Nutritional Therapies for Ulcerative Colitis: Literature Review, Chart Review Study, and Future Research

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Few clinical studies suggest a significant influence of diet or nutritional supplementation on ulcerative colitis. One reason is that ulcerative colitis, like many chronic diseases, is multifactorial. This article will describe and review the relevant literature on ulcerative colitis, including studies of (1) diet and intravenous therapy, (2) nutritional status and nutritional supplementation, and (3) bowel flora and immune function and their influences. Also, results of a retrospective chart review study that was done at a complementary medicine office will be presented. Finally, suggestions for future research will be discussed based on a nutritional model of ulcerative colitis. Taken together, it is hoped that these areas will clarify the current status of ulcerative colitis research and promote the types of investigations that are necessary to establish the validity of nutritional influences on ulcerative colitis as well as the mechanisms that are involved. (Altern Ther Health Med. 2000:6(1):55-63)

It is surprising that so few clinical studies have found that dietary or nutritional factors significantly influence ulcerative colitis (UC). It is noteworthy, however, that a range of factors have been researched including dietary components such as refined sugars, allergic foods, fast foods, as well as nutritional supplement effects from fish oil, zinc, glutamine, folate, and α-tocopherolquinone. Investigators have also examined the interrelationships between bowel flora and UC, including factors such as flora changes, endotoxemia, and supplementation effects with Lactobacillus species. These studies, combined with a review of UC, suggest that nutritional influences on UC are multifactorial.

The multifactorial nature of UC—common in many chronic disorders—helps to explain why few clinical studies have suggested beneficial effects from nutritional approaches. The unfortunate result, however, is that many practitioners in medicine do not accept the importance or benefit of diet and nutritional supplementation, and those who do must develop empirical therapies based on what patients are willing to do and what seems to be helpful. Although this approach has been effective for many patients, it is now necessary for researchers and complementary and alternative medicine (CAM) practitioners to substantiate these significant effects through well-designed prospective research. In addition, these investigations should clarify involved mechanisms and establish criteria for the use of specific nutritional guidelines.

With these points in mind, this article will (1) review and discuss the relevant literature concerning UC, (2) describe a chart review study that was performed in an outpatient complementary medicine office, and (3) discuss the necessary future research based on a proposed nutritional model for UC.

ULCERATIVE COLITIS LITERATURE REVIEW

Diet and Intravenous Therapy

In research on diets that were followed prior to acute exacerbations of UC, it has been shown that individuals eating higher levels of sugar, fast food, and bread were at greater risk. Investigations of food sensitivity or allergy showed elevated levels of cow's milk antibodies in UC patients in one study, and in another study 70% of subjects reported concomitant symptoms that were judged to be possibly allergic. A 1997 study of self-reported food intolerance found that 64% of UC patients believed they developed specific UC symptoms from one or more foods. A more thorough review of dairy allergy or sensitivity in inflammatory bowel disease (IBD) suggests multiple potential reactions that may include sensitivity to dairy proteins, lactose intolerance, and possible intolerance to long-chain triacylglycerol content.

A clinical trial of a dairy-free diet showed a decreased relapse rate in UC patients. This effect was more pronounced in those patients with a history of UC of less than 3 years. This study estimated that approximately 20% of patients may benefit from this restriction. An unconfirmed report suggested a correlation between responses to rectally injected antigens and disease improvement with dietary antigen withdrawal. However, no studies in the last 30 years have examined therapeutic influences of diet in UC, and other findings have not confirmed pre-illness diet or...
allergic effects that influence UC development or treatment.12,23-25

In contrast to UC, however, dietary studies of Crohn’s disease have consistently found increased levels of sugar intake.2,28,27 As a result, a few more studies of Crohn’s disease have explored therapeutic dietary effects. One study found that a sugar-free diet significantly reduced relapse rates,29 whereas another did not.30 A third investigation found that it was the hypoallergenic or exclusion diet that produced the benefits for ongoing patients and not the sugar-free diet.31 More consistent dietary effects may be observed in Crohn’s disease compared with UC, because dietary sugars and antigenic proteins may be more likely to reach involved intestinal mucosa and gut-associated lymphatic tissues that may influence mechanisms of disease activity.

Investigations of intravenous therapy as a primary treatment for UC among hospitalized patients have examined the extent to which total parenteral nutrition (TPN), bowel rest, and small amounts of intravenous medication might be helpful.32,33 One study34 found that the severity of inflammation and the amount of colonic involvement affected whether the intravenous therapy was helpful in promoting remission. Less severity of disease and less involvement was associated with more frequent short-term benefit, even though no effect on the relapse time or long-term prognosis was found. These 2 factors may therefore be important determinants for evaluating the success of nutritional factors and therapies, and may help to explain nutritional research inconsistencies. This TPN research also suggests that the level of disease activity and colonic involvement should be taken into account in future research, and that long-term studies are required to examine maintenance of remission.

Nutritional Status and Nutritional Supplementation

The chronic symptoms of UC, such as diarrhea, bloating, pain, and blood loss, as well as nutrient-drug interactions, suggest that nutritional deficiency might be common and have a role in UC pathology; however, studies generally have not found this to be the case. Folate deficiency was observed in one large study of chronic IBD patients,11 with anti-folate effects of sulfasalazine having a significant effect.35 In addition, a study of colorectal cancer and IBD showed a significantly lower level of serum retinol in UC patients compared with controls.14 Other studies suggest that UC patients may have subclinical or clinical deficiency of zinc, magnesium, calcium, and/or iron, especially with greater severity of disease.36-38 Finally, research on UC mucosa samples have shown altered ascorbic acid status,33 decreased antioxidant defenses,40 and low coenzyme A activity despite normal pantothenic acid levels.41,42

Few clinical studies examining the effects of nutritional supplementation have been done in UC. Probably the most significant investigation evaluated the influence of fish oil on UC and observed anti-inflammatory effects that may have derived from decreased leukotriene B4 levels.2 This result was accompanied by improved histology indices and significant weight gain. A subgroup on prednisone also showed a nonsignificant average decrease from 12.9 mg/d to 6.1 mg/d. Only modest clinical improvements were noted, however, so researchers concluded that fish oil could not be recommended as a simple treatment for UC.

Another example of “nutritional supplementation” benefit was illustrated in a clinical study of distal UC in which butyrate enemas were found to significantly reduce stool frequency and bleeding as well as improve endoscopic scores and histologic measures of inflammation.43 Butyrate is the primary energy substrate for colonocytes and its use was the likely mechanism through which significant benefit was produced. A related study showed that butyrate oxidation is impaired even in quiescent UC.44

The amino acid glutamine may also be beneficial for UC because it is also an energy substrate for colonocytes, though to a significantly lesser extent.45 Interestingly, an animal model of UC found that glutamine supplementation significantly decreased portal vein endotoxin levels46—this may be another potential mechanism of benefit. This effect may have been explained by an investigation of glutamine-supplemented TPN that found a significant increase in biliary secretory immunoglobulin (Ig) A.47 Further study showed that oral glutamine had more beneficial effects on secretory IgA than did intravenous glutamine,48 suggesting a localized effect that might be derived from oral supplementation.

A case-control study49 of folate supplementation in UC showed a decrease in the incidence of dysplasia and cancer. Whereas several biologically plausible mechanisms were mentioned in this study, one involved cell replication processes such as methylation pathways, purine synthesis, and DNA formation. A related clinical study50 suggested that after 6 months of supplementation with 10000 µg of folate per day, significant increases in methylation pathways were found. It also may be plausible that folate status and function as well as cell replication and turnover could influence UC pathology. If this were true, arguments could be made for an effect of vitamin A and zinc because they may also influence cell replication. Interestingly, these nutrients also have immune effects, suggesting the potential for dual mechanisms in UC. Zinc supplementation in a double-blind study51 of UC, however, was not found to significantly influence UC treatment, though this was a short-term study and there may have been a trend toward some benefit.

Flora Composition, Immune Function, and Associated Influences

Although there have been no highly significant studies showing an influence of bowel flora in UC, some research supports several potential mechanisms by which flora may be important. For example, one study of mucosa-associated microflora in active UC compared to those with inactive disease showed significantly reduced counts of total flora, obligate anaerobes (eg, bifidobacteria), facultative organisms, and microaerobes (eg, lactobacilli).52 The differences were also more significant in patients suffering their first UC attack compared to those with relapses. Although other studies have found associations between UC and Escherichia coli,53-55 this study found E. coli less frequently and in smaller amounts. This study further suggested that other species found—such as bacteroides as well as...
aerobic and anaerobic gram-positive cocci—were more common and might be promising candidates for potential influences in future UC research. A more thorough discussion of this area of investigation can be found elsewhere. The possibility of influencing bowel flora was suggested by a case report of UC showing beneficial results from supplementation with α-tocopherolquinone, in which the benefits were thought to have been produced from bowel flora effects. In addition, more general probiotic “nutritional supplementation” research has shown the following:

- supplementing with freeze-dried Lactobacillus casei GG reduced the susceptibility of subjects to traveler’s diarrhea
- Lactobacillus GG yogurt reduced antibiotic-associated diarrhea
- a milk concentrate of Lactobacillus GG effectively treated relapsing Clostridium difficile colitis
- Lactobacillus GG significantly benefited pouchitis, a complication of ileal reservoir surgery in UC patients who have had a proctocolectomy

Possible mechanisms by which probiotic supplementation may be beneficial include increased gut immune responses and decreased intestinal permeability.

Another potentially important aspect of bowel flora influence was shown in a clinical study of 25 UC patients in which it was determined that 88% had systemic endotoxemia, which positively correlated with anatomic extent of disease and disease activity. Other studies have also found endotoxemia in UC and its correlation with disease activity.

Part of the difficulty in assessing bowel flora effect comes not only from the significant variety of microflora species present in the gut, but also from the range and complexity of immunological measures and mediators that may suggest immune reactivity or mediate UC pathology. For example, there is evidence of circulating antibodies to bacterial, dietary, and self-antigens in UC, especially of the IgG subtype. In addition, increased intestinal permeability has been reported in IBD, though this has been better documented in Crohn’s disease than in UC. With regard to the IgG subtype of immunoglobulins found in UC, it is involved with complement activation that may mediate acute UC episodes. As for relevant cellular immunity responses, one study showed that IBD mesenteric lymph node mononuclear cell responses (gut-associated lymphatic tissue cells) were generally greater to most flora antigens than they were to peripheral blood mononuclear cells, which were often undetectable.

Whereas a discussion of the immunopathological aspects of UC are beyond the scope of this article, a more thorough review may be found elsewhere. This area is important, however, to the further understanding of nutritional and bowel flora influences in UC because this is where some specific mechanisms will be found. Future nutritional researchers will need to monitor general UC research to evaluate these investigations, and future nutritional research must include some of these immunological measures.

In summary, there is a wide range of nutritional and medical research of UC that has examined dietary factors, nutritional status, nutritional supplement effects, flora composition and effects, immunological factors, and intestinal factors. A concerted effort is now required to develop comprehensive nutritional protocols that can be shown to produce consistent benefits and provide clarification of involved mechanisms. The following retrospective chart review study illustrates the type of work that is required.

**CHART REVIEW STUDY**

A retrospective chart review study was conducted of 24 consecutive UC patients who presented to the Atkins Center for Complementary Medicine in New York, NY. Treatment emphasized a comprehensive nutritional regimen including a sugar-free hypoallergenic diet and nutritional supplementation.

**Methods**

Subjects were included in this study who presented for treatment of UC between March 10, 1992, and January 20, 1995. All subjects had at least 2 follow-up appointments to monitor compliance with dietary and nutritional supplementation recommendations, and to assess disease status through reported symptoms and medication dosage changes. Exclusion criteria were as follows:

- inadequate follow-up visits (9 patients)
- aged more than 70 years (7 patients)
- other major illnesses (3 patients)
- noncompliance (2 patients)
- medical complications during treatment (2 patients)

Twenty-four subjects (15 male, 9 female) were enrolled in the study. At time of presentation, subjects were aged 15 to 67 years (average, 41.3 years). Although all subjects sought UC treatment, 14 (58.3%) specifically reported having colonoscopy and/or sigmoidoscopic tests done by previous physicians to confirm their diagnosis. At presentation, 17 subjects were on 1 or more medications. Eight patients were on sulfasalazine (dose range, 1000-5000 mg/d), 7 were on prednisone (dose range, 2.5-25 mg/d), 5 were on Dipentum (olsalazine sodium) (dose range, 500-2000 mg/d), 3 were on Asacol (mesalamine) (dose range, 600-2400 mg/d), 1 was on Imuran (azathioprine) (50 mg/d), 1 was on cyclosporine (200 mg/d), 4 were having cortisone enemas (1-2 times per day), 1 was having a lidocaine gel enema (2 times per day), and 1 was on Imodium (loperamide hydrochloride) (2 times per day). The other 7 subjects had reported being on a course of prednisone and/or sulfasalazine at least once before their visit. Symptoms at presentation included the following: 19 with diarrhea (79.2%), 13 with bleeding (54.2%), 10 with pain or cramping (41.7%), 10 with mucus (41.7%), 5 with bloating (20.8%), and 4 with gas (16.7%). Subjects reportedly had their UC diagnosis from 2 months to 20 years (average, 6.2 years). They were followed in this study from 1 to 26 months (average, 7.2 months). Monitoring of subject progress and data collection ended July 31, 1995.

At the first visit after a complete medical work-up that included a history, physical examination, and comprehensive...
blood analysis, 1 of 2 staff medical doctors prescribed a specific nutritional regimen. The subjects then met with a clinical nutritionist who carefully explained a sugar-free, hypoallergenic diet. All forms of sugar and foods that contained sugar were excluded from the patients’ diet. Allergenic foods such as dairy products, peanuts, citrus, and yeast were excluded from all subjects’ diets. In addition, some patients had food sensitivity testing that suggested a further restriction for wheat (7 subjects) and corn (3 subjects).

Nine subjects had stool and rectal mucosa samples collected for microbial and parasite analyses (Great Smokies Diagnostic Laboratories, Asheville, NC). Parasite evaluations used enzyme immunoassays with monoclonal antibodies, immunofluorescence assays with monoclonal antibodies, and computer-enhanced video microscopy. The presence of possible pathogens was assayed by culture techniques using standard media and incubation guidelines, and the Vitek system for colorimetric identification of bacteria.

Initial nutritional supplementation included (1) a multivitamin and mineral supplement (2-6 tablets per day) (Table 1); (2) an oil formula containing w-3 and w-6 fatty acids derived from fish oil (400 mg), borage oil (400 mg), and flax oil (400 mg) (3-8 softgels per day) (Table 1), with 2 subjects instead taking separate fish oil and borage oil supplements; and (3) a probiotic. For the probiotic, 12 subjects took a Bacillus laterosporus supplement (2-3 capsules per day, 280 mg each) and 12 subjects took a Lactobacillus formula containing L acidophilus, L bifidus, and L bulgaricus strains (2-8 capsules per day, approximately 500,000 spores each). In addition, 22 of 24 subjects took vitamin A (20000-40000 IU/d), vitamin D3 (15 IU) (3-8 softgels per day) (Table 1), with 2 subjects instead taking separate fish oil and borage oil supplements; and (3) a probiotic. For the probiotic, 12 subjects took a Bacillus laterosporus supplement (2-3 capsules per day, 280 mg each) and 12 subjects took a Lactobacillus formula containing L acidophilus, L bifidus, and L bulgaricus strains (2-8 capsules per day, approximately 500,000 spores each). In addition, 22 of 24 subjects took large doses of folate (20-60 mg/d), 22 of 24 subjects took pantethine (450-900 mg/d), 20 of 24 subjects took beta carotene (25000-75000 IU/d), and 18 of 24 subjects took vitamin A (20000-40000 IU/d). In addition, 7 subjects took calcium carbonate (500-1000 mg/d) and 3 subjects took extra zinc (30-60 mg/d). Also, some subjects received supplements for specific symptoms or disorders unrelated to UC and 4 subjects received intravenous nutrients. Finally, it should be noted that glutamine was not a significant part of the regimen, because recognition of its effects in intestinal function is more recent; only 3 subjects took it toward the end of their study participation.

A sign test was used for evaluating clinical improvement in medicated and nonmedicated subjects.24 Medication dose changes in subject subsets were assessed by paired t tests and by nonparametric Wilcoxon rank sum test.

**Results**

Eighteen of 24 subjects (75%) with UC improved on a sugar-free hypoallergenic diet with nutritional supplementation (Table 2). This included 12 of 17 subjects on various UC medications at presentation who had symptomatic improvement and/or medication reduction, and 6 of 7 nonmedicated subjects who had symptomatic improvement. Using a simple sign test and a 1-sided alternative hypothesis against the null hypothesis (ie, that the procedures were equally likely to help the subjects or not help them), the P value associated with 12 of 17 improvements was .015—a statistically significant result. In addition, a simple statistical sign test demonstrated that the treatment, which resulted in 0 of the 7 nonmedicated subjects deteriorating, was significant (P=.016). (Table 3 lists the specific symptom changes for medicated and nonmedicated subjects.)

<table>
<thead>
<tr>
<th>TABLE 1 Nutritional supplementation among study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nutrient</strong></td>
</tr>
<tr>
<td>Vitamin A</td>
</tr>
<tr>
<td>Beta carotene</td>
</tr>
<tr>
<td>Vitamin D3</td>
</tr>
<tr>
<td>Thiamine</td>
</tr>
<tr>
<td>Riboflavin</td>
</tr>
<tr>
<td>Niacin</td>
</tr>
<tr>
<td>Niacinamide</td>
</tr>
<tr>
<td>Pantethine</td>
</tr>
<tr>
<td>Pantothenic acid</td>
</tr>
<tr>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Pyridoxal 5 phosphate</td>
</tr>
<tr>
<td>Cyanocobalamin</td>
</tr>
<tr>
<td>Folate</td>
</tr>
<tr>
<td>Biotin</td>
</tr>
<tr>
<td>Choline</td>
</tr>
<tr>
<td>Inositol</td>
</tr>
<tr>
<td>Para-aminobenzoic acid</td>
</tr>
<tr>
<td>Ascorbate</td>
</tr>
<tr>
<td>Citrus bioflavinoids</td>
</tr>
<tr>
<td>Alpha-tocopherol</td>
</tr>
<tr>
<td>Copper</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Manganese</td>
</tr>
<tr>
<td>Chromium</td>
</tr>
<tr>
<td>Molybdenum</td>
</tr>
<tr>
<td>Vanadium</td>
</tr>
<tr>
<td>Selenium</td>
</tr>
<tr>
<td>Octacosanol</td>
</tr>
<tr>
<td>N-acetylcyesteine</td>
</tr>
<tr>
<td>Reduced glutathione</td>
</tr>
</tbody>
</table>

**Oil formula composition**

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Per softgel</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid</td>
<td>152 mg</td>
<td>456-1216 mg</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>180 mg</td>
<td>540-1440 mg</td>
</tr>
<tr>
<td>Gamma linolenic acid</td>
<td>96 mg</td>
<td>288-768 mg</td>
</tr>
<tr>
<td>Alpha linolenic acid</td>
<td>164 mg</td>
<td>492-1312 mg</td>
</tr>
<tr>
<td>Eicosapentaenoic acid</td>
<td>120 mg</td>
<td>360-960 mg</td>
</tr>
<tr>
<td>Docosahexaenoic acid</td>
<td>80 mg</td>
<td>240-640 mg</td>
</tr>
</tbody>
</table>

* Subjects took 2 to 6 tablets per day.
† Subjects took 3 to 8 softgels per day; also contained 5 IU of vitamin E per softgel.
There was a trend toward reducing subject prednisone dose during the study period, whereas the sulfasalazine dose was significantly lower. The prednisone dose decreased from 14.8 mg/d to 9.0 mg/d (Figure 1). Despite the small sample size, this decrease in prednisone was close to statistical significance. A 1-sided, paired t test resulted in a P value of .065. Similarly, the nonparametric Wilcoxon rank sum test yielded a P value of .066.

Sulfasalazine dose decreased significantly, from 2814 mg/d to 1375 mg/d (Figure 2). As measured by a number of statistical tests, this decrease in sulfasalazine was significant. A 1-sided, pooled t test yielded a P value of .028. Although a normal probability plot showed no evidence of nonnormality, the nonparametric Wilcoxon rank sum test was also used to assess the treatment effects on subjects taking sulfasalazine. This test had a P value of .0004, which is highly significant.

The prednisone analysis did not include 1 subject who was not controlled on the protocol and pursued further treatment elsewhere. This subject's presentation dose was 2.5 mg/d and the ending dose was 75 mg/d (more medication than the ending dose of the other 6 prednisone subjects combined).

Five subjects improved sufficiently to allow discontinuation of their medication. Two of these subjects had to restart medication again, though their symptoms were controlled at lower doses than at their initial presentation. The 3 remaining patients were controlled without medication at the end of the study period.

Table 4 presents the results of a subset of subjects (9/24) with microflora analyses before treatment. As indicated, 2 of 9 patients had a parasite and 3 of 9 had possible pathogens. In addition, 6 of 9 patients had imbalanced flora as indicated by
inadequate amounts of Lactobacillus species and/or E.coli (5/9), and excessive amounts of Enterobacter cloacae, hemolytic E.coli, and/or Morganella morganii (2/9). Unfortunately, no follow-up analyses were performed.

DISCUSSION

The results of this retrospective chart review study suggest that a dietary and nutritional supplementation regimen may significantly benefit UC patients. This study finding is based on significant improvements in symptoms and medication dosage needed to control symptoms. In the context of few positive clinical studies, these results suggest that a comprehensive therapeutic nutritional program will more likely help UC patients and produce more consistent study results than will a single dietary factor or nutritional supplement. Future research is necessary, however, to confirm these results, clarify the relationship between specific nutritional factors and UC, and further evaluate the possible multifactorial nutritional influence in this disorder. Also, because sulfasalazine is used for both treatment and maintenance of remission in UC, longer-term studies are necessary to determine whether sulfasalazine reduction will adversely affect the relapse rate.

These data are reported with the understanding that chart review studies include several weaknesses. Weaknesses in this study include the following: nutritional regimes varied by subject, variations in duration of subjects' study period, self-reporting of symptoms and lack of an objective disease activity index, potential for selective recording of symptom self-reports, possible sample selection bias, lack of a control group, inability to draw conclusions concerning the relative importance of specific dietary guidelines followed and nutritional supplements taken, and inability to assess specific mechanisms involved.

The sample selection bias resulted from the 11 subjects who were excluded from the study due to inadequate follow-up (n=9) or noncompliance (n=2). The often severe dietary restrictions and large requirement for supplement ingestion could have selected more highly motivated subjects. Therefore, the results may not be generalizable to all subjects with UC.

This research does not meet the standards required to draw conclusions about the effects of nutritional therapies; however, it does illustrate important research parameters such as inclusion and exclusion criteria, the need for a standardized nutritional regimen, and the requirement for assessment of objective symptom scores and disease activity measures. These and other issues will be more thoroughly discussed in the following section.

TABLE 4 Microbial analysis in sample subset (n=9)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Parasite</th>
<th>Possible pathogen</th>
<th>Excess</th>
<th>Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Chilomastix mesnili</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Citrobacter freundii</td>
<td>Klebsiella pneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Blastocystis hominis</td>
<td>Citrobacter freundii</td>
<td>Klebsiella pneumoniae</td>
<td>Proteus vulgaris</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Lactobacillus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>Lactobacillus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>Lactobacillus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>Lactobacillus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>Hemolytic E.coli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>Klebsiella pneumoniae</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FUTURE RESEARCH

Considerable additional research concerning nutritional influences on UC should be undertaken. First and foremost, there should be outcome-type research to show that nutritional approaches are beneficial. Such research should include an ability to examine dietary and nutritional supplementation approaches both individually and as part of a combined treatment. More refined investigations of UC must clarify various aspects of the contributing factors. This research may be more clearly examined with the use of a model like the one in Figure 3. This model shows that dietary guidelines and nutritional supplementation may influence 2 primary categories: (1) bowel flora composition and related factors such as endotoxin secretion and colonization resistance, and, more importantly, (2) intestinal parameters at the cellular and tissue level as well as immunological measures that are integrated into both. This latter category includes a wide range of histologic measures and sigmoidoscopic indices as well as eicosanoid production, intestinal permeability, immune reactivity, and so on. These categories may then influence systemic factors such as endotoxemia and liver detoxification—all of which combine to influence UC symptoms.

Future investigations should include a prospective design; an adequate sample size; a control group; a standard diet and nutritional supplement regimen; an adequate study length;
objective measures of UC activity such as sigmoidoscopy scores, histology indices, disease activity indices, and relapse rates; and appropriate study designs that examine multifactorial disorders. In addition, it will be necessary to examine individual nutritional factors and their effect on some of the intermediary measures discussed in this article such as (1) intestinal factors (eg, cellular measures, mucosal indices, and immunological parameters), (2) bowel flora composition and related factors, and (3) systemic factors (eg, endotoxemia and liver detoxification). These types of studies may show influences of these factors on UC measures.

### Nutritional Therapies for Ulcerative Colitis

**Dietary factors**
- Sugars
- Food antigens
- Others

**Nutritional supplements**
- ω-3 oils
- Probiotics
- Glutamine
- Folate
- Zinc
- Vitamin A
- Carotinoids
- Calcium
- Pantethine
- Others

**Intestinal effects**

**Cellular**
- Histology measures:
  - Loss of polarity
  - Mucin content of surface epithelium
  - Denudation or erosion
  - Superficial and deep inflammatory cell infiltrate
  - Architectural distortion
  - Fibrosis
  - Impaired antioxidant defenses

**Mucosal tissue**
- Inflammation and ulceration
- Anatomic extent of disease
- Intestinal permeability
- Sigmoidoscopy measures
  - Granularity
  - Friability
  - Mucopurulent exudate

**Bowel flora composition**
- Species types and amount
- Toxic secretion
- Colonization resistance
- Bacterial fermentation/synthesis of short chain fatty acids
- pH
- Rule out parasites
- Other flora influences

**Immuneologic**
- Secretory IgA
- Mesenteric lymph node mononuclear cell reactivity
- Eicosanoid production
- Other GALT functions and immunologic parameters

**Systemic effects**
- Endotoxemia, acute phase proteins, circulating TNF
- Liver detoxification

**Ulcerative colitis symptoms**
- Bleeding
- Diarrhea
- Mucus
- Pain and cramps
- Gas

**FIGURE 3** Multifactorial model of nutritional therapy in ulcerative colitis. GALT indicates gut-associated lymphoid tissue; TNF, tumor necrosis factor.
but they may not be large enough to affect clinical symptoms. Such studies may, however, help to identify more subtle relationships, of which there may be several.

Examples of some specific intermediary investigations in UC would include the following:
- the effects of variation of dietary macronutrients, and sugar content on bowel flora
- the colonization potential of probiotic supplementation in UC as well as its influence on immune function, intestinal permeability, endotoxemia, and antibodies to flora and food antigens
- influence of a hypoallergenic diet on circulating IgG levels to specific food antigens, followed by evaluation of levels with food reintroduction
- effects of various nutritional supplements such as zinc, glutamine, folate, and vitamin A on mucosal nutritional status, secretory IgA, histologic measures, intestinal permeability, and endotoxin levels
- other potentially important interrelationships

Because of these varied interrelationships, there may be subsets of UC patients who may be more affected by some intermediary factors than by others. The most effective nutritional regimen may need to be uniquely developed for each UC patient based on reliable measures of these intermediary factors. Also, there may be many more dietary factors and nutritional or herbal supplements that may be helpful in UC; these should be examined. The model itself may need to be enlarged beyond nutrition to include other factors such as stress as well as other modalities such as relaxation techniques, acupuncture, and homeopathy.

It would be counterintuitive to suggest that diet and nutritional supplementation do not influence UC. Whereas research has not supported such an association, not thorough or comprehensive investigations have been conducted to better understand the causes, contributing factors, or range of potentially beneficial therapeutic approaches. This presents the CAM community with an opportunity to show that CAM treatments are significantly helpful and that the CAM model of healthcare is more preventive, less prone to side effects or complications, and includes more patient involvement and responsibility than does a conventional approach. Conducting this important research for UC will be generally helpful if the research model can then be applied to other chronic diseases as well.

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