Chapter 11
Dietary Supplements in Celiac Disease

Michelle Maria Pietzak

Why Are There Nutritional Deficiencies in Patients with Celiac Disease?

Celiac disease (CD) is more than just an "allergy" or "sensitivity" to wheat and gluten. It is a lifelong, permanent intolerance to the gliadin fraction of wheat protein and its related alcohol-soluble proteins (prolamins) found in rye and barley. In patients with the genetic susceptibility to CD, ingesting these proteins leads to an autoimmune enteropathy that will self-perpetuate as long as these foods remain in the diet. The good news is that, unlike most autoimmune conditions, removal of the environmental trigger (gluten) from the diet of a biopsy-proven celiac results in complete symptomatic and histologic resolution of the disease in the majority of patients [1, 2].

Differentiating CD from wheat allergy, gluten sensitivity, and other autoimmune gastrointestinal (GI) diseases (such as Crohn's disease) can be challenging. Likewise, CD can present at any age with "classic" GI features, such as diarrhea and weight loss, or outside the GI tract with anemia, rashes, infertility, osteoporosis, joint pain, short stature, delayed puberty, and even malignancy. It is common that patients experience chronic ill health and nutritional deficiencies prior to the correct diagnosis being made. These patients commonly incur high healthcare costs because of the multiple subspecialists and tests performed on them prior to the confirmation of CD [3].

The duodenum and proximal small bowel play an important role in the digestion and absorption of many key nutrients, such as carbohydrates, protein, lipids, and iron. The bulk flow of water occurs primarily through the porous junctions of the proximal

M.M. Pietzak, M.D. (✉)
Department of Pediatric Gastroenterology, University of Southern California Keck School of Medicine, Intern's and Resident's Building Room 124, 2020 Zonal Avenue, Los Angeles, CA, USA
e-mail: Pietzak@usc.edu

S.D. Rampertab and G.E. Mullin (eds.), *Celiac Disease*, Clinical Gastroenterology,
DOI 10.1007/978-1-4614-8560-5_11, © Springer Science+Business Media New York 2014

small intestinal epithelial cells. The distal part of the small bowel, the terminal ileum, is preferentially responsible for the absorption of B_{12} and bile acids. In a patient with CD, depending upon the severity of intestinal damage, there may be varying amounts of edema, atrophy, and loss of disaccharidases (in particular, lactase) within the villous structures. This can lead to malabsorption of the above nutrients, as well as excessive osmotic load by undigested sugars, causing watery diarrhea.

The colon is an important salvage organ and is mainly responsible for the reabsorption of water. Also, indigestible fibers are broken down by enzymes in the colonic bacteria, producing short-chain fatty acids (acetate, proprionate, and butyrate), which are then efficiently absorbed by the colon. Some patients with CD will also have a lymphocytic colitis if biopsies are taken during a colonoscopy. Patients with CD-associated lymphocytic colitis may experience urgency and tenesmus in addition to watery diarrhea.

Lifelong compliance with the gluten-free diet (GFD) is challenging, with frequent temptations towards dietary transgressions, which will lead to further enteropathy and malabsorption. Adherence to the GFD is improved by patient education, close supervision by an interested physician, and regular nutritional counseling by a registered dietician with expertise in CD [4]. Compliance can be improved, even in adolescents, who are seen by a physician on a regular basis [5, 6]. One of the best and least expensive markers for dietary compliance is assessment by a trained interviewer (either a physician or dietician) due to the low cost, noninvasiveness, and a strong correlation to intestinal damage [6]. Healthcare providers should encourage the patient to join local chapters of national support organizations (see Appendix 1), which can aid in finding local resources such as supermarkets, food manufacturers, literature, and restaurants that are familiar with the GFD [4]. It is important to be familiar with the recommended dietary allowances of micronutrients of CD patients who are at risk for deficiencies. Likewise, the practitioner caring for the patient with CD should be able to recognize the signs of micronutrients deficiency, be able to provide guidelines for corrective supplementation, and monitor safety of therapy. We have provided the Food and Nutrition Board and the Institute of Medicine's Dietary Reference Intakes (DRI) for vitamins and elements in Appendix 10 and the DRI for Tolerable Upper Intake for vitamins and elements in Appendix 11 (http://www.iom.edu/About-IOM/Leadership-Staff/Boards/Food-and-Nutrition-Board.aspx).

Anemia in CD: Iron, B_{12}, and Folic Acid Deficiencies

Background

A routine complete blood cell count may reveal many hematologic abnormalities in an untreated patient with CD. Anemia, leukopenia, and thrombocytopenia have all been reported. The anemia is usually microcytic and hypochromic, due to iron

deficiency [7]. Iron is absorbed by villus enterocytes in the proximal duodenum [8]. A macrocytic anemia should warrant an investigation into deficiencies of B12 (cobalamin) and/or folic acid. A large study in a cohort of patients with newly diagnosed CD found anemia in 20 %, with iron deficiency in 33 % of men and 19 % of women, folate deficiency in 12 % of the total, and B_{12} deficiency in 5 % of the total [9]. In addition to malabsorption, inflammation and poor dietary intake may explain these deficiencies since the GFD in and of itself may be deficient in nutrients such as folate. Since elevated ferritin and sedimentation rates were seen in some, these authors hypothesized that inflammation may be responsible for this anemia of chronic disease. In a 3-day GFD survey, only 44 % of the female respondents consumed the daily recommended amounts of iron [10]. In addition, research done on gluten-free cereals indicates that these products contain lower amounts of iron and folic acid than their gluten-containing counterparts [11].

Symptoms

Common symptoms of anemia include pallor, fatigue, frontal headache, decreased appetite, and shortness of breath on exertion. Iron deficiency, in particular, is associated with abdominal pain, disturbed sleep, sore red tongue, and brittle hair and nails. Patients may demonstrate pica, which is a strong desire to eat nonfoods such as ice, paint, dirt, and hair. Iron-deficiency anemia may also lead to problems with fertility and maintenance of pregnancy. Profound B_{12} deficiency may also manifest as mania, impaired balance, depression, and peripheral neuropathy.

Diagnosis

A complete blood cell count with peripheral smear, mean corpuscular volume, and other red cell indices is a routine screen for these anemias. The degree of iron deficiency can be further delineated by serum iron, ferritin, percent saturation, and total iron binding capacity. Since serum B_{12} levels are not very sensitive for B_{12} function, a serum methylmalonic acid (MMA) level is recommended. Serum folic acid is easily measured in red blood cells.

Treatment

Dietary sources rich in iron include meats (beef, shrimp, turkey, and liver), seafood (oysters, clams, and scallops), beans (lentils, chick peas, soybeans), dark green leafy vegetables, and iron-fortified cereals. Iron supplements come in liquids, tablets, and slow-release capsules. Dosages range from 1 to 5 mg/kg/day of iron for 3–6 months,

depending upon the severity of the anemia. Foods rich in folic acid include green leafy vegetables (spinach, lettuce, broccoli, asparagus), soybeans, salmon, bananas, fortified cereals, and orange and tomato juice. Since folate is heat sensitive, it may be inactivated in overcooked foods. Medications that may lower folic acid levels include metformin, anti-inflammatory drugs (aspirin), and acid blockers (Pepcid, Tagamet, Zantac). The typical dose of folate for megaloblastic anemia and malabsorption ranges from 250 to 1,000 μg per day. B_{12} is found in high concentrations in eggs, liver, beef, lamb, cheese, and seafood (clams, oysters, mussels, caviar, octopus, crab, lobster, and bony fish). Supplementation of B_{12} can be done via oral, sublingual, intramuscular, intravenous, or nasal routes, depending upon the degree of malabsorption. Doses range from 10 μg per day for prevention of anemia to upwards of 1,000–2,000 μg in scheduled doses to treat severe anemia. Fortification of folate to gluten-free dietary products should be strongly considered [12].

Deficiencies of the Fat-Soluble Vitamins (A, E, D, K) in CD

Background

The fat-soluble vitamins are solubilized into micelles in the intestinal lumen by bile acids, which are then absorbed through the duodenal epithelium into the bloodstream [13, 14]. Fat malabsorption may occur in CD due to intestinal damage, liver disease, underlying pancreatic insufficiency, or drugs that bind to bile acids such as cholestyramine [15]. The inability to properly digest and absorb fat can lead to deficiencies in vitamins A, E, D, and K, some of which have profound lifelong morbidities. Requirements and recommended daily allowances for these and all vitamins and minerals are dependent upon age, reproductive status, and underlying health conditions and are provided in Appendix 10 and Appendix 11. The reader is also encouraged to refer to the intake recommendations for nutrients developed by the Food and Nutrition Board at the Institute of Medicine of the National Academies (http://www.iom.edu/About-IOM/Leadership-Staff/Boards/Food-and-Nutrition-Board.aspx) as well as the NIH Office of Dietary Supplements (http://ods.od.nih.gov/).

Vitamin A (Retinol and Provitamin A Carotenoids)

Symptoms

Vitamin A is important for epithelial cell development in the eyes, heart, lungs, and kidneys [16]. It also plays a role in the maintenance of the skin and mucous membranes of the mouth, nose and sinuses, bone formation, reproduction, and collagen synthesis and wound healing [17–19]. Deficiency often presents during periods of

high nutritional demand, such as during pregnancy, lactation, infancy, and childhood. Vitamin A deficiency increases the risk of diarrhea; while chronic diarrhea can also lead to excessive losses [13]. The most common symptoms are xerophthalmia and night blindness [20]. In fact, vitamin A deficiency is one of the leading causes of blindness in children worldwide [21]. Vitamin A deficiency also increases the severity and mortality risk of infections, especially with measles [13, 21]. Higher intakes of carotenoids may be associated with lower risks of lung cancer, prostate cancer, cataracts, and macular degeneration [22–24].

Diagnosis

Retinol and carotenoid levels can be measured in plasma; however, their value for assessing marginal vitamin A status is limited, as they do not decline until hepatic stores are almost depleted [25].

Treatment

Preformed vitamin A is found in animal sources, such as meat (especially liver), dairy, and fish, as well as fruits, leafy green vegetables, orange and yellow vegetables, and tomato products [25]. In the USA, the top food sources of vitamin A are dairy products, liver, fish, and fortified cereals, while the top sources of provitamin A are carrots, broccoli, cantaloupe, and squash [22]. Dietary supplements are available as retinyl acetate or retinyl palmitate (preformed vitamin A), beta-carotene (provitamin A), or a combination of the two. Caution must be used with preformed vitamin A supplementation to avoid hypervitaminosis A, which has been associated with pseudotumor cerebri, skin irritation, joint pain, fractures, coma, and even death [13, 16, 26]. Fortification of GF foods with vitamin A should be considered [12].

Vitamin E (Alpha-Tocopherol)

Symptoms

Vitamin E is an antioxidant that protects cells from the damaging effects of free radicals. It also plays a role in immune function and the inhibition of platelet aggregation [22, 27]. Deficiency symptoms include peripheral neuropathy, ataxia, skeletal myopathy, retinopathy, and impairment of the immune response [22, 28]. Vitamin E is being studied for the prevention of coronary heart disease, cataracts, age-related macular degeneration, Alzheimer's disease, and prostate, bladder, and colon cancers [22, 24, 29–33].

Diagnosis

Alpha-tocopherol and beta-gamma-tocopherol are easily measured in serum. Early manifestations of vitamin E deficiency include hyporeflexia, ataxia, limitations in upward/outward gaze, and deficits in proprioception and vibratory sense. Late symptoms of continued deficiency include severe ataxia, diffuse muscle weakness, nystagmus, dysphagia, dysarthria, blindness, and dementia [34].

Treatment

The vitamin may be administered via oral, intramuscular, or parenteral routes. Overdose, though rare, is associated with decreased platelet aggregation and possible increased risk for hemorrhagic stroke [35]. In the USA, most vitamin E in the diet is in the form of gamma-tocopherol from vegetable oils (soybean, canola, corn), although small amounts of alpha-tocopherol are found in nuts, tomato, kiwi, mango, spinach, and broccoli [36].

Vitamin D

Symptoms

There is a long list of potential benefits with vitamin D, including improved bone health and resistance to infections, cancer, and cardiovascular diseases. In children, the classic diseases associated with deficiency are rickets and osteomalacia. Adults may also manifest with bone pain, muscle weakness, dental disease, limited joint mobility, osteopenia, and osteoporosis [37, 38]. Ongoing research is exploring the impact of vitamin D on diabetes, multiple sclerosis, hypertension, and rheumatoid arthritis [39–44].

Diagnosis

The best test to determine vitamin D status is serum 25-hydroxy vitamin D. Levels less than <20 ng/mL (<50 mmol/L) are consistent with vitamin D deficiency, while levels of 21–29 ng/mL (52.5–72.5 mmol/L) are considered consistent with vitamin D insufficiency [45]. Serum parathyroid hormone levels are often elevated, indicating secondary hyperparathyroidism. Skeletal radiographs and bone density measurements may reveal rickets, osteopenia, or osteoporosis (see subsequent section “Issues in Bone Health in CD”).

Treatment

There are a limited number of foods that naturally contain vitamin D. Some of the best sources are fish liver oil and bony fish (salmon, tuna, mackerel, herring, sardines) [37]. Small amounts are found in cheese, egg yolk, mushrooms, and beef liver. The majority of vitamin D in the U.S. diet comes from fortified foods. These include milk as well as some breakfast cereals, orange juice, yogurt, and margarine. Of note, products made from milk, such as cheese and ice cream, are not generally fortified in the United States [46]. Vitamin D supplements, which are readily available over the counter, can vary widely in their potencies [47], and thus caution should be used to avoid overdose. Excessive vitamin D intake can be associated with anorexia, arrhythmias and calcifications in the renal and cardiovascular systems [37]. Vitamin D is also made by the body as a result of exposure to the sun.

Vitamin K

Symptoms

This vitamin is absorbed mainly in the terminal ileum and is important for the synthesis of vitamin K–dependent clotting factors, which are made in the liver [48]. It is also important for the formation of the bone matrix. There are three types: phylloquinone from plants, menaquinone from bacteria in the GI tract, and menadione, which is synthetic and water soluble. Deficient patients have increased risk for spontaneous bruising and bleeding as well as osteoporosis [49, 50].

Diagnosis

A significant amount of this vitamin in the human body is synthesized by bacteria in the colon; therefore, overuse of broad-spectrum antibiotics can lead to deficiency. Prothrombin time (PT) and prothrombin antigen assay readily detect deficiencies of factor VII, a vitamin K-dependent factor with a very short half-life of only 30 min. Although plasma vitamin K can be measured, checking a PT is less expensive and more readily available.

Treatment

The vitamin K deficiency found in malabsortive GI disorders such as CD is easily treated and monitored by the correction of the PT [51]. Oral VK-3, a menadione,

is a synthetic, water-soluble form used to treat deficiency associated with GI malabsorption. IV or IM preparations can be administered for more severe cases. However, the IV form must be given very slowly as it can be associated with hypersensitivity, anaphylaxis, shock, and cardiopulmonary arrest. This nutrient can be found in green leafy vegetables and vegetable oils (soybean, cottonseed, olive, canola) [52].

Malabsorption of Minerals and Trace Metals in CD: Zinc, Selenium, Copper, Calcium, and Magnesium

High percentages of magnesium, calcium, and phosphorous deficiencies have been reported in both adolescents and adults with CD [10, 53].

Zinc

Background

This trace element is absorbed throughout the small intestine by a number of transporters and binding proteins located in the villus epithelial cells [54]. As zinc is important for DNA synthesis, it plays a role in wound healing and maintenance of the intestinal mucosa. It is a coenzyme for over 100 enzymes, some of which are involved with the immune system, linear growth, hemoglobin synthesis, male fertility, and taste and smell. Deficiency of zinc has been reported in newly diagnosed and severely malnourished adults and children with CD [55, 56]. GF breads may not be routinely fortified with zinc.

Symptoms

Patients may complain of anorexia, fatigue, depression, diarrhea, and compromised taste and smell discrimination. Physical exam may reveal hypothyroidism, short stature, white spots in the nail beds, and various skin rashes (psoriasis and eczema). As zinc is stored intracellularly, including in enterocytes, excessive amounts can be lost through diarrhea.

Diagnosis

Serum levels of zinc, red blood cells, and alkaline phosphatase can all be used as indices for zinc status [57]. Fractional absorption of oral or IV zinc isotopes can be used as a research tool for measuring gut integrity [58].

Treatment

Food products containing zinc include meats, fish, shellfish (especially oysters), and nuts, beans, and seeds. The supplement is readily available over the counter as either separate pills or in multivitamins. Zinc absorption is increased by red wine and decreased by copper, iron, calcium, folic acid, and phytates from plants (corn, rice) [59]. Toxicity with zinc has been associated with nausea, and emesis is rare if more than 100 mg a day are ingested. Given the competition of cooper and zinc for binding sites in the gut lining, zinc excess can cause copper deficiency.

Selenium

Background

Selenium is absorbed in the proximal small bowel. Severe GI malabsorptive disorders, such as CD, may result in its depletion or deficiency [60]. This nutrient is important for the function of muscle, the immune system, and thyroid hormone.

Symptoms

Although rare in the USA, three specific conditions have been reported with severe selenium deficiency: Keshan disease (enlarged heart with poor function in children), Kashin–Beck disease (osteoarthropathy), and myxedematous endemic cretinism (hypothyroidism with mental retardation) [61].

Diagnosis

CD patients deficient in selenium may complain of generalized fatigue and muscle weakness. Physical exam and labwork may reveal low serum selenium levels, hypertension, cardiomyopathy, elevated transaminases, autoimmune thyroid disease, and perhaps even psychiatric manifestations (schizophrenia) [62, 63].

Treatment

Selenium is found in high amounts in nuts (Brazil nuts), beans, organ meats (kidney, liver), fish, shellfish, and mushrooms. GFD sources include products made from corn and rice flour where the grains were grown in selenium-rich soil [64]. As opposed to zinc, selenium toxicity (selenosis) is relatively easy to develop, with symptoms including diarrhea, fatigue, nerve damage, and brittle hair and nails [65, 66].

Copper

Background

Copper deficiency can be seen in severe malabsorption states, but it is uncommonly screened for in CD. One report describes five CD patients with neurologic complaints, three of which also had hematological abnormalities due to copper deficiency [67].

Symptoms

The most common complaints of copper deficiency are neurologic and include ataxia and sensory loss in the limbs which could be confusing in the CD patient who may present with diverse neurological sequale [68]. Hypochromic anemia (despite iron sufficiency), neutropenia, and thrombocytopenia may present as fatigue, increased infections, and easy bruising and bleeding. Other findings include bone and joint issues, osteoporosis, and changes in skin color [67].

Diagnosis

Serum copper and ceruloplasmin (the major copper carrying protein) can be used to measure levels. A CBC with differential may show the above hematologic abnormalities.

Treatment

Dietary copper comes from liver, shellfish, legumes, chocolate, nuts, and sun-dried tomatoes. Oral copper sulfate is usually adequate to correct mild deficiencies seen in malabsorption. Parenteral copper histidine can be given subcutaneously for severe deficiency. Most copper in the blood is bound to proteins. Free copper is toxic, and overdose results in nausea, vomiting, diarrhea, and even fatal kidney and liver disease. Absorption is decreased by taking zinc and calcium. A hidden source of zinc is denture creams which are frequently ingested by consumers in significant and toxic quantities enough to cause serious sequale [69].

Calcium

Background

Calcium deficiency is common in untreated CD, as its ionized form is actively transported through the duodenum. Comorbid vitamin D deficiency, as described prior, also decreases calcium absorption. A 3-day diet history showed that less than one-third of females with CD consumed the daily-recommended amounts of calcium [10].

Symptoms

Oral paresthesias are often the earliest symptom of hypocalcemia. Acutely low levels of serum calcium are associated with muscle cramps and mental status changes (anxiety and insomnia). Severe hypocalcemia can be life threatening, and is associated with bone pain, convulsions, arrhythmias, tetany, and numbness of the extremities.

Diagnosis

Measurements of total serum calcium, ionized calcium, albumin, magnesium, phosphorus, PTH, and vitamin D can be revealing for the etiology of hypocalcemia. On physical exam, hyperactive tendon reflexes, Trousseau sign (carpal spasm with inflation of the blood pressure cuff), and Chvostek's sign (facial spasms with tapping the cheek) may be elicited. Other physical findings can include petechiae, purpura, and hand tetany. EKG may reveal intermittent prolongation of the QTc, which puts the patient at risk for torsades de pointes, a specific type of ventricular fibrillation. Skeletal radiographs and bone density measurements may reveal rickets, osteopenia, or osteoporosis (see subsequent section "Issues in Bone Health in CD").

Treatment

Calcium-rich foods include dairy products (milk, yogurt, cheese, ice cream), dark-green leafy vegetables (broccoli, spinach, bok choy), boney fish (salmon, sardines), firm tofu, and those which are fortified (orange juice, soymilk, some juices). Vitamin D helps with the absorption of calcium. Intestinal absorption of calcium is interfered by the ingestion of soda, proton pump inhibitors, and diets high in fiber, phytic acid (whole grains), and oxalic acid (green vegetables, berries, nuts, grains, and seeds) [70–73]. Oral calcium citrate and calcium carbonate are available and are dosed by sex, age, and severity of deficiency, along with vitamin D supplementation. For severe, life-threatening, acute hypocalcemia, IV calcium gluconate and calcium chloride can be used. Excessive calcium ingestion can interfere with the absorption of iron, magnesium, and manganese. Hypercalcemia leads to nausea, vomiting, constipation, delirium, kidney stones, and excessive calcification of the soft tissues [74].

Magnesium

Background

Hypomagnesima occurs commonly in CD due to both malabsorption and inadequate dietary intake from the GFD, which is naturally low in this mineral. Most magnesium is absorbed, along with fat, in the jejunum. Multiple studies have shown

inadequate dietary intake of magnesium in both newly diagnosed CD patients and those who have been on the GFD for years [12, 75, 76].

Symptoms

Magnesium is important in all nerve conduction and muscle contraction, including those in the heart and GI tract. Patients may complain of vague symptoms, including anorexia, fatigue, vomiting, constipation, insomnia, anxiety, and depression. Chronic deficiency contributes to hypertension, osteoporosis, impaired PTH secretion (leading to hypocalcemia), hypertension, and myocardial ischemia and dysrhythmias [77, 78].

Diagnosis

Serum magnesium, calcium, PTH, and fat-soluble vitamins may be measured concomitantly. In research studies, magnesium status has been examined by intravenous Mg loading test, serum and erythrocyte magnesium concentrations, and urinary excretion [75]. Bone density measurements may reveal osteoporosis (see subsequent section "Issues in Bone Health in CD").

Treatment

Foods that naturally contain magnesium include seafood, nuts, and beans. Patients with CD should embrace GF dietary sources such as buckwheat, quinoa, amaranth, and flours made from soy, corn, and brown rice. Oral supplements are available as liquid, powder, and capsules and are dosed based upon sex and age. A parenteral form can be used for severe deficiency. Hypermagnesemia can occur with supplements, with symptoms such as diarrhea and lethargy. Drugs that inhibit magnesium absorption include proton pump inhibitors, some antibiotics, diuretics, warfarin, steroids, cyclosporin, and oral contraceptives. Fortification of GF foods with magnesium should be considered [12, 79, 80].

Fiber

Background

Patients on the GFD often go "fiber-free" when they eat "gluten-free." One study reported that less than half of the females surveyed during a 3-day GFD history consumed the daily-recommended amounts of fiber [10]. In addition, the dietary

fiber content of GF cereals do not compare favorably to gluten-containing flours, breads, and pastas made from whole wheat sources [11].

Symptoms

CD patients who do not get enough fiber in their diet will often complain of constipation, nausea, fatigue, and irritable bowel syndrome-like symptoms. Since fiber contributes to satiety, and non-fiber carbohydrates are more easily absorbed and digested, weight gain may also be an issue. Studies show that a diet high in whole grains is preventative for diabetes, hypertension, cancer, and hypercholesterolemia.

Diagnosis

Patients may appear bloated and distended, as well as have hemorrhoids, due to constipation. A flat plate X-ray of the abdomen may reveal obstipation.

Treatment

It is recommended that adults consume at least 25 g of fiber per day. The two most commonly prescribed fiber supplements include psyllium and inulin/fructo-oligosaccharide containing compounds (prebiotics). Other sources include cellulose, dextrins, guar gum, and acacia fibers. Gluten-free dietary sources of fiber should be strongly encouraged as part of the GFD. Fruits, vegetables, and legumes are excellent sources of fiber. Gluten-free sources include enriched, fortified, whole grain gluten-free cereals and breads and pastas made from brown rice, bean flour, corn, millet, nuts, quinoa, buckwheat, teff, tapioca, amaranth, flax, soybean, and sorghum [11]. Unfortunately, products made from these inherently gluten-free grains, seeds, and flours can become contaminated with wheat, barley, or rye anywhere from the field to the packaging plant, making them unsafe for those on a GFD [81]. Improvements in gluten-free labeling, as per the "Food Allergen Labeling and Consumer Protection Act of 2004 (Title II of Public Law 108–282)" will hopefully address these issues with contamination [82].

It remains controversial whether or not oats should be eliminated from the GFD. The prolamin of oats, avenin, only accounts for 5–15 % of the total seed protein. This is in marked contrast to gliadin, which comprises about 50 % of the wheat protein [83]. Since avenin does not elicit the same immune response as gliadin, it is thought by some to be safe for patients with CD to ingest. Children with newly diagnosed CD in a U.S. study were provided oats as part of the GFD and demonstrated symptomatic and histologic resolution of the disease comparable to those who were denied oats [84]. However, since oats are often crop rotated, harvested, and milled with wheat, the risk for contamination with wheat gluten is potentially somewhat greater than with other grains such as quinoa.

Are Probiotics Useful in CD?

Background

The intestinal barrier plays an important role in various inflammatory diseases of the GI tract, including CD. Alterations in the intestinal microbiota that are normally involved in gut-associated lymphoid tissue (GALT) homeostasis may also play a role in CD [85]. Probiotics have shown benefit in a number of disorders such as ulcerative colitis, antibiotic-associated diarrhea, *Clostridium difficle* colitis, infectious diarrheas, and the irritable bowel syndrome (IBS), but not specifically in CD in humans to date. Basic science studies show that specific probiotics may have preservative effects on the intestinal epithelial barrier in regard to increasing mucus, defensins, and tight junction protein expression, and an inhibition of epithelial apoptosis, proinflammatory cytokines, and pathogenic bacterial adhesion [86].

A combination of bacterial probiotic supplement, VSL#3, has shown ability to decrease the toxicity of wheat flour by completely hydrolyzing the alpha2-gliadin-derived epitopes 62–75 and 33-mer *in vitro* [87]. The probiotic *yeast Saccharomyces boulardii* has been shown to hydrolyze the 28-kDa-gliadin fraction and improve enteropathy and inflammation in gluten sensitive mice [88].Oral administration of probiotic bacteria *Lactobacillus casei* induced a complete recovery of villus blunting and improved GALT homeostasis in a mouse model of gliadin-induced enteropathy [85]. As reviewed in Chap. 7, dysbiosis may be a key etiologic factor in the pathobiology of CD.

Symptoms

Symptoms of IBS and dysbiosis such as small intestine bacterial overgrowth (SIBO) commonly include gassiness, bloating, diarrhea, and abdominal distension.

Diagnosis

SIBO can be measured by breath hydrogen testing or via culture of jejunal aspirates obtained during endoscopy.

Treatment

Probiotics can be ingested via foods and supplements. Fermented products containing live active cultures, such as yogurts with Bifidobacteria and *Lactobacillus* strains, can alleviate IBS symptoms. Oral probiotic bacterial and yeast supplements in sachets, liquids, and capsule form are commonly available that promote “GI health.”

Issues for Bone Health in CD

Background

Low bone density is a common morbidity in CD, and it can lead to vertebral fractures, kyphosis, hip fractures, and Colles fracture of the lower radius. One review summarized the published literature to state that, at diagnosis, approximately one-third of adult CD patients have osteoporosis, one-third have osteopenia, and one-third have normal bone mineral density [89]. Although osteopenia can begin in early childhood, prompt initiation of the GFD can halt progression, and may even reverse bone loss and low height velocity in pediatric patients [90–92]. Severe osteoporosis, however, from CD diagnosed late in life will not improve on the GFD and puts the patient at increased risk of fracture over the general population [93]. The prevalence of CD among osteoporotic individuals has been reported as high as 17-fold higher than among nonosteoporotic individuals, justifying a recommendation to screen all those with low bone density for CD [94].

Diagnosis

Bone density should be measured in newly diagnosed CD, as numerous studies have documented low bone density in both children and adults at the time of initial diagnosis. Plain bone radiographs may reveal osteopenia, but this is not a sensitive measure of bone density. Bone mineral density can be measured via dual-energy X-ray absorptiometry (DXA, previously DEXA) or quantitative CT (QCT) of the spine and femur. Abnormal scans should be repeated 1–2 years after initiation of the GFD. Serum measurements of calcium, phosphorus, albumin, copper, and vitamins A, D, and K (as outlined prior) and 24 h urine calcium can reveal specific nutrient deficiencies [89]. Parathyroid hormone (PTH) may be high due to hypocalcemia (secondary hyperparathyroidism) [95]. Serum alkaline phosphatase may be elevated due to a high bone fraction.

Treatment

The most important treatment for CD-associated bone disease in both pediatrics and adults is the GFD [96]. The GFD can improve bone mineral health even in postmenopausal women and those with incomplete mucosal recovery [97]. Oral calcium, magnesium, and vitamin D supplements may be prescribed. Impact sports and weight-bearing exercises can also improve bone density. Moderation of alcohol and caffeine, and cessation of smoking, also improves bone health. Supplemental antiresorptives, which prevent excessive bone remodeling (bisphosphonates, estrogen

replacement, selective estrogen receptor modulators [raloxifene], and denosumab (a human antibody that inactivates RANKL)), may be required in those at high fracture risk despite the GFD such as postmenopausal women and older men [89, 98].

Special Issues for Women: Pregnancy and Fertility

CD is diagnosed at a higher rate in women than in men [99]; however, a large serologic screening in the USA showed that the prevalence rates in both sexes are the same [100].

Background

Women with CD have been reported older at menarche, younger at menopause, having a lower mean number of children, and having more spontaneous miscarriages [101]. GFD in CD women reduced the relative risk of abortion ninefold, reduced the number of low birth weight babies from 29 % to zero ($p<0.05$), and increased duration of breast-feeding twofold [102].

Symptoms

Failure to follow a GFD during pregnancy can have effects on the fetus, including increased risk for spina bifida and other neural tube defects due to poor folic acid absorption [103]. The fatigue associated with iron-deficiency anemia can make pregnancy and newborn care more difficult. Depression in CD can interfere with maternal-child bonding. Duration of breast-feeding has been reported to be three times shorter in untreated mothers with CD [102]. Low levels of maternal plasma zinc are associated with toxemia, vaginitis, prolonged labor, and a history of previous stillbirth [57].

Diagnosis

Serology for CD should be performed in idiopathic infertility cases, as initiation of a GFD during pregnancy can decrease the risk of spontaneous abortions and low birth weight infants [102, 104]. Levels of the above vitamins and nutrients, especially iron, folate and zinc, should be measured in the pregnant women with CD [99, 102].

Treatment

Women with known CD should follow a strict GFD during pregnancy and ensure that iron, folic acid, zinc, calcium, B and D vitamins, and gluten-free sources of fiber are included in the diet (or supplemented) in addition to routine prenatal vitamins. Supplementing magnesium and calcium may decrease the risk of preeclampsia (high blood pressure, proteinuria, edema) [105]. In the GFD, the major source of dietary folic acid is lost because fortified commercial cereals, breads, and pasta products are excluded. Without supplementation during the child-bearing years, women with CD might not receive enough dietary folate to maintain protective levels against neural tube defects [106]. Fortification of gluten-free foods with folate should be considered.

Nutritional Issues in Refractory Celiac Disease

Background

A minority of CD patients will continue to have GI symptoms and biopsy-proven enteropathy, despite vigorous adherence to the GFD.

Symptoms

Patients with refractory celiac disease (RCD) have profound diarrhea and malabsorption, exhibiting many of the nutritional deficiencies described prior in this chapter.

Diagnosis

Non-adherence to the GFD accounts for the majority of patients who are not better on the GFD. In those unresponsive to the GFD, a thorough dietary history should exclude inadvertent gluten ingestion; compliance should be assessed with serum antibodies; workup including endoscopic evaluation should be performed to exclude other causes of continued symptoms despite strict compliance with a GFD [2, 107].

Treatment

In addition to the GFD, these patients often require immunosuppression with steroids, azathioprine, cyclosporine, and methotrexate [107–112]. Oral or parenteral supplementation with iron, copper, magnesium, folic acid, zinc, and albumin has been used with some benefit. With proven osteopenia (and steroid use), vitamin D, calcium, and biphosphonates have been utilized [113, 114]. A 4-week elemental (amino acid-based) diet has been shown in one study to reduce inflammatory cytokines and improve clinical symptoms, histology, and serum albumin in RCD [115]. If malabsorption and weight loss are severe, total parenteral nutrition may be required [107].

References

1. Rubin CE, Brandborg LL, Flick AL. Biopsy studies on the pathogenesis of celiac sprue. In: Wolstenholme GEW, Cameron CM, editors. Intestinal biopsy. Boston: Little, Brown & Co; 1962. p. 67.
2. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. Gastrointest Endosc. 2003;57:187–91.
3. Hankey GL, Holmes GK. Coeliac disease in the elderly. Gut. 1994;35:65–7.
4. Pietzak M. The follow-up of patients with celiac disease – achieving compliance with treatment. Gastroenterology. 2005;128:S135–41.
5. Ljungman G, Myrdal U. Compliance in teenagers with coeliac disease—a Swedish follow-up study. Acta Paediatr. 1993;82:235–8.
6. Mäki M, Lähdehaho ML, Hällström O, Viander M, Visakorpi JK. Postpubertal gluten challenge in coeliac disease. Arch Dis Child. 1989;64:1604–7.
7. Carroccio A, Iannitto E, Cavataio F, Montalto G, Tumminelo M, Campagna P, et al. Sideropenic anemia and celiac disease: one study, two points of view. Dig Dis Sci. 1998;43:673–8.
8. Wessling-Resnick M. Iron transport. Annu Rev Nutr. 2000;20:129–51.
9. Harper JW, Holleran SF, Ramakrishnan R, Bhagat G, Green PHR. Anemia in celiac disease is multifactorial in etiology. Am J Hematol. 2007;11:996–1000.
10. Thompson T, Dennis M, Higgins LA, Lees AR, Sharrett MK. Gluten-free diet survey: are Americans with celiac disease consuming recommended amounts of fibre, iron, calcium and grain foods? J Hum Nutr Dietet. 2005;18:163–9.
11. Thompson T. Folate, iron, and dietary fiber contents of the gluten-free diet. J Am Diet Assoc. 2000;100:1389–96.
12. Shepherd SJ, Gibson PR. Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease. J Hum Nutr Diet. 2012. doi:10.1111/jhn.12018.
13. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press; 2001.
14. Hofmann AF, Borgström B. The intraluminal phase of fat digestion in man: the lipid content of the micellar and oil phases of intestinal content obtained during fat digestion and absorption. J Clin Invest. 1964;43(2):247.
15. Carroccio A, Iacono G, Lerro P, Cavataio F, Malorgio E, Soresi M, et al. Role of pancreatic impairment in growth recovery during gluten-free diet in childhood celiac disease. Gastroenterology. 1997;112:1839–44.

16. Ross CA. Vitamin A. In: Coates PM, Betz JM, Blackman MR, editors. Encyclopedia of dietary supplements. 2nd ed. London: Informa Healthcare; 2010. p. 778–91.
17. Alberts D, Ranger-Moore J, Einspahr J. Safety and efficacy of dose-intensive oral vitamin A in subjects with sun-damaged skin. Clin Cancer Res. 2004;10:1875–80.
18. National Institutes of Health, Office of Dietary Supplements. Facts about dietary supplements: vitamin A and carotenoids. Bethesda: National Institutes of Health; December 2001.
19. Ribaya-Mercado JD, Blumber JB. Vitamin A: is it a risk factor for osteoporosis and bone fracture? Nutr Rev. 2007;65(10):425–38.
20. Sommer A. Vitamin A, deficiency and clinical disease: an historical overview. J Nutr. 2008;138:1835–9.
21. World Health Organization. Global prevalence of vitamin A deficiency in populations at risk 1995–2005: WHO global database on vitamin A deficiency. Geneva: World Health Organization; 2009.
22. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000.
23. Neuhouser ML, Barnett MJ, Kristal AR, Ambrosone CB, King IB, Thornquist M, et al. Dietary supplement use and prostate cancer risk in the carotene and retinol efficacy trial. Cancer Epidemiol Biomarkers Prev. 2009;18:2202–6.
24. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001;119:1417–36.
25. Ross A. Vitamin A and carotenoids. In: Shils M, Shike M, Ross A, Caballero B, Cousins R, editors. Modern nutrition in health and disease. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2006. p. 351–75.
26. Villamor E, Fawzi WW. Vitamin A supplementation: implications for morbidity and mortality in children. J Infect Dis. 2000;182 Suppl 1:S122–33.
27. Traber MG. Vitamin E. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins R, editors. Modern nutrition in health and disease. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2006. p. 396–411.
28. Kowdley KV, Mason JB, Meydani SN, Cornwall S, Grand RJ. Vitamin E deficiency and impaired cellular immunity related to intestinal fat malabsorption. Gastroenterology. 1992;102:2139–42.
29. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol. 1994;139:1180–9.
30. Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, et al. Supplemental and dietary vitamin E, β-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst. 2006;98:245–54.
31. Bostick RM, Potter JD, McKenzie DR, Sellers TA, Kushi LH, Steinmetz KA, et al. Reduced risk of colon cancer with high intakes of vitamin E: the Iowa women's health study. Cancer Res. 1993;15:4230–17.
32. Jacobs EJ, Henion AK, Briggs PJ, Connell CJ, McCullough ML, Jonas CR, et al. Vitamin C and vitamin E supplement use and bladder cancer mortality in a large cohort of US men and women. Am J Epidemiol. 2002;156:1002–10.
33. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Opthalmol. 2011;119:1439–52.
34. Sokol RJ, Guggenheim MA, Heubi JE. Frequency and clinical progression of the vitamin E deficiency neurologic disorder in children with prolonged neonatal cholestasis. Am J Dis Child. 1985;139(12):1211–5.
35. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA. 2007;297:842–57.

36. Dietrich M, Traber MG, Jacques PF, Cross CE, Hu Y, Block G. Does γ-tocopherol play a role in the primary prevention of heart disease and cancer? A review. Am J Coll Nutr. 2006;25:292–9.
37. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academy Press; 2010.
38. Wharton B, Bishop N. Rickets. Lancet. 2003;362:1389–400.
39. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001;358:1500–3.
40. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care. 2006;29:650–6.
41. Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. Lancet. 1998;352:709–10.
42. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004;79:820–5.
43. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006;296:2832–8.
44. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag K. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa women's health study. Arthritis Rheum. 2004;50:72–7.
45. Hollis BW, Wagner CL. Normal serum vitamin D levels. N Engl J Med. 2005;352(5):515–6.
46. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. Am J Clin Nutr. 2004;80:1710S–6S.
47. LeBlanc ES, Perrin N, Johnson JD, Ballatore A, Hillier T. Over-the-counter and compounded vitamin D: is potency what we expect? JAMA Intern Med. 2013;173(7):585–6.
48. Udall JA. Human sources and absorption of vitamin K in relation to anticoagulation stability. JAMA. 1965;194(2):127–9.
49. Ozdemir MA, Karakukcu M, Per H, Unal E, Gumus H, Patiroglu T. Late-type vitamin K deficiency bleeding: experience from 120 patients. Childs Nerv Syst. 2012;28(2):247–51.
50. Vermeer C, Theuwissen E. Vitamin K, osteoporosis and degenerative diseases of ageing. Menopause Int. 2011;17(1):19–23.
51. Krasinski SD, Russell RM, Furie BC. The prevalence of vitamin K deficiency in chronic gastrointestinal disorders. Am J Clin Nutr. 1985;41(3):639–43.
52. Suttie JW. Vitamin K. In: Machlin L, editor. Handbook of vitamins. New York: Marcel Dekker; 1984. p. 147.
53. Sdepanian VL, de Miranda Carvalho CN, de Morais MB, Colugnati FA, Fagundes-Neto U. Bone mineral density of the lumbar spine in children and adolescents with celiac disease on a gluten-free diet in São Paulo, Brazil. J Pediatr Gastroenterol Nutr. 2003;37(5):571–6.
54. Krebs NF. Overview of zinc absorption and excretion in the human gastrointestinal tract. J Nutr. 2000;130:1374S–7S.
55. Singhal N, Alam S, Sherwani R, Musarrat J. Serum zinc levels in celiac disease. Indian Pediatr. 2008;45(4):319–21.
56. Solomons NW, Rosenberg IH, Sandstead HH. Zinc nutrition in celiac sprue. Am J Clin Nutr. 1976;29(4):371–5.
57. Lazebnik N, Kuhnert BR, Kuhnert PM, Thompson KL. Zinc status, pregnancy complications, and labor abnormalities. Am J Obstet Gynecol. 1988;158(1):161–6.
58. Tran CD, Katsikeros R, Manton N, Krebs NF, Hambidge KM, Butler RN, et al. Zinc homeostasis and gut function in children with celiac disease. Am J Clin Nutr. 2011;94(4):1026–32.
59. Lonnerdal B. Dietary factors influencing zinc absorption. J Nutr. 2000;130:1378S–85S.
60. Rannem T, Ladefoged K, Hylander E, Hegnhoj J, Staun M. Selenium depletion in patients with gastrointestinal diseases: are there any predictive factors? Scand J Gastroenterol. 1998;33:1057–61.
61. National Institutes of Health Office of Dietary Supplements. Dietary Supplement Fact Sheet: Selenium. http://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/#en20.

62. Stazi AV, Trinti B. Selenium deficiency in celiac disease: risk of autoimmune thyroid diseases [Article in Italian]. Minerva Med. 2008;99(6):643–53.
63. Brown JS, Foster HD. Schizophrenia: an update of the selenium deficiency hypothesis. J Orthomol Med. 1996;11(400):211–2.
64. Longnecker MP, Taylor PR, Levander OA, Howe M, Veillon C, McAdam PA, et al. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. Am J Clin Nutr. 1991;53:1288–94.
65. Koller LD, Exon JH. The two faces of selenium-deficiency and toxicity are similar in animals and man. Can J Vet Res. 1986;50:297–306.
66. Goldhaber SB. Trace element risk assessment: essentiality vs. toxicity. Regul Toxicol Pharmacol. 2003;38:232–42.
67. Halfdanarson TR, Kumar N, Hogan WJ, Murray JA. Copper deficiency in celiac disease. J Clin Gastroenterol. 2009;43(2):162–4.
68. Goodman PB, Mistry MD. Copper deficiency myeloneuropathy due to occult celiac disease. Neurologist. 2009;15(6):355–6.
69. Hedera P, Peltier A, Fink JK, Wilcock S, London Z, Brewer GJ. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin II. The denture cream is a primary source of excessive zinc. Neurotoxicology. 2009 Nov;30(6):996–9.
70. Kopic S, Geibel JP. Gastric acid, calcium absorption, and their impact on bone health. Physiol Rev. 2013;93(1):189–268.
71. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947–53.
72. Krittaphol W, Bailey KB, Pongcharoen T, Winichagoon P, Gibson RS. Low zinc, iron, and calcium intakes of Northeast Thai school children consuming glutinous rice-based diets are not exacerbated by high phytate. Int J Food Sci Nutr. 2006;57(7–8):520–8.
73. Thomas E, von Unruh GE, Hesse A. Influence of a low- and a high-oxalate vegetarian diet on intestinal oxalate absorption and urinary excretion. Eur J Clin Nutr. 2008;62(9):1090–7.
74. Legrand SB. Modern management of malignant hypercalcemia. Am J Hosp Palliat Care. 2011;28(7):515–7.
75. Rujner J, Socha J, Syczewska M, Wojtasik A, Kunachowicz H, Stolarczyk A. Magnesium status in children and adolescents with coeliac disease without malabsorption symptoms. Clin Nutr. 2004;5:1074–9.
76. Wild D, Robins GG, Burley VJ, Howdle PD. Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. Aliment Pharmacol Ther. 2010;32(4):573–81.
77. al-Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis. 1994;24(5):737–52.
78. Ramsay JG. Cardiac management in the ICU. Chest. 1999;115(5):138S–44S.
79. Horn EJ. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis. 2010;56(1):112–6.
80. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci. 2011;56(4):931–50.
81. Thompson T, Lee AR, Grace T. Gluten contamination of grains, seeds, and flours in the United States: a pilot study. J Am Diet Assoc. 2010;110(6):937–40.
82. Pietzak M. Gluten-free food labeling in the United States. J Pediatr Gastroenterol Nutr. 2005;41(5):567–8.
83. Holmes G, Catassi C, editors. Coeliac disease. Oxford: Health Press; 2000.
84. Hoffenberg EJ, Haas J, Drescher A, Barnhurst R, Osberg I, Bao F, et al. A trial of oats in children with newly diagnosed celiac disease. J Pediatr. 2000;137:361–6.
85. D'Arienzo R, Stefanile R, Maurano F, Mazzarella G, Ricca E, Troncone R, et al. Immunomodulatory effects of Lactobacillus casei administration in a mouse model of gliadin-sensitive enteropathy. Scand J Immunol. 2011;74(4):335–41.
86. Mennigen R, Bruewer M. Effect of probiotics on intestinal barrier function molecular structure and function of the tight junction. Ann NY Acad Sci. 2009;1165:183–9.

87. De Angelis M, Rizzello CG, Fasano A, Clemente MG, De Simone C, Silano M, et al. VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for celiac sprue. Bioenergetics. 2006;1762(1):80–93.
88. Papista C, Gerakopoulos V, Kourelis A, Sounidaki M, Kontana A, Berthelot L, et al. Gluten induces coeliac-like disease in sensitised mice involving IgA, CD71 and transglutaminase 2 interactions that are prevented by probiotics. Lab Invest. 2012;92(4):625–35.
89. Fouda MA, Khan AA, Sultan MS, Rios LP, McAssey K, Armstrong D. Evaluation and management of skeletal health in celiac disease: position statement. [Review]. Can J Gastroenterol. 2012;26(11):819–29.
90. Valdimarsson T, Lofmano O, Toss G, Strom M. Reversal of osteopenia with diet in adult coeliac disease. Gut. 1996;38:322–7.
91. Mora S, Barera G, Beccio S, Proverbio MC, Weber G, Bianchi C, et al. Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. Am J Gastroenterol. 1999;94:398–403.
92. Prader A, Tanner JM, von Harnack GA. Catch-up growth in coeliac disease. Acta Paediatr Scand. 1969;58:311.
93. Meyer D, Stavropolous S, Diamond B, Shane E, Green PH. Osteoporosis in a North American adult population with celiac disease. Am J Gastroenterol. 2001;96:112–9.
94. Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. Arch Intern Med. 2005;165:393–9.
95. Valdimarsson T, Toss G, Löfman O, Ström M. Three years' follow-up of bone density in adult coeliac disease: significance of secondary hyperparathyroidism. Scand J Gastroenterol. 2000;35:274–80.
96. Mora S, Barera G, Beccio S, Menni L, Proverbio MC, Bianchi C, et al. A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. J Pediatr. 2001;139:516–21.
97. Sategna-Guidetti C, Grosso SB, Grosso S, Mengozzi G, Aimo G, Zaccaria T, et al. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult coeliac disease patients. Aliment Pharmacol Ther. 2000;14:35–43.
98. Recker RR, Armas L. The effect of antiresorptives on bone quality. Clin Orthop Relat Res. 2011;469(8):2207–14.
99. Danowski L, Brand LG, Connolly J. Selections from current literature: gluten-free diets, coeliac disease and associated disorders. Fam Pract. 2003;20:607–11.
100. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S. Prevalence of celiac disease in at-risk and not at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163:286–92.
101. Sher KS, Mayberry JF. Female fertility, obstetric and gynaecological history in coeliac disease: a case control study. Acta Paediatr Suppl. 1996;412:76–7.
102. Ciacci C, Cirillo M, Auriemma G, Di Dato G, Sabbatini F, Mazzacca G. Celiac disease and pregnancy outcome. Am J Gastroenterol. 1996;91:718–22.
103. Wald NJ, Hackshaw AD, Stone R. Blood folic acid and vitamin B12 in relation to neural tube defects. Br J Obstet Gynaecol. 1996;103(4):319–24.
104. Kumar A, Meena M, Begum N, Kumar N, Gupta RK, Aggarwal S, et al. Latent celiac disease in reproductive performance of women. Fertil Steril. 2011;95(3):922–7.
105. Zerfu TA, Ayele KT. Micronutrients and pregnancy; effect of supplementation on pregnancy and pregnancy outcomes: a systematic review. Nutr J. 2013;12:20.
106. Hancock R, Koren G. Celiac disease during pregnancy. Can Fam Physician. 2004;50:1361–3.
107. Daum S, Cellier C, Mulder CJJ. Refractory coeliac disease. Best Pract Res Clin Gastroenterol. 2005;19:413–24.
108. Stuart BM, Gent AE. Atrophy of the coeliac mucosa. Eur J Gastroenterol Hepatol. 1998;10:523–5.

109. Mitchison HC, al Mardini H, Gillespie S. A pilot study of fluticasone propionate in untreated coeliac disease. Gut. 1991;32:260–5.
110. Vaidya A, Bolanos J, Berkelhammer C. Azathioprine in refractory sprue. Am J Gastroenterol. 1999;94:1967–9.
111. Rolny P, Sigurjonsdottir HA, Remotti H. Role of immunosuppressive therapy in refractory sprue-like disease. Am J Gastroenterol. 1999;94:219–25.
112. O'Mahony S, Howdle PD, Losowsky SM. Management of patients with non-responsive coeliac disease. Aliment Pharmacol Ther. 1996;10:671–80.
113. Mulder CJ, Wahab PJ, Moshaver B, Meijer JW. Refractory coeliac disease: a window between coeliac disease and enteropathy associated T cell lymphoma. Scand J Gastroenterol Suppl. 2000;232:32–7.
114. Love A, Elmes M, Golden M, McMaster D. Zinc deficiency and coeliac disease. In: McNicholl B, McCarthy C, Fottrell P, editors. Perspectives in coeliac disease. Lancaster: MTP; 1978. p. 335–42.
115. Olaussen RW, Løvik A, Tollefsen S, Andresen PA, Vatn MH, De Lange T, et al. Effect of elemental diet on mucosal immunopathology and clinical symptoms in type 1 refractory celiac disease. Clin Gastroenterol Hepatol. 2005;3(9):875–85.