Nutritional Deficiencies in Vegetarian, Gluten-Free, and Ketogenic Diets

Erik Andrewski, MD,* Katherine Cheng, MD,† Charles Vanderpool, MD*

*Riley Hospital for Children and Indiana University School of Medicine, Indianapolis, IN
†UCSF Benioff Children's Hospital, San Francisco, CA

EDUCATION GAPS

Pediatricians should be aware of the increased prevalence of infants, children, and young adults on restrictive diets, including vegan, ketogenic, and gluten-free diets. Although inadequately monitored vegetarian and gluten-free diets can lead to poor growth, the ketogenic diet carries severe risks, including hypoglycemia and cardiomyopathy, if not managed properly.

OBJECTIVES *After completing this article, readers should be able to:*

1. Understand medical indications for a gluten-free or ketogenic diet.
2. Recognize presenting signs and symptoms of nutritional deficiencies associated with the vegetarian, gluten-free, and ketogenic diets.
3. Gain knowledge regarding dietary changes and common foods or fortified products that can help reduce the risk of deficiency.

ABSTRACT

Previously, medical diets, including the ketogenic and gluten-free diets, were rare outside of their target population. Subspecialists more familiar with risks and benefits often managed nutrition and any associated shortcomings. With more patients electively following a gluten-free or ketogenic diet for nonmedical needs, as well as the increasing prevalence of vegetarian diets, general pediatricians are seeing more followers of restrictive diets with general well-child care. Increasingly, general pediatricians can be the first provider to witness presenting signs or symptoms of associated nutritional deficiencies. This article reviews signs and symptoms of possible nutrient deficiencies seen with the vegetarian, ketogenic, and gluten-free diets.

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ABBREVIATIONS

AA	amino acid
AED	antiepileptic drug
CD	celiac disease
DHA	docosahexaenoic acid
DRI	dietary reference intake
GF	gluten-free
GFD	gluten-free diet
KD	ketogenic diet

INTRODUCTION

Adults and children can follow restrictive diets for various reasons, including medical necessity, perceived health benefits, trendiness, animal rights, environmental impact, or a desire for weight loss. Nearly half of American adults and 40% of teens report attempted weight loss annually. (1)(2) Various diets come in

and out of favor, with some originating as medical therapies for specific ailments or disease states. Ketogenic (KD), gluten-free (GFD), and vegetarian diets are generally safe when closely supervised by trained health-care providers. Patients adapting these diets regardless of reason could unknowingly place themselves at risk for nutrient deficiency without proper monitoring and supplementation. In contrast to vegetarian and GF diets, the KD is additionally associated with serious, and potentially lethal, adverse effects, including cardiac arrhythmia, growth failure, and nephrolithiasis, necessitating close supervision by a trained medical expert. (3) This article reviews common restrictive diets, with a focus on medical evidence for need and potential deficiencies that can be encountered with each diet.

KETOGENIC DIET

The KD was developed in the 1920s for treatment of seizures; although effective, the rigidity of the diet led to a steep drop in popularity after the introduction of antiepileptic drugs (AEDs) in the mid-20th century. (4) The KD enjoyed a recent resurgence in popularity after being found efficacious for seizure reduction or cessation in epileptic patients with seizures refractory to multiple frontline medications. The KD is also effective treatment for pyruvate dehydrogenase deficiency and glucose transporter type 1 deficiency. (5) Recently, the KD has been investigated for weight loss and management of type II diabetes mellitus. (3)

Diet

The KD consists of low carbohydrate intake, leading to ketosis; multiple regimens exist and are based on varying lipid-to-nonlipid ratios by weight, commonly 4:1 g, 3:1 g, or less. These ratios provide high fat, low carbohydrate, and adequate protein, with the ultimate goal to imitate a fasting state. (6) In the classic KD, nearly 90% of daily calorie intake is from fat. (7) Some patients may opt for an initial fast to achieve ketosis more quickly. Medium-chain triglycerides can be used and are more ketogenic than their long-chain counterparts, allowing for a more flexible ratio, but can be associated with increased rates of diarrhea, vomiting, and abdominal pain. (8) The Atkins diet, originally devised for weight loss, offers a less restrictive path to ketosis that is often equally effective for seizure management. (9) Children are allowed up to 30% of caloric intake from protein, 10% from carbohydrates, and the remaining 60% from fat. The increased protein and carbohydrate allowance is more palatable, and the increased flexibility allows consumption of school lunches or dining out. (9)(10) Irrespective of ratio, children on a KD are at increased risk for kidney stones due to hypercalciuria as a result of serum acidosis. (11)

Nutritional Deficiencies

Due to a decreased variety of food options, nutritional deficiencies, including thiamine, vitamin D, magnesium, phosphorous, copper, zinc, selenium, and carnitine, can be associated with the KD. Studies have shown the stricter the lipid-to-nonlipid ratio, the higher the likelihood of nutrient deficiencies, with children on a 4:1 ratio meeting only 3 of 28 daily dietary reference intakes (DRIs) and those on a 1:1 ratio meeting 12 of 28 DRIs. (5) KD plans can include specialty commercial formulas, solid foods, or a mixture of both. Typically, a multivitamin is prescribed with the diet, but none have been specifically designed to treat KD deficiencies, and supplementation varies among institutions. (12)

Selenium, a trace element found in high quantity in meats and grains, especially if grown in areas with high soil concentration, is required for the production of more than 25 proteins in humans and can be protective against some forms of cancer. (13)(14)(15) The typical KD is selenium-deficient, and without proper supplementation, serum levels can be depressed within a few months of KD initiation. Keshan disease, a cardiomyopathy, is a rare but serious complication of selenium deficiency. (16) Selenium-associated cardiomyopathy is caused by decreased action of the antioxidant enzyme glutathione peroxidase, leading to inflammation and tissue damage. (17) Restoration of appropriate levels can help prevent progression of the disease but will not reverse the damage. (18) Those with concurrent gastrointestinal disease are especially at risk.

Other minerals, including magnesium, phosphorous, and zinc, can be deficient in patients on a KD, with hair loss, diarrhea, or poor growth being notable symptoms of zinc deficiency. (7)(19)

Carnitine, a cofactor responsible for moving acyl–coenzyme A from the mitochondria to peroxisomes in long-chain fatty acid metabolism, is another possible deficiency associated with the KD. Nearly three-quarters of required daily value is obtained via diet, mostly from meat and dairy. (20) A carnitine deficiency would be particularly concerning for children on the KD due to its critical role in fatty acid oxidation. Studies of carnitine deficiency on a KD are sparse and limited by small sample size. When starting a KD, carnitine levels should be checked because

deficiency has been associated with hypoglycemia during the initial fast. During the maintenance phase, symptoms associated with secondary carnitine deficiency from a KD include mild muscle weakness, hypotonia, apathy, listlessness, anorexia, nausea or vomiting, and constipation. (21) In a prospective study, Coppola et al (22) found 11 patients who were simultaneously on carnitine-reducing AEDs and KD therapy and showed no deficiency after 3 and 12 months. The remainder of their cohort was exclusively on AED therapy, and carnitine deficiency was primarily associated with valproate use. In a second study, Berry et al (6) found that 18% of patients on a KD became carnitine-deficient, but no patients became symptomatic or had elevated alanine aminotransferase levels. Those who were deficient responded quickly to supplementation. Carnitine deficiency can be a rare complication of KD therapy, and serum levels likely do not need to be monitored unless patients become symptomatic. (21) Reassuringly, cardiomyopathy does not seem to be associated with secondary carnitine deficiency from a KD, unlike primary carnitine deficiency syndromes. (23)

Other possible deficiencies include a case report of pureed, homemade KD with insufficient copper causing neutropenia, which resolved with appropriate replacement therapy. (24) Two reports of optic neuropathy secondary to thiamine deficiency have also been reported. (25)

Interestingly, fat-soluble vitamin D deficiency has been found in patients on a KD and shown via imaging to lead to bone demineralization in this population. (26) Complicating these findings, most children on a KD are also treated with AEDs, a known cause of vitamin D deficiency. A lack of sufficient calcium, phosphorous, and magnesium in the KD can exacerbate the effects of low vitamin D. (5) Further study is needed to establish what proportion of deficiency can be attributed to diet alone.

VEGETARIAN DIET

Veganism, or avoidance of all animal products, is on the rise, with an estimated 2% of all Americans and 1% of children ages 8 to 18 years following this strict diet. (27)(28)(29) Vegetarians avoid all meat products, although some subtypes can eat fish, eggs, dairy, or honey (Fig 1). Although not strictly vegetarian, most macrobiotic dieters avoid red meats, poultry, butter, lard, eggs, and dairy entirely, and some followers allow rare consumption of fish. They also emphasize avoidance of genetically

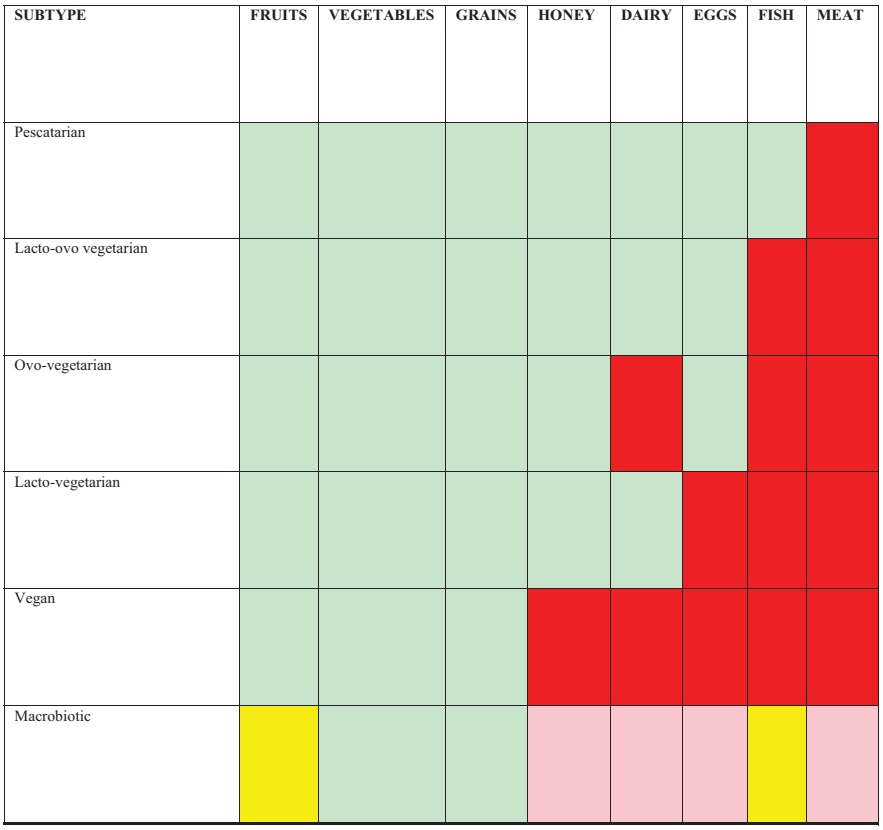


FIGURE 1. Subtypes of vegetarian diets. Green denotes no restrictions; yellow, limited consumption; pink, general avoidance; and red, total avoidance.

modified organisms and local sourcing of foods. (30) Their combined number is anticipated to grow as climate change, animal rights concerns, and perceived nutritional benefits lead more Americans to cease consuming some, or all, animal products. These diets have been described as safe for all life stages, including pregnancy, infancy, childhood, and adolescence, so long as they are "well-balanced." (31)

Nutritional Deficiencies and Adverse Effects

Vitamin, mineral, and macronutrient deficiencies have been reported in patients limiting animal product consumption.

Vitamin B_{12} is produced exclusively by microorganisms and found in high concentrations in animal product. Vitamin B_{12} deficiency is a well-known complication of veganism but can also be seen in nonvegans with low egg, dairy, fish, or meat intake; without adequate supplementation, deficits occur and can cause macrocytic anemia and neurologic deficits of the dorsal column. (32) One study followed strict macrobiotic vegan infants into adolescence; even after animal dietary product was reintroduced as teens, more than one-third continued to have depressed cobalamin levels, showing that transition in diet alone might not replete serum vitamin B_{12}. (33) Deficiency of vitamin B_{12} can also be seen in the breastfeeding infant of a vegan mother, and infant supplementation of vitamin B_{12} should be considered.

Vitamin D is essential for bone health, with fortified cow milk serving as a great source for children. This is not universally true of soy and nondairy milks, and the vitamin D content of cow milk substitutes should be confirmed (Table 1). A Polish study found that vegan patients had average vitamin D levels 50% under the lower limit of normal. (35) Another study comparing standard vegetarians and macrobiotic vegetarians stratified by animal food intake found stricter macrobiotic tendencies associated with lower vitamin D intakes. Overall, the macrobiotic group was severely vitamin D–deficient, averaging less than 50 IU of a recommended 400 IU daily intake. Eighty-eight percent consumed less than 100 IU per day, the minimum necessary for rickets prevention, compared with 18% of the control vegetarian group. (36) Cases of rickets in vegans consuming homemade formula or unfortified milk alternatives are not uncommon, with children at greatest risk in winter and early spring, when they are unable to synthesize vitamin D via sunlight exposure. (36)(37)(38)

Retinol, the active form of fat-soluble vitamin A, is exclusive to animal products; however, humans can convert other carotenoids, or members of the vitamin A family, to the active form. For those avoiding animal products, good sources of carotenoids include spinach, carrots, sweet potato and other yellow and orange fruits or vegetables. Provitamin carotenoids are measured in retinol activity equivalents and require a larger intake to meet daily goals than retinol. Vitamin A is essential for vision, skin health, immune function, and the developing embryo. (39)(40) If dietary intake of yellow and orange vegetables is low, supplementation should be considered.

Mineral deficiencies can arise from inadequate intake, decreased bioavailability, and high concentrations of oxalate and phytate. Phytate is a storage molecule commonly found in cereals, oil seeds, legumes, and nuts that acts as a reservoir of phosphorous, calcium, and magnesium. (41) Oxalate, a known contributor to kidney stones, is found in especially high concentration in taro root, beets, spinach, rhubarb, and sweet potato. (42) In the digestive tract, phytate and oxalate can complex with divalent cations, rendering them poorly absorbable and leading to potential deficiencies of calcium, iron, and zinc. (43)(44) Absorption is most adversely affected when calcium-, iron-, or zinc-rich foods are eaten in the same meal as high phytate or oxalate foods. Although zinc absorption is decreased in

Table 1. Milk and Milk Substitute Nutrition Information (34)

MILK TYPE	VITAMIN D, % DRI	CALCIUM, % DRI	PROTEIN, g	CALORIES
Whole milk	10–25	20–30	8	150
Skim milk	10–25	25–30	8	80
Almond	10	30	1–5	30–40
Cashew	25	10–45	0–1	25
Coconut	10	10–45	0–1	40–45
Flax	30	30	0–7	55–80
Hemp	10	20–40	2–4	60
Oat	0–25	2–35	1–4	70–80
Pea	30	35–45	8	70
Rice	25	25–30	0–1	70
Soy	15–30	20–40	6–7	80–90

Content per 8-oz serving; the unsweetened versions of milk substitutes were used for nutrition information. Ranges are provided when significant variation was found between brands. DRI=dietary reference intake.

patients on vegetarian diets, it is currently unclear whether serum concentrations are reduced enough to precipitate any adverse effects.

Dairy products provide up to two-thirds of total calcium intake in the United States. (45) A study using computer-generated diets concluded that nonfortified foods in a vegan diet could not meet the DRIs of calcium without producing other nutrient deficiencies or caloric excess. Including calcium-fortified foods, the same study examined real diet logs of 127 dairy-free 9- to 18-year-olds; only 1 had adequate intake, and on average consumption was less than 40% of DRIs. (46) In addition to decreased intake, high oxalate contents of leafy greens and cruciferous vegetables inhibit calcium absorption. This can be mitigated by combining calcium-rich foods with a source of vitamin C. If intake is still below recommended levels, daily supplementation is recommended.

Adult vegans have been found to have lower iron stores but typically do not have increased rates of anemia. Similar data are not available for the pediatric population. Caution should be taken because even children reaching 100% of the DRI of iron may be deficient due to lower bioavailability of nonheme iron, a phytate-heavy diet, and decreased dietary vitamin C, which has a synergistic effect on iron absorption.

Both absolute intake and composition of protein should be closely monitored in a vegetarian diet. Although animal products are a complete source of essential amino acids (AAs), a mixture of nonanimal products is required to obtain all essential AAs. Legumes and fruits provide adequate threonine, an essential AA lacking in most grains, but are deficient in methionine and cysteine. Plant-based protein is often less bioavailable as well. For these reasons, increased protein intake with a vegetarian diet by up to 35% of daily recommended value is suggested. (47)

Protein deficiency from inappropriate milk substitute is well documented. Certain milk substitutes, such as rice milk and almond milk, have little to no protein. Some cases of Kwashiorkor have been reported secondary to milk substitution. In these specific instances, dairy avoidance was related to perceived milk allergy or parental choice to avoid animal products. (27) If dairy substitutes are used, close attention should be given to protein content (Table 1).

In terms of overall growth, no studies have shown vegan children to be at increased risk for failure to thrive, but mildly decreased weight and stature among teenage boys has been demonstrated. (48) In particular, The Farm Study examined more than 400 children, with vegans' average height 0.7 cm less than that of their omnivorous peers. Of note, participants in The Farm Study cohort were supplemented with multiple vitamins and minerals, possibly lessening the growth suppression that could be seen with less vigilant intake. (49)

A final concern is children who choose vegetarian diets while their families remain omnivorous. Teens pursuing a vegan or vegetarian diet can do so for weight loss with overly restrictive eating, limiting nutritional variety and increasing the risk of deficiency.

Special Considerations in Infants and Toddlers

Vegan diets can begin at birth, with breast feeding by a vegan mother or exclusive soy formula use. Vitamin and mineral concentrations in human milk are dependent on maternal levels. (50)

Concentrations of vitamins A, C, D, and the B group in human milk are especially maternal diet–dependent. (51)(52) Although vitamin B_{12} is frequently supplemented in vegans, nursing mothers can have borderline levels. Case reports have found symptomatic vitamin B_{12} deficiency in both breastfed infants of vegan mothers and those who have started weaning. In its most severe form, prolonged vitamin B_{12} deficiency can cause irreversible neurologic damage from decreased myelination. (50)(53) To ensure adequate vitamin B_{12}, mothers should take an approved supplement or infants should be supplemented directly. In addition, low maternal iron stores in vegan or vegetarian mothers can lead to deficiency in breastfed infants. Guez et al (54) described a case of normocytic anemia, hepatosplenomegaly, and developmental delay secondary to severe iron deficiency and vitamin B_{12} deficiency in a strict vegan mother not actively supplementing. Term infants born to iron-deficient vegetarian mothers are not only more likely to become deficient but also onset of deficiency can occur as early as 6 months of age, or 3 months sooner than infants born to moms with adequate iron stores. (55)

Lack of docosahexaenoic acid (DHA) in vegan mothers' milk has become a concern, with studies showing a lower human milk concentration than in their nonvegan peers. DHA is critical for the developing retina and brain in preterm infants, although benefit to term infants is less clear. (56)(57) Some studies support that higher early consumption correlates with better long-term developmental outcomes. Note that although omnivorous mothers have higher concentrations of DHA, until recently DHA was not added to formula, which had a lower level than vegan human milk. (27)(58)(59)

Standard soy formulas available on the market are nutritionally complete and appropriate for use in healthy

term infants. However, soy formulas are not appropriate for use in preterm infants, especially infants with weight less than 1,800 g, due to concerns regarding reduced calcium and phosphorous absorption, bone mineralization, and growth. (60) There is a lack of preterm or completely hydrolyzed vegan formulas on the market, leading some parents to use home mixtures that might not be nutritionally appropriate. Families might also look to using formulas outside of their country of location, leading to the potential for limited quality and safety monitoring and limited recall notification for quality concerns.

Finally, weaning to standard soy milk and vegan diet places infants at risk for insufficient caloric intake. Soy milk contains many of the same vitamins and minerals as whole milk, but fat content is more comparable with that of 2% milk. (59) Other milk substitutes have varying nutritional profiles (Table 1). High-fiber foods, including fruits, vegetables, and whole grains, the cornerstone of a vegan diet, are filling but have poor energy density. A vegan diet can easily exceed the 0.5 g/kg of daily fiber recommended by the American Academy of Pediatrics, leading to early satiety, caloric insufficiency, and poor growth. Until the child is age 2 years, parents should provide adequate energy by offering nut butters, avocado, legumes, and refined grains to meet daily caloric goals. (59)

GF DIET

Gluten, a family of proteins high in glutamine and proline residues known as prolamins, is a viscoelastic substance that enhances the flavor and texture of baked goods. Many gastrointestinal disorders require partial or total gluten avoidance. Nearly 1% of Americans and Europeans are affected by celiac disease (CD), an autoimmune enteropathy triggered by gluten. The GF diet (GFD) was discovered in 1953; it consists of strict avoidance of wheat, barley, and rye and is the only known treatment for CD (Fig 2). (61)(62)

Wheat, barley, and rye all contain high concentrations of gluten and must be strictly avoided by patients with CD on a GFD. Oats are less clear cut; aside from frequent contamination by other grains during processing, a small subset of patients with CD might have a reaction to a protein contained in oats that is structurally similar to gluten. Oats should be avoided after initial diagnosis of CD and reintroduced only after presenting symptoms have resolved. After reintroduction of oats, patients should be clinically and serologically monitored. (63)

Other gastrointestinal diseases for which patients can follow a GFD include wheat allergy, nonceliac gluten sensitivity, and irritable bowel syndrome. Wheat allergy, mediated by an IgE reaction to various proteins found in wheat, affects up to 0.5% of the population. Wheat allergy typically requires elimination of only wheat products rather than a true GFD, although some portion of patients can have cross-reactivity to proteins in other grains (Fig 3). (65)

The number of Americans following a strict GFD is increasing, with patients without CD now composing most of those purchasing GF foods. (66) Many nonceliac purchasers of GF products are nonwhite individuals, have

VITAMIN	VEGAN	KETOGENIC	GLUTEN-FREE	SOURCES	SIGNS AND SYMPTOMS OF DEFICIENCY
B_1 (thiamine)				Whole grains, pork	Neuropathy, confusion, heart failure, weight loss
B_9 (folate)				Leafy greens, oranges, nuts, beans, peas	Megaloblastic anemia, fatigue, headaches, palpitations
B_{12} (cobalamin)				Animal product	Macrocytic anemia, neuropsychiatric symptoms
Vitamin D				Fish liver, fortified dairy	Osteomalacia, rickets, hypocalcemia
Vitamin A				Animal product, orange/yellow vegetables (as carotene)	Xeropthalmia, vision changes, night blindness
Calcium				Dairy, fortified foods, leafy greens	Osteopenia, osteoporosis arrhythmia, numbness, tingling
Iron				Heme: fish, poultry, meat; nonheme: iron-fortified cereals/breads	Anemia, fatigue
Magnesium				Leafy vegetables, whole grains, legumes	Nausea, vomiting, seizures, arrhythmia
Phosphorous				Dairy, breads, vegetables	Osteopenia, muscle weakness
Copper				Oysters, chocolate, potatoes	Anemia, neutropenia, abnormal hair, osteopenia, muscle weakness
Zinc				Seafood, meat, poultry, whole grains	Poor growth, hypogonadism dysgeusia, diarrhea, alopecia, dermatitis (especially perioral and perianal), poor wound healing
Selenium				Seafood, organ meats, beans, Brazil nuts	Cardiomyopathy, skeletal muscle deficiency
Carnitine				Meat	Cardiomyopathy, weakness, hypoglycemia
Docosahexaenoic acid				Human milk	Poor neurodevelopment
Fiber				Fruits, vegetables, grains	Constipation, elevated cholesterol

FIGURE 2. Deficiencies associated with the ketogenic, vegan, and gluten-free diets. Shading denotes increased risk of deficiency.

DISEASE STATE	WHEAT	BARLEY	RYE	OATS	CORN	RICE
Wheat allergy (64)						
Nonceliac gluten sensitivity						
Celiac disease						

FIGURE 3. Grain avoidance in gluten-limiting disease states. Red denotes need for avoidance; yellow, potential avoidance based on individual symptoms; and green, no restrictions.

a high school diploma or less, and earn less than $30,000 a year, which are all groups that may have decreased access to medical care relative to the general population and thus potentially are more prone to nutrient deficiency. (67)

The decision to avoid gluten in patients without CD is multifold, with more than 1 in 5 US consumers viewing "gluten-free" as important when selecting food. (67) In some international areas, up to 5% of children avoid it entirely. (68) Reasons for adopting a GFD include perceived healthiness, trendiness, concerns over genetically modified wheat, behavioral changes in children, or nonspecific symptoms such as chronic abdominal pain, fatigue, and headaches that patients might relate to gluten.

A GFD can be nutritionally incomplete due to avoidance of wheat, rye, and barley. These products naturally contain vitamins, minerals, and fiber, and many wheat products have government-mandated micronutrient fortification that is not required of their GF equivalents.

Many studies report concern about low fiber and, to a lesser extent, decreased protein intake with a GFD. (69)(70) Wheat, barley, rye, and oats are naturally good sources of fiber; GF substitutes for breads, pastas, and baked goods are often heavily refined, which entails removing the bran and mill and substantially decreasing fiber content. (71) One study looked specifically at adolescent fiber intake and found lower daily intakes in the GFD group relative to their peers. (72) Although most studies still support inadequate intake, some newer papers report increasing fiber content of packaged GF foods. (73) Non–gluten-containing pseudocereals such as amaranth, buckwheat, and quinoa are also becoming increasingly popular and have high fiber content.

Use of refined flours and lack of mandatory fortification also contribute to vitamin and mineral deficiencies with a GFD. In many Western countries, including the United States, governments mandate that wheat-based products be fortified, as evidenced by packaging listing "enriched wheat flour." The Food and Drug Administration (FDA) requires the addition of thiamine, niacin, riboflavin, folate, and iron to enriched grain products. (74) For products listing calcium-fortified, the FDA has also set minimum standards. Nonwheat flours are not held to the same controls, with only 5% of GF breads having the mandatory amount of calcium, iron, niacin, and thiamine present. (75) Thiamine is of particular concern, with one study showing that serum levels actually decreased in patients with CD after initiation of a GFD and mucosal healing, likely due to the low thiamine content of the GFD. (76) Packaged GF goods have also been shown to have lower folate levels than their gluten-based equivalents, with deficiency being found in up to 20% of patients with CD on a GFD. (76)

Concerns for vitamin B_{12} deficiency have also been well-documented in the GF population, with up to 40% having inadequate serum levels. (75) Vitamin B_{12} is essential for the production of methionine from homocysteine. If vitamin B_{12} levels are low, homocysteine levels can rise. (77) A multicenter trial compared 2 groups of patients with CD on a GFD using homocysteine levels as a proxy for adequacy of intake; 1 group received vitamin B_{12}, folic acid, and vitamin C supplementation, and the control group received only placebo. With the vitamin B_{12} regimen, serum homocysteine levels dropped, and patients reported an overall improved sense of wellness. (78) Megaloblastic anemia, psychiatric symptoms, and thromboemboli should all raise suspicion for vitamin B_{12} deficiency in patients on a GFD. (79) Interestingly, one study also found increased rates of vitamin A deficiency in some subsets of patients with CD after GFD initiation, but those results have not yet been replicated elsewhere. (80)

Mineral deficiencies associated with GFD include selenium and magnesium, which are consumed in significantly smaller amounts on a GFD. (69) Selenium is known to be high in wheat products, and intake is inadequate by DRIs with a GFD, but evidence of serum deficiency is lacking. Serum levels of magnesium remained depressed after initiation of a GFD. With evidence of mucosal healing after GFD initiation, this seems likely to

be related to inadequate intake with packaged GF foods and naturally GF grains, both being poor sources. (76)

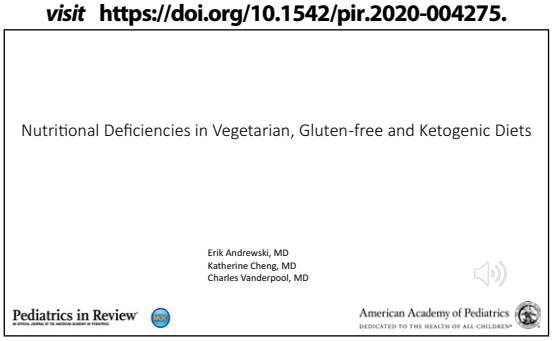
In children, inadequate iron intake raises concerns for anemia, and zinc is crucial for adequate growth and is involved in protein synthesis. Studies on patients with CD suggest that iron and zinc intake is decreased on a GFD relative to the general population but mixed regarding whether true deficiency occurs. Iron data range from normal serum levels to up to 40% of patients with CD having an iron deficiency. (69)(73)(75) Impaired absorption of iron in the duodenum in patients with active CD enteropathy complicates interpretation of results and extrapolation to nonceliac patients. For calcium, adult intake was higher on a GFD compared with that of their gluten-consuming counterparts, but still only 18% to 32% of women met calcium DRIs. (69) In a cohort of children, 3.6% were calcium-deficient when adherent to a GFD. (81)

Many limitations exist in studies of potential GFD-associated nutritional deficiencies in children. Most available data focus on adult populations, which might not be accurately extrapolated to children. Studies looking at nonceliac patients on a GFD are also sparse. Studies focused only on patients with CD might artificially increase the number of observed deficiencies of a GFD due to complicating factors from CD, including impaired absorption from chronic mucosal injury, that would not be generalizable to non-CD populations. Other authors suggest that the literature's focus on patients with CD might actually underestimate GFD nutrient deficiencies in the nonceliac population, as patients without CD might be more likely to avoid multiple food groups for perceived health benefits. Finally, many studies examined cohorts outside of the United States, who likely have different dietary patterns, access to different brands of GF foods, and varying laws regarding mandatory fortification.

Summary

- The ketogenic diet (KD) is an effective therapy for antiepileptic drug–refractory seizure disorders, pyruvate dehydrogenase deficiency, and glucose transporter type 1 deficiency. Currently, there is no standardized KD multivitamin available, and the stricter the lipid-to-nonlipid ratio in a KD, the higher the risk of nutrient deficiencies, with selenium being of particular concern. (5)(12)(26) (Evidence quality D)
- If well-balanced or supplemented, vegan and vegetarian diets can be safe for all ages, including pregnancy, infancy, and childhood. However, patients who are highly restrictive in eating might be at increased risk for micronutrient and macronutrient deficiency, with vitamin B_{12}, iron, folate, and zinc deficiency being of particular concern. (82) (Evidence quality B)
- In the pediatric population, vegetarian diets should be closely monitored for fiber and protein content. The American Academy of Pediatrics recommends no more than 0.5 mg/kg per day of fiber to promote increased intake of energy-rich foods that promote growth. Plant-based protein is less bioavailable than that of animal origin, with vegetarian children requiring varying amounts above the standard recommended daily allowance depending on patient age. (47)(82) (Evidence quality D)
- Plant-based milks are not universal in nutritional status and often are not a suitable replacement for cow milk; in particular, protein, calcium, and vitamin D content can be of concern. (34) (Evidence Quality D)
- Strict avoidance of gluten is the only known treatment for celiac disease. Patients following a gluten-free diet, whether for medical needs or personal preference, can be at increased risk for micronutrient deficiency, including iron, folate, and B vitamins, with monitoring decisions made on a patient by patient basis. (83) (Evidence Quality B)

To view teaching slides that accompany this article, visit **https://doi.org/10.1542/pir.2020-004275.**



References for this article can be found at https://publications.aap.org/pediatricsinreview/43/2.

PIR QUIZ

1. A 6-year-old boy who consumes a ketogenic diet due to parental preference presents to your office for a health supervision visit. His mother feels his stools are very loose and watery, with him stooling up to 8 times per day. There is no blood in the stools. She also notes he has very thin hair. His weight for age is at the 5th percentile, whereas he was at the 45th percentile before initiating the ketogenic diet 3 years ago. Testing for celiac disease is negative. His symptoms are the result of deficiency of which of the following substances?

   A. Carnitine.
   B. Selenium.
   C. Vitamin B_{12}.
   D. Vitamin E.
   E. Zinc.

2. The family of a 9-year-old girl with epilepsy decides to start her on a ketogenic diet without consulting a provider. She is in the initial fasting phase when she develops new signs and symptoms. The family brings her to urgent care due to sweating, confusion, shakiness, and an elevated heart rate. She is found to have a serum glucose level of 52 mg/dL (2.89 mmol/L), which corrects with oral glucose therapy. Her hypoglycemia is likely associated with a deficiency of which of the following substances?

   A. Carnitine.
   B. Glutamine.
   C. Retinol.
   D. Selenium.
   E. Vitamin B_{12}.

3. A 4-year-old girl is being seen for a health supervision visit. The entire family observes a vegan diet and consumes almond milk as a milk substitute. With this knowledge, the pediatrician should pay close attention to possible deficiency of which of the following substances?

   A. Oxalate.
   B. Protein.
   C. Vitamin A.
   D. Vitamin B_{12}.
   E. Vitamin D.

4. You are rounding in the NICU and seeing a 14-day-old neonate who was born at 32 weeks' gestational age with a birthweight of 1,700 g. The family is vegan and wants to feed the baby exclusively soy formula. You advise them that soy formula would not be recommended because it places their child at risk for which of the following?

   A. Hypercalcemia.
   B. Hypermagnesemia.
   C. Hypophosphatemia.
   D. Hypovitaminosis E.
   E. Zinc deficiency.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

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5. You are seeing a 12-year-old boy with abdominal pain, nonbloody diarrhea, bloating, and fatigue. Laboratory evaluation is notable for a microcytic anemia and a tissue transglutaminase IgA antibody level of 235 ChmU (reference range, <20 ChmU). After referral to a pediatric gastroenterologist, endoscopically obtained biopsies show duodenal villous blunting and intraepithelial lymphocytosis, confirming the diagnosis of celiac disease. Which of the following special diets is indicated in this patient?

   A. Free of animal products.
   B. Free of red meats, poultry, butter, eggs, and dairy.
   C. Free of wheat, barley, and rye.
   D. High in fat and low in carbohydrates.
   E. High in soy-based products.