Seymour Katz, M.D., Series Editor

Nutritional Therapy for Crohn's Disease

by Alan L. Buchman

NUTRIENT DEFICIENCIES AND REPLETION

Vitamin, mineral, and trace element deficiencies may result from inadequate intake and/or increased losses (Table 1). Water soluble vitamin deficiencies are uncommon with the exception of vitamin B_{12} and to a lesser degree, folate deficiency. Vitamin B_{12} deficiency will result when ≥60 cm of terminal ileum has been resected (or is diseased) (1). Bacterial overgrowth may occur proximal to small intestinal strictures and may result in vitamin B_{12} deficiency because bacteria compete for nutrient absorption. The serum vitamin B_{12} concentration may be normal during the early stages of vitamin B_{12} deficiency; an elevation in serum methylmalonic acid (MMA) concentration may be a more sensitive indicator of vitamin B_{12} deficiency. Vitamin B_{12} deficiency should be treated with daily intramuscular injections, sublingual, or intranasal administration of vitamin B_{12} (1000 g) over a seven-day period followed by monthly maintenance injections. Low serum folate concentration may be observed in up to 30% of patients with Crohn's disease (2), although is more likely in the subset of patients with proximal jejunal involvement and in addition, those treated with sulfasalazine for colonic disease. Treatment as well as prevention of deficiency can be successfully accomplished with a daily folic acid supplement of 1–2 mg/day, although given that wheat flour in now supplemented with folate by law, it is unclear if supplementation will still be necessary. The use of folate supplementation to prevent colonic dysplasia in patients with Crohn's colitis is controversial. Deficiency in other B vitamins or in vitamin C have rarely been reported.

Fat soluble vitamin deficiencies (A, D, E, K) are more common because normal fat absorption is generally necessary to effect normal fat soluble vitamin absorption. A reduced bile salt pool from bile salt malabsorption induced by terminal ileal disease or resection leads to impaired fat digestion. Vitamin D deficiency is the most common fat soluble vitamin deficiency encountered, and may result in calcium malabsorption and subsequent osteopenia. Deficiency may be treated with sufficient sunlight exposure (3) or

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Table 1.

Water-Soluble Vitamins	Calcium
Folate	Iron
B12	Potassium
Fat-Soluble Vitamins	Magnesium
A	Zinc
D	Selenium
E	

Common vitamin and mineral deficiencies in patients with Crohn's disease (reprinted with Permission from Buchman AL Dietary Manipulations—Enteral Therapy for Crohn's Disease. IBD: *The Complete Guide to Medical Management,* Gary Lichtenstein, Editor. SLACK Incorporated, Thorofare NJ. in press, 2006)

vitamin D supplementation (1000 IU/day; care should be taken in order to avoid overshooting normal by measurement of weekly or bi-weekly serum ionized calcium supplementation. Sixteen percent of patients may also develop vitamin A or vitamin E deficiencies (4). Early vitamin A deficiency most commonly manifests in difficulty with night vision. Vitamin E deficiency is uncommon although low serum concentration may be encountered. In many cases this reflects only a decreased serum total lipid concentration.

Calcium deficiency may develop because of malabsorption in the setting of vitamin D deficiency and/or corticosteroid use. Patients at risk should take a supplement of 1500 mg elemental calcium daily. Iron deficiency develops most commonly in relationship to chronic blood loss and less likely if duodenal involvement of Crohn's disease is present, given the duodenum is the site of iron absorption. The most reliable indicator of iron deficiency is a low serum ferritin concentration, although as an acute phase reactant, it may be elevated in the setting of active Crohn's disease. Zinc is lost at a rate of 16 mg per liter of stool (5). Deficiency may be found in up to 40% of patients with Crohn's disease (6). Because serum zinc is bound to albumin and other proteins, which may be low in patients with active Crohn's disease, a combination of low serum and urinary zinc concentrations is highly suggestive of zinc deficiency. Replacement may be undertaken with 1–2 tablets daily of zinc sulfate or zinc gluconate. Potassium and magnesium deficiencies may also occur in patients with significant diarrhea.

GENERAL DIETARY THERAPY

The most important advise for patients without an intestinal obstruction is to consume a diet liberal in protein, with sufficient energy to either gain weight if necessary, or to maintain a normal weight. This might typically consist of 25–35 kcal/kg/day and 1–1.5 g/kg/day of protein. There is no benefit to a low-residual diet in the absence of a bowel obstruction (7). Diets with increased amounts of soluble fiber, which are fermented to short chain fatty acids by enteric bacteria in the colon, may be of value to patients with colonic disease (8). However, there is no proven benefit from a general increase in unrefined carbohydrate for the maintenance of remission (9).

Lactase deficiency, in the absence of Crohn's disease affecting the duodenum or proximal jejunum, is no more common in patients with the disease than the population as a whole. Because lactose-containing diets are excellent sources of calcium, lactose restriction should not be prescribed in the absence of documented lactase deficiency. Many patients with symptoms consistent with lactose intolerance are not actually lactose intolerant (10). There is data to support the contention that diets high in saturated long chain triglycerides may increase the likelihood for clinical relapse (11). The idea is that the more linoleic acid present in the diet, the more "pro-inflammatory" prostaglandins are produced.

Dietary oxalate should be restricted in patients with steatorrhea who have colon in continuity for their small intestine because of the risk of calcium oxalate nephrolithiasis. Normally, calcium binds to oxalate in the diet and is excreted unabsorbed in the stool, but in the presence of significant fat malabsorption, calcium preferentially binds to free fatty acids, allowing free oxalate to pass into the colon where it is absorbed. The absorbed oxalate is subsequently filtered by the kidneys where it is complexed with calcium.

Patients often report that specific foods tend to trigger the symptoms of active Crohn's disease. From that arose the concept that elimination diets might be useful for the treatment of Crohn's disease or the maintenance of remission. Alun Jones, et al queried a group of 20 patients with Crohn's disease as to which particular foods triggered symptoms of their Crohn's disease. The patients were then

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admitted to a research center, made *nil per os*, and each of these foods were then added back to their diet a day at a time and it was noted whether specific foods triggered gastrointestinal complaints in the research setting (12). Patients listed foods, primarily wheat, dairy products, and some vegetables that triggered diarrhea and abdominal cramping. However, wheat bran is an excellent stool-bulking agent, dairy products may cause diarrhea and cramping in lactose interolerant individuals, and vegetables such as mustard greens have a significant amount of biomass. A larger, multicenter study was then completed in which patients that had achieved remission using an elemental diet were randomized to receive maintenance therapy with either a regular diet with corticosteroids followed by drug taper or an elimination diet (13). Common food intolerances included corn, wheat, milk, yeast, eggs, potatoes, rye, tea, and coffee. Seventy nine percent of patients in the corticosteroid group relapsed versus only 62% in the elimination diet group although 25% of those patients were withdrawn due to noncompliance. The median remission time was 7.5 months in the elimination diet group and 3.8 months for those that received a regular diet. The "fast food" diet of hamburgers, hotdogs, fries, and a soft drink

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Table 2.
Enteral Feeding in Crohn's Disease

Author and Series	*No. of Patients*	*Short-Term Remission (%)*	*Long-Term Remission (%)*	*Length of Follow-up (months)*
Prospective, Uncontrolled Studies				
O'Morain (1980)	27	24 (89)	18 (67)	6
Lochs (1984)	25	15 (60)	1 (48)	6–24
O'Brien (1991)	16	10 (62)	4 925)	12

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Table 3.
Elemental Diets in Crohn's Disease

Author and Series	*No. of Patients*	*Short-Term Remission (%)*		*Long-Term Remission (%)*		*Length of Follow-up (months)*
Prospective, Uncontrolled Studies						
		Steroids	**Enteral**	**Steroids**	**Enteral**	
O'Morain (1984)	21	8/10 (88)	9/11 (82)	7/10 (70)	8/11 (73)	3
Saverymuttu (1985)*	37	16/16 (100)	15/21 (71)			
Sanderson (1987)	17	7/8 (88)	8/9 (89)			
Malchow (1990)	95	32/44 (73)	21/51 (41)	32/44 (73)	21/51 (41)	3
Lochs (1991)**	107	41/52 (79)	29/55 (53)	5/8 (63)***		
Lindor (1992)	19	7/10 (70)	3/9 (33)			

*Diet also includes antibiotics, **Peptide, ***Diet + steroids

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Table 4.
Diet vs. Steroids in Crohn's Disease

Author and Series	*No. of Patients*	*Short-Term Remission (%)*		*Long-Term Remission (%)*		*Length of Follow-up (months)*
Prospective, Controlled Studies						
		Steroids	**Enteral**	**Steroids**	**Enteral**	
O'Keete (1989)	6	2/3 (67)	1/3 (33)			
Seidman (1991)	19	6/9 (67)	8/10 (80)	9/9 (100)	6/10 (60)	2.5
		Steroids	**Peptide**	**Steroids**	**Peptide**	
Engelman (1993)	11	4/4 (100)	7/7 (100)	4/4 (100)	7/7 (100)	6.5
Seidman (1993)	68	31/34 (90)	26/34 (76)			
Gorard (1993)	42	19/22 (86)	11/22 (50)	13/19 (67)	3/11 (28)	6
		Steroids	**Polymeric**	**Steroids**	**Polymeric**	
Ruuska (1994)	20	8/9 (89)	9/10 (90)	7/9 (78)	8/10 (80)	5

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Table 5.
Enteral Diets in Crohn's Disease

Author and Series	*No. of Patients*	*Short-Term Remission (%)*		*Long-Term Remission (%)*		*Length of Follow-up (months)*
Prospective, Controlled Studies						
		TPN	**Elemental**	**TPN**	**Elemental**	
Alun-Jones (1987)	36	17/19 (89)	15/17 (88)			
Cravo (1991)	39	18/24 (75)	11/15 (73)	12/23 (52)	4/22 (18)	34
		Peptide	**Elemental**	**Peptide**	**Elemental**	
Middleton (1991)	29	11/15 (73)	11/14 (79)			
Royall (1994)	40	15/21 (71)	16/19 (84)	6/21 (20)	5/19 (26)	12
Mansfield (1995)	44	8/22 (36)	8/22 (36)			
		Polymeric	**Elemental**	**Polymeric**	**Elemental**	
Gaiaffer (1990)	30	5/14 (36)	12/16 (75)	8/17 (47)		6
Rigaud (1991)	30	11/15 (73)	10/15 (67	4/15 (27)	3/15 (20)	12
Raouf (1991)	24	8/11 (73)	9/13 (69)	9/24 (38)		3–9
Park (1991)	14	5/7 (71)	2/7 (20)	1/7 (14)	0/7 (0)	12
Verma (2000)	21	6/11 (55)	8/10 (80)			
		Peptide	**Hosptial Diet**	**Peptide**	**Hosptial Diet**	
Munkholm-Larsen (1989)	19	6/11 (55)	8/10 (80)			0.5

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Table 6.
TPN in Crohn's Disease

Author and Series	*No. of Patients*	*In-Hospital Remission (%)*	*TPN Duration (days)*	*Long-Term Remission (%)*	*Length of Follow-up (months)*
A. Prospective Studies					
Elson (1980)	20	13 (65)	36	8 (40)	12
Meryn (1983)	25	20 (80)	27		
Muller (1983)	30	25 (83)	21	17 (57)	3–48
B. Prospective, Controlled Studies					
		Medication	**TPN**	**Medication**	**TPN**
Dickinson (1980)	9	3/3 (100)	4/6 (67)	0/3 (0)	1/6 (17)
Lochs (1983)	20	6/10 (60)	6/10 (60)	6/10 (60)	5/10 (50)
McIntyre (1986)	16	5/7 (71)	9/9 (100)	2/7 (29)	3/9 (33)
Alun-Jones (1987)	36	15/17 (88)	17/19 (89)		
Greenberg (1988)	32	9/15 (60)	12/17 (71)	6/15 (40)	8/17 (47)

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has also been associated with a risk for development of Crohn's disease. The risk was 3.4 times more likely in individuals that consumed at least 2 meals weekly (14). Proof of association however is not proof of cause, and this epidemiologic observation may have reflected a certain lifestyle that may have included smoking, sedentary behavior, occupational toxin exposure, education level, etc. Current dietary behaviors may also not reflect either past or future behaviors. In fact, given the often frequent delay between the time of onset of symptoms of Crohn's disease and diagnosis, individuals may have made intentional changes to their dietary habits.

THERAPEUTIC DIETARY INTERVENTION

Specific Nutrient Supplementation

Fish Oils

Omega-3 fatty acids, so named because of a double bond between the third and fourth carbon atoms away from the methyl end of the fatty acid chain, are a insignificant part of a typical Western diet. *In vivo* data has suggested fish oils may possess "anti-inflammatory" properties that result in decreased neutrophil aggregation, chemotaxis, and epithelial cell adherence, as well as decreased IL-1 and TNF synthesis (15–17). Eicosanoids also competitively inhibit arachadonic (omega-6) metabolism to "pro-inflammatory" prostaglandins. Fish oil supplements have been used in a attempt to prolong remission in patients with Crohn's disease. Belluzi, et al found 2.7 g (3 capsules t.i.d.) of an enteric-coated preparation maintained remission in 59% of patients at one year when compared to only 26% in the placebo group that had maintained remission (18). However, a larger study failed to reproduce this finding (19). A larger, multicenter study of fish oil for the maintenance of remission of Crohn's disease is underway in the USA and Canada.

Glutamine

A non-essential amino acid, glutamine is synthesized from glutamate and glutamic acid by the enzyme glutamine synthetase. Because glutamine has been thought to be the "preferred" fuel (although it is actually glutamate [20,21]) for the small intestine and observations that in rodent models of TPN use, radiation, trauma, intestinal resection, and burn injury, dietary glutamine supple-

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mentation prevented villus hypoplasia and improvements in gut barrier function. Four small, placebo-controlled human studies have shown no benefit of glutamine supplementation (15–21 g/day) on Crohn's disease activity, mucosal permeability, or various nutritional parameters (22–25) and in fact, data from a rodent model of colitis suggested glutamine supplementation may worsen intestinal inflammation (25,26).

Enteral Nutritional Support

Enteral nutritional support may be used for two reasons: 1) correct or prevent under-nutrition and weight loss, and 2) induction of remission. In the absence of intestinal obstruction, proximal fistula (but sufficiently distal as to preclude placement of a feeding tube distal to it), ileus, or toxic megacolon, enteral nutrition is generally the preferred route for nutritional support. The available data suggests the provision of enteral formula as the sole dietary constituent for 3–6 weeks will achieve a remission rate of approximately 68%, which is similar to the remission induction rate reported for TPN although somewhat lower than that reported for corticosteroids (Tables 2,3,4). Remission is unrelated to the protein content of the formula and remission rates are similar for free amino-acid-based, di- and tripeptide-based, and polymeric (intact protein)-based formulas (27); (Table 5) formula are more palatable or less expensive. Enteral nutritional support may be more likely to induce remission in patients with small intestinal disease (28). Induction of remission may be however related to the fact all of these formula are sterile (Figure 1). Data also suggest remission rate may relate to the formula's long chain triglyceride content; studies using formula with a high concentration of long chain fatty acids had lower remission rates (11,29). A recent study from Spain however has suggested formulas with a higher concentration of omega-6 polyunsaturated fats (low oleate, high linoleate) were more effective for the induction of remission regardless of the long chain triglyceride content (30). This observation may also apply to fat content of meals.

Total Parenteral Nutrition

There are few prospective and prospectively-controlled trials that have evaluated the use of total parenteral nutrition (TPN) for induction of remission in Crohn's disease; most studies have been open-labeled case series (Table 6). TPN, much like enteral nutritional support, has been used to induce remission as well as for adjunctive therapy to correct or prevent nutritional deficiency. Specific indications for TPN in patients with Crohn's disease include intestinal obstruction, bowel perforation, prolonged postoperative ileus, as part of a regimen to treat entero-enteric or proximal enterocutaneous fistula, severe malabsorption from widespread disease, and short bowel syndrome secondary to numerous surgical resections or mesenteric thrombosis related to the hypercoagulable state observed in patients with inflammatory bowel disease. In general, TPN should be used only when sufficient nutrients and fluid cannot be delivered via the gastrointestinal tract. Retrospective observations have suggested preoperative TPN may lead to increased albumin concentration and weight gain (31) and decreased postoperative infection risk in patients with Crohn's disease although it is unclear as to whether similar results could have been obtained with enteral feeding (32). TPN is more expensive than standard polymeric formula, but similar or less expensive than many of the "elemental" and "immune-enhancing" formulas. The actual costs for TPN, including the pharmacist's time to mix the bag, vary between $16–$25/day, although actual charges are substantially greater.

As primary therapy for Crohn's diease, the composite data from the literature (consisting primarily of retrospective and uncontrolled trials and studies in which corticosteroids may have been used together with TPN) would indicate a short-term remission rate of approximately

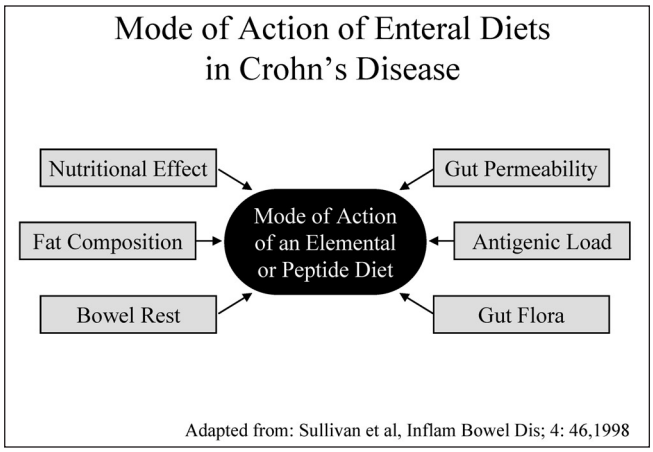

Figure 1. Mode of Action of Enteral Diets in Crohn's Disease

64% after 3–6 weeks with *nil per os* and TPN (33). Results appear better for patients with disease limited to the small intestine (34). Long-term remission rates however, as with corticosteroid as well, were very low. These results are similar to those achieved with enteral nutritional therapy. Indeed, several studies have shown remission rates are similar with either TPN or enteral nutritional therapy, although for the most part, enteral nutritional therapy is safer if patients are appropriately monitored. The natural history of Crohn's disease does not appear affected by either mode of therapy. The short term results of TPN as primary therapy in patients with enterocutaneous fistula are historically similar to that of infliximab, although long-term closure is rare (35). ■

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