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THE EMERGING ROLE OF NUTRITIONAL SUPPLEMENTATION IN CELIAC DISEASE

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Introduction

Celiac disease (also known as gluten intolerance, celiac sprue, non-tropical sprue, or gluten-sensitive enteropathy) is a life-long autoimmune genetic digestive disorder in which there is an abnormal response to gliadin, a protein fraction of gluten naturally found in some grains. Unaddressed, celiac disease can damage the small intestine and, over time, may predispose to other associated diseases and disorders.

For affected patients, the presence of gliadin triggers a T-cell-mediated immune response, initiating a damaging inflammatory process in the lining of the small intestine. This inflammatory response blunts or destroys intestinal villi (tiny finger-like projections on the inner intestinal wall that enable nutrients to pass from the digestive tract into the bloodstream). Villous destruction reduces the surface area, limiting absorption of nutrients, which can lead to malnutrition and a host of associated secondary symptoms and conditions.

Gluten is found in wheat, barley and rye and in wheat's close relatives, spelt, triticale and kamut. Most people sensitive to gluten can tolerate rice, soy, millet, buckwheat, quinoa and possibly uncontaminated oats.¹

Prevalence and symptoms.

Gluten intolerance is one of the most common genetic diseases in the United States and Europe.² It most commonly affects individuals of European descent and is less frequently diagnosed in Africans, Chinese and Japanese, but has been reported in Asian Indian populations. A recent study at the University of Maryland School of Medicine revealed that about 1 in 133 Americans has celiac disease and the prevalence among first-degree relatives of celiacs is 1 in 22.³ Some researchers believe that historically, there has been a conservative under-diagnosing and under-reporting of the condition's actual prevalence.^{3,4} If we include all forms of gluten sensitivity and gluten allergy, the prevalence in the general population may well exceed 5%,⁵ and may be as high as 30% according to one researcher.⁶⁰

The most common symptoms of celiac disease may include abdominal bloating and pain, chronic diarrhea, weight loss, foul-smelling stools, gas, bone or joint pain, unexplained anemia, fatigue, and delayed growth or failure to thrive in children due to secondary malnutrition. Constipation and/or difficulty losing weight may be seen in some patients. Some people with celiac disease may lack observable symptoms for years but still suffer from low-level nutrient malnutrition or other effects that, over time, can cause complications. Such presentations are classified as either silent (exhibiting no symptoms) or subclinical (exhibiting extra-intestinal symptoms only). Examples of extra-intestinal symptoms include osteoporosis, iron deficiency anemia, hair loss, and infertility.⁶⁻¹⁰

Detection and diagnosis.

Early detection is critical, yet the diagnosis of celiac disease is often overlooked, as symptoms of gluten intolerance can be confused with those of other chronic diseases (e.g. diverticulitis, intestinal infections, chronic fatigue syndrome, and various forms of colitis, such as irritable bowel syndrome). Timely diagnosis is especially important in children, as adequate nutrition is critical during times of active growth. Thus, in Italy for example, every child is routinely screened by age six so that even asymptomatic cases can be found early. In the U.S., however, the average time between first symptom appearance and diagnosis is about ten years.¹¹ As we will see later, this delay in diagnosis increases the risk for developing malnutrition and other complications.^{11,12}

Screening tests that detect and measure antibodies to gliadin as well as genetic screening are presently available for suspected cases of celiac disease. Health professionals can run blood tests to measure levels of IgA endomysial antibodies (EmA), IgA tissue transglutaminase (tTG) and IgA and IgG anti gliadin antibodies. IgA endomesial antibody testing has not proven usefully sensitive in detecting mild or early cases as it correlates mainly with total villous atrophy and not with mild intestinal damage. A serum IgA should be obtained because around 10% of celiacs may have an IgA deficiency. Genetic screening for DQ2/DQ8 enables clinicians to rule out, but not rule in celiac disease and is now being used in combination with the celiac antibody screening mentioned above. Consensus among most gastroenterologists is that a small intestine biopsy is required to confirm the diagnosis of celiac disease.

Treatment – easier said than done!

Treatment is both basic and effective, but somewhat difficult to accomplish, as the patient must completely avoid all foods that contain gluten, i.e. follow a strict gluten-free diet (GFD).

Significant improvement usually occurs within weeks or, in some cases, months to years. More severe symptoms may require longer recovery times. Severely damaged digestive tracts (as found especially in older persons and in long-untreated cases) may not be able to heal completely with the GFD alone.¹³ In such patients, intravenous nutrition and/or possibly higher oral doses of nutritional supplements may be required.^{14,15} However, most people with this condition are able to become symptom-free as long as they maintain strict avoidance of gluten-containing foods. Refractory celiac disease, which is non-existent in children, may be seen rarely in adults.

Unfortunately for some, ingesting even small amounts of gluten can reinjure the delicate lining of the intestine, and compliance to a restricted diet can be challenging. The standard American diet is replete with products that feature wheat or other gluten-containing foods. [See **TABLE 1: GLUTEN-FREE & GLUTEN-CONTAINING FOODS.**] Gluten is found in most snack foods, fast foods and convenience food products, while other foods may harbor hidden sources of gluten (e.g. thickeners and stabilizers). Patients should look for the words "gluten-free" or "contains no gluten" on the labels of questionable products.

Those diagnosed with gluten intolerance and their families can significantly benefit from gluten-free meal planning with a compassionate, nutritionally-oriented healthcare professional. Support groups are especially helpful in making the transition to a gluten-free life. We cannot stress too emphatically the importance of becoming comfortable with and maintaining a 100% gluten-free life and overall healthful lifestyle. In the short term, a celiac treated with the GFD will likely feel significantly better. In the long run, dietary compliance can significantly reduce the chance for malignancies, osteoporosis and many other diseases.^{5,16}

Importance of nutritional supplementation.

In **THE BOOK OF GLUTEN**, author Stephen Gislason, MD states, "As a general rule, celiac and many other gluten-sensitive patients have nutrient deficiencies until proven otherwise."¹⁷ Studies have shown that nutrient deficiencies are commonplace in persons with active stages of celiac disease, and occur during silent or subclinical stages as well.^{6,18}

In general, nutrient deficiencies may occur as a result of inadequate nutrient intake, increased need for nutrients, or malabsorption of nutrients. Since this last factor is a defining characteristic of gluten intolerance, it is not surprising that suboptimal levels of fat-soluble vitamins D and E, water-soluble vitamins B12, folic acid and other B vitamins, and minerals such

as calcium, magnesium, iron and zinc have all been observed in persons with active celiac disease.¹⁸⁻²¹ Usually, as healing progresses, a patient's ability to absorb most nutrients returns. However, the degree of recovery is dependent on age at onset, extent and duration of the condition and other concomitant health factors.

TABLE 1: GLUTEN-FREE & GLUTEN-CONTAINING FOODS		
GLUTEN-FREE GRAINS		GLUTEN-CONTAINING GRAINS
Rice	Millet	Wheat & Wheat Family (<i>semolina, triticale, spelt, kamut, bulgur, cous-cous, etc.</i>)
Corn	Teff	Rye
Buckwheat	Quinoa	Barley
Amaranth	Sorghum	
OTHER GLUTEN-FREE FOODS		POSSIBLY GLUTEN-CONTAINING
Whole Beans/Bean Flours (<i>soy beans, lentils, black beans, chick pea, aduki, lima, etc.</i>)		Oats (<i>technically gluten-free, but may be contaminated with wheat</i>)
Whole/Ground Seeds & Nuts (<i>flax, poppy, sunflower, sesame, pumpkin, almond, walnut, etc.</i>)		
Some Examples of GLUTEN-FREE & GLUTEN-CONTAINING FOODS		
TYPE OF FOOD	GLUTEN-FREE (GF)	CONTAINS (OR MAY CONTAIN) GLUTEN
FLOURS	rice, corn meal, GF baked goods	wheat, barley, rye, most baked goods
PASTA	rice, corn, polenta	durum, semolina, ramen, cous-cous
BREAKFAST CEREALS	cream of rice, GF oatmeal	cream of wheat, muesli, cereal
DAIRY	milk, most yogurt & cheese	some blue cheeses, malted milk
FATS & OILS	most vegetable oils, butter, coconut	wheat germ oil, salad dressings, mayonnaise, suet
MEAT & FISH	fresh or frozen meat and fish	breaded/fried/processed meat and fish, imitation crab
VEGETABLES	fresh or frozen vegetables	breaded/creamed/fried vegetables
FRUITS	fresh, dried or frozen fruits	canned in sauce
NUTS & SEEDS	raw or naturally roasted	dry roasted, flavored
BEVERAGES	tea, coffee, fruit juice	beer, some soy & rice milks, roasted grain coffee substitute
SOUPS & SAUCES	GF canned soups, GF dry mixes	canned and dry mixes, gravy
SEASONINGS	salt, pepper, pure herbs & spices	herb or spice mixes, soy sauce, tamari
Sources: "Safe and Forbidden Lists for Celiac Diets" (www.celiac.com); British Nutrition Foundation (http://www.nutrition.org.uk/education/pupilcentre/projectareas/coeliac.htm)		
READ LABELS CAREFULLY. WHEN IN DOUBT, CONTACT MANUFACTURER.		

Again, the only effective treatment for active, subclinical and silent celiac disease is avoidance of gluten. Without a GFD, celiac disease can lead to osteoporosis, neurological conditions (such as congenital neural tube defects in children born to mothers with celiac-induced folic acid deficiency), short stature and a plethora of other nutrient-deficiency diseases. It is our opinion that adequate replenishment of nutrients lost to inefficient absorption is essential to minimizing secondary health problems caused by gluten intolerance.

Some celiacs and gastroenterologists specializing in celiac disease take the position that the GFD alone is sufficient for "cure" and avoid the connection between celiac disease and optimal nutrient supplementation. Conversely, other researchers suggest that to compensate for the celiac patient's compromised nutrient assimilation, targeted supplementation at doses significantly greater than the RDA is required. For instance, a 2002 study concludes, "Overall, calcium supplementation must be higher than the RDA in order to obtain the correct amount of calcium in the presence of latent malabsorption which exists

in many celiac disease patients. However, no studies have investigated what the calcium requirement of celiac disease patients actually is. Further investigation is advisable.”²² In modern science, research data on any given topic is virtually never complete. This axiom became critically apparent when we undertook a literature search, covering the past 20 years, for nutritional supplement intervention studies documenting dose-response in celiacs. We were unable to find any such intervention studies.

While there is an urgent need for studies looking at optimum nutrient intake levels in the treatment of both active and silent celiacs, there is already ample research suggesting a crucial value to lifelong nutrient supplementation. We postulate that in most persons with celiac disease, optimum intestinal repair, healing and return to normal health are possible only with total abstention from gluten-containing foods, a healthful lifestyle and diet, and supplement intervention with appropriate levels of vitamins, minerals and other nutritional cofactors.

Presented below are eight arguments supporting nutritional supplements for celiacs from current research and reviews.

EIGHT RATIONALES FOR THE INCLUSION OF DIETARY SUPPLEMENTS IN THE TREATMENT PROTOCOL FOR CELIAC DISEASE

1. Most people do not consume an optimal nutrient intake by diet alone.

Supplementation is not only for those with active celiac disease. The Journal of the American Medical Association has recently endorsed the position that all adults take at least a multivitamin/mineral supplement daily. The authors conclude, “Most people do not consume an optimal amount of all vitamins by diet alone... it appears prudent for all adults to take vitamin supplements.”²³ The proactive use of vitamins and minerals is part of a preventive approach to health that anyone might consider to reduce the opportunity for common preventable chronic diseases such as cardiovascular disease, osteoporosis and cancer.²³⁻²⁵

Virtually thousands of clinical studies have shown wide-ranging health benefits from daily use of single and multi-nutrient supplements – from improvements in non-verbal intelligence,²⁶⁻²⁷ to decreased risk for cardiovascular disease and cancer,^{24,28} to fewer acute health problems and improved quality of life. In a one-year, placebo-controlled study looking at infections in adult diabetics, there was a four-fold decrease in absenteeism due to infection in those subjects who took a multivitamin/

multimineral supplement.²⁹

2. People with celiac disease are at higher risk for insufficient absorption and uptake of certain nutrients.

One of the critical long-term sequelae of celiac disease is an increased probability for nutrient deficiencies throughout life compared to persons without this condition.^{6,18,20,22,30} It appears that as long as damage from inflammation in the intestines persists, the efficiency of nutrient assimilation will be compromised. In a study looking at plasma levels of vitamins B6, B12 and folic acid, the authors found, “Half of the adult celiac patients carefully treated with a gluten-free diet for several years showed signs of a poor vitamin status...when following up adults with celiac disease, vitamin status should be reviewed.”²⁰

What constitutes a reasonable daily intake of nutrients for a healthy person may not be sufficient or optimum for a person with celiac disease. The Recommended Daily Allowances set by the Food and Nutrition Board of the National Research Council are meant to apply to healthy, average Americans. The RDAs (and more recent DRIs) have never been intended for “individuals with special nutritional needs.”³¹

In a comprehensive review of research that looked at 35 years of studies linking chronic disease prevention to vitamins, the authors concluded: “...patients with malabsorption are at higher risk for inadequate intake or absorption of several vitamins, ...vitamin deficiency and suboptimal vitamin status.”²⁸

Similarly, the American Dietetic Association states that taking vitamins and minerals can be beneficial ... “If you eat a special diet...which has limited variety because of food allergies or intolerance to certain foods, [or] if your body can’t absorb nutrients properly [due to] a disease of your intestines.”³²

Our presumption is this: Because of the inefficiency of absorption in celiac disease, higher doses of vitamins, minerals and other nutrients will allow higher levels of nutrients to find their way through or between the enterocytes, compensating for the nutrient deficiencies caused by the inhibiting effects of malabsorption.

3. Many people don’t fully comply with a 100% GFD – a diet critical for repair and improved nutrient absorption.

For most celiacs, healing and a return to normal or near-normal digestive and absorptive potential and optimum health depends on maintaining a strict gluten-free diet for life.

However, it is very challenging to comply with a 100% GFD. About 30-40% of adult celiacs and more than half of children and adolescents are not able to completely maintain such a diet.³³⁻³⁸ For this non-compliant group, it is likely that some degree of compromised absorptive function remains a possibility, whether symptoms are observable or not.⁸ Where there is continued absorptive dysfunction, nutrient deficiencies are likely to persist. When the health professional is adequately informed, closely follows patient progress and engages in patient education, support, guidance and nutritional counseling, compliance is likely to be considerably higher.⁵⁹

4. An unguided GFD can skew eating choices and may induce nutritional imbalances and other health conditions.^{34,45}

The “Standard American Diet” (SAD) (i.e. the diet typically consumed by many Americans – not the diet recommended by nutrition professionals) is by most measures nutrient deficient and unbalanced,²³ while childhood and adolescent versions of the SAD tend to be even less optimal.^{34,39} In one diet study of children ages 2 to 19, only 1% met all the national recommendations for food group intake and 16% did not meet any.⁴⁰ In attempting to comply with a gluten-free diet, people accustomed to eating the SAD often further skew their intake of fats, proteins, carbohydrates and other nutrients, resulting in a suboptimal diet higher in fat calories and lower in complex carbohydrates.⁴¹

Over time, eating such a skewed diet can favor the onset of metabolic diseases including obesity³⁴ and diabetes³³ – conditions already genetically correlated with celiac disease. (About 5-10% of Type 1 diabetics have genetic markers of celiac disease, while the risk for developing Type 2 diabetes is slightly higher among celiacs than in the general population.)^{42,44} Certain metabolic diseases may be at least partially due to imbalanced gluten-free food choices over time. Celiac children on a GFD have been noted to have low caloric and carbohydrate intakes, a high fat intake, and an imbalance toward simple sugar and saturated fat.³³ Lifelong protraction of such unbalanced dietary habits may encourage the development of metabolic diseases in later life.³³

In another study, what appeared to be a balanced children’s GFD diet was found to be calcium deficient. “The lower calcium content of [the] gluten-free diet...can lead to increased parathyroid secretion which can cause retardation of bone growth even in treated patients with celiac disease.”⁴⁵ Professional dietary guidance coupled with proper supplementation are useful in ensuring balanced nutritional adequacy for the celiac patient.

5. Patients with continued compromised absorption or other symptoms, despite following a gluten-free diet, may need further evaluation and treatment.

Healing from active celiac disease isn’t always neat and tidy. The GFD treatment is always necessary, but sometimes insufficient for complete recovery.⁴⁶ A small percentage (7% to 30%)⁴⁷ fail to fully respond to treatment with a GFD. This may stem from unrecognized inadequate compliance to the GFD – probably the main reason.⁴⁸ In patients with continued symptoms one should address other possible etiologies or contributing factors. These may include sensitivity to dietary constituents in addition to gluten (e.g. lactose intolerance, soy, etc.), pancreatic insufficiency, microscopic or lymphocytic colitis, bacterial overgrowth, enteropathy-associated T-cell lymphoma or other causes.^{47,48,59} A small subset of patients may have an overlap with an inflammatory bowel disease such as Crohn’s Disease or ulcerative colitis.⁵⁹ Identifying the root cause(s) is paramount and requires time and patience.

Age also plays a key role in recovery. A 2002 study found that although children recovered up to 95% within two years, and nearly 100% ultimately achieved recovery after starting and maintaining a GFD, recovery was incomplete or absent in a substantial subgroup of older patients (10.1% villous atrophy after 5 years).¹³

Dietary levels of specific nutrients such as calcium, vitamin E and iron can be lower in GFD-compliant children and adolescents than in healthy subjects.^{9,34} In adults, folic acid, calcium and other nutrient deficiencies may persist even when the patient is GFD compliant.^{45,49,51}

One study on bone mineral density (BMD) in celiacs found that “...approximately 70% of adults with celiac disease have abnormally low BMD values. Since celiac disease may not be discovered in most patients until adulthood, the failure to reach normal BMD even after [GFD] treatment can be explained in part by a failure in the patient to reach peak bone mass during developmentally important years.”¹² At any age, nutrient supplementation may help improve nutrient status in the face of persistent challenges to intestinal function.

6. Silent (symptomless) celiacs can still have compromised digestion and absorption.

“Silent” celiacs fall into two categories – those who have already been diagnosed with celiac disease but are free of observable symptoms, and those who are unaware that they have the condition because they have not experienced any classic symptoms.

Improved diagnosis in recent years has revealed that celiac disease doesn't always show up as an observable digestive tract symptom.⁵² Often, the first symptoms appear as bone demineralization, anemia, hair loss or the skin condition dermatitis herpetiformis.^{6,7} Some silent celiacs may have no discernable symptoms, digestive or otherwise. Nevertheless, lack of symptoms does not exclude secondary deficiency conditions.⁸

Without a thorough examination and comprehensive testing for nutrient level deficiencies, it is difficult to determine the health status of a person with silent celiac disease. Meanwhile, clinicians are less inclined to work-up a patient who lacks overt symptoms. A sensible program of broad-spectrum nutrient supplementation may help to counteract undetected deficiencies.

7. Nutrient supplementation may speed recovery, providing the necessary cofactors for growth and repair.

Studies of celiac patients who are complying with a GFD have found that persisting nutrient deficiencies may impede the rate of healing. "The correction of vitamin and mineral deficiencies may be helpful in aiding recovery; vitamin D and calcium supplementation often is recommended."⁵³ Likewise, it has been shown that "Zinc deficiency may complicate many gastrointestinal malabsorptive states."⁵⁴ And in a study of children it was suggested that clinicians "add zinc supplementation in patients with diminished zinc values... because zinc deficiency could inhibit the recovery of the intestinal mucosa."⁵⁵

8. Risk/Benefit: Treating with vitamins and minerals is safe, beneficial and cost effective.

Clearly, the potential for inefficient absorption is considerably higher in people with gluten intolerance than in the general population. Providing supplementation within the upper limits of safety based on Upper Intake Levels as determined by the Food and Nutrition Board of the National Academies of Science makes sense, as it can do little harm and may be critically helpful. [See TABLE 2: RECOMMENDED DAILY ALLOWANCES AND UPPER LIMITS OF SAFETY FOR SELECTED NUTRIENTS.]

Some celiac healthcare advocates hold the position that proof of vitamin and mineral deficiencies must be demonstrated in a patient before a trial of supplementation is undertaken.³⁸ While in theory this might be a good idea, in practice it is a very involved, costly and impractical venture to attempt to identify every nutrient level through blood, urine and tissue testing. Few clinicians routinely test in this way.

	DIETARY REFERENCE INTAKE* (DRI)	UPPER LIMIT OF SAFETY (UL)
VITAMINS	A	.900 mcg (3000 IU) 3000 mcg (10,000 IU)
	C	.90 mg 2000 mg
	D	.15 mcg (600 IU)50 mcg (2000 IU)
	E	.15 mg (22 IU natural vitamin E) 1000 mg (1466 IU natural vitamin E)
	Thiamin (B-1)	.12 mg ND
	Riboflavin (B-2)	.13 mg ND
	Niacin (B-3)	.16 mg35 mg
	Pyridoxine (B-6)	.17 mg100 mg
	Cobalamin (B-12)	.24 mcg ND
	Folate	.400 mcg (from food; 200 mcg synthetic) 1000 mcg (synthetic)
MINERALS	Calcium	1300 mg 2500 mg
	Iron	18 mg 45 mg
	Iodine	150 mcg 1100 mcg
	Magnesium	420 mg (RDA) 350 mg**
	Zinc	11 mg 40 mg
	Selenium	.55 mcg 400 mcg
	Chromium	.35 mcg ND

*Values for adult males, aged 31-50 **From supplements only. Magnesium UL does not include intakes from food and water.

ND: Upper Limit not determined. No adverse effects observed from high intakes of the nutrient. (Author note: It is our position that due to their rapid excretion and lack of toxicity, some water-soluble vitamins and minerals are safe at levels higher than the ULs.)

Source: Institute of Medicine of the National Academy of Science, 1997-2001 (www.iom.edu)

The potential benefits of giving optimum levels of all essential vitamins, minerals and macro- and micronutrients to those with gluten intolerance in all stages of their lives and of their disease far outweigh the risks. When given within the upper limits of safety there are relatively few cases of ill effects, side effects or toxicity from supplemental vitamins and minerals – far fewer than for most drugs or even aspirin, for example.⁵⁶

The adage "what you don't use, you excrete" applies to most water-soluble nutrients, and as long as fat-soluble nutrients are given in therapeutically appropriate levels, there ought to be little concern with excess storage in tissues.

Vitamins and minerals have proven extremely safe for over 75 years when taken in appropriate doses. Furthermore, the total cost of taking every daily-required vitamin and mineral in bioavailable forms, dosed within the upper limits of safety, is only about 75 cents to \$1.50 per day. This sum is most likely far less expensive than treating an evolved nutrient-related chronic disease later in life.

Conclusion

There have been few dose-dependent studies of nutritional supplementation in celiacs, though some researchers are calling for more, and investigation is ongoing.^{22,57,58} Until additional research data becomes available, it is our opinion that for the reasons presented in this article, a reasonable and therapeutically prudent course of action is to recommend nutritional supplementation to all persons with gluten intolerance. In addition to addressing specifically identified nutrient deficiencies as per individual need, we suggest 1) that supplementation include all known vitamins and minerals, 2) that supplementation be given

on a daily basis, and 3) that supplementation be given within and near the upper limits of safety as established by the Food and Nutrition Board of the Institute of Medicine.

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