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INVITED REVIEW

Update on the management of vitamins and minerals in cystic fibrosis

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Abstract

Advancements in respiratory and nutrition management have significantly improved the survival of patients with cystic fibrosis (CF). With the availability of several nutrition interventions such as oral/enteral nutrition supplements, enteric-coated pancreatic enzymes, and water-miscible CF-specific vitamin supplements, frank vitamin deficiencies—with the exception of vitamin D—are rarely encountered in current clinical practice. Whereas they were previously considered as micronutrients, our current understanding of fat-soluble vitamins and minerals as antioxidants, immunomodulators, and disease biomarkers has been evolving. The impact of highly effective modulators on the micronutrient status of patients with CF remains elusive. This narrative review focuses on the updates on the management of fat-soluble vitamins and other micronutrients in CF in the current era and identifies the gaps in our knowledge.

KEYWORDS

calcium; cystic fibrosis; iron; magnesium; vitamin A; vitamin D; vitamin E, vitamin K; zinc

INTRODUCTION

When cystic fibrosis (CF) was first recognized as a distinct entity in the 1930s by Dr Dorothy Andersen, most infants died from consequences of severe malnutrition.[1] Advancements primarily in respiratory and nutrition therapies have led to significant improvements in the median life span of individuals with CF over the past five decades. The Cystic Fibrosis Foundation (CFF) Registry data are released annually, and the latest data for the year 2020, published in 2021, showed a predicted median reported survival of approximately 50 years.[2] The role of registered dietitians is pivotal in the multidisciplinary CF team, and common nutrition interventions include individualized nutrition counseling utilizing weight, body mass index, and/or body composition to frame recommendations; exercise/activity to promote optimal body composition; pancreatic enzyme replacement therapy (PERT) for individuals with exocrine pancreatic insufficiency (EPI); and appropriate micronutrient supplementation.[3–5] The CFF 2020 Registry data revealed approximately 40% of patients with CF required oral nutrition supplements and 10% received enteral nutrition.[2]

The nutrition state of individuals with CF has significantly improved and is mainly attributed to early CF diagnosis through newborn screening, use of effective enteric-coated pancreatic enzymes, optimization of

fat-soluble vitamin supplementation, implementation of systematic quality-improvement interventions, and availability of newer CF-targeted therapies such as the highly effective modulators (HEMs).[6,7] HEMs are postulated to positively impact nutrition status in several ways, such as reduction in energy requirement, decrease in intestinal inflammation, improvement of intestinal dysbiosis, and improved fat absorption.[8] Lately, the landscape of nutrition management of CF, especially in adult patients, is drifting toward newer nutrition challenges such as overweight/obesity and associated comorbidities, such as cardiovascular disease, hypertension, and metabolic syndrome.[6,9–11] In the past, there were several reports of deficiencies in fat-soluble vitamins in CF, including Dr Andersen's first description of CF.[1] In the current era, frank micronutrient deficiencies of vitamin A and vitamin E are rarely encountered in patients with CF, presumably owing to early diagnosis and initiation of pancreatic enzymes, CF-specific vitamin supplementation, and possibly improved absorption with HEMs. On the contrary, instances of elevated vitamin levels are now seen.[12–17] Also, once solely considered as micronutrients, our latest understanding of the role of fat-soluble vitamins and trace minerals has evolved. Currently, they are increasingly recognized for their various functions as antioxidants, immunomodulators, and disease biomarkers.[18–26] In other words, rather than a focus on their status as deficient vs sufficient in CF, there is recognition of optimal vs suboptimal status impacting disease outcome in CF.[18,27,28]

Ivacaftor (VX-770 [Kalydeco; Vertex Pharmaceuticals Inc]) was the first HEM approved in 2012 for gating mutations, which account for approximately 15% of patients with CF. Two trials (ARRIVAL and KIWI studies) noted improving pancreatic function in young children with gating mutations.[29,30] In 2019, the US Food and Drug Administration (FDA) approved the first triple combination therapy (elexacaftor/tezacaftor/ivacaftor [TRIKAFTA; Vertex Pharmaceuticals Inc]) for patients with at least one delta F508 mutation, which is present in up to 90% of individuals with CF. Currently, elexacaftor/tezacaftor/ivacaftor is approved for patients ≥6 years of age. It is yet unclear whether this triple combination will significantly impact pancreatic function; studies are underway. Currently, PERT dosage is not adjusted in patients after the initiation of elexacaftor/tezacaftor/ivacaftor, owing to concerns of complications such as micronutrient deficiencies and worsening of gastrointestinal (GI) symptoms (including distal intestinal obstruction syndrome) and lack of data to guide any changes in PERT. However, there is a concern that individuals with CF may lower PERT dosage on their own after starting HEMs for reasons such as GI symptoms and concerns of excessive weight gain.[31] It is important to keep the line of communication open and approach these topics in a supportive manner.

A recent study by Sommerburg and colleagues has shown that lumacaftor/ivacaftor in CF could significantly alter vitamin levels.[13] In a small cohort of patients who have CF and are homozygous for delta F508, the median plasma vitamin A level improved from 1.2 to 1.6 μmol/L in a 2-year period. None of the patients had levels in the toxicity range. This change also correlated with reduction in lung inflammation, as demonstrated by significant decrease in serum immunoglobulin G. Here, the authors postulated that improved intestinal absorption of vitamin A along with reduction in lung exacerbations could be the reason for this increase. At the same time, the plasma vitamin E/cholesterol ratio decreased from 6.2 to 5.5 μmol/mmol, and a competitive decrease in intestinal absorption, redistribution of vitamin E from plasma to adipose tissue, and increased degradation were proposed as causes of this decrease. The effect of HEMs such as elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin and other micronutrient status is unclear, and the literature remains sparse. Preliminary evidence has shown that elexacaftor/tezacaftor/ivacaftor could improve vitamin D levels.[32] The exact reason for these improving levels is unclear but could be related to improved intestinal absorption and/or optimization of vitamin D utilization with concomitant decrease in inflammation in CF patients.[32] This review focuses on the basic principles in current practice of vitamins and minerals in CF in the era of HEMs and identifies the gaps in our knowledge.

Fat-soluble vitamins

Reports of deficiencies in fat-soluble vitamins A, D, E, and K in CF are commonly attributable to fat malabsorption, particularly in patients with poorly controlled EPI. The original description of CF by Dr Andersen in 1938 included references to vitamin A deficiency.[1] In a multicenter study, deficiencies in fat-soluble vitamins were documented in up to one-third of children with CF and EPI but rarely noted in patients with pancreatic sufficiency.[33] CF-specific vitamins are available, most of which contain fat-soluble vitamins in a water-miscible form, as well as water-soluble vitamins and zinc. Regular monitoring of fat-soluble vitamins and appropriate supplementation are necessary to prevent these deficiency states. In people with CF and EPI, fat-soluble vitamins can be deficient owing to uncontrolled fat malabsorption, suboptimal adherence to therapy, and comorbid issues such as short bowel syndrome and/or CF-related liver disease (CFLD).[34,35] Recommendations

for doses of fat-soluble vitamins in CF are mostly from expert consensus rather than evidence-based practice.[3] The CFF recommends regular screening for deficiencies in fat-soluble vitamins at the time of diagnosis and then annually and after any dose change. The important functions of fat-soluble vitamins and minerals and their interpretation are noted in Table 1. Also, Table 2 outlines the micronutrient status in specific populations affected by CF.

Vitamin A

Vitamin A is a crucial component in many physiological functions, including embryonic development, vision, bone health, cellular proliferation and differentiation, immunity, and antioxidant function. Importantly in CF, vitamin A protects respiratory epithelial cells against oxidation.[47] Better vitamin A status is linked with better pulmonary status in people with CF.[48] Vitamin A can be consumed in two forms, preformed vitamin A (retinol, retinyl esters) and provitamin A carotenoids such as beta-carotene. Preformed vitamin A is found in dairy, liver, eggs, and fortified foods, such as breakfast cereal. Provitamin A is found in plant-based foods, such as fruits and vegetables. Provitamin A is only converted to retinol if needed by the body; and this is an important difference between the two forms of vitamin A, given that there is concern for vitamin A deficiency as well as vitamin A toxicity in people with CF.[27]

Vitamin A supplementation in CF is standard clinical practice, and the recommended dosage in the US varies from 450 to 3000 mcg retinol activity equivalents per day (equivalent to 1500–10,000 IU)[49]; however, these guidelines are not based on clinical studies.[50] Even though vitamin A deficiency has been reported to be independent of pancreatic function,[51] most studies reported vitamin A deficiency in patients with EPI either before initiation of PERT and supplementation of fat-soluble vitamins or due to poor adherence to therapy.[33,52] Vitamin A deficiency is becoming rare in people with CF, whereas elevated serum retinol levels have become more prevalent.[15] Elevated serum vitamin A is associated with liver and bone disease and increased intracranial pressure.[53,54]

A serum retinol value below a cutoff of 20 mcg/dl represents biochemical vitamin A deficiency.[47] Although obtaining fasting annual laboratory values may be burdensome, nonfasting levels may reflect recent intake of vitamin A. Thus, serum retinol levels are ideally assessed in the fasting state.[36] Vitamin A is a negative acute-phase reactant and therefore can result in falsely low levels when assessed during acute illness.[55] Vitamin A is transported bound to retinol-binding protein (RBP), which is produced in the liver and often low in patients with liver disease and/or malnutrition. When there is not enough RBP to transport vitamin A, it accumulates in the liver. Therefore, preformed vitamin A can cause toxicity if RBP is low. In patients with liver disease or malnutrition, assessing the molar ratio of retinol to RBP can help guide the need for vitamin A supplementation. A ratio of <0.8 indicates true vitamin A deficiency that requires vitamin A supplementation.[56] Measurement of serum retinyl esters can be more useful for estimating vitamin A toxicity if >10% of total vitamin A is in the form of retinyl esters.[36,57]

Zinc is necessary for synthesis of RBP, and therefore, zinc deficiency may lead to inadequate RBP available to circulate retinol.[58] Vitamin A absorption and conversion of beta-carotene take place in the small intestine; therefore, a history of small bowel resection may lead to low serum levels of vitamin A. CF-specific multivitamins are commonly the first choice for vitamin A supplementation with the content predominantly as beta-carotene,[59] which decreases the risk of toxicity. Individualized vitamin A supplementation based on estimation of serum levels is important to prevent vitamin A deficiency and toxicity.[60] Higher retinol levels with possible toxicity may be encountered in patients treated predominantly with retinol-based supplements, patients who have chronic kidney disease, and patients posttransplant.[15,42,61-63] There are case reports of hypervitaminosis A in patients treated with CFTR modulator therapy, and more studies are needed to elucidate the effect of HEMs on vitamin A status in patients with CF.[12-14]

Vitamin D

Vitamin D serves an important role in bone health by regulating circulating calcium and phosphorus levels to promote normal bone mineralization.[64] There is also evidence for its role in immunity,[64] microbiome,[65] inflammation, and pulmonary health.[28,66] Vitamin D deficiency and insufficiency are common in people with CF.[18,67] Factors that contribute to deficiency in CF include decreased intestinal absorption, inadequate intake of vitamin D–containing foods or supplements, low sunlight exposure, treatment with glucocorticoids, impaired hydroxylation of vitamin D in the liver or kidneys, and reduced fat stores.[67]

Vitamin D can be obtained orally through diet or supplementation with ergocalciferol or cholecalciferol and by skin production through sunlight exposure. Vitamin D is not naturally present in many foods, with the exception of the flesh of fatty fish and fish liver and in

TABLE 1 Summary of functions and evaluation of vitamins and minerals in cystic fibrosis

Fat-soluble vitamins	Functions	Evaluation and interpretation of serum levels[4,36,37]	Daily vitamin and mineral recommendations[3,4,38,39]
Vitamin A	Vision, immune function, epithelial integrity; beta-carotene is an antioxidant	• Negative acute-phase reactant (falsely decreased during illness and inflammatory states).[40,41] • Interpret with retinol-binding protein in setting of liver disease. • Check zinc level if vitamin A (serum retinol) is persistently low. • Toxicity possible; can cause hepatotoxicity and bone toxicity.	Infants: 1500 IU; toddlers: 5000 IU; 4–8 years: 5000–10,000 IU; >8 years: 10,000 IU (Dosage recommendations based on retinol form) 10,000 IU retinol = 3000 mcg RAE; 15 mg beta-carotene = 7500 mcg RAE = 25,000 IU retinol
Vitamin D	Bone health/calcium absorption, immune function	• Negative acute-phase reactant.[28] • Serum 25-hydroxyvitamin D is used to measure vitamin D status. • Levels may be influenced by season (higher in late summer or early fall because of increased sun exposure). • Toxicity increases risk for hypercalciuria and hypercalcemia.	Infants: 400–500 IU; 1–10 years: 800–1000 IU; >10 years: 800–2000 IU (Cholecalciferol or vitamin D_3 is the preferred form for supplementation in CF. Minimum daily doses are depicted here. Dosage can be increased based on serum levels and after ensuring compliance.) 1 IU = 0.025 mcg 400 IU/ml = 10 mcg/ml
Vitamin E	Antioxidant, cellular membrane stability, important for cognitive function	• Level may be decreased in pulmonary exacerbations.[41] • Serum alpha-tocopherol levels reflects supplementation. • Lipid level abnormalities may influence level.	Infants: 40–50 IU; toddlers: 80–150 IU; 4–8 years: 100–200 IU; >8 years—200–400 IU. 1 IU of the synthetic form is equivalent to 0.45 mg of alpha-tocopherol.
Vitamin K	Blood clotting, bone formation, cell growth regulation	• Serum vitamin K levels do not reflect stores. • PT/INR are late and nonspecific indicators of vitamin K deficiency. • PIVKA-II or uc-OC level is a sensitive indicator of early vitamin K deficiency.	0.3–0.5 mg for all age groups
Salt	Hyponatremic dehydration; salt loss is one of the reasons for poor weight gain in infants	• Patients with CF have 2–4 times higher sodium chloride in the sweat, resulting in enhanced loss. • Urine sodium: creatinine ratio can be utilized to evaluate enhanced sodium loss.	Historically, infants <6 months of age are provided one-eighth teaspoon of table salt (approximately 11 mEq sodium), and infants beyond 6 months of age are given one-fourth teaspoon of table salt. Patients with CF who exercise or play outside in hot weather also may need one-eighth teaspoon of salt added to 12 ounces (360 ml) of beverage.
Zinc	Immune function, growth, tissue healing, component of almost 300 enzymes, and structural role as zinc fingers in certain proteins.	• Plasma zinc levels may not reflect deficiency. • Consider empiric supplementation if deficiency is suspected or persistent poor weight gain despite adequate calorie and PERT supplementation. • Patients with ileostomy are at increased risk of zinc deficiency.	No consensus on routine zinc supplementation. Dosing: infants up to 2 years receive 1 mg/kg/day, children receive 15 mg/day, and adults receive 25 mg/day.

(Continues)

TABLE 1 (Continued)

Fat-soluble vitamins	Functions	Evaluation and interpretation of serum levels[4,36,37]	Daily vitamin and mineral recommendations[3,4,38,39]
		• **Patients at risk of zinc deficiency can be empirically supplemented for 6 months.**	
Calcium	Bone health, muscle and nerve functions, clotting; functions as coenzyme in many metabolic processes	• In patients with a low serum albumin level, calcium levels should be corrected for low serum albumin level status. • Calcium levels should be screened annually, and recommended calcium intake is similar to that in patients without CF.	Dietary reference intake of calcium for general population is recommended for CF population.
Magnesium	Muscle and nerve function, bone health, and a cofactor for many enzymatic reactions.	• Low magnesium levels are increasingly recognized in patients with CF due to many factors.	No formal guidelines available regarding evaluation or treatment of magnesium in CF.

Abbreviations: CF, cystic fibrosis; PERT, pancreatic enzyme replacement therapy; PIVKA, protein induced in vitamin K antagonism/absence; PT/INR, prothrombin time/international normalized ratio; RAE, retinol activity equivalent; uc-OC, undercarboxylated osteocalcin.

TABLE 2 Micronutrients status in specific populations affected by CF

Special populations	Micronutrient considerations
Lung transplant recipients	Elevated levels of vitamin A and vitamin E have been documented.[42] Renal dysfunction due to the use of immunosuppressive medications can further complicate the vitamin levels and should be monitored closely. CF-specific vitamins should be discontinued, and over-the-counter multivitamins can be given. Vitamin D and vitamin K status should be optimized. Higher vitamin A can adversely affect bone health and can can liver fibrosis.
Pancreatic-sufficient CF	Vitamin D deficiency is noted to be similar to that in populations with pancreatic insufficiency.[18] There is sparse literature on routine supplementation of other fat-soluble vitamins.
Pregnancy	Fat-soluble vitamin levels ideally should be tested before conception and monitored every trimester to ensure levels are optimized. Vitamin A supplementation should continue at <10,000 IU/day.[43,44] Also, clinicians should ensure patients are taking adequate amounts of folic acid, iron, calcium, and phosphorus.
Liver disease	Concomitant liver disease further predisposes patients to deficiencies in fat-soluble vitamins and needs close monitoring. Higher vitamin A levels can worsen liver disease.
Short bowel syndrome	Pancreatic enzymes, specifically trypsin, also play a significant role in cleaving R-binders produced in the salivary glands. This enhances vitamin B_{12}–intrinsic factor coupling and later aids in B_{12} absorption in the ileum.[45] In patients with extensive ileal resection related to meconium ileus, B_{12} deficiency has been reported.[46]

Abbreviation: CF, cystic fibrosis.

smaller amounts in beef liver, dairy products, and egg yolk in the form of cholecalciferol and its metabolite 25-hydroxyvitamin D_3 [25(OH)D]. Some mushrooms are a source of ergocalciferol.[68] Supplemental cholecalciferol has been shown to be superior at improving serum 25(OH)D levels compared with ergocalciferol,[69] and current CFF guidelines recommend treatment with cholecalciferol and offer specific dosing guidelines.[38] Ergocalciferol may be considered for individuals who avoid the use of animal products, although higher doses may be required.[38] Vitamin D absorption may be improved when taken with pancreatic enzymes before meals. The CFF recommends that individuals with difficult-to-treat vitamin D deficiency be referred to a specialist with expertise in vitamin D therapy.[38]

Additionally, levels will be influenced by time of year/exposure to sunlight, with peak levels likely to be during the summer months.[70] The CFF recommends yearly screening for vitamin D status using serum 25(OH)D, preferably at the end of winter when sun exposure is lowest.[38] Vitamin D

status is considered sufficient when 25(OH)D concentrations are ≥30 ng/ml, insufficient when concentrations are ≥20 and <30 ng/ml, and deficient when concentrations are <20 ng/ml. Optimal vitamin D status is defined as a 25(OH)D concentration between 30 and 50 ng/ml, and the CFF recommends a minimum 25(OH)D level of 30 ng/ml (75 nmol/L) for individuals with CF. Levels should not exceed 100 ng/ml given the increased risk for associated hypercalcemia. Vitamin D status should be reevaluated roughly 3 months after changes to vitamin D dosing.[38] Serum 25(OH)D is a negative acute-phase reactant and is an unreliable marker of vitamin D status during acute illness.[71]

Despite routine supplementation with vitamin D, serum vitamin D levels remain insufficient in many individuals with CF.[72,73] A recent study found that reported sunlight exposure was significantly associated with higher serum vitamin D levels at admission for pulmonary exacerbation, whereas total oral vitamin D intake was not significantly associated with vitamin D levels, suggesting that sun exposure is a major source of vitamin D production in individuals with CF and malabsorption.[74] Given these findings, sunlight may provide an alternative or synergist benefit to oral vitamin D treatment when feasible. There are limitations to sun-induced synthesis; some patients may not be able to tolerate sun exposure because of increased photosensitivity to certain medications. Other factors, including season, time of day, latitude, skin pigmentation, and sunscreen use, influence the amount of vitamin D absorbed by the skin.[16,75] In the general population, exposing 20% of the body surface to sunlight for half the time it would take to cause mild sunburn is equivalent to ingesting roughly 1400–2000 IU (35–50 mcg) of vitamin D_3 and is effective for all skin types.[75]

Numerous studies have demonstrated the impact of vitamin D deficiency and insufficiency status in CF outcomes. Simoneau and colleagues noted increased association of *Pseudomonas aeruginosa* colonization in vitamin deficient/insufficient patients.[18] Increased serum vitamin D levels were found to be associated with better lung function tests in both children and adults with CF.[28,76,77] However, a recent meta-analysis evaluated eight randomized controlled trials and showed that the intervention group (receiving vitamin D supplementation) had no difference in bone disease, pulmonary status, and immunological outcomes when compared with the placebo group.[78]

Vitamin E

Vitamin E is a fat-soluble antioxidant that is found in foods such as nuts, seeds, and oils, but it is also an additive to some foods and available as a supplement. There are eight chemical forms of vitamin E found naturally in foods; however, alpha-tocopherol is the only form recognized to meet human requirements, has the highest biological activity, and is the form most commonly found in supplements.[79,80] Alpha-tocopherol serves as an antioxidant preventing the deleterious effects of free oxygen radicals on unsaturated fatty acids.[81] It is unclear whether there are subclinical benefits of vitamin E supplementation for individuals with CF, including those with pancreatic sufficiency; there may be increased need from higher oxidative stress from chronic inflammation and bacterial infections.[81] A recent Polish study involving young children and adults with CF identified vitamin E deficiency in 8% of participants and high levels in 11.4%.[17]

Severe hemolytic anemia can result from vitamin E deficiency and can be seen in infants with CF as young as 6 weeks of age who are not receiving supplements.[82] Vitamin E deficiency can also manifest as neurological problems, including sensorimotor neuropathy, and cognitive impairment.[83,84] Deficiencies are uncommon in individuals treated with enzymes and CF vitamins, and supplementation may not be needed for individuals with pancreatic sufficiency.[84,85] Supplementation is associated with improved vitamin E levels; however, there is a lack of research indicating improved clinical outcomes associated with supplementation.[84]

Annual measurement of alpha-tocopherol levels in individuals with CF is recommended, with more frequent follow-up if abnormalities are noted. Aggressive supplementation may lead to elevated serum alpha-tocopherol vitamin levels and/or suppression of gamma-tocopherol levels.[86] The clinical significance of this suppression in CF is unknown, and there are no recommendations to assess other tocopherol levels besides alpha-tocopherol. Elevated levels of vitamin E are particularly common in individuals after transplant and may predispose them to risk of hemorrhage.[42] Altered lipid levels may be associated with elevated or low vitamin E levels. Vitamin E circulates in the blood bound to lipoproteins. A more accurate assessment of vitamin E deficiency can be obtained using the vitamin E to total lipid ratio, which has a sensitivity of 95% and a specificity of 99%.[87] A lipid panel is recommended in situations when abnormal vitamin E levels are noted. High-dose vitamin E supplementation has been noted to antagonize the effect of vitamin K in populations without CF.[88] When taken with pancreatic enzyme replacement,[89] a water-soluble form of vitamin E does not appear to have any advantage over fat-soluble vitamin E in terms of absorption.[81]

Vitamin K

Vitamin K is the least studied of all fat-soluble vitamins in terms of dosing (type and amount) and optimal methods for monitoring vitamin K status. Vitamin K is also unique because it is produced by intestinal bacteria (menaquinones or vitamin K_2) in addition to food (phylloquinone or vitamin K_1) and supplemental sources.[81,90] Dark green and leafy vegetables such as broccoli, kale, and spinach are good sources of vitamin K. Vitamin K is a cofactor for the enzyme gamma-glutamyl carboxylase, which is involved in the posttranslational modification of peptidyl gamma-carboxyglutamic acid (Gla) from specific glutamyl residues. Gla residues are found in coagulation factors (II, VII, IX, and X), and these proteins are synthesized in the liver.[90,91] Whereas vitamin K is most commonly known for its importance in synthesizing proteins necessary for blood clotting, the other proteins involved in bone metabolism and cell growth regulation such as osteocalcin, matrix Gla protein, transmembrane Gla proteins, and proline-rich Gla proteins also contain Gla.[90,91] In vitamin K deficiency, undercarboxylated proteins are formed, which are functionally defective because they cannot bind either calcium or phospholipids. These abnormal coagulation factors are called protein induced by vitamin K absence or antagonism (PIVKA) and des-gamma-carboxy-prothrombin (otherwise known as PIVKA-II). PIVKA-II and undercarboxylated osteocalcin (uc-OC) are sensitive markers of vitamin K deficiency and are available mostly for research settings and not for clinical utility.[3,91-93] Serum vitamin K levels reflect intake over the prior 24 h and are not useful in estimating deficiency status. Prothrombin time (PT) is not useful to identify vitamin K deficiency in the early stages, and PT levels become abnormal when prothrombin levels fall below 50% of normal values.[94] Also, the liver is capable of utilizing vitamin K better than bone in early stages of vitamin K deficiency, and thus, deficiency status may increase risk of poor bone health and cancer.[90,95,96] Rashid and colleagues demonstrated mild vitamin K deficiency in 75% of their patients with CF, both children and adults. They demonstrated increased levels of PIVKA-II.[97] Similarly, Wilson and colleagues showed that vitamin K at a mean daily dose of 0.18 mg demonstrated a significant decrease in PIVKA-II.[98] In a study by Hubert and colleagues, decreased bone mineral density and high PIVKA-II levels were noted both before and after lung transplant.[99]

Patients with concomitant CFLD have increased susceptibility to vitamin K deficiency.[98] Similarly, patients with short bowel syndrome and patients with frequent antibiotic use are at increased risk of vitamin K deficiency.[100] The CFF consensus guidelines recommend a vitamin K dose of 0.3–0.5 mg daily for the pediatric age group and 2.5–10 mg weekly for adults.[3,101] The guidelines from the European Society for Clinical Nutrition and Metabolism; European Society for Paediatric Gastroenterology, Hepatology and Nutrition; and the European Cystic Fibrosis Society (ESPEN-ESPGHAN-ECFS) recommended a daily dose of 0.3–1 mg in infants and 1–10 mg in patients beyond infancy.[4] Adverse effects from excessive vitamin K supplementation are not reported.[102] Also, vitamin K intake should be carefully monitored in patients on medications such as warfarin.[103]

Iron

Iron deficiency anemia is more commonly seen in individuals with CF who have more advanced lung disease and may be related to iron losses into the airway, which may facilitate *Pseudomonas* infection.[104] Incidence of hypoferremia varies widely based on publication, likely owing to the difficulty in interpreting iron studies because iron studies are influenced by inflammation.[105] Despite the association between iron and *Pseudomonas*, oral iron supplementation does not seem to lead to an increase in pulmonary exacerbations or negatively affect the lung microbiome.[105] Also, patients can be encouraged to consume foods that are good sources of iron, such as liver, meat, and lamb. Further studies are warranted to examine the incidence of iron deficiency in CF, as well as an optimal way to monitor and treat deficiency.

Iron deficiency may be a concern among some people with CF and is associated with anemia, deficiencies in fat-soluble vitamins, and worse lung function.[106,107] Loss of iron in the GI tract and sputum may contribute to the prevalence of iron deficiency in CF.[104] There are currently no guidelines for screening, diagnosing, and treating iron deficiency and anemia in CF. Assessing iron status is challenging because of the lack of standardized values used to define iron deficiency. Furthermore, infection and inflammation are known to affect iron studies, leading to elevated of levels of ferritin and transferrin and low levels of iron and percent transferrin saturation.[108] Management of iron deficiency in CF is challenging because it is hard to distinguish between anemia of chronic disease and anemia due to iron deficiency. Another concern is that supplementing iron may cause harm. When surveyed, about a quarter of CF clinicians reported concern that supplemental iron could enhance the growth of lung bacteria despite lack of evidence between iron supplementation and pulmonary status.[105,109]

Because iron studies are affected by inflammation, it is best to use multiple laboratory values to assess iron status, including serum iron, transferrin saturation, and soluble transferrin receptor. Checking C-reactive protein may help improve the interpretation of results.[110] Studies of iron status in patients with CF found that a ferritin

cutoff of 12 ng/ml, which is the World Health Organization (WHO) classification for iron deficiency, showed poor sensitivity and underestimated iron deficiency.[106,111] It may be more reasonable to use a ferritin cutoff of 30 ng/ml, which is used in guidelines for other chronic inflammatory diseases. The American Gastroenterology Association recommends using a ferritin cutoff of 45 ng/ml in patients with anemia (hemoglobin <13 g/dl in men and <12 g/dl in women, as defined by WHO).[111] Iron supplementation has been shown to be helpful in adults with CF who suffer from restless leg syndrome regardless of iron status.[112]

When deciding how to treat iron deficiency, the clinician should assess for anemia of chronic disease and treat the underlying disease first. In most patients, an initial trial of oral iron should be given because it is readily available, inexpensive, and safe.[110] Available evidence does not support any available formulation as being more effective or better tolerated than the others.[113] However, GI intolerance to oral iron supplements is common, and patients with malabsorption syndromes may have limited response.[110] Although there are no dosing guidelines specific to CF, traditionally, a daily elemental iron dose of 150–200 mg has been recommended for adults, and a dose of 3–6 mg/kg/day elemental iron divided two or three times per day for children. Recent studies suggest that lower dosing or every-other-day dosing may improve tolerability and absorption.[114,115] Oral iron supplements acutely increase serum hepcidin that persists for about 24 h. Hepcidin is a regulator of iron balance and negatively correlates with iron bioavailability, therefore decreasing iron absorption from supplements given later that day or the next day. One study found that hepcidin was significantly increased at 24 h with oral iron doses of 60 mg or more and returned to baseline after 48 h.[115] Vitamin C can enhance iron absorption, and phytates, calcium, and tannins can reduce absorption. In patients who have intolerance to oral iron, intravenous iron infusions have been reported in CF, but the efficacy and adverse effects of this intervention remain unclear.[116]

Salt (sodium)

An old adage depicts the fate of an infant born with CF before identification of the diagnosis: "Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon will die." Sodium is important in fluid balance and maintenance of blood volume. It is found ubiquitously in food because it is used as a preservative and flavor enhancer. Abnormal transport of sodium and chloride across sweat gland epithelial cells has long been recognized as a consequence of CF. Di Sant'Agnese and colleagues documented a twofold to fourfold higher sweat sodium and chloride content in individuals with CF compared with that of controls.[117] Sodium chloride deficits can be particularly problematic in infancy because of increased requirements due to rapid growth as well as the low sodium content of first foods and breast milk. Infants also have increased salt losses through their skin, especially in warm climates.[3]

Chronic clinical consequences of salt include poor growth and failure to thrive, particularly in young children.[118] Sodium deficit can be detected via urine sodium excretion and may be particularly useful in infants with persistent growth issues.[119] Past the age of 2 years, the CFF has no specific recommendations for salt intake for individuals with CF, other than using the salt shaker at meals and providing additional sources of salt when exercising and/or exposed to excessive heat. However, other guidelines outside of the USA have more specific recommendations for salt intake.[120] Measurement of chloride levels during sweat tests has traditionally been the method of confirming the diagnosis of CF.[117,121] Cases of hyponatremic dehydration have been described in individuals with CF during infancy and during periods of excessive sweating, mainly during heat waves.[122,123] Changes in sweat chloride levels have been the basis of ongoing research, used as a secondary outcome examining the efficacy of modulator therapy. Although ivacaftor causes an overall significant decrease in sweat chloride levels, the changes are variable and, so far, do not seem to be associated with improvements in lung function.[124] It is yet unknown whether salt recommendations should be modified in individuals with CF after starting HEM therapy. Additionally, some patients experienced only mild decreases in chloride levels, and it is unknown whether there is variation in losses from day to day or during periods of increased sweating.[119,120] There is some evidence that ivacaftor raises blood pressure in adults with CF,[125] and hypertension may be problematic in the posttransplant population as well. Individuals with portal hypertension may be advised to limit salt intake owing to ascites; however, this recommendation is met with controversy.[126] Additionally, not all individuals are "salt sensitive," and it can be challenging to identify those who have a significant blood pressure response to excess sodium intake.[127] Individualized recommendations may be needed in these situations, focusing on extra salt intake only in situations in which excess salt loss is expected to occur (ie, exercise, heat).

Zinc

Zinc is essential for many metabolic pathways and several enzymes. It has significant antioxidant and

anti-inflammatory activity.[128] Zinc has been shown to influence growth and development, protein and DNA synthesis, wound healing, oxidation, and cellular immune responses.[128,129] Common dietary sources of zinc include meat, fish, and fortified foods. Most CF-specific vitamins contain zinc. Zinc deficiency is a risk in infants who are exclusively breastfed beyond 6 months of age, and meat/fortified cereal can be considered as a first food in this scenario. Young children who consume excessive soy-based beverages may have lower bioavailability of zinc due to the presence of phytates.[130,131]

Zinc deficiency can occur in the setting of diarrhea, including steatorrhea caused by untreated or undertreated pancreatic insufficiency.[132] Acrodermatitis enteropathica–like presentation has been reported in infants newly diagnosed with CF who have not yet started enzyme replacement; however, reports of this condition are rare since the advent of newborn screening.[133] Zinc deficiency has been associated with growth failure and reduced growth velocity.[132] In a cross-sectional study of 30 infants with CF diagnosed by newborn screen, plasma zinc was significantly lower in one-third of the infants and improved after initiating PERT.[134,135] In adults with CF, low zinc levels were associated with adverse clinical outcomes.[136] Measurement of zinc (Red blood cell or plasma zinc level) does not necessarily reflect zinc status.[137] In 62 children with CF, plasma zinc did not correlate with growth and pulmonary status.[138]

Both CFF and European guidelines recommend an empiric trial of zinc for 6 months in infants < 2 years of age with unexplained growth failure despite adequate caloric intake and PERT.[3,39] However, studies also demonstrated no improvement of growth with zinc supplementation.[139] In a double-blinded placebo-controlled study of 26 children with CF, intake of 30 mg of zinc daily for a year decreased the requirement of oral antibiotics for pulmonary infections.[140] The effect of zinc supplementation was higher in children who had low plasma zinc levels at baseline compared with those children who had higher levels at baseline.[140] Also, prolonged high doses of zinc supplementation can lead to copper deficiency and should be carefully monitored.[141] Serum zinc levels are not sensitive in early stages of deficiency, and lower levels are noted in cases of prolonged and severe zinc deficiency.[142]

Calcium and bone health

Along with vitamin D and vitamin K, calcium intake should be optimized for bone health.[143] Patients with CF have poor bone health secondary to many factors such as CFTR dysfunction, corticosteroids use, poor nutrition, decreased physical activity (particularly, reduced weight-bearing exercise), pubertal delay, and systemic inflammation.[144] Patients with CF may have deficient calcium status due to multiple reasons, such as vitamin D deficiency or reduced calcium intake or absorption.[4,36] Recommended calcium intake depends on age and sex.[4,36] Some patients with respiratory problems are hesitant to include milk in the diet because of perceived concerns regarding increased mucus production, and clinicians should thoroughly counsel against this perception.[145] In patients with ongoing fat malabsorption, the unabsorbed intestinal fat can chelate unbound calcium, which decreases the calcium available to sequestrate intestinal oxalate, thereby promoting intestinal oxalate absorption.[146] This enhanced oxalate absorption can possibly predispose patients with CF to renal stones. Also, clinicians should be aware that calcium is not included in any of the CF-specific vitamin products and calcium intake should be screened annually.[36]

Magnesium

Magnesium is essential for muscle and nerve function and bone health and is a cofactor for many enzymatic reactions. Low magnesium levels in patients with CF are increasingly recognized, and the causes could be multifactorial—eg, increased renal loss secondary to proximal convoluted tubular damage from frequent aminoglycosides (used for *Pseudomonas* infections), decreased absorption, malnutrition, CF-related diabetes, and medications such as calcineurin inhibitors in transplant recipients.[147,148] Recombinant human deoxyribonuclease efficacy can be decreased in the presence of concomitant magnesium deficiency.[149] Higher doses of oral magnesium supplements can result in diarrhea, and intravenous magnesium may be needed to rapidly replenish the magnesium levels if the levels are severely low. Hypomagnesemia could predispose critically ill patients to recalcitrant hypokalemia and hypocalcemia.[150] There is no evidence to recommend routine monitoring and evaluation of magnesium status in CF.

Water-soluble vitamins

There are no recommendations for specific doses of water-soluble vitamin supplementation in CF.[3] Most CF vitamin preparations contain multivitamins, including water-soluble vitamins, listed as daily values. As nutrition intake and nutrition status improve in CF owing to HEMs, it would be beneficial to reexamine the CF vitamin preparations and necessity to include water-soluble vitamins.

CONCLUSIONS AND FUTURE DIRECTIONS

Except for vitamin D deficiencies, overt deficiencies in fat-soluble vitamins and trace minerals are not seen commonly in routine clinical practice. Higher levels of vitamins, particularly vitamin A, are increasingly recognized in selective populations such as those after lung transplant and after initiation of HEMs. Currently, the FDA has approved the elexacaftor/tezacaftor/ivacaftor combination for children ≥6 years of age. If this modulator is approved for younger children, one may expect some restoration of pancreatic function specifically in patients with heterozygous delta F508 mutation and the presence of a concomitant milder mutation.[151] In this scenario, the macronutrient recommendations, dosing of PERT, and dosing of fat-soluble vitamins may also need to be revised. Vitamin K is the least-studied fat-soluble vitamin, and an accurate test for detecting the deficient status such PIVKA-II or uc-OC is needed for clinical use. The role of many vitamins and minerals as antioxidants and immunomodulators is emerging, and further studies are needed to explore these roles.

AUTHOR CONTRIBUTIONS

Senthilkumar Sankararaman, Sara J. Hendrix, and Terri Schindler contributed to the conception and design of this review. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

CONFLICT OF INTEREST

Senthilkumar Sankararaman is a consultant for Nestlé. Sara J. Hendrix has no conflicts to declare. Terri Schindler has the following to declare: Chiesi (advisor and speaker's bureau), AbbVie (speaker's bureau), and Nestlé (advisor).

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