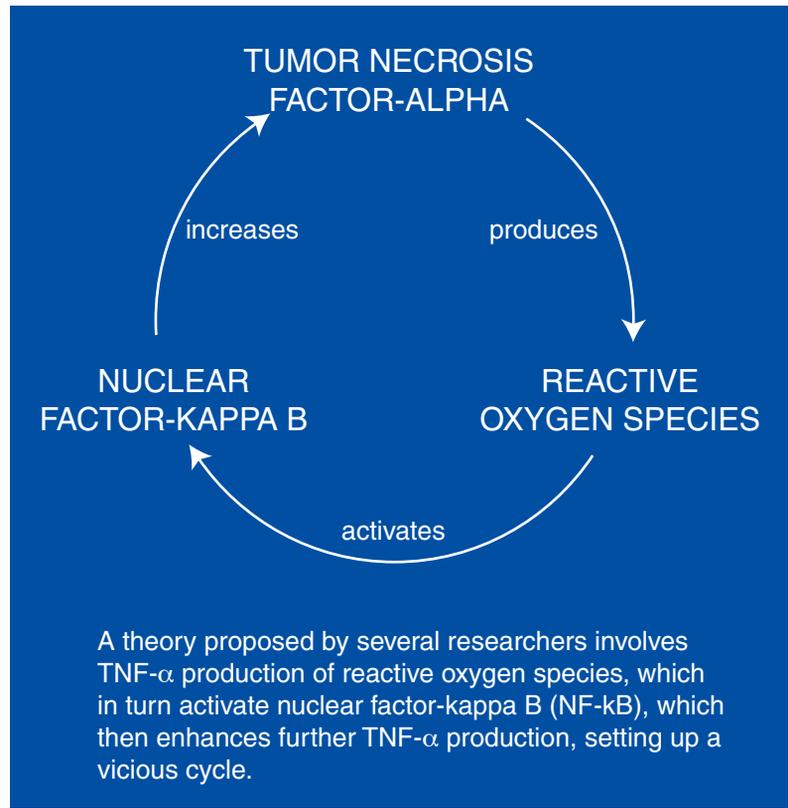
*The Role of Glycosaminoglycans*

The gastrointestinal (GI) extracellular matrix is composed of the proteins collagen and elastin, and ground substance that includes glycosaminoglycans (GAGs). GAGs are abundant in the basement membrane, lamina propria, and submucosa of the GI tract. The composition of GAGs may significantly affect both the permeability of the colon and immune/inflammatory reactions. Analysis of diseased, resected colons yielded altered GAG content in the colon of patients with IBD and colonic neoplasia compared to tissue from undiseased colons. In histologically normal colon tissue the majority of GAG content consists of chondroitin- and dermatin sulfate, with smaller amounts of hyaluronic acid and heparan sulfate. Ulcerative colitis yielded a distinctly abnormal distribution of GAGs, with significantly greater amounts of total glycosaminoglycans, heparan sulfate, and hyaluronic acid than control tissue. Colonic neoplasias were also found to contain these abnormal GAG profiles, but to a greater extent than UC tissue.<sup>32</sup>

Other researchers report the alterations are limited to the mucosa in UC, with substantial loss of GAGs from the subepithelial basal lamina. These researchers hypothesize that alterations in negatively charged sulfated compounds could significantly affect the passage of substances through the colonic mucosa, contributing to leakage of proteins and fluids, thrombosis, and extensive remodeling observed in UC and other inflammatory bowel conditions.<sup>33</sup>

The importance of altered glycosaminoglycan content of colonic tissue to the pathogenesis of UC is not completely understood. Whether it is a result of, or cause of, inflammation remains to be determined. Some researchers hypothesize these alterations may contribute to the inflammatory process since hyaluronic acid can

*Figure 1. The Potential Role of Reactive Oxygen Species in Inflammation*



interact directly with lymphocytes, inhibit macrophage response to cytokines, and enhance phagocytosis. GAG content has been associated with alteration in the distribution of macrophages reactive to TNF- $\alpha$ .<sup>34</sup>

Extracellular matrix proteins are important for maintaining the integrity of the gut wall as it is constantly challenged by antigens and microbes.

### *Colonic Milieu: Bacterial Profile, Effect on Gut Permeability, Sulfur, Nitric Oxide, and Short Chain Fatty Acids*

#### **The Significance of the Colonic Microflora**

Despite considerable study of fecal microflora in inflammatory bowel disease, no consistent pathogenic enteric bacteria have been identified, with the exception of *Clostridium difficile* (specific to patients with antibiotic-associated colitis).

Research results have varied and may, at least in part, be due to differences in specimen location. Some researchers have linked various Enterobacteraceae, especially *Escherichia coli*, with colitis. An examination of fecal samples collected from 23 patients with active ulcerative colitis, 15 with UC in remission, and 20 from patients with other types of colitis, found 35 percent of patients with active UC and 27 percent of patients with UC in remission harbored one or more invasive or adhesive fecal coliform bacteria, compared with five percent of patients with other types of colitis and five percent of normal controls ( $p < 0.05$ ).<sup>35</sup>

Researchers examining stool, sera, and gut tissue samples from 59 patients with IBD (14 with UC) concluded mycobacteria did not play a role in IBD. They found *Yersinia* species in tissue from IBD patients, and pathogenic *E. coli*, particularly in patients with UC.<sup>36</sup>

Another group of researchers examined diseased tissue from patients with IBD and did not find signs of a primary role for *E. coli*, *Listeria monocytogenes*, or *Klebsiella pneumoniae*. *E. coli* antigens were detected in ulcerous tissue and were suspected to be due to secondary infection in these lesions.<sup>37</sup>

On examination of stool samples and rectal biopsies from 30 patients with IBD and 20 controls, Schultz et al concluded that potentially pathogenic adherent *E. coli* were just as commonly seen in the large intestine of healthy controls than patients with IBD.<sup>38</sup>

Some researchers hypothesize that fecal samples are influenced by such things as rectal bleeding and diarrhea, and as such are not the best sources for flora investigation. They examined, instead, the rectal mucosa-associated flora (MAF) of patients with ulcerative colitis: 25 with newly diagnosed UC, 20 with relapse of existing disease, and 44 in remission. Interestingly, they found total bacterial counts as well as counts of specific groups (facultative anaerobes, obligate anaerobes, and micro-aerobes) actually decreased in patients with active disease, especially those suffering their first attack, compared to those in remission. With treatment the numbers increased. Unlike other research, *E. coli* was not isolated as frequently as other bacterial strains including *Bacteroides* species and aerobic and anaerobic gram-positive cocci.<sup>39</sup>

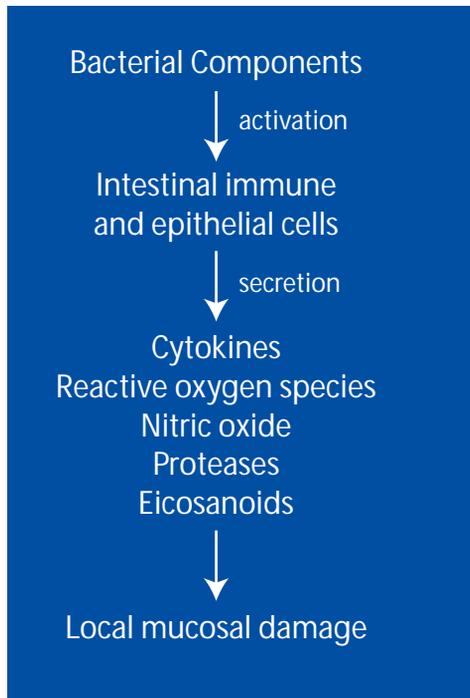
**Table 4. Pathogens with Potential Association with Ulcerative Colitis**

*Escherichia coli*  
*Diplostreptococcus*  
*Costridium difficile*  
*Fusobacterium necrophorum*  
*Shigella sp.*  
*Helicobacter hepaticus*  
 RNA virus  
*Bacteroides vulgatus*  
*Yersinia sp.*

On the other hand, researchers examining the mucosal microflora have found increases in bacterial counts for both aerobes and anaerobes in UC patients, with the highest counts and most frequent isolation for *Bacteroides vulgatus*. The researchers concluded that an antibody response to these bacteria could play an etiological role in ulcerative colitis.<sup>40</sup> Table 4 summarizes potential pathogens associated with UC.

Despite the inability to isolate a specific pathogen, there is considerable evidence that bacteria play a role in colitis: (1) bowel lesions apparently occur more frequently in areas of highest bacterial concentration; (2) normal enteric bacteria are necessary for disease expression in animal models; (3) patients with UC who have had ileal pouch-anal anastomosis surgery develop mucosal lesions only after bacterial colonization; and (4) therapeutic manipulation of colonic flora with anti- or probiotics can result in symptom improvement.<sup>41</sup>

**Figure 2. The Potential Effect of Bacteria on Inflammation and Gut Permeability**



There are several mechanisms whereby colonic bacteria may influence the course of ulcerative colitis. The beneficial effects are discussed in the treatment section. Pathogenic mechanisms may involve: (1) an overwhelming presence of

specific pathogenic bacteria; (2) subtle imbalances in the ratio of beneficial to pathogenic bacteria (dysbiosis); (3) a defective mucosal barrier; and (4) alterations in the gut immune response.<sup>41</sup> Pathogenic bacteria may secrete enterotoxins capable of altering gut permeability and causing systemic effects, elaborate immunosuppressive proteins that interfere with normal gut immune responses, and may directly interfere with epithelial cell metabolism (e.g., metabolism of SCFAs). A possible cascade of events is illustrated in Figure 2.

Because no specific pathogen has been implicated in UC, alterations in gut immunity may play a significant role. A popular theory among researchers is that UC is characterized by an abnormal host response to normal colonic bacteria, i.e., a cross-reactivity between antibodies produced against bacteria and mucosal proteins. Animal models and human studies of colitis support this theory, demonstrating inflammatory reactions to commensal anaerobes. In a mice study an abnormal T-cell response to an enteric bacterial strain was implicated as a mechanism for colitis pathogenesis. The researchers further demonstrated a bacterial antigen could contribute to either an abnormal Th1 or Th2 response that progressed to colitis.<sup>27</sup>

Subjects with normal bowel function elaborate IgA as the primary immunoglobulin in the intestines, offering the first line of defense against antigens (bacteria, allergens, etc.). Researchers have found patients with IBD tend to produce high concentrations of IgG by intestinal lymphocytes, when compared to controls with IBS. IgG antibodies, directed at cytoplasmic proteins from normal commensal bacteria, were evident in patients with UC but not in controls.<sup>42</sup> An overreaction to normal enteric microflora, resulting in an autoimmune response, may be an important aspect of chronic ulcerative colitis.

### Gut Permeability

An impaired colonic mucosal barrier leading to increased intestinal permeability has been demonstrated in patients with UC. Local leaks due to apoptosis of colonic epithelium comprise the primary lesion in mild UC. Moderate-to-severe

UC is characterized not only by extensive local leaks but also by highly permeable ulcerous lesions.<sup>43</sup>

Patients with UC have also demonstrated decreased colonic mucin species IV compared to biopsy specimens from normal controls.<sup>44</sup> An *in vitro* study demonstrated a possible interaction between bacterial peptides and the mucosa in UC, resulting in depletion of mucus secretion by goblet cells.<sup>45</sup>

Medical therapy (unspecified) leading to remission not only results in decreased inflammation but also improved gut barrier integrity.<sup>46</sup>

### The Sulfur-Butyric Acid Connection

Butyric acid, a four-carbon short chain fatty acid, and several other SCFAs, including propionic and acetic acids, are produced in a healthy colon by fermentation of fiber and other carbohydrates. Butyric acid provides the primary fuel for colonocytes. Proper ion transfer, mucus synthesis, phase II detoxification, and lipid synthesis for cell membrane integrity in the colonocytes depend on butyrate oxidation.<sup>47</sup> Impaired metabolism of SCFAs has been implicated as a factor in UC.

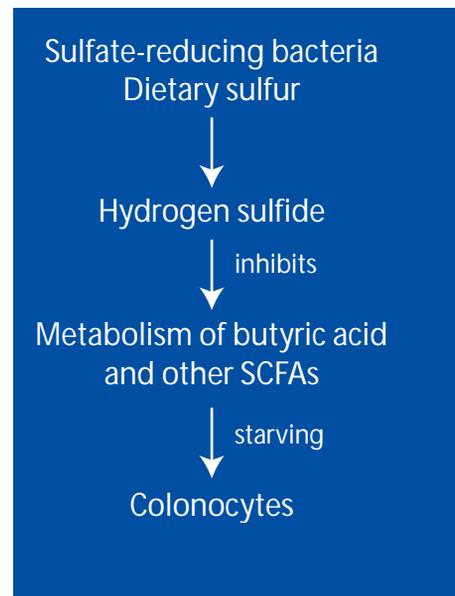
Hond et al compared butyrate metabolism in healthy controls with that of 25 hospitalized patients with severe ulcerative colitis and 11 UC patients in remission. They measured butyrate metabolism after rectal instillation of <sup>14</sup>C-labeled butyrate by measuring <sup>14</sup>CO<sub>2</sub> in the breath. Patients with active UC had significantly lower butyrate oxidation than patients in remission (who had normal butyrate oxidation) or controls. Three patients with inactive disease had decreased butyrate oxidation and interestingly, all three relapsed within a few weeks.<sup>48</sup> Perhaps decreased oxidation of SCFAs is a good predictor of possible relapse and occurs before other signs of inflammation. Because normal oxidation was observed in patients in remission, faulty SCFA oxidation is likely to be a result rather than a primary cause of ulcerative colitis.

Other researchers compared the rate of butyrate, glucose, and glutamine oxidation to carbon dioxide in colonoscopy biopsy specimens from 15 patients with quiescent or mild colitis to specimens from 28 controls with normal colonic

mucosa. Butyrate, but not glucose or glutamine, oxidation was significantly impaired in the UC patients compared to controls, even though the disease was mild.<sup>49</sup>

High concentrations of sulfate-reducing bacteria with concomitant elevation of hydrogen sulfide have been noted in patients with UC. Hydrogen sulfide can potentially damage the gut mucosa by inhibiting butyrate oxidation in the mitochondria, essentially starving the colonocyte (Figure 3). In experiments on human colonocytes isolated from colectomy patients, hydrogen sulfide and other sulfur compounds inhibited butyrate oxidation by 75 percent in the distal colon and 43 percent in the ascending colon. The authors of the study conclude that the “metabolic effects of sodium hydrogen sulfide on butyrate oxidation along the length of the colon closely mirror metabolic abnormalities observed in active ulcerative colitis.”<sup>50</sup>

*Figure 3. A Potential Mechanism for Hydrogen Sulfide Toxicity*



Animal studies on rabbits and guinea pigs have demonstrated that feeding sulfated polysaccharides (such as carrageenan), but not unsulfated polysaccharides, can induce lesions similar to ulcerative colitis.<sup>51</sup>

Researchers note higher counts of sulfur-reducing bacteria in the feces of patients with active UC than in patients in remission.<sup>52</sup> A commonly used drug for treatment of ulcerative colitis, 5-aminosalicylic acid (5-ASA; mesalamine) has been shown to lower sulfide concentrations in feces.<sup>53</sup>

Methylation is believed to be an important route for sulfide detoxification in the colonocyte.<sup>54</sup> A study was conducted to determine if methyl donors could reverse the damaging effect of sulfides on colonocytes. Isolated colonocytes from rat and human specimens were tested by measuring the oxidation of butyrate in the presence of hydrogen sulfide, followed by introduction of methyl donors to the suspension. Sulfide toxicity was reversible most potently by S-adenosylmethionine 1,4 butane disulfonate (stable form of SAME), followed by DL-methionine-S-methyl-sulfonium and L-methionine. Methyl donors may have therapeutic value in UC.<sup>55</sup>

Interestingly, hyperhomocysteinemia, a condition of inadequate methylation, has been found to occur more commonly in patients with IBD (17 of 64; 26.5%) than controls (4 of 121; 3.3%).<sup>56</sup> Other researchers confirm homocysteine levels tend to be higher in IBD (8.7 mmol/L) than in healthy controls (6.6  $\mu$ mol/L).<sup>57</sup> While hyperhomocysteinemia may likely be, at least in part, a result of folate or vitamin B12 deficiency associated with the disease process or medications used, it may also be a contributing factor to the pathogenesis of UC.

At least two *in vitro* studies have attempted to determine whether activity of certain enzymes involving sulfur metabolism are up- or down-regulated in UC. One found thiolmethyltransferase (TMT) activity did not seem to be associated with sulfide-induced colonocyte toxicity.<sup>54</sup> A second *in vitro* study found TMT activity was significantly higher in UC. The authors speculate TMT might be up-regulated in UC in an attempt to detoxify excess hydrogen sulfide.<sup>58</sup>

Potential sulfate toxicity may have implications for diet as both an etiological and therapeutic factor. The Western diet, which by one analysis contains an average of 16.6 mmol sulfate/day compared to the rural African diet that contains an average of 2.7 mmol sulfate/day,<sup>51</sup> has been implicated as one of the risk factors in ulcerative colitis. Sulfur may be acquired in the diet by consumption of food preservatives and additives such as sulfites, sulfur dioxide, and carrageenan, and foods high in sulfur amino acids (eggs, whole milk, cheese, meat, cruciferous vegetables, onions, and garlic). The effects of low-sulfur diets on UC are discussed in the dietary treatment section.

Similar to sulfides, nitrogen derivatives may inhibit butyrate metabolism. An *in vitro* study found nitric oxide interfered with fatty acid metabolism in colonocytes. However, co-administration of peroxide and sulfide was necessary to cause injury to the colonocyte.<sup>59</sup>

### *NSAIDs as a Causative Factor*

Non-steroidal anti-inflammatory drugs (NSAIDs) are believed to cause colitis as well as exacerbate existing disease by increasing permeability and contributing to colonic bleeding. Based on previous animal studies demonstrating ibuprofen inhibited SCFA oxidation in isolated mitochondria of mouse liver,<sup>60</sup> Roediger and Millard studied ibuprofen's effect on colonocytes from rats and humans and found that, at concentrations of 2.0-7.5 mmol/L, ibuprofen selectively inhibited oxidation of butyrate.<sup>61</sup> This concentration may not occur at doses typically consumed.

Other NSAIDs have been implicated in acute episodes and relapses of proctocolitis. Four cases were reported, involving flufenamic acid, mefenamic acid, naproxen, and ibuprofen.<sup>62,63</sup>

### *Dietary Factors in the Etiology of Colitis*

Several studies have examined dietary risk factors for the development of ulcerative colitis. Table 5 summarizes the results.

*Table 5. Dietary Risk Factors for Ulcerative Colitis*

Study	Subjects	Method	Increased Risk	Decreased Risk
Italian	104 UC and CD patients compared to healthy controls	Dietary recall questionnaire	Refined sugar Starch Total protein	
Dutch	43 UC patients compared to 43 age- and gender-matched controls	Cross-check dietary history	Mono- and polyunsaturated fats Vitamin B6 (artifact?)	
Israeli	54 UC patients, 33 CD patients, and 144 controls	Pre-illness dietary history	Sucrose Fat (especially animal fat)	Fructose
Swedish	145 UC patients, 152 CD patients, and 305 controls	Dietary recall questionnaire	Fast food (twice weekly resulted in relative risk of 3.9)	Coffee (artifact?)

An Italian study of 104 patients with UC and CD found, using a dietary recall questionnaire, that total carbohydrate, refined sugar, and starch intakes immediately prior to onset of the disease were significantly higher in both UC and CD patients than in healthy controls. Total protein intake was significantly higher in UC but not Crohn's patients.<sup>12</sup>

A case-control Netherlands study of 43 recently-diagnosed (within the previous six months) UC patients and 43 age- and gender-matched controls examined dietary intakes for five years prior to the study using a cross-check dietary history method. Fat intake was determined by adipose tissue fatty acid composition. In this study, high intakes of vitamin B6 and mono- and polyunsaturated fats were associated with increased risk. No significant differences in composition of adipose tissue were noted. The connection between vitamin B6 and increased UC risk is baffling and may be an anomaly.<sup>64</sup>

A study in Israel compared the pre-illness diet of 87 recently diagnosed IBD patients (54 with UC and 33 with CD) with 144 controls. Odds ratios for developing IBD were determined for various foods. High sucrose intake was associated with risk for both UC and CD, while fat (especially animal fat) was associated with increased risk for UC only. Interestingly, fructose intake was negatively associated with risk for IBD.<sup>65</sup>

Pre-illness dietary habits of Swedish patients with IBD (145 with UC, 152 with CD, and 305 controls) were examined in a case-control study. The most significant finding was an increased relative risk for IBD associated with fast food consumption. Eating fast food twice weekly resulted in a relative risk of 3.9 for UC. Coffee intake was associated with protection, although the researchers believed this could have been merely an artifact. Because the questionnaire was sent to participants as long as four years after the date of diagnosis asking them to recall what they had eaten five years previously, the data may be flawed.<sup>10</sup>

Cow's milk sensitivity has been evaluated as an etiology of UC. Serum from patients with several conditions, including 51 with UC, was compared to that of 38 healthy controls. Antibodies to the principal cow's milk proteins were analyzed, including casein,  $\alpha$ -lactalbumin, and  $\beta$ -lactoglobulin. Antibody titers from patients with UC did not differ from controls or patients with other conditions. The authors conclude, "At the present time there is little evidence to suggest that milk allergy is a factor in the etiology of ulcerative colitis."<sup>66</sup> Other researchers have found no increase in IgG antibodies to folate-binding protein of cow's milk in patients with UC compared to controls.<sup>67</sup>

### Conventional Treatment of Ulcerative Colitis

Conventional drugs for ulcerative colitis include aminosalicylates, corticosteroids, antibiotics, and immunomodulators. The most common protocols include aminosalicylates for maintaining remission and corticosteroids during acute episodes.

Aminosalicylates include sulfasalazine (azulfadine) and 5-ASA-only medications – mesalamine, balsalazide, and olsalazine. Sulfasalazine consists of a 5-ASA molecule bound to sulfapyridine. Sulfapyridine is absorbed systemically after being cleaved from 5-ASA and is responsible for the majority of side effects associated with sulfasalazine. Drugs in this class have anti-inflammatory effects by inhibition of IL-1, IL-2, and NF-kB.<sup>68,69</sup> In addition, they impair monocyte and lymphocyte function and provide antioxidant activity.<sup>70</sup> Another potential mechanism may involve inhibition of sulfide production. *In vitro*, 5-ASA has been found to inhibit sulfide production. Patients with UC not on 5-ASA drugs appear to have higher fecal levels of sulfide than controls,<sup>71</sup> although 5-ASA appears to inhibit oxidation of butyrate, potentially interfering with normal SCFA metabolism.<sup>72</sup> The implications for long-term use remain to be elucidated. These drugs may also be used as suppositories or enemas for distal colitis and proctitis.

Side effects occur in 30 percent of patients taking sulfasalazine and include nausea, vomiting, headaches, rash, fever, agranulocytosis, pancreatitis, nephritis, hepatitis, and male infertility. In addition, the sulfa portion of the drug interferes with folic acid absorption, so this vitamin should be supplemented in patients taking sulfasalazine. The 5-ASA medications lacking the sulfa moiety are associated with fewer side effects, although diarrhea and abdominal pain have been reported with these medications.<sup>70</sup>

Corticosteroids are the mainstay for acute episodes of UC. Their potent immunosuppressive effects include inhibition of the arachidonic acid cascade, IFN- $\gamma$ , and IL-1, -2, -4, -5, -6, and -8. While a dose-response curve is evident with prednisone, doses over 40 mg/day do not confer increased benefit.<sup>70</sup> Topical steroids may be administered rectally via suppository or enema for distal proctocolitis.

Side effects of short-term steroid use include fluid retention, weight gain, and mood swings. Long-term use increases the risk for cataracts, osteoporosis, myopathy, conditions associated with immune suppression, and adrenal insufficiency.

Antibiotics have been prescribed for UC; however, unlike with Crohn's disease, they have been largely ineffective. Among the drugs tried are vancomycin, metronidazole, tobramycin, and ciprofloxacin. In some studies antibiotics have resulted in initial improvement that has not been maintained over the long term.<sup>70</sup>

A new category of drugs, immune modulator drugs, including azathioprine and 6-mercaptopurine, is being explored for patients dependent on steroids. These drugs exert their effects by inhibiting proliferation of lymphocytes and ribonucleotide synthesis. Their anti-inflammatory effects are due to suppression of natural killer (NK) cell activity and T-cell function. While effective, they are associated with significant side effects, including pancreatitis, fever, rashes, arthralgias, nausea, and diarrhea.<sup>70</sup>

Cyclosporin, billed as "the greatest treatment advance for UC in 10 years," inhibits T-helper activity by blocking IL-2, -3, and -4, TNF- $\alpha$ , and IFN- $\gamma$ . It is particularly useful for patients

with severe UC for whom steroids are no longer effective. Not only does it have a higher response rate than steroids, its remission rate is considerably more impressive. Cyclosporin has significant potential toxicity, including paresthesias, tremor, hypertension, nausea, vomiting, headaches, seizures, and nephrotoxicity. The combination of cyclosporin with steroids and immunomodulators increases the risk for opportunistic infections such as *Pneumocystis carinii*.<sup>70</sup>

## Less Conventional Treatments for Ulcerative Colitis

### *Connection between Smoking, Nicotine, and UC*

Epidemiological data have found smoking may confer some level of protection from UC. Thirty newly diagnosed UC patients were matched for age, sex, and marital and economic status with healthy controls. Patients with UC were three times less likely to smoke but seven times more likely to have quit smoking an average of 27 months prior to diagnosis.<sup>73</sup>

Because of the possible link between smoking and protection from UC, a number of studies have been conducted using transdermal nicotine patches or nicotine gum for the treatment of ulcerative colitis. A small, double-blind, crossover trial examined seven UC patients individually (single-patient trial) for eight weeks. Therapy was alternated every two weeks between nicotine gum (20 mg/day) and placebo gum. Evaluation was on the basis of self-reported symptoms and proctoscopic exam. Three of seven patients, all former smokers, demonstrated significant enough improvement to warrant incorporating nicotine gum into their treatment regimens.<sup>74</sup>

The effectiveness of transdermal patches has been examined in several double-blind trials. Seventy-two patients with active UC were randomized to receive either daily 15-25 mg transdermal nicotine patches or placebo patches for six weeks. All patients remained on previous medications – mesalamine in all patients and low-dose glucocorticoids in 12 patients. Seventeen of 35 patients in the nicotine group experienced

complete remission, compared to nine of 37 in the placebo group. The nicotine group also had greater improvement in clinical signs, symptoms, and histological findings, and decreased stool frequency, abdominal pain, and urgency. Twenty-three patients in the nicotine group experience side effects (mainly lightheadedness, nausea, headache, and sleep disturbances), compared to only 11 in the placebo group.<sup>75</sup>

A study published the following year, involving some of these same researchers, did not find significant positive effects from the use of transdermal nicotine. Eighty UC patients in remission were assigned in double-blind fashion to either transdermal nicotine (15 mg patch for 16 hours daily) or placebo patch for six months. As soon as a maintenance dose of nicotine was reached, mesalamine was discontinued in all patients. No significant differences in number of relapses were noted between groups. The researchers observed serum nicotine levels were lower than expected in the active treatment group, which may reflect poor compliance.<sup>76</sup>

Several small Italian studies yielded some positive findings. In seven of 10 patients with relapsing UC on mesalamine who did not tolerate steroids well, 15 mg transdermal nicotine daily for four weeks resulted in clinical remission that persisted for as long as three months after nicotine withdrawal.<sup>77</sup>

Another small study compared the effects of transdermal nicotine with those of prednisone in patients on mesalamine maintenance therapy. Patients in clinical relapse were randomly assigned to add either prednisone or transdermal nicotine to mesalamine for five weeks. The first 15 in each group with clinical and endoscopic signs of remission were followed for six months. The relapse rate was 20 percent in the nicotine group and 60 percent in the prednisone group.<sup>78</sup> In a further evaluation, follow-up continued for 12 months with patients in remission due to either nicotine or prednisone. If patients relapsed, they were crossed over to the other treatment regimen. After 12 months, relapse occurred in 14 of 15 patients originally on prednisone and seven of 15 on nicotine.<sup>79</sup>

Transdermal nicotine has been compared to oral mesalamine in the treatment of distal colitis. Thirty patients who failed to respond to mesalamine enemas (4 g at bedtime) were randomly assigned to 15 mg transdermal nicotine daily or 800 mg mesalamine three times daily for four weeks. Clinical and sigmoidoscopic remission was observed in 12 of 15 patients on nicotine, but only five of 15 on oral mesalamine.<sup>80</sup>

Transdermal nicotine appears to offer effective co-treatment for UC, both for patients during relapse and for maintaining remission. In the negative study, patients were asked to discontinue mesalamine, unlike other studies where patients remained on their maintenance treatment. Although nicotine's mechanism of action is unknown, it may exert its effects through inflammatory mediators,<sup>81</sup> changes in mucus production,<sup>82</sup> or alterations in blood flow.<sup>83</sup>

### *Heparin: An Unexpected Find*

Patients with UC have a greater risk of developing coagulation problems such as deep vein thrombosis (DVT). In treating patients for DVT with heparin, an unexpected improvement in UC was noted. Heparin consists of a group of GAGs that have anticoagulant as well as potential anti-inflammatory effects.

In a pilot study, 16 hospitalized UC patients unresponsive to high-dose steroid treatment were given intravenous (IV) heparin at standard anticoagulant dosages. Within one week, 12 of 16 experienced significant clinical improvement; and within four weeks these 12 were in complete remission.<sup>84</sup>

In a prospective study, 13 patients with severe UC and four with CD in a hospital setting were treated with sulfasalazine (which they had already been taking at the time of hospitalization) and continuous heparin IV for two weeks, followed by home injections of heparin for another six weeks. Significant improvement in clinical symptoms and laboratory signs of inflammation – C-reactive protein and erythrocyte sedimentation rate – were seen in patients with UC, but not CD. Seven UC patients achieved complete remission after four weeks.<sup>85</sup>

Another small pilot study examined the safety and effectiveness of heparin in an outpatient setting. Twelve UC patients, who had not responded well to steroids, self administered heparin (dalteparin sodium 5,000 units by subcutaneous injection) twice daily. Eleven of the 12 patients improved; six attained complete remission after 12 weeks. No serious adverse events occurred.<sup>86</sup>

Based on positive results from small, pilot trials, a multicenter, randomized trial was conducted. Hospitalized patients received either IV heparin or methylprednisolone for 10 days. After 10 days, 69 percent in the steroid group but none in the heparin group had achieved remission. C-reactive protein was decreased in the steroid but not heparin group. Thirty-one percent of the steroid group experienced rectal bleeding by day 10 compared to 90 percent in the heparin group. Two patients in the heparin group experienced rectal bleeding severe enough to require a blood transfusion.<sup>87</sup> More extensive study to examine the effectiveness and safety of heparin for UC is indicated.

### *Melatonin and the Gastrointestinal Tract*

The amount of melatonin found in the GI tract can be 10-100 times the levels found in the blood and 400 times that found in the pineal gland. Although the GI tract may act as a sink for extragastrointestinal derived melatonin, there is evidence pointing to *de novo* synthesis in the GI tract as well.<sup>88</sup>

While it is still theoretical and no clinical studies have been conducted to determine its efficacy, melatonin may provide some benefit in ulcerative colitis. Intraperitoneal injections (150 µg/kg) of melatonin to mice with dextran-induced colitis resulted in resolution of rectal bleeding and occult blood in all cases. Frequency and severity of lesions in the mucosa were significantly reduced on histological exam.<sup>89</sup>

There are several mechanisms whereby melatonin might exert potential benefit. Location of melatonin in the intestinal villae supports the

hypothesis that it is integral in transport of electrolytes across cell membranes. Melatonin has been noted *in vitro* to relieve spasm in isolated rat intestinal tissue.<sup>90</sup>

Melatonin may exert benefit in IBD by interacting with inflammatory mediators. Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is induced by TNF- $\alpha$  and believed to be involved in inflammation associated with IBD. In an *in vitro* study, melatonin, in amounts 5-50 times the usual 3 mg nightly dose, inhibited TNF- $\alpha$ -induced MAdCAM-1.<sup>91</sup> Furthermore, oxidative stress is considered to be important in the pathogenesis of UC, and melatonin is a significant free radical scavenger.<sup>88</sup>

### *Effect of Estrogens in UC*

Data on the relationship between estrogen and ulcerative colitis has been conflicting, with pregnancy increasing risk of UC flare-ups in severe, uncontrolled colitis, but not in milder cases or those in remission.<sup>92</sup> In animals 17 $\beta$ -estradiol has been found to decrease inflammation in some experimental models of colitis, but to increase inflammation in others.<sup>93</sup> Whether exogenous estrogen would be beneficial or detrimental to women with ulcerative colitis remains to be determined.

### *Dehydroepiandrosterone (DHEA)*

Dehydroepiandrosterone sulfate (DHEAS) levels have been found to be low in people with chronic inflammatory conditions. A study examined serum DHEAS and cortisol levels in 64 patients with UC, 115 patients with CD, and 66 healthy subjects. DHEAS levels were lower in both groups of IBD patients than in controls, and even lower in patients with a history of corticosteroid use.<sup>94</sup>

Another controlled study compared the effects of acute and chronic inflammation on DHEA levels. Thirteen patients undergoing cardiothoracic surgery (representing acute inflammation) were compared to 61 patients with IBD (21 with UC; representing chronic inflammation) and 120 controls. While DHEA was elevated in patients with acute inflammation, it was decreased in IBD patients with chronic inflammation.<sup>95</sup>

DHEA, at least in animal models, has been shown to inhibit proinflammatory cytokines, including TNF- $\alpha$ , providing a potential beneficial mechanism of action in chronic inflammation.<sup>96</sup>

## **Diet, Probiotics, Specific Nutrients, and Botanicals in the Treatment of UC**

### *Correcting Nutrient Deficiencies or Excesses*

Ulcerative colitis is associated with several nutritional deficiencies. Geerling et al demonstrated, in a clinical study of 69 patients with IBD (46 with UC), that beta-carotene, magnesium, selenium, iron, copper, and zinc were significantly lower in newly diagnosed patients than in controls.<sup>97</sup> The low levels of antioxidants, such as carotenoids, selenium, and zinc, may be attributed to increased oxidative stress contributing to increased consumption of antioxidants by the inflamed intestinal tissue.

### **Vitamin A and Carotenoids**

Carotenoids and retinol play an essential role in enhancing the mucosal integrity of the gut. Low levels of retinol binding protein (RBP) are seen in IBD, resulting in a secondary decrease in serum retinol levels. Decreases in RBP may be due to excessive protein loss from diarrhea associated with IBD. Patients with most active disease demonstrated the lowest levels of serum retinol and RBP. Because zinc is required for the synthesis of RBP, a zinc deficiency may negatively impact vitamin A metabolism and result in hypovitaminosis A. Retinol absorption rates were also decreased in patients with severe UC, but not in patients with mild-to-moderate disease.<sup>98</sup> In the Geerling study, serum beta-carotene concentrations were significantly lower in UC patients than in controls.<sup>97</sup>

A study of IBD patients, including 35 with UC, examined serum retinol and carotenoid levels as well as the prevalence of the Leiden mutation, a newly discovered genetic marker of UC and CD. Mozsik concluded that (1) retinoids and carotenoids play an essential role in maintaining

mucosal integrity in the gastrointestinal tract; (2) serum levels of vitamin A are significantly lower in UC, while alpha- and beta-carotene levels are nearly the same as that of controls; and (3) an inverse relationship exists between the prevalence of the Leiden mutation and serum retinol values.<sup>99</sup>

One study found beta-carotene was the carotenoid most significantly reduced in UC, with only 50 percent of the plasma concentration of controls. The extent of disease activity also influenced some antioxidant levels to varying degrees, with lycopene and zeaxanthin demonstrating the largest difference between active disease and remission in ulcerative colitis patients.<sup>30</sup> In an animal model of colitis, lycopene, but not beta-carotene, significantly reduced signs of inflammation.<sup>100</sup>

### Vitamin E

Vitamin E levels have also been found to be low in some patients with IBD. One study found low levels only during active disease, possibly reflective of increased oxidative stress observed during inflammation.<sup>30</sup>

### Vitamin C

Much of the research on IBD has focused on the etiology of the inflammatory process and the role oxidative stress plays in damaging intestinal tissue. An Australian study examined colonic biopsies from IBD patients and measured mucosal concentrations of reduced and total ascorbic acid. In UC patients, mucosal total ascorbic acid content decreased by 73 percent and reduced-ascorbic acid by 41 percent. Enzymatic reduction of dehydroascorbic acid decreased significantly in inflamed mucosa of UC patients, indicating inflamed mucosa is less able to maintain reduced-ascorbic acid concentrations. The researchers postulated that oxidative stress caused by inflammatory cells contributed to significant loss of antioxidant buffering capacity, retarding tissue recovery.<sup>101</sup>

### Vitamin K

Inflammatory bowel disease has also been shown to be associated with vitamin K deficiency that can result in abnormal prothrombin.<sup>102,103</sup> Consequently, a highly sensitive antigen assay, using this prothrombin abnormality, was developed for the diagnosis of vitamin K deficiency. In a study of 58 patients with chronic GI disease or resection, 31 percent (18 patients) demonstrated a vitamin K deficiency. All patients had either conventionally treated UC or CD involving the ileum. Abnormal prothrombin levels returned to normal with vitamin K administration. Vitamin K deficient patients also demonstrated significantly lower plasma vitamin E levels.<sup>103</sup>

### Folic Acid

Folic acid status in ulcerative colitis patients may be influenced by a number of factors, including reduced dietary intake, red cell hemolysis secondary to chronic drug therapy,<sup>104</sup> chronic diarrhea,<sup>105</sup> and sulfasalazine therapy that interferes with absorption of folate.<sup>106</sup> Impaired intestinal transport and absorption results in structural alteration of intestinal mucosal cells, thus promoting further malabsorption and cell transformation.<sup>105,107</sup>

As mentioned, folate deficiency may be associated with high homocysteine levels often seen in UC patients. A Greek study examined serum folate and homocysteine levels in 108 IBD patients, 53 of whom had UC. It was determined that UC patients had significantly higher homocysteine levels, while folate levels were lower when compared to control subjects.<sup>108</sup>

### Calcium

Calcium deficiency in UC patients may result from a variety of factors, including decreased dietary intake, malabsorption, enteric losses, associated vitamin D deficiency, and corticosteroid treatment.<sup>109</sup> In a study of 152 patients with IBD (73 controls), males especially had lower calcium intakes than control subjects. The daily dietary calcium intake was below 1,000 mg in 53 percent of patients and below 400 mg in 9.2 percent of patients. Forty-seven percent of patients

avoided lactose in their diet, compared to 11 percent of control subjects.<sup>110</sup>

### Iron

Iron deficiency and resultant anemia is frequent in UC due to chronic GI bleeding.<sup>109</sup> Iron status in UC patients is most accurately measured by serum ferritin, with levels below 18 ng/mL being highly predictive of iron deficiency. In a study of 24 patients with UC, plasma iron levels were significantly reduced compared to controls, particularly in patients with moderately severe UC.<sup>111</sup>

Conversely, the mucosal iron concentration has been observed to be significantly increased in the presence of inflammation, at least in part due to overproduction of free radicals via increased levels of free hemoglobin from mucosal ulceration and bleeding.<sup>112</sup> Furthermore, research on preneoplastic colonic mucosa of UC patients has demonstrated immunoreactivity to the major iron-binding proteins, lactoferrin, transferrin, and ferritin. Increased expression of these proteins and subsequent iron accumulation may trigger a self-perpetuating cycle, resulting in further tissue damage and a trend toward neoplastic progression. Iron chelation has been found effective in experimental models of inflammation.<sup>111</sup> In view of higher iron concentrations in intestinal mucosa, iron supplementation in UC should be avoided if possible. Treatment goals should be to curb iron loss by healing the gut, providing antioxidants to counter pro-oxidant effects of mucosal iron, and chelate free iron if necessary.

### Magnesium

Magnesium deficiency is prevalent in UC patients, but whether it is a result of disease via malabsorption and intestinal loss, or a causative factor from decreased intake remains unclear. In a dietary history study of 54 UC patients, high magnesium intake was shown to reduce the risk of inflammatory bowel disease, suggesting an association between low pre-illness dietary intakes and subsequent development of UC.<sup>65</sup> Another study demonstrated that in 46 newly diagnosed UC patients, serum magnesium concentrations

were significantly lower than in controls, suggesting a possible etiological role for magnesium deficiency.<sup>97</sup> Despite sometimes-normal serum magnesium levels, intracellular magnesium concentrations are frequently low in UC patients.<sup>109</sup>

### Selenium

Like magnesium, serum and plasma selenium levels are significantly ( $p < 0.05$ ) lower in newly diagnosed UC patients than in controls.<sup>97</sup> Another study assessing mineral status in patients with IBD (117 with UC) found men had significantly lower serum selenium than controls. After adjusting for age and sex, low selenium levels also increased the risk for development of UC, suggesting a deficiency as a potential etiological factor.<sup>113</sup> Selenium's potential role in colorectal cancer prevention highlights its importance in UC.

### Zinc/Metallothionein

Studies assessing zinc status in UC patients have generated mixed results. The most current research shows a significant decrease in serum zinc levels compared to controls.<sup>98</sup> Conversely, other studies report increased serum zinc levels in both men and women compared with controls.<sup>113,114</sup>

Colonic inflammation may contribute to reduced local availability of zinc in mucosal tissue, resulting in a reduction in antioxidant zinc-dependent enzymes, such as metallothionein. A growing body of evidence supports metallothionein's role in maintaining cellular defense mechanisms in the face of oxidative stress.<sup>115,116</sup>

Italian researchers demonstrated that, while there were no changes in plasma zinc levels of 24 UC patients, mucosal zinc and metallothionein concentrations were often decreased, particularly at inflammatory sites.<sup>117</sup>

### Copper

Serum copper levels are often increased in patients with IBD<sup>113,118</sup> and, during inflammation, may be accompanied by increased ceruloplasmin (the carrier molecule for copper) levels.<sup>119</sup> Excess copper may increase oxidative stress in the

colonic mucosa resulting in a continuous cycle of inflammation in IBD.<sup>120</sup> Zinc supplementation may result in a copper deficiency; therefore, supplementing small amounts of copper may be indicated.

See Table 6 for suggested supplementation of vitamins and minerals.

**Dietary Treatment**

**Elemental Diet**

An elemental diet is comprised of free-form or predigested amino acids. Some improvement in UC has been noted in patients on these diets, but is thought to be a result of the diet’s influence on intestinal microflora composition rather than enhanced nutritional status. Evidence of the effectiveness of elemental diets is limited. A review of 11 randomized trials evaluating various diets used in UC patients revealed no positive treatment effect in the two trials utilizing elemental diets.<sup>121</sup> Compliance is also difficult. Hospitalization is often necessary for proper administration, and relapse is common once the patient resumes a normal diet. The diets are also unpalatable to many patients and the hyperosmolality frequently causes diarrhea.

**Elimination/Hypoallergenic Diet**

Food allergies have long been considered in the etiology of UC, with most research focusing on allergy to cow’s milk protein. Recent research demonstrates, however, there is no consistent evidence of lactose intolerance among patients with active ulcerative colitis.<sup>122-124</sup>

Other highly allergenic foods may be responsible for exacerbation of UC, and elimination diets seem to hold the most promise for therapeutic benefit. A small study of 18 UC patients demonstrated an elimination diet excluding commonly known allergenic foods resulted in significantly fewer UC symptoms (primarily diarrhea and rectal bleeding) in nine patients on the elimination diet compared to nine patients consuming a normal diet. Foods that seemed to elicit

**Table 6. Correcting Nutrient Deficiencies in UC**

Nutrient	Suggested Supplementation
Vitamin A	10,000-25,000 IU daily*
Beta carotene	25,000-100,000 IU daily
Vitamin E	400-800 IU daily
Vitamin C	500-1,000 mg daily
Vitamin K	500 mcg-1 mg daily
Folic acid	400 mcg-1 mg daily
Calcium	500-1,000 mg daily**
Iron	30-60 mg daily***
Magnesium	300-500 mg daily
Selenium	200-400 mcg daily
Zinc	15-45 mg daily
Copper	1-3 mg daily

\* Do not exceed 7,500 IU if pregnant  
 \*\* Citrate or citrate malate forms  
 \*\*\* Supplement only if anemic

symptoms included citrus fruits, dairy, pork, tomatoes, pineapple, shellfish, spiced or curried foods, apples, grapes, and melon. In addition to the decrease in symptoms, four patients in this study attained remission on the elimination diet and eight months later three were still symptom free, despite reverting to a normal diet.<sup>125</sup>

### Elimination of Sulfur-containing Amino Acids

Based on the known contribution of sulfides to the pathogenesis of UC, a pilot study was conducted on eight patients taking sulfasalazine for maintenance and prednisolone for acute attacks (four who had suffered a first acute attack and four with chronic UC). The patients were asked to eliminate dietary sources of sulfur-containing amino acids, including eggs, cheese, whole milk, ice cream, mayonnaise, soy milk, mineral water, sulfited drinks such as wine and cordials, nuts, and cruciferous vegetables. They were also asked to decrease intake of red meat, substituting chicken, fish, and skim milk as protein sources. During the 12-month follow-up, the patients experienced no relapses or attacks (expected relapse rate on sulfasalazine was 22.6 percent). In addition, all showed marked histological improvement. The number of bowel movements daily in the four chronic UC patients decreased from an average of 6/day to 1.5/day. Two patients stopped the diet, but resumed it when they noticed adverse effects.<sup>126</sup> A larger controlled trial is warranted.

### Fiber in the Diet

Fiber can be therapeutically beneficial for people with UC. Diets with a low fiber content have been associated with increased risk of UC, suggesting a high-fiber diet may protect against disease or relapse.<sup>127</sup> Low-fiber diets are frequently high in refined carbohydrates thought to promote muscle spasm, resulting in increased pressure in the colonic lumen, further facilitating the disease process.<sup>128</sup> This suggests that a high-fiber diet, composed of complex rather than refined carbohydrates, may be a better option for UC patients. During periods of disease exacerbation, however, the amount and type of fiber may have to be decreased until overt inflammation subsides. Diets high in fiber may also promote advantageous intestinal flora composition via increased butyrate production.<sup>129</sup>

The effects of specific types of fiber have been examined in both animal models and clinical studies of UC. In a rat model, animals receiving five-percent *Plantago ovata* (PO; psyllium)

seeds experienced an increase in SCFA production (mainly butyrate), restored colonic glutathione levels, lower TNF- $\alpha$  and nitric oxide synthase levels, and recovery of damaged colonic mucosa, when compared with untreated colitic rats.<sup>130</sup>

In a randomized clinical trial of 105 ulcerative colitis patients in remission, subjects were given 10 g PO seeds twice daily, 500 mg mesalamine three times daily, or a mesalamine and PO combination, with the desired outcome being remission for 12 months. In the PO group, 13 of 35 patients relapsed, compared to 13 of 37 patients in the mesalamine group. In the PO plus mesalamine group, only seven of 30 patients relapsed, suggesting a greater benefit with the combination treatment than either PO or mesalamine alone. To determine the effect of PO intake on SCFA production, a separate group of seven patients was given the seeds for three months. Fecal SCFA were measured at trial entry and at three months. PO administration resulted in significantly higher butyrate, acetate, and total SCFA levels. It has been suggested butyrate has a protective effect against colon carcinogenesis.<sup>131</sup>

Psyllium husk (referred to as ispaghula husk in the study) has the ability to absorb 40 times its own weight in moisture. A double-blind, placebo-controlled trial of 29 UC patients in remission, but reporting disturbances in bowel habits, demonstrated 4 g psyllium husk twice daily (or placebo – low-fiber crushed crispbread) for four months resulted in symptomatic improvement in 69 percent of patients on psyllium compared to 24 percent in the control group. Symptom assessment was by questionnaire at onset and at two and four months.<sup>132</sup>

Germinated barley foodstuff (GBF) is a protein-rich insoluble prebiotic fiber made from brewer's spent grain, containing glutamine-rich protein and hemicellulose. Prebiotics enhance production of beneficial microflora. GBF is produced by the Kirin Brewing Company in Japan and has received approval from the Japanese Ministry of Health and Welfare as a food for specific use in ulcerative colitis therapy. Animal and human studies by a group of Japanese researchers have shown GBF to increase stool butyrate levels and inhibit

pro-inflammatory cytokine production,<sup>133,134</sup> increase levels of beneficial intestinal bacteria,<sup>135</sup> increase stool-forming ability in the colon,<sup>136</sup> decrease diarrhea,<sup>137</sup> prevent mucosal damage,<sup>138</sup> and possibly improve the mucosal barrier of the colon.<sup>139</sup>

Larch arabinogalactan is a polysaccharide powder derived from the wood of the larch tree (*Larix* species) and comprised of approximately 98-percent arabinogalactan. Arabinogalactans are most abundant in *Larix occidentalis* (Western larch), a deciduous pine tree native to the Pacific and Inland Northwest.<sup>140</sup> Larch arabinogalactan is approved by the U.S. Food and Drug Administration as a source of dietary fiber, and has been shown to increase SCFA production (primarily butyrate) via its vigorous fermentation by intestinal microflora.<sup>141</sup> Because butyrate is a primary energy source for colonic epithelial cells, it may protect the intestinal mucosa from disease.<sup>142</sup> Although no studies have been conducted to date, larch arabinogalactan administration may be of benefit in UC patients by virtue of increased fecal butyrate levels and improved intestinal microflora composition.

### Probiotics

As previously discussed, an abnormal host immune response to certain intestinal microflora is believed to play a part in the pathogenesis of UC. In addition, UC patients with active disease frequently have reduced amounts of obligate anaerobes such as Bifidobacteria, Eubacteria, and Clostridia, as well as reductions in facultative organisms and micro-aerobes, when compared to UC patients in remission.<sup>39</sup> Consequently, researchers have examined the effects of probiotic supplementation in UC patients. Probiotic bacteria may include Lactobacilli, Streptococci, Bifidobacteria, and certain *E. coli* subspecies. Probiotics may be effective in UC because of lactic acid production, which reduces luminal content pH, inhibiting growth of putrefactive or harmful bacteria.<sup>143</sup> Another possible explanation is bacteriocin production, resulting in a direct antibacterial action.<sup>144</sup> For a probiotic to be effective, it must be safe and well-tolerated, arrive in the intestinal tract in a viable form, and adhere securely to the intestinal mucosa.<sup>145</sup>

Both animal and clinical studies reveal several probiotics may aid in achieving UC remission. Nineteen UC patients were treated with *Lactobacillus plantarum* 299v or placebo after four weeks of being unresponsive to conventional therapies. Of the 10 patients receiving the probiotic solution, seven achieved clinical and colonoscopic remission. No patients in the placebo group achieved remission.<sup>146</sup>

In an uncontrolled, open trial Venturi et al administered a combination probiotic preparation called VSL-3, which contained three strains of Bifidobacteria, four Lactobacilli strains, as well as *Streptococcus salivarius*, subspecies thermophilus, to UC patients in remission. Patients were supplemented for a period of 12 months. Of the 20 patients in the treatment group, 15 remained in remission for one year, four relapsed, and one was lost to follow-up. Levels of fecal *Streptococcus salivarius* ssp. thermophilus, Lactobacilli, and Bifidobacteria were significantly increased in all 20 patients, as compared to baseline. These results suggest that colonization of the intestinal tract by the VSL-3 preparation may aid in maintaining remission in UC patients.<sup>147</sup>

In a double-blind study, Kruis et al gave *E. coli* (Nissle strain 1917) or mesalazine to 116 patients with quiescent UC and demonstrated that the *E. coli* strain was as effective as mesalazine in preventing relapse.<sup>148</sup> The two agents were also compared in a study of 120 patients with active disease, and it was concluded the *E. coli* strain was equally effective to mesalazine in preventing relapse in these patients.<sup>149</sup>

A small, randomized clinical trial examined the use of Bifidobacteria-fermented milk (BFM) as a dietary adjunct in the treatment of UC. Eleven patients received 100 mL/day BFM for one year, at which time colonoscopies, blood markers, and examinations of intestinal flora were performed. Statistical analysis revealed a significant reduction in disease exacerbation in the BFM group compared to controls, suggesting BFM supplementation was successful in preventing relapse and maintaining remission.<sup>150</sup>

### *Specific Nutrients*

#### **Essential Fatty Acids**

Changes in omega-3 and -6 fatty acid profiles have been observed in UC patients.<sup>151,152</sup> These changes may influence fatty acid synthesis by colonic tissue as well as membrane lipid composition of luminal cells,<sup>153</sup> potentially playing a part in disease pathogenesis. A study of 73 patients with active IBD assessed plasma fatty acid patterns and actually found a marked increase in omega-3 fatty acids, particularly docosahexanoic acid (DHA), suggesting that during active disease increased biosynthesis may accompany increased consumption resulting from a response to inflammation. Omega-6 fatty acids, especially dihomo-gammalinolenic acid (DGLA), were found to be decreased in UC patients.<sup>152</sup>

With few exceptions, a review of omega-3 fatty acid studies demonstrates they exert a beneficial effect in UC patients.<sup>154-157</sup> In a randomized, double-blind, controlled trial of 96 ulcerative colitis patients, 4.5 g eicosapentanoic acid (EPA) was administered daily for one year. Control subjects were given an olive oil placebo. Twenty of 96 patients entered the trial during relapse, and 16 of that 20 achieved remission with EPA. Patients receiving EPA attained remission sooner than patients in the placebo group (median 102 days versus 141 days on placebo), although the results were not statistically significant. Patients receiving EPA, however, experienced a significant reduction in steroid medication requirement and a 50-percent reduction in leukotriene B4 (LTB4) synthesis throughout the trial.<sup>158</sup>

Three separate studies conducted by Almallah et al examined various effects of a six-month supplementation with 3.2 g EPA and 2.4 g DHA in 18 patients with distal proctocolitis; control subjects received sunflower oil. The earliest of the three studies investigated the role of omega-3 fatty acids in the modulation of natural cytotoxicity and disease activity. Over the six-month period, analysis revealed omega-3 supplementation significantly reduced the number of circulating NK cells and lymphokine activated killer (LAK) cells when compared to the placebo group.<sup>159</sup>

Some of the same researchers examined histological and clinical effects of omega-3 supplementation and found a significant reduction in the number of certain T-lymphocyte subsets (CD3) and activated cells (HLA-DR) in the intestinal mucosa. The supplemented group also had a significantly reduced percentage of rectal mucosal cells containing IgM when compared to controls. Histological scores, disease activity, and sigmoidoscopic scores also improved in the omega-3 supplemented group compared to placebo. The researchers concluded omega-3 supplementation for six months suppressed immune reactivity as well as disease activity in proctocolitis patients receiving omega-3 fatty acids.<sup>160</sup>

A third evaluation examined the possible mechanisms involved in the inhibition of natural cytotoxicity observed in the earlier studies. After six months of supplementation with omega-3 fatty acids, laboratory assessment revealed that key humoral mediators, specifically LTB4 and IL-2, both known to enhance NK-cell activity, were significantly reduced in serum samples of patients with proctocolitis when compared to patients receiving placebo. Clinical assessment showed a reduction in disease activity as evidenced by reduced symptomatology and improved sigmoidoscopy scores.<sup>161</sup>

Not all studies have found positive benefits from supplementation with omega-3 fatty acids. In a double-blind, placebo-controlled study of 63 UC patients with quiescent disease, administration of EFAs (1.6 g gamma-linolenic acid, 270 mg EPA, and 45 mg DHA per day) for one year failed to prolong remission when compared to controls (500 mg/day sunflower oil).<sup>162</sup> It should be noted, however, the dosages in this study were extremely low.

In a second study, omega-3 fatty acids (5.4 g daily) were compared to sulfasalazine (2 g daily) in 10 patients with mild-to-moderate UC over a two-month period. Treatment with omega-3 fatty acids resulted in an increase in disease activity as evidenced by increased platelet counts, erythrocyte sedimentation rate, C-reactive protein, and total fecal nitrogen excretion. Patients in the sulfasalazine group did not experience any significant changes in these laboratory parameters.

*Table 7. Summary of Omega-3 Fatty Acids for Ulcerative Colitis*

Authors	Subjects	Duration	Design	Dosage	Outcome
Middleton et al. 2002	63 patients with quiescent disease	12 months	Randomized, double-blind, placebo-controlled	1.6 g GLA, 270 mg EPA, 45 mg DHA daily	Did not prolong the period of disease remission
Dichi et al. 2000	10 with mild to moderate active UC	4 months	Randomized, cross-over study	5.4 g fish oil daily	Increased disease activity compared to sulfasalazine; (increased pH, ESR, CRP, fecal nitrogen)
Almallah, El-Tahir et al. 2000	18 with active distal proctocolitis	6 months	Double-blind, randomized, placebo-controlled study	3.2 g EPA and 2.4 g DHA daily	Decreased serum LTB4 and IL2; inhibition of NK cytotoxicity
Almallah et al. 1998	18 with active distal proctocolitis	6 months	Double-blind, randomized, placebo-controlled study	3.2 g EPA and 2.4 g DHA daily	Decreased circulating levels of LAK and NK cells; suppressed cytotoxicity and reduced disease activity
Hawkey et al. 1992	96 patients in remission or relapse	12 months	Double-blind, randomized, placebo-controlled study	4.5 g EPA daily	Decreased serum LTB4 levels and decreased steroid use
Almallah, Ewen et al. 2000	18 patients with active distal proctocolitis	6 months	Double-blind, randomized, placebo-controlled study	3.2 g EPA and 2.4 g DHA daily	Decreased CD3, HLA, and IgM expression (in situ immune reactivity); improvement in disease activity and histological scores
Stenson et al. 1992	18 with active UC	4 months	Multi-center, randomized, double-blind, placebo-controlled, cross-over study	3.24 g EPA and 2.16 g DHA daily	Decreased LTB4 levels; improved histological scores; weight gain
Lorenz et al. 1989	10 with active UC	7 months	Double-blind, placebo-controlled, cross-over study	1.8 g EPA and 1.3 g DHA daily	Decreased disease activity; improved morphological scores on endoscopy
Loeschke, Uberschaer et al. 1996	64 with active but quiescent disease	24 months	Double-blind, placebo-controlled study	5.1 g daily omega-3 fatty acids	Increased time to relapse initially; did not prevent relapse over long-term
Salomon et al. 1990	10 patients with mild-to-moderate UC	2 months	Uncontrolled, open trial	2.7 g EPA daily	Decreased disease activity; improved morphological score on endoscopy.; reduced steroid dosages

It was concluded that sulfasalazine treatment was superior to omega-3 fatty acids in patients with mild-to-moderate UC.<sup>163</sup> See Table 7 for a summary of omega-3 fatty acid studies in ulcerative colitis.

### **Short Chain Fatty Acids**

Because of the vital role they play in the maintenance of colonic integrity and energy metabolism, SCFA supplementation using butyrate enemas has been the focus of several studies in UC patients. Enema administration is thought to enhance and prolong the contact of butyrate with the colonic cells when compared to other routes of administration. The use of butyrate enemas in UC patients has produced varied results, making conclusions regarding their effectiveness difficult. Harig et al administered enemas containing sodium salts of butyrate, propionate, and acetate to patients with diversion colitis (microscopically indistinguishable from UC) twice daily over a six-week period and demonstrated an improvement in inflammation and a significant reduction in symptoms.<sup>164</sup>

In a multicenter trial, 51 patients with chronically active mild-to-moderate distal UC received enemas of either butyrate plus 5-ASA or saline plus 5-ASA twice daily. After eight weeks endoscopic and histological parameters, laboratory data, stool frequency and consistency, and other UC symptoms were assessed. The administration of 5-ASA plus butyrate was significantly more effective than 5-ASA plus saline in achieving disease improvement or remission.<sup>165</sup>

Two six-week studies reported either statistically insignificant<sup>166</sup> or no improvement<sup>167</sup> in UC disease activity or remission status in patients supplemented with butyrate enemas, when compared to a saline enema placebo.

### **Glutamine**

In addition to being the main fuel source for the mucosal cells in the ileum,<sup>168</sup> glutamine is also utilized by colonocytes as a respiratory fuel source.<sup>169</sup> A rat study investigated the effect of various agents (prednisolone, 5-ASA, L-glutamine, or SCFAs) applied by enema twice

daily for seven days after induction of colitis with trinitrobenzene sulfonic acid in ethanol. L-glutamine enemas provided the most benefit when compared to the other agents, resulting in a decrease in severity of colitis and lipid peroxidation, without altering mucosal absorption capacity. None of the other three agents yielded such comprehensive benefit.<sup>170</sup>

Research using other animal models of UC has shown glutamine addition to elemental diets decreases endotoxin levels<sup>171</sup> and promotes more rapid healing of colonic lesions.<sup>172</sup>

### **Phosphatidylcholine/Phosphatidylinositol**

Research using a rat model of induced colitis indicates oral supplementation with phosphatidylcholine (PC) prevents collagen deposition and subsequent stricture formation in inflamed colonic tissue. Two of 15 rats fed 100 mg PC daily developed strictures, compared to 12 of 16 colitic rats not receiving PC. Non-colitic control rats had no stricture development. In addition, collagenase activity in colonic tissue was significantly higher in colitic rats given PC than in non-colitic rats and colitic rats receiving no PC. The authors conclude the reduced rate of stricture formation in the treated rats was due to PC enhancement of collagen breakdown.<sup>173</sup>

A study of rats with acetic-acid induced colitis investigated the therapeutic benefits of colonically administered PC and phosphatidylinositol (PI). Both phospholipids were found to have therapeutic benefit when given in a dose-dependent and time-dependent manner over a three-day period. Beneficial effect (prevention of colitis induction and reduction of mucosal permeability) was most pronounced when either PC or PI was given to rats immediately after colitis induction (acetic acid administration). Both phospholipids resulted in significant mucosal recovery and decreased permeability.<sup>174</sup>

### **Superoxide Dismutase**

UC is characterized by signs of increased oxidative stress in the intestinal mucosa that may be secondary to inflammation. Superoxide dismutase (SOD) is a scavenger of free radicals,

and as such may have therapeutic application in UC. An animal study examined the effects of lecithinized-SOD (PC-SOD) administered intravenously to 114 rats with induced UC; control rats were given purified water. The SOD was bound to lecithin to enhance tissue affinity. Rats receiving PC-SOD showed a decrease in bloody stools as well as decreased inflammatory cell infiltration and erosion in the colon. Blood leukocyte levels were also decreased. By scavenging oxygen free radicals, PC-SOD is thought to prevent colonic tissue damage in this UC model.<sup>175</sup>

### **Botanicals and Flavonoids**

Over 20 different botanicals have been used alone or in combination in both animal models and clinical trials of UC. Clinical trials have been conducted on a *Ginkgo biloba* extract (Cedemin), *Boswellia serrata*, and a botanical combination. Animal studies or case reports offer preliminary information on the potential efficacy of flavonoids, bromelain, and other plant extracts.

#### ***Ginkgo biloba***

In a small open trial, 10 patients with mild-to-moderate UC were given Cedemin enemas nightly for three weeks. Three of 10 patients achieved remission and two experienced some improvement, but these results were not statistically better than placebo.<sup>176</sup> It was hypothesized that the mechanism responsible for Cedemin's effect in patients who improved or attained remission was due to the extract's inhibition of platelet-activating factor (PAF), which mediates mucosal inflammation.<sup>177</sup>

#### ***Boswellia serrata***

An open, non-randomized clinical trial of 30 patients with chronic colitis investigated the effect of *Boswellia serrata* gum resin (BWGR) for six weeks on various UC disease parameters. Achieving remission was the primary goal of treatment. Stool properties, histopathology of colonic mucosa, sigmoidoscopic scores, and various laboratory markers of anemia and inflammation were assessed at the beginning and end of the trial. Twenty of 30 patients received 900 mg daily of

BWGR in three divided doses. Ten control patients received 3 mg daily sulfasalazine in divided doses. Eighteen of 20 patients receiving BWGR showed an improvement in one or more of the parameters assessed, particularly in sigmoidoscopic scores, and 14 achieved remission. This was compared to four of 10 patients in the control group receiving sulfasalazine. After statistical analysis of results for all parameters measured, the degree of improvement was not statistically significantly better for BWGR-treated patients than for patients receiving sulfasalazine.<sup>178</sup>

### **Combination Herbal Treatment**

Another study examined the effectiveness of an herbal combination, containing *Taraxacum officinale*, *Hypericum perforatum*, *Melissa officinalis*, *Calendula officinalis*, and *Foeniculum vulgare*, on 24 patients with chronic non-specific colitis. By day 15 of the study, 23 patients had a complete resolution of pain in the large intestine. In addition, diarrhea resolved and fecal content normalized.<sup>179</sup>

#### ***Peumus boldus***

A rat study compared the efficacy of boldine – an alkaloid from *Peumus boldus*, an evergreen tree found in Chile – to 5-ASA. The study investigated boldine's cytoprotective and anti-inflammatory properties in mucosal tissue of rats with induced colitis. Boldine was found to have an anti-inflammatory effect in the colon as evidenced by reduced colonic neutrophil infiltration, protection against edema and cell death, and enhanced fluid absorption in the colon.<sup>180</sup> Clinical studies may be indicated.

### **Plant Sterols and Sterolins**

Sterols and sterolins (phytosterols) are fats present in all plants, including fruits and vegetables. Beta-sitosterol (BSS) is the major phytosterol in higher plants, along with its glycoside beta-sitosterolin (BSSG). In *in vitro*, animal, and human studies a proprietary BSS:BSSG mixture has shown promise in normalizing T-cell function and dampening overactive antibody responses. Since T cells from patients with UC manifest a

cytokine profile compatible with an over-active Th2 response, it is possible that administration of a BSS:BSSG mixture might prove beneficial in UC patients. Dampening of Th2 leads to decreased levels of IL-4, IL-6, and IL-10, which are involved in B-lymphocyte differentiation and inflammation.<sup>181</sup>

### **Bromelain**

Bromelain is a proteolytic enzyme obtained from the pineapple stem. Its anti-inflammatory properties are attributed to fibrinolysis and inhibition of platelet aggregation. Two case reports indicate it may be of benefit in UC patients. Two women with UC refractive to conventional treatment reported a reduction in diarrhea after taking bromelain and one reported a decrease in the number of bowel movements and the appearance of blood in the stool when compared to pre-bromelain status. In both cases, endoscopy performed after bromelain supplementation revealed healed mucosa.<sup>182</sup> Although these anecdotal reports are of interest, more extensive clinical investigation is indicated.

### **Flavonoids: Quercetin and Rutin**

Quercetin and rutin have both been the subject of study in patients with UC, based on their antioxidant, anti-inflammatory, mast-cell stabilizing, and free-radical scavenging properties. Quercetin and its glycosides, rutin and quercitrin, were found to counteract glutathione depletion in colonic tissue and inhibit colonic inflammation in a rat model of induced colitis. Quercitrin also reduced adhesions, colonic weight, and colonic surface damage by 30-45 percent, although it did not attenuate disease severity. This study indicates a potential protective effect in the intestinal mucosa meriting further study.<sup>183</sup>

### **Potential Sequelae of Ulcerative Colitis**

Patients with UC are at higher risk for developing a number of secondary conditions, including colon cancer, osteoporosis, kidney stones, gallstones, and liver disease.

### **Colon Cancer**

Persons with UC have an increased risk for colon cancer. Although aspects of the disease itself, such as inflammation and alterations in GAG content, may be partially responsible for the increased risk, certain medications used in its treatment may be co-carcinogens. In a dimethylhydrazine (DMH) rat model of colitis, metronidazole, sulfasalazine, and low-dose 5-ASA (30 mg/kg daily) increased number and/or size of tumors. On the other hand, high-dose 5-ASA (60 mg/kg daily) inhibited tumor size. Olsalazine at 60 mg/kg daily had no effect.<sup>181</sup> Another study of sulfasalazine on DMH-induced carcinogenesis found sulfasalazine, at doses similar to human therapeutic doses, altered the character of the tumors without affecting incidence.<sup>185</sup>

Sulfasalazine was chosen by the National Cancer Institute for carcinogenicity and toxicity studies. The two-year NTP Toxicology and Carcinogenesis Study for Salicylazosulfapyridine found large doses of sulfasalazine (ranging from 84-337.5 mg/kg) increased the incidence of urinary tract and hepatocellular carcinomas.<sup>186</sup> Potential mutagenicity of sulfasalazine has also been observed, both in patients on the therapy for up to 21 months and in animal models.<sup>187</sup>

Several substances may prevent progression of UC to dysplasia and cancer. High-dose 5-ASA (mesalamine) may provide benefit. The 60 mg/kg dose mentioned above as potentially providing protection is larger than the therapeutic dose generally suggested for treatment. A dose of 2.4 g daily is generally recommended during acute flare-ups, with a dose of 1.2-2.4 g daily as the maintenance dose during remission.

Sulfasalazine results in inhibition of folic acid absorption, a deficiency implicated in dysplasia. In a case-control study of UC patients on sulfasalazine, 35 patients with neoplasia were compared to 64 without neoplasia to determine the effects of folate supplementation (400 mcg-1 mg daily). Folate supplementation was associated with a 62-percent decreased incidence of dysplasia. There was no increased protection for doses higher than 400 mcg daily. Folate supplementation, particularly in patients on sulfasalazine, would seem prudent.<sup>188</sup>

Members of this same research team performed further study on the effects of folate in colon cancer prevention. Records of 98 patients with UC were examined. This study found a dose-response effect on relative risk (RR=0.54 in patients taking 1 mg daily versus 0.76 in patients taking 400 mcg in a multiple vitamin) compared to those taking no folate.<sup>189</sup>

Primary sclerosing cholangitis (PSC) is seen more commonly in patients with UC than healthy controls. A placebo-controlled study of ursodeoxycholic acid (UDCA) in 52 patients with both UC and PSC, followed for 355 patient years, found a significant decrease in risk of developing colon dysplasia or cancer (RR=0.26) with the use of UDCA.<sup>190</sup>

A full discussion of prevention and treatment of colon cancer is outside the scope of this article. Nutrients that may hold promise for the prevention and treatment of colon cancer, a significant risk for patients with UC, include omega-3 fatty acids (especially DHA),<sup>191,192</sup> quercetin chalcone, fractionated citrus pectin,<sup>193</sup> calcium, selenium, vitamin C, mixed antioxidants,<sup>194</sup> lycopene, vitamins D and E, curcumin, green tea, N-acetylcysteine, indole-3-carbinol, inositol hexaphosphate, and calcium d-glucarate.<sup>195</sup> Refer to the review articles by Lamson and Brignall cited above for a more in-depth discussion of the chemopreventive effects of nutrients and botanicals.

### ***Osteoporosis***

Some research has found patients with IBD have an increased risk for osteoporosis, at least in part due to corticosteroid therapy. A study examined bone mineral density in 79 patients – 35 with UC and 44 with CD. A high incidence of low bone mineral density was seen in patients despite the diagnosis and use of corticosteroids. The hip was more frequently affected than the lumbar spine. Patients in this study exhibited a greater degree of bone resorption without compensatory bone formation. The authors of this study noted other research pointing to a higher rate of osteoporosis in patients with small bowel involvement, steroid use, those who had undergone intestinal resection, and postmenopausal or amenorrheic women.<sup>196</sup>

A large Danish study examining 16,416 patients with IBD – 8,323 with UC – found no increased fracture rate in this subgroup, except for a small increase at the time of diagnosis.<sup>197</sup>

### ***Liver/Gall Bladder Disease***

A study examining the records of 113 patients with UC found 27 percent had elevated liver enzymes: GGT > ALAT > AP > ASAT > bilirubin. Gallstones were diagnosed in four percent of patients.<sup>198</sup> Primary sclerosing cholangitis is frequently associated with ulcerative colitis.

### ***Kidney Stones***

The same record examination of 113 patients found four percent of UC patients had kidney stones.<sup>198</sup> Another study examined the urine of stone formers, taking into account history of IBD. Scanty urine was associated with UC, leading to more concentrated urine, lower pH, and greater chance for uric acid or mixed stones.<sup>199</sup>

### ***Discussion and Future Direction***

Several research projects are being conducted through the National Institutes of Health. In one study, patients with UC or CD ages 8-75 are being observed to determine inflammatory responses to the two conditions.<sup>200</sup> Another study is examining the effect of interferon- $\beta$  to block inflammatory cytokines in UC.<sup>201</sup> Other drugs being investigated include infliximab (an anti-TNF agent),<sup>202</sup> rhIL-11 that alters gene expression of disease,<sup>203</sup> and visilizumab (a potent immunosuppressive agent).<sup>204</sup> Another study is currently assessing the viability of oral methotrexate compared to IV methotrexate.<sup>205</sup>

The potential toxicity of many of the drugs presently being studied suggests the need for extensive investigation of less invasive treatments. An animal study found inhibition of poly (ADP-ribose) polymerase (PARP) down-regulated proinflammatory mediators associated with chronic colitis and decreased intestinal permeability.<sup>206</sup> A study of niacinamide, a natural inhibitor of PARP, is recommended.

*Table 8a. Summary of Alternative Therapies for Ulcerative Colitis*

Intervention	Therapeutic Benefit	Dosage
Diet Elimination/hypoallergenic	Decreases symptoms and disease exacerbation; may result in remission	N/A
Low sulfur-containing amino acid	Decreases relapses; symptomatic and histological improvement	N/A
Fiber Psyllium husk	Increases stool butyrate levels; decreases bowel disturbances in patients in remission	4-10 g twice daily
Germinated Barley Foodstuff (GBF)	Increases stool butyrate levels; increases beneficial intestinal flora; improves stool forming ability; decreases diarrhea; prevents mucosal damage; and may improve colonic mucosal barrier	10 g twice daily
Larch arabinogalactan	Increases stool SCFA levels (primarily butyrate); protects intestinal mucosa	No clinical studies in UC; consider 4-5 g once or twice daily
Nicotine: gum or transdermal patches	More rapid achievement of remission and increased remission time; decreased stool frequency, abdominal pain, and urgency; better relapse rate than prednisone group	15-mg patch or 20 mg nicotine gum daily
DHEA	Inhibits pro-inflammatory cytokines including TNF-alpha; tends to be low in patients with UC	No clinical studies to date; suggest testing and if low, supplement with 15-50 mg daily
Melatonin	High levels of melatonin normally in the GI tract; resolution of rectal bleeding in experimental colitis (animal study); relieves intestinal spasm in animal model; has anti-inflammatory and antioxidant effects	No clinical studies; consider 1-3 mg at bedtime for patients in remission and perhaps a higher dose for active cases

**Table 8b. Summary of Alternative Therapies for Ulcerative Colitis**

Intervention	Therapeutic Benefit	Dosage
Probiotics	Reduce luminal pH and normalize intestinal flora; direct antibacterial action via bacteriocin production; may aid in achieving remission and preventing relapse	1.5-3 billion CFUs twice daily
Essential Fatty Acids	Histological improvement of colonic mucosa; decreased disease activity; decreased immune reactivity due to anti-inflammatory effects; reduced steroid use	1-2 g three times daily
Short Chain Fatty Acids	May help maintain colonic integrity and energy metabolism, resulting in a reduction in symptoms	Butyrate (40-80 mM/L) enemas twice daily
Glutamine	May decrease disease severity; decreases lipid peroxidation; promotes healing of ulcerated mucosa	1.5-3 g daily
Phosphatidylcholine	Reduces colonic strictures via collagenase activity	Animal studies only; consider 2-3 g daily of each
Phosphatidylinositol	Increases mucosal recovery and decreases permeability	Animal studies only; consider 200 IU twice daily
Superoxide Dismutase	Decreases bloody stools; decreases inflammatory cell infiltration and colonic erosion; decreases blood leukocyte levels	300 mg three times daily
<i>Eoswellia serrata</i>	Improvement on sigmoidoscopic exam; increases rate of remission	Theoretical, needs investigation; 20 mg sterols/200 µg sterolins three times daily between meals
Plant Sterols and Sterolins	Dampen over-active Th-2 response, decreasing inflammatory cytokines	0.5-1 g twice daily
Bromelain	Reduces number of bowel movements, diarrhea, and blood in stool; subsequent mucosal healing	500 mg 2-3 times daily
Quercetin and Rutin	Counteracts glutathione depletion; reduces colonic inflammation and damage, thereby protecting the intestinal mucosa	

Promising treatments that might be considered as adjuncts to conventional treatment or as part of a comprehensive natural approach to UC include transdermal nicotine, hormones such as melatonin and DHEA, probiotics, omega-3 fatty acids, dietary modification, specific fiber, flavonoids, and anti-inflammatory botanicals (Table 8a and 8b). Long-term studies involving larger populations are indicated.

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