Review Article

Digestive and Nutritional Considerations in Celiac Disease: Could Supplementation Help?

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Abstract

Due to the increased immune activation in the intestinal tract of people with celiac disease, the digestive and absorptive processes of those affected may be compromised. Individuals with celiac disease are more susceptible to pancreatic insufficiencies, dysbiosis, lactase insufficiencies, and folic acid, vitamin B_{12}, iron, and vitamin D deficiencies, as well as accelerated bone loss due to an increase in inflammatory signaling molecules. Beyond strict maintenance of a gluten-free diet, research has shown benefit with additional nutritional supplementation to assist in regulation of several of these complications. (*Altern Med Rev* 2009;14(3):247-257)

Introduction

Celiac disease (CD) is an autoimmune condition characterized by damage to intestinal cells leading to ultimate deterioration. Emphasis is often put on the degradation of the finger-like projections (villous atrophy) in the duodenal and jejunal regions, as these are the most frequently observed dysfunctional tissues in this disorder (Figure 1). A derangement in the upper intestinal morphology and alterations in the local chemical environment surrounding the immunological responses to gliadin (a protein fragment found in wheat, barley, and rye) may lead to increased susceptibility to a variety of adverse consequences.[1] Well-known are the deficiencies of folic acid, vitamin B_{12}, iron, and vitamin D associated with subsequent elevated homocysteine levels, iron deficiencies, and bone and immune disorders. Lesser known are possible pancreatic insufficiencies, dairy intolerances, dysbiosis, dyspepsia, and accelerated bone loss due to an increase in inflammatory signaling molecules. This article reviews these concerns in conjunction with considering supplementation as an adjunct to a gluten-free diet.

Pancreatic Insufficiency

Postprandial hormone secretion signals the exocrine pancreas to secrete enzymes that assist in the digestion of partially digested foodstuffs (chyme) in the upper intestines. The primary hormonal signal for pancreatic enzyme secretion is cholecystokinin (CCK). The enteric neurons and I-cells responsible for the secretion of CCK are found in the crypts and villi of both the duodenum and jejunum. Peptides, amino acids, and fats in the chyme stimulate the secretion of CCK that binds to CCK-A receptors found on vagal afferent neurons. Once these receptors are bound, a neuronal reflex is stimulated that inhibits gastric and duodenal motility, as well as initiates suppression of appetite and a decrease in acid secretion.

Simultaneously, the exocrine pancreas is stimulated to secrete digestive enzymes, and the gallbladder is signaled to secrete bile (Figure 2). Therefore, any condition that causes mucosal tissue damage to the duodenum or jejunum, or an alteration in the function of the necessary cells in these locations, can contribute to a reduction in pancreatic enzyme secretion. This has been documented in gluten, dairy, and bacterial enteropathies.[2-4]

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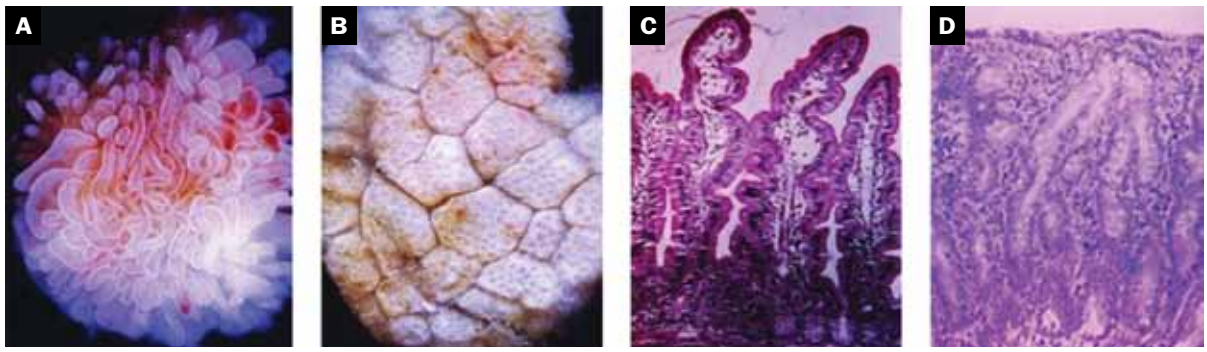
Figure 1. Small Intestinal Mucosal Biopsies



(A and B) Small-intestinal mucosal biopsy viewed through a dissecting microscope. The normal biopsy (A) shows numerous surface villi; whereas, a biopsy from an individual with CD and total villous atrophy shows, in place of the villi, numerous surface openings to underlying crypts and surface ridges (B). (C) Stained section of a normal small-intestinal mucosal biopsy. (D) Stained section of a small-intestinal mucosal biopsy from an individual with CD and total villous atrophy.

From: Kagnoff MF. Celiac disease: pathogenesis of a model immunogenetic disease. *J Clin Invest* 2007;117:41-49. Used with permission.

In 2001, researchers examined fecal elastase-1 (E1) values in celiac patients. E1 is a marker of exocrine pancreatic function often used in cystic fibrosis patients, a population known to have compromised pancreatic function, to determine the severity of their dysfunction. Of the 16 celiac patients studied, nine (56%) had abnormal values (cut-off level of 200 mcg/g) indicating insufficient exocrine pancreatic function. All nine subjects had normal E1 levels after one year on a gluten-free (GF) diet.[3]

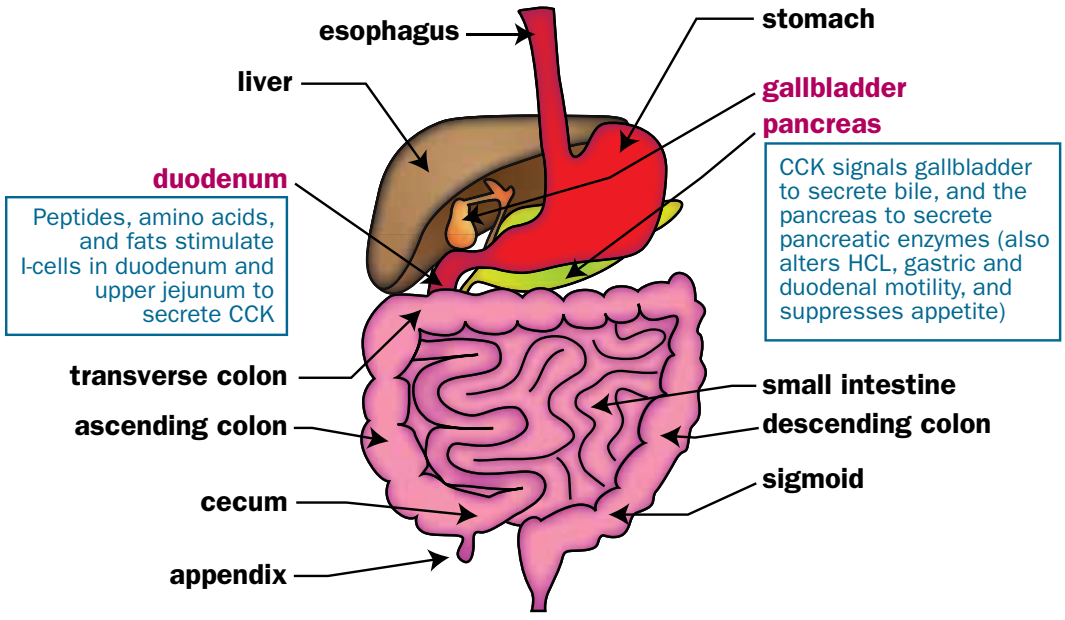
A group of researchers in Greece demonstrated a significant inverse correlation between the severity of villous atrophy and decrease in both CCK and fecal elastase in patients with either CD or cow's milk protein enteropathy. They also found that CCK and pancreatic enzyme secretion return to normal when the intestinal morphology normalized.[5]

A 2002 article in *Regulatory Peptides* examined whether CCK secretion was impaired by villous atrophy itself or by other factors. The researchers examined plasma CCK in 20 celiac patients divided into three groups and compared to nine controls. They looked at six celiac patients with normal mucosa after a GF diet, six CD patients with increased epithelial lymphocytes and little atrophy, and eight CD patients with significant villous atrophy, and compared them with controls. Significant decreases in basal CCK in the plasma (B 0.6 [95% CI, 0.3-1.3] pmol/L; $p<0.003$) and postprandial CCK area under the curve (AUC 34 [19-61] pmol/L x 120 min, $p<0.0001$) were observed in the patients with villous atrophy compared to the GF-diet treated patients with normal villi, as well as the healthy controls (B 1.0 [0.7-1.4] pmol/L; AUC 186 [131-264] pmol/L x 120 min). There was also a significant decrease in CCK in the CD patients with intraepithelial lymphocyte infiltration but little atrophy (B 0.4 [0.2-0.7] pmol/L; AUC 56 [31-101] pmol/L x 120 min; $p<0.0001$). This evidence implies that more than villous atrophy might be causing a disruption of the CCK signaling network in celiac patients.[6]

In addition, this article found that fasting gallbladder volumes were higher in group B and C compared to controls, while postprandial gallbladder emptying was less in both of these groups, indicating compromised gallbladder function in both the subjects with significant villous atrophy and in subjects with residual intraepithelial lymphocyte infiltration but little villous atrophy.[6]

Leeds et al examined the effect of pancreatic enzyme supplementation on CD patients who had persistent symptoms (diarrhea), even though they were following a gluten-free diet.[7] The study tested

Figure 2. CCK: The Primary Hormone Signal for Pancreatic Enzyme Secretion



the hypothesis that pancreatic insufficiencies may be a contributing factor to this persistent diarrhea and that pancreatic enzyme supplementation may assist in the reduction of its frequency. The study compared four groups: (1) (n=57) newly diagnosed individuals (no GF diet); (2) (n=86) CD patients on a GF diet absent of GI symptoms; (3) (n=66) CD patients on a GF diet with chronic diarrhea; and (4) (n=50) subjects with chronic diarrhea without diagnosed CD. Low fecal elastase was found in 11 percent of the newly diagnosed CD patients, six percent of CD patients with no GI symptoms, 30 percent of CD patients with diarrhea even after a GF diet, and four percent of the group with chronic diarrhea and no CD. The difference between low elastase levels in the CD patients with diarrhea after a GF diet compared to the other subgroups was significant ($p \leq 0.0001$), as was the difference compared to controls ($p \leq 0.003$). The use of pancreatic enzyme supplementation significantly reduced diarrhea frequency. The authors stated, "In 18 of 20 stool frequency reduced following pancreatic enzyme supplementation from four per day to one ($p \leq 0.001$)." The researchers concluded that, "…low fecal elastase levels are common in adult celiac disease and occur predominantly in those patients with chronic diarrhea when compared with controls. This is suggestive of exocrine pancreatic insufficiency. For those celiac patients with diarrhea and a low fecal elastase, pancreatic enzyme supplementation may provide symptomatic benefit."[7]

Bacterial overgrowth is a barrier to effective pancreatic enzyme therapy. Some researchers report that up to 40 percent of patients with chronic pancreatitis or pancreatic exocrine insufficiency have bacterial overgrowth.[8]

Dysbiosis

Collado et al noticed the species of organisms that survive and thrive in the intestines of untreated pediatric celiac patients, treated (GF diet) pediatric celiac patients, and pediatric healthy controls are significantly different. From biopsies and fecal samples, they found elevated levels of Bacteroides and *Clostridium leptum* more abundantly in celiac patients whether they were treated with a gluten-free diet or not. Fecal and biopsy levels of *E. coli* and Staphylococci were elevated in untreated celiac patients compared to controls; treat-

ment with a GF diet normalized these levels. In the fecal samples of all CD patients (treated and untreated) and the biopsies of untreated celiacs, Bifidobacterium levels were lower compared to controls.[9-11] Summarizing these points, Nada et al concluded, "The ratio of Lactobacillus – Bifidobacterium to Bacteroides – *E. coli* was significantly reduced in coeliac patients with either active or inactive disease compared with controls." They continued, "Overall, the higher incidence of gram-negative and potentially pro-inflammatory bacteria in the duodenal microbiota of coeliac children was linked to the symptomatic presentation of the disease and could favour the pathological process of the disorder."[12]

As a gluten-free diet does not appear to normalize microflora levels, evidence is beginning to point to supplementation with probiotics and prebiotics as potential tools for beneficially modifying the intestinal microflora populations of celiac patients to reduce inflammatory responses and increase positive clinical outcomes.[9-13]

When 15 celiac patients who had persistent GI symptoms in spite of being on a GF diet for 6-8 months were evaluated, it was found that two-thirds had small intestinal bowel overgrowth (SIBO). The authors state, "This study showed that SIBO affects most celiacs with persistence of GI symptoms after gluten withdrawal." Other causes of persistent GI symptoms included parasitic infections (n=2), accidental gluten consumption as a hidden ingredient in an antibiotic (n=1), and lactose intolerance (n=2).[14]

Dairy and Lactose Intolerance

With the majority of global populations (approximately 70%) having a lactase insufficiency, lactose intolerance is a relatively common issue. Lactase is naturally secreted from cells located in the brush border of the upper intestinal tract where physiological damage is likely to take place in gluten enteropathies (Figure 1). The lactase enzyme also relies on a pancreatic enzyme, trypsin, to modify this protein into the active enzyme form.[15]

As previously stated, celiac patients are susceptible to pancreatic insufficiencies and upper intestinal damage. Therefore, a person with celiac disease may have an increased chance of being lactose intolerant, as a study from Serbia confirms.[16]

Lactose intolerance may be responsible for continued symptoms in refractory celiac disease patients,[14] and lactose malabsorption may improve on a gluten-free diet.[17]

One of the most common excipients used in pharmaceuticals is lactose. Examining this issue in a paper entitled, "Quantifying the 'hidden' lactose in drugs used for the treatment of gastrointestinal conditions," Eadala et al conclude, "Lactose is present in a range of medications and may contribute towards symptoms. This may not be recognized by the prescribing doctor…."[18]

As well as pharmaceuticals, nutritional supplements often contain this potentially irritating excipient. One vitamin D study disclosed that the supplement used contained 98.75-percent lactose.[19]

Beyond lactose intolerance, some researchers speculate there may be an additional immunological response to various proteins found in cow's milk. As Goldfarb comments in the *Journal of Proteome Research*, "Milk is species-specific. Between 2 and 3% of children under two years have cow's milk allergy, an IgE moderated disease. It is speculated that most adults have some IgG antibodies to cow milk proteins…."[20]

Based on earlier studies using a rectal challenge of antigens in celiac patients and measurement of inflammatory markers,[21-23] Kristjánsson et al tried to elicit an immunological response to cow's milk (CM) protein in 20 CD patients similar to a gluten response.[24] CD subjects had been on a GF diet for two years, tested negative to serologic markers at the beginning of the study, and were compared with 15 age-matched controls. The authors stated, "A mucosal inflammatory response similar to that elicited by gluten was produced by CM protein in about 50 percent of the patients with coeliac disease. Casein, in particular, seems to be involved in this reaction." None of the controls responded to the challenge. Both IgG and IgA antibodies were measured on the antigenic peptides challenged, with the results indicating an innate immune response caused some of the increased inflammation. However, a recent article in *Nutrition* noted the increase in milk intolerance in the celiac population could involve IgA reactions to both alpha- and beta-caseins.[25]

Gastric Complications

Studies demonstrate 30-40 percent of celiac patients suffer from dyspepsia.[26] Due to the commonality of occurrence, some researchers recommend that clinicians test for celiac disease in dyspeptic patients.[27] Reflux is a common symptom of celiac disease as cases of silent celiac disease have been diagnosed after endoscopies for this disorder.[28]

One study found 29 of 105 CD patients (28%) presented with nonerosive reflux disease.[29] Since proton pump inhibitors (PPIs) are the most common pharmaceutical agents recommended for reflux, PPIs may be commonly recommended drugs in celiac patients presenting with these symptoms.[29] A short course of acid blocking medication has been shown to increase stomach pH from the normal 1.6-2.0 pH (similar to the pH of battery acid) to a pH of 5.0 (similar to the pH of table vinegar).[30]

This might be unfortunate for celiac patients for two reasons. First, adequate pH is needed to break down protein fragments in foods (including gliadin and cow's milk protein) to avoid further excitation of the immune system. One study found allergenic antigens were reduced up to 10,000-fold by adequate gastric acid.[30] Subjects on acid-blocking medications were also 10.5 times more susceptible to IgE-mediated food reactions, with an elevation in IgE antibodies remaining five months after a three-month course of acid blocker therapy.[31]

Second, adequate pH is necessary to facilitate nutrient digestion, to limit the entry of non-beneficial organisms, to activate digestive enzymes, and to activate proton pump-dependent transporters for nutrient absorption. Due to the risk of increased fractures, vitamin B_{12} deficiency, *Clostridium difficile*-associated diarrhea, and other complications of proton pump inhibitor therapies, clinicians are calling for prudent utilization of these medications.[32]

Nutrient Deficiencies

Corazza et al found that 67 percent of patients with overt celiac disease and 31 percent of those with a silent or subclinical case had malnutrition at the time of diagnosis.[33]

A Swedish group followed celiac patients for 10 years who were on a gluten-free diet and noted they continued to have vitamin deficiencies regardless of their gluten-free status. They concluded, "Half of the adult coeliac patients carefully treated with a gluten-free diet for several years showed signs of a poor vitamin status. This may have clinical implications considering the linkage between vitamin deficiency, elevated total plasma homocysteine levels and cardiovascular disease. The results may suggest that, when following up adults with coeliac disease, the vitamin status should be reviewed."[34]

Folic Acid

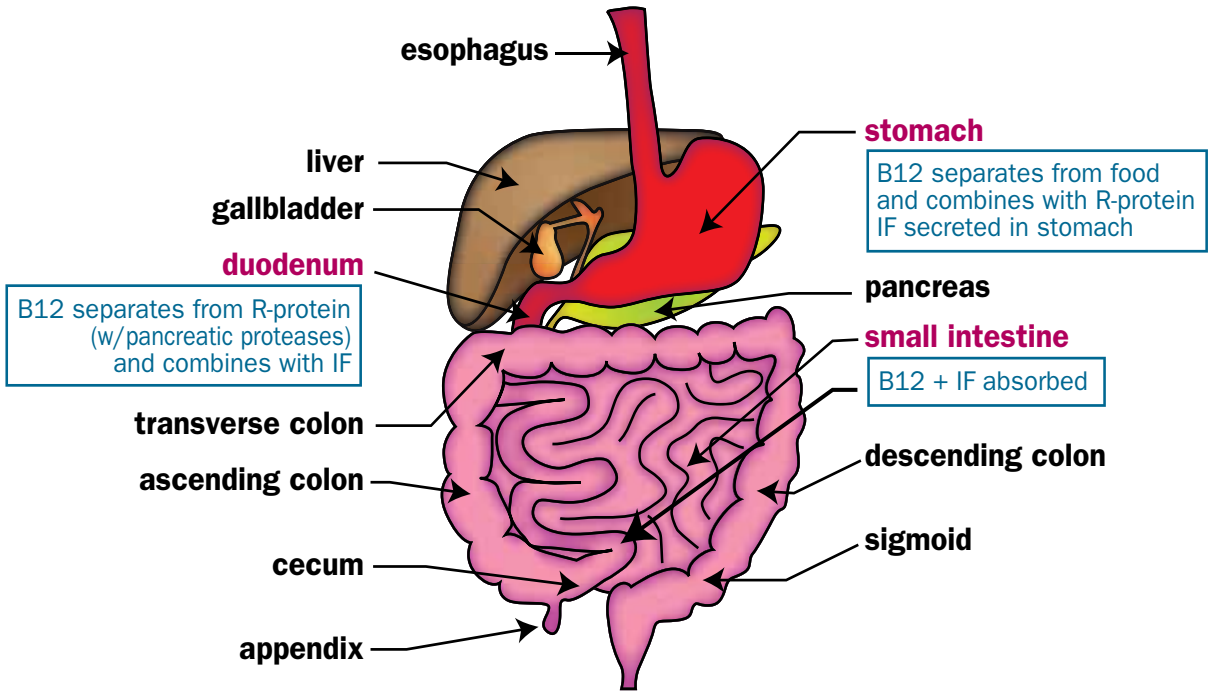
Folic acid, vitamin B_{12}, and vitamin B_6 are the most common deficiencies associated with elevated homocysteine (Hcy) levels. It has been hypothesized that compromised absorptive capacities in CD patients make them more susceptible to Hcy abnormalities. Consequently, when intestinal morphology returns to normal after a gluten-free diet, Hcy levels often decrease to normal.[35] Wilcox and Mattia showed in several case studies that Hcy levels are elevated in celiac patients and that folic acid supplementation and a gluten-free diet could normalize these values.[36]

However, Hadithi et al observed that, in comparison to non-supplemented CD patients and controls, patients supplementing vitamins B_6 and B_{12} and folic acid had Hcy levels consistently lower regardless of the presence of villous atrophy. The markers they studied showed no association with genetics; both CD groups and controls had an approximate 50-percent prevalence of the common 5,10-methylenetetrahydrofolate reductase thermolabile variant T-allele.[37]

Food fortified with folate cannot sufficiently be relied upon for the celiac population as folate levels have been found to be lower in gluten-free products, with only three cold cereals out of 58 products (including gluten-free pastas, breads, and cold cereals) fortified with folic acid.[38]

A recent article in *Cell* reports the discovery of an acid-dependent, proton-coupled folate transporter in the apical brush border of the upper intestinal tract. Upon challenges, it became clear this is the primary transporter for folate in the body. The authors note that as pH in the duodenum increases, the absorption of folic acid decreases significantly, indicating the importance

Figure 3. Digestion and Absorption of Vitamin B_{12}



of acidic chyme from the stomach. The researchers also found the methylated form of folic acid, 5-methyltetrahydrofolate (5-MTHF), was better absorbed across a broader pH range, indicating 5-MTHF may be a better choice for supplementation in gastric acid-compromised individuals.[39]

The recent findings of a role for 5-MTHF as an antioxidant may call for preference of this supplement in inflammatory disorders also associated with folate deficiencies.[40,41] Some medications used in inflammatory conditions of the gastrointestinal tract, such as sulfasalazine, are known to be folate depleting, potentially increasing the need for folic acid in those administered these medications.

Vitamin B_{12}

Vitamin B_{12} deficiency is relatively common in the U.S. adult population, with prevalence increasing with age. The most common causes of this deficiency are destruction of the intrinsic-factor secreting gastric parietal cells (associated with pernicious anemia) and an inability to release cobalamin from food or binding proteins (food-cobalamin malabsorption syndrome).[42]

The digestive and absorptive process by which vitamin B_{12} enters the body is complex. Adequate gastric acid is needed for vitamin B_{12} to separate from protein sources and attach to salivary R-protein (haptocorrin) in the stomach. Gastric parietal cells secrete intrinsic factor (IF) that binds to B_{12} in the upper intestines after pancreatic proteases cleave the bond between R-protein and B_{12}, and the intestinal environment is closer to a pH of 7. The terminal ileum is where the bulk of vitamin B_{12} is absorbed – bound to intrinsic factor via a receptor requiring the pairing of IF and B_{12} (notwithstanding the approximate 1% of B_{12} that is absorbed via passive diffusion) (Figure 3). Because the terminal ileum and not the duodenum or proximal jejunum are the sights of primary absorption, it was originally assumed that vitamin B_{12} deficiency could not be directly associated with celiac disease, although studies continue to demonstrate a direct correlation between CD and vitamin B_{12} deficiency.[43-45]

Allen et al theorize that deranged pancreatic enzyme function might be responsible for the lower levels of vitamin B_{12} commonly seen in conditions that have pancreatic insufficiency as a co-morbidity or potential side-effect.[46] As described previously, evidence shows celiac disease to be such a condition. Allen et al suggest the cause of dysfunctional vitamin B_{12} metabolism may be decreased pancreatic protease production, which is needed to separate R-protein from vitamin B_{12} in the upper intestines. If R-protein is not able to separate, then IF cannot bind and B_{12} absorption in the terminal ileum is consequently inhibited.[46]

Since autoimmunity is common in celiac disease, some researchers have implicated auto-antibodies including those to the gastric parietal cells and/or intrinsic factor as the primary cause of B_{12} deficiencies, but the results supporting this theory have been less than convincing.[45]

Regardless of the cause, 11-41 percent of celiac patients have vitamin B_{12} deficiencies,[43-45] and some studies have shown B_{12} supplementation and a gluten-free diet to be effective at treating a subset of neurological complications associated with CD.[43,47]

Although intramuscular shots of vitamin B_{12} are often used in deficient populations, studies have demonstrated oral dosing to be as effective as injections in regulating vitamin B_{12}-associated neurological and hematological functions.[48,49]

The use of PPIs may be contraindicated in patients with vitamin B_{12} deficiencies as PPIs are associated with significantly lower serum B_{12} levels compared with controls ($p=0.00005$). Vitamin B_{12} supplementation concurrent with PPIs is only able to slow but not cease the decline in vitamin B_{12} status.[50]

Iron

A 2007 article in *American Journal of Medicine* discussed a 30-year-old female diagnosed with iron deficiency anemia during her first pregnancy at age 17. After numerous trials of oral iron supplementation failed to correct her anemia, she was referred to a hematologist for further evaluation. Her symptoms included mild fatigue, a craving for ice, restless legs syndrome, lightheadedness, occasional left-hand numbness and tingling, and one pre-syncopal (dizziness) episode. The laboratory values showed a low serum ferritin of 3 ng/mL (normal: 10-300), elevated serum erythropoietin of 107 mIU/mL (normal: 4-19), and absent iron stores on a bone marrow exam. An endoscopy was performed after positive serology yielded multiple gluten-sensitivity markers, including elevated IgG antibody of 39 (negative <11), elevated IgA gliadin antibody of >100 (negative <11), endomysial IgA antibody titer of 1:160, and anti-tissue transglutaminase IgA antibody of 83 M/mL (positive >8). Biopsies of the duodenum showed villous blunting, increased intraepithelial lymphocytes, crypt hyperplasia, and increased chronic inflammation consistent with celiac disease.[51]

Iron deficiency anemia is the most common extra-intestinal symptom of CD, with a significant fraction of patients testing positive. The converse also appears to be true; i.e., a significant fraction of individuals with iron deficiency also have celiac disease.

An investigative group in Spain performed jejunal biopsies of 66 patients with iron deficiency to identify potential malabsorptive disorders associated with the deficiency. CD was the most commonly identified cause for malabsorption in this patient population, comprising 32 percent (21 patients) of the diagnoses.[52]

Annibale et al examined 190 consecutive adult patients presenting with iron deficiency anemia and screened them for celiac disease via duodenal biopsies at 6, 12, and 24 months.[53] Of the 190 patients, 26 (14%) tested positive for celiac disease (24 women, 2 men). All patients had been referred because of anemia symptoms, including tiredness, asthenia, and pallor; only nine patients of the 26 (35%) had the "classic" CD presentation of loose stools. CD patients were advised to consume a gluten-free diet and were tested for iron deficiency at 6, 12, and 24 months. After six months on a gluten-free diet, using hemoglobin levels and red blood cell distribution width as a reference for anemia, 78 percent of the CD patients recovered from iron deficiency anemia; 94 percent recovered after 12 months.[53]

When serum ferritin levels are used as a reference for recovery from iron deficiency, the authors suggest at least one year on a gluten-free diet is needed for normalization without iron supplementation. After 12 months on a GF diet, 50 percent of the patients still had low serum ferritin levels, and 45 percent were still low at 24 months. This may be an indication that further supplementation is needed. However, the authors recommend avoiding supplementation until completing

six months on a gluten-free diet with the recommendation that iron supplements may not be utilized until the intestinal morphology has normalized. This study did not include histological exams prior to six months to indicate whether or not the morphology was improving steadily during this time. A previous study of nutrient deficiencies in celiac patients indicated supplementation may help even in the presence of villous atrophy.[37,53]

Harper et al suggest the increase in inflammation associated with celiac disease is involved in the pathology of iron deficiency anemia in these patients as well.[54]

Vitamin D

Bone disorders are common in celiac disease, with some studies indicating reduced bone mineral density in up to 70 percent of celiac patients.[55,56] An increase in malabsorption of bone-building nutrients and an upregulation of inflammatory signals are thought to be responsible for the high incidence of bone disorders in CD.[56]

Vitamin D, primarily absorbed in the duodenum, is a secosteroid molecule that utilizes the same digestive and absorptive mechanisms as other fat-soluble substances (i.e., bile, pancreatic lipase, and micelle formation).[57] If the CCK mechanism responsible for signaling bile and pancreatic lipase is not functioning correctly, and the absorptive surface area for vitamin D is compromised, it could be hypothesized that deficiency is more likely.

When 54 children (average age seven) with celiac disease were compared with 60 age-matched controls, deficiencies in essential bone-building nutrients, including calcium (<9.2 mg/dL, 41% versus 0%), magnesium (<1.8 mg/dL, 12% versus 0%), and 25-hydroxyvitamin D (<20 ng/mL, 36% versus 5%) were more common. Furthermore, parathyroid (PTH) levels (117.44±70.80 versus 53.5131±27) were more elevated; 29 (54%) of the CD children had hyperparathyroidism compared with only six (10%) controls.[58] Parathyroid hormone activation occurs when serum 25-hydroxyvitamin D levels are 30 ng/mL or lower. At this approximate level, osteoclasts are activated to remove calcium and other minerals from the bone.[57]

The activity of vitamin D to change gene expression in the enterocytes and allow for absorption of intestinal calcium is so important that serum calcium and PTH levels are direct indicators of vitamin D status. When there is sufficient 25-hydroxyvitamin D, 30-40 percent of intestinal calcium can be absorbed; whereas, in 25-hydroxyvitamin D deficiency, only 10-15 percent of calcium is absorbed.[57]

Atrophy in the upper intestines, common in CD, can compromise vitamin D activity and function. Colston et al noted that vitamin D receptors are expressed in the mucosa of the duodenum and may be damaged by villous atrophy.[59] According to Staun et al, damaged areas of the intestine may also be lacking vitamin D-regulated proteins calbindin and calcium-binding protein that increase uptake of calcium from the intestines.[60]

It has been observed that calcium absorption can be 45-percent less in untreated CD patients compared to controls.[61] Valdimarsson et al noted bone mineral density (BMD) normalizes after a gluten-free diet only in patients without secondary hyperparathyroidism.[62] The same research group earlier demonstrated that BMD in celiac patients on a GF diet for one year only increased in patients also receiving calcium and 25-hydroxyvitamin D supplements.[63]

To accommodate new findings that demonstrate elevated vitamin D levels may be protective in a host of diseases, researchers are now calling for an increase in recommended serum 25-hydroxyvitamin D levels – to 40-70 ng/mL.[64] When this number is compared to currently observed global values, the vast majority of the world's population is at risk for vitamin D deficiencies.[65]

The recommended daily allowances established in 1997 for vitamin D are 200 IU (ages birth to 50 years), 400 IU (ages 51-70), and 600 IU (ages 71+). The daily upper tolerable limit is set at 1,000 IU (ages birth to 12 months) and 2,000 IU for all other age groups.[66] These levels have been deemed far too low by many researchers who recognize that daily adult needs for vitamin D may be closer to 3,800 IU in a sufficient state (serum 25-hydroxyvitamin D >22 ng/mL) and 5,000 IU in an insufficient state.[67]

Vitamin D is of particular importance in the maintenance of bone in celiac patients. Not only is it essential to decrease bone resorption via PTH and increase serum calcium levels, but vitamin D is an important immune modulator with a capability of lowering inflammatory damage in the intestinal tract.[68-72]

Anti-inflammatory Botanical Extracts: Curcumin

Monocytes are immune cells activated by inflammatory cytokines. These same sentinels of the immune system are precursor cells for the formation of osteoclasts that facilitate the breakdown of bone. CD is characterized by upregulation of inflammatory cytokines interleukin (IL) -1, tumor necrosis factor-alpha (TNF-α), IL-6, and the receptor for nuclear factor kappaB ligand, all of which are associated with an increase of bone loss via formation and activation of osteoclasts.[73-75] Some have suggested that TNF-α inhibitors may be beneficial in minimizing bone loss in CD and irritable bowel syndrome.[76]

Natural components, such as curcumin derived from turmeric, have promising regulatory effects on each of these inflammatory mediators.[77] Due to the modulatory effect it has on the inflammatory cascade in the intestinal tract, curcumin is being considered for the treatment of inflammatory bowel disease.[78-81] Future research is needed to see if the anti-inflammatory effect of curcumin may benefit CD patients as well.

Conclusion

Biochemical components from food must be digested and absorbed properly before they can be utilized by the body. Due to changes in physiological function in celiac disease, these processes may be challenged and may not normalize completely on a gluten-free diet. Therefore, further studies are needed to determine the benefit of substances like pancreatic enzymes, prebiotics, probiotics, vitamin B_{12}, vitamin D, iron, 5-MTHF, and curcumin to aid in the treatment of this disorder.

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