



An Argument for Vitamin D, A, and Zinc Monitoring in Cirrhosis

Andree H. Koop,^{*,♦} Omar Y. Mousa,^{*,♦}

Ly Elaine Pham,^{**} Juan E. Corral-Hurtado,^{*} Surakit Pungpapong,^{*,***} Andrew P. Keaveny^{*,***}

^{*} Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA.

^{**} Department of Internal Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, USA.

^{***} Department of Transplantation, Mayo Clinic, Jacksonville, FL, USA.

[♦] Contributed equally.

©2018 Mayo Foundation for Medical Education and Research.

ABSTRACT

Malnutrition is prevalent in cirrhosis. Vitamin and mineral deficiencies, including vitamin D, vitamin A, and zinc, are common and have been shown to correlate with survival. Our aim was to review the mechanisms of vitamin D, vitamin A, and zinc deficiencies in cirrhosis and the clinical assessment of affected patients, their outcomes based on the current literature, and management. This is a narrative review including the relevant literature for cirrhosis and vitamin D, vitamin A, and zinc deficiencies. Vitamin D deficiency has important effects in cirrhosis, regardless of the cause of chronic liver disease. These effects include associations with fibrosis and outcomes such as infections, hepatocellular carcinoma, and mortality. Vitamin A deficiency is associated with liver disease progression to cirrhosis and clinical decompensation, including occurrence of ascites or hepatic encephalopathy. Zinc deficiency can lead to hepatic encephalopathy and impaired immune function. Such deficiencies correlate with patient survival and disease severity. Caution should be applied when replacing vitamin D, vitamin A, and zinc to avoid toxicity. Identification and appropriate treatment of vitamin and mineral deficiencies in cirrhosis may reduce specific nutritional and cirrhosis-related adverse events. Routine monitoring of vitamin A, vitamin D and zinc levels in cirrhosis should be considered.

Key words. Cirrhosis. Vitamin A deficiency. Vitamin D deficiency. Zinc deficiency.

INTRODUCTION

Severe malnutrition has been associated with adverse outcomes among patients with cirrhosis and following liver transplantation.¹⁻³ The prevalence of malnutrition in cirrhosis is reported to be 50% to 90%, and the nutritional status predicts morbidity and mortality in this patient population. Multiple factors contribute to malnutrition, including increased resting energy expenditure and hypermetabolism, fat maldigestion and malabsorption, altered macronutrient metabolism, anorexia and micronutrient deficiencies. Fat malabsorption, use of diuretics, and anorexia contribute to micronutrient deficiencies.⁴

Vitamin and mineral deficiencies are common in cirrhosis regardless of the etiology. Previous studies investigated the effect of vitamin D, vitamin A, and zinc

deficiencies individually in patients with cirrhosis.⁵⁻¹⁰ Vitamin D deficiency was associated with hepatic decompensation and higher mortality rates.^{6,8,10} Vitamin A deficiency was frequent in patients with cirrhosis and may also have predicted a more severe disease course.¹¹ Zinc deficiency correlated with survival and the severity of disease.⁹ Although these micronutrients have been studied individually in cirrhosis, to our knowledge there has not been a comprehensive review of these deficiencies to date. Furthermore, specific recommendations regarding the clinical assessment and treatment of these deficiencies in cirrhosis are poorly standardized. The current guidelines from the American Association for the Study of Liver Diseases (AASLD) regarding liver transplantation evaluation recommend measuring vitamin D with no further recommendations on measurement of vitamin A and zinc levels.¹²

In this narrative review, we discuss the mechanisms of vitamin D, vitamin A, and zinc deficiencies in cirrhosis and the clinical assessment of affected patients, their outcomes based on the current literature, and appropriate further management.

VITAMIN D DEFICIENCY IN CIRRHOSIS

Vitamin D deficiency occurs in up to 1 billion people worldwide and approximately 25% to 50% of the adult population in the United States.^{13,14} Vitamin D is an important secosteroid most widely known for its role in calcium homeostasis and bone mineralization, but has gained recognition for its extraskelatal effects, including the pathophysiology and treatment of chronic diseases, the immune system, and cellular proliferation and differentiation.¹⁵⁻¹⁷ First reported in patients with cirrhosis in the 1970s, inadequate levels of vitamin D are common in cirrhosis, occurring in up to 93% of patients, with severe vitamin D deficiency being present in as many as one-third of patients.¹⁵ Epidemiologic, clinical, and diagnostic information regarding deficiency of vitamin D are listed in table 1.^{8,10,15,18-23} Vitamin D deficiency occurs in cirrhosis of all etiologies, and is not limited to patients with cholestatic liver disease (Table 2).^{5,15,24-53} Prior to the year 2000, the majority of studies on vitamin D deficiency in cirrhosis focused on bone demineralization and metabolism. Over the past 2 decades, there have been advances in the understanding of the pathophysiology of vitamin D deficiency and its relation to chronic liver disease.²⁵ Vitamin D deficiency has important implications in chronic liver disease, including associations with the degree of fibrosis and outcomes, such as infections, hepatocellular carcinoma, and mortality.^{8,10,37,54-56}

Vitamin D Metabolism

The liver plays an important role in the metabolism of vitamin D, where it is hydroxylated into 25-hydroxyvitamin D (25[OH]D), the major circulating form, which is generally tested to determine a patient's vitamin D status. 25(OH)D is transported to the kidneys where it undergoes a second hydroxylation to the active form 1,25-dihydroxyvitamin D (1,25[OH]D).¹⁶

Mechanisms for Deficiency

The etiology of vitamin D deficiency in liver disease is generally multifactorial, including decreased oral absorption (eg, cholestatic liver disease or portal hypertensive enteropathy) and decreased exposure to ultraviolet light. Patients with severe cholestasis have decreased absorption of vitamin D compared to patients with milder disease.²³

Patients with severe parenchymal disease or obstructive hepatic disease may have reduced synthesis of 25(OH)D. However, the majority of the liver must be dysfunctional before synthesis is reduced.⁵⁷ Other risk factors for vitamin D deficiency include high latitudes, seasonal variation with decreased sun exposure, obesity, medications increasing vitamin D metabolism, and chronic medical conditions, such as chronic kidney disease, leading to decreased synthesis of 1,25(OH)D.⁵⁸ Cirrhosis, non-white race, acute decompensation of cirrhosis, and triceps skin fold thickness (a measurement for estimating body fat) are associated with lower vitamin D levels.⁵⁹

Clinical Assessment and Laboratory Testing

The symptoms of vitamin D deficiency are nonspecific and include fatigue, weakness, anxiety, depressed mood, and bone, muscle, or joint pain. The symptoms may overlap with other medical comorbidities, including cirrhosis, fibromyalgia, myopathy, or chronic fatigue.⁶⁰ Vitamin D is important for bone mineralization, and severe deficiency is associated with rickets in children and osteomalacia in adults.¹⁶

In the general population, optimal vitamin D levels range from 30 to 50 ng/mL. Vitamin D deficiency is generally defined as serum 25(OH)D levels < 20 ng/mL. Levels of 25(OH)D < 30 ng/mL are associated with an increase in parathyroid hormone, and 25(OH)D levels between 20 to 32 ng/mL are associated with an increase in intestinal calcium transport.^{61,62} As such, a vitamin D level of 21 to 29 ng/mL is generally considered a relative deficiency.¹³ There is no consensus definition regarding the optimal vitamin D level for patients with chronic liver diseases, including cirrhosis.²⁵

Cellular Changes and Clinical Outcomes

Vitamin D deficiency correlates with the severity of underlying chronic liver disease and is associated with worse outcomes.^{20,50,63,64} In patients with cirrhosis and vitamin D deficiency, levels improve with oral vitamin D supplementation and fall without supplementation.⁶⁴ In a study of 75 cirrhotic patients in an outpatient liver clinic, vitamin D deficiency correlated with the Child-Pugh score and Model for End-Stage Liver Disease scores and was associated with hepatic decompensation and mortality.⁸ In a prospective study of 65 patients with cirrhosis over a 24-month period, low vitamin D levels were associated with increased mortality.¹⁰ In a study of 88 hospitalized patients with cirrhosis, a severe deficiency (vitamin D < 10 ng/mL) occurred in 56.8% of patients, with low levels of 25(OH)D being independently associated with

Table 1. Epidemiology, Clinical Findings, and Diagnosis of Vitamin D, Vitamin A, and Zinc Deficiency in Cirrhosis.

Epidemiologic, clinical, diagnostic information	Vitamin D	Vitamin A	Zinc
Prevalence	68%-86% ^{8,10,15,19,20}	- 28 - 35% ^{18,22} - 50% in HCV Child-Pugh class A-B - 70% in HCV Child-Pugh class C ²¹	- 83% of cirrhotics, mostly decompensated - 91% Child-Pugh class B - 94% Child-Pugh class C - 95% >15 MELD scores ²³
Risk factors	- Northern latitudes - Increasing age - Reduced sun exposure - Increased skin pigmentation - Obesity - Malabsorption syndromes - Cholestatic liver disease - Use of medications affecting vitamin D metabolism - Nephrotic syndrome - Chronic kidney disease - Heritable disorders - Primary hyperparathyroidism - Granulomatous disorders - Hyperthyroidism ^{58,92}	- Female sex - Poor nutritional intake - Endemic areas - Alcohol abuse - Cholestatic liver disease: PBC, CFLD, Alagille syndrome.	- Poor nutritional intake - Hypoalbuminemia - Alcohol abuse - Diuretic use - Low zinc absorption - Portacaval shunt
Clinical findings	- Symptoms: bone pain, muscle weakness, fatigue, fractures, falls - Laboratory abnormalities: hypocalcemia, hypophosphatemia, secondary hyperparathyroidism. - Nonskeletal actions of vitamin D: increased risk of cancer; cardiovascular disease; and autoimmune diseases, including type 1 diabetes, multiple sclerosis, Crohn's disease.	- Ocular: xerophthalmia, Bitot spots, corneal xerosis, keratomalacia, night blindness, and retinopathy ^a - Musculoskeletal: poor bone growth. - Skin: nonspecific dermatologic problems, like hyperkeratosis, phrynoderma (follicular hyperkeratosis), and destruction of hair follicles with replacement by mucus glands. - Immune: impaired humoral and cell-mediated immunity via direct and indirect effects on the phagocytes and T cells.	- Poor wound healing - Bullous pustular dermatitis - Alopecia - Diarrhea - Psychologic impairment-hepatic encephalopathy - Weight loss - Infections secondary to cell-mediated immunity dysfunction - Hypogonadism in men - Impaired night vision - Acrodermatitis enteropathica - Necrolytic acral erythema - Anorexia with altered taste/smell
Best diagnostic test	25-hydroxyvitamin D	Visual dark adaptation test Fasting serum vitamin A level	- Fasting serum/plasma zinc level

CFLD: cystic fibrosis-related liver disease. HCV: hepatitis C virus. MELD: Model For End-Stage Liver Disease. PBC: primary biliary cholangitis. ^a Advanced stages may be irreversible.

bacterial infections, including bacteremia, urinary tract infections, and spontaneous bacterial peritonitis.⁵⁴

Vitamin D Replacement in Cirrhosis

Treatment recommendations for vitamin D deficiency are listed in table 3.⁶⁵⁻⁶⁹ The Endocrine Society Clinical

Practice Guidelines (ESCPG) recommend screening for vitamin D deficiency in patients at high risk, including those with hepatic failure, although this term is not specifically defined.⁶⁶ The European Association for the Study of the Liver (EASL) and the AASLD recommend consideration of supplementation of vitamin D for all patients with cholestatic disease for the prevention of osteoporosis.^{70,71} In their guidelines, the two societies

Table 2. Vitamin D deficiency in different etiologies of chronic liver disease.

Liver Disease Etiology	Study	Conclusions
Hepatocellular carcinoma	Finkelmeier, <i>et al.</i> 2014 ³⁷	- Severe vitamin D deficiency correlated with the highest mortality risk. Very low vitamin D levels were associated with mortality, independent of the MELD score and high α -fetoprotein levels (> 400 ng/mL).
	Hepner, <i>et al.</i> 1976 ²⁴	- 200 patients with HCC; mean serum vitamin D level was negatively correlated with the stage of cirrhosis and stages of HCC.
Alcoholic steatohepatitis	Anty, <i>et al.</i> 2015 ²⁷	- In 101 patients with alcohol abuse who underwent liver biopsy, 85.4% of patients with alcoholic steatohepatitis and 80% with bridging fibrosis had vitamin D deficiency. 60.4% of the patients had a severe 25(OH)D deficiency (< 10 ng/mL).
	Savic, <i>et al.</i> 2018 ⁵⁰	- In 50 patients with alcoholic cirrhosis, a higher level of vitamin D was related to a lower Child-Pugh score. Supplementation of vitamin D 1000 IU per day was associated with an increase in vitamin D levels and decrease in Child-Pugh score.
Nonalcoholic fatty liver disease	Hyponen, <i>et al.</i> 2008 ⁴³ Ford, <i>et al.</i> , 2005 ³⁸	- Vitamin D may play a role in NAFLD; vitamin D deficiency has been associated with a higher incidence of metabolic syndrome and insulin resistance.
	Eliades, <i>et al.</i> 2013 ³³ Barchetta, <i>et al.</i> 2011 ²⁹	- Patients with NAFLD have lower serum 25(OH)D levels when compared to those without NAFLD.
	Targher, <i>et al.</i> 2007 ⁵¹	- In 60 patients with NAFLD, decreased levels of vitamin D were associated with hepatic steatosis, necroinflammation, and fibrosis on biopsy.
	Dasarathy, <i>et al.</i> 2014 ³¹	- Plasma vitamin D was significantly lower in patients with nonalcoholic steatohepatitis compared to steatosis alone. Lower plasma vitamin D concentrations were associated with increasing scores of steatosis, fibrosis, and hepatocyte ballooning.
	El-Sherbiny, <i>et al.</i> 2018 ³⁴	- In a rat model of NAFLD, vitamin D administration reduced liver enzymes, attenuated liver inflammation and fibrosis, and improved lipid profiles. Compared to conventional vitamin D therapy, vitamin D nanoemulsion was superior in prevention of high fat diet-induced liver injury.
Chronic hepatitis C	Backstedt, <i>et al.</i> 2017 ²⁸	- In a study of 218 patients with chronic hepatitis C who completed direct acting antiviral therapy, neither the pre-treatment vitamin D level nor the change in level during treatment were predictive of treatment response.
	Gentile, <i>et al.</i> 2015, ⁴⁰ Terrier, <i>et al.</i> 2012 ⁵²	- Severe vitamin D deficiency has been associated with extrahepatic manifestations of HCV, including mixed cryoglobulinemia and vasculitis.
	Gal-Tanamy, <i>et al.</i> 2011, ³⁹ Matsumura, <i>et al.</i> 2012 ⁴⁹	- Two <i>in vitro</i> studies on hepatocytes suggest that vitamin D may have direct antiviral activity against HCV, occurring at the level of virus assembly. - Further research is needed into the role of vitamin D deficiency and supplementation with newer HCV antiviral therapies.
Chronic hepatitis B	Kong, <i>et al.</i> 2013, ⁴⁵ Farnik, <i>et al.</i> 2013, ³⁶ Maggi, <i>et al.</i> 2015, ⁴⁸ Wong, <i>et al.</i> 2015, ⁵³	Vitamin D deficiency is common in chronic hepatitis B infection.
	Farnik, <i>et al.</i> 2013 ³⁶	- Lower levels of vitamin D are associated with greater hepatitis B virus replication.

Primary biliary cholangitis	Gossard, <i>et al.</i> 2014 ⁴¹	- Increased risk of fat soluble vitamin deficiencies due to decreased availability of bile salts necessary for absorption in the intestinal lumen.
	Barchetta, <i>et al.</i> 2011 ²⁹	- In a study of 79 patients with PBC, 33% had a vitamin D level of 10 ng/mL or lower vs. 7% of controls.
	Agmon-Levin, <i>et al.</i> 2015 ²⁶	- Vitamin D levels correlated with advanced liver disease, as defined by stage III or IV fibrosis on liver biopsy.
	Luong, <i>et al.</i> 2013 ⁴⁷	- Vitamin D has been implicated in the pathogenesis of PBC. Specifically, vitamin D has a role in regulating cell signaling mechanisms, including matrix metalloproteinases, prostaglandins, reactive oxygen species, and transforming growth factor β , which may be implicated in the disease process.
	Li, <i>et al.</i> 2014, ⁴⁶ Fang, <i>et al.</i> 2015 ³⁵	- The vitamin D receptor is expressed by human immune cells and exerts a modulatory influence on T- and B-cell function. Polymorphisms in the vitamin D receptor have been associated with increased risk for PBC.
	Guo, <i>et al.</i> 2015 ⁴²	- Patients with PBC and lower baseline 25(OH)D levels may be less likely to respond to treatment.
Primary sclerosing cholangitis	Jorgensen, <i>et al.</i> 1995 ⁴⁴	- In a study of 56 patients with PSC and 87 patients with advanced PSC under evaluation for LT, vitamin D deficiency occurred in 14% and 57% of patients, respectively.
Autoimmune hepatitis	Efe, <i>et al.</i> 2014 ³²	- In patients with autoimmune hepatitis, severe deficiency of 25(OH)D has been associated with advanced fibrosis and severe interface hepatitis. Lower levels of 25(OH)D have been associated with treatment nonresponders.
Liver transplantation	Chaney, <i>et al.</i> 2015 ⁵	- Common in cirrhotic patients awaiting liver transplantation, occurring in up to 84%.
	Bitetto, <i>et al.</i> 2010 ³⁰	- In 133 liver transplant recipients, moderate to severe rejection episodes were independently associated with progressively lower pretransplant serum 25(OH)D levels. Early supplementation with vitamin D was independently associated with a lack of liver allograft cellular rejection.

HCC: hepatocellular carcinoma. HCV: hepatitis C virus. LT: liver transplantation. MELD: Model for End-Stage Liver Disease. NAFLD: nonalcoholic fatty liver disease. PBC: primary biliary cholangitis. PSC: primary sclerosing cholangitis.

indicated that the cutoffs for vitamin D deficiency and insufficiency are a serum 25(OH)D level < 20 ng/mL and a level between 21 to 29 ng/mL, respectively. According to the ESCPG, all adults who have vitamin D deficiency should be treated with 50,000 IU/week of vitamin D2 or D3 for 8 weeks or 6,000 IU/day of vitamin D2 or D3 to achieve a serum level of 25(OH)D > 30 ng/mL.⁶⁶ This should be followed by maintenance therapy of 1,500 to 2,000 IU/day. Higher daily doses (6,000-10,000 IU) are recommended in patients with obesity, a history of malabsorption syndromes, and patients on medications affecting vitamin D metabolism to achieve a 25(OH)D level above 30 ng/ml, followed by mainte-

nance therapy of 3,000 to 6,000 IU/day.⁶⁶ In patients with cholestatic liver disease, the EASL recommends 400 to 800 IU/day and the AASLD recommends 1,000 IU/day for the prevention of osteoporosis.⁷⁰⁻⁷³ Other than these recommendations, there are not specific guidelines for vitamin D supplementation in cirrhosis. A Cochran review, which included 15 randomized clinic trials and 1,034 participants, was performed to assess the effects of vitamin D supplementation on individuals with chronic liver diseases. They found that the evidence was uncertain regarding vitamin D supplementation and its effects on mortality or other adverse events.⁷²

Table 3. Treatment of vitamin D, vitamin A, and zinc deficiency in cirrhosis.

Treatment	Vitamin D	Vitamin A	Zinc
Daily intake and replacement recommendations	<ul style="list-style-type: none"> - Adequate daily intake: age 19-50: 600 IU/day, age 50-70: 600-800 IU/day - Deficiency (25-hydroxyvitamin D < 20 ng/mL): 50,000 IU/week vitamin D2 or D3 for 8 weeks or 6,000 IU/day of vitamin D2 or D3, with goal level > 30 ng/mL, followed by maintenance therapy 1,500-2,000 IU/day.⁶⁶ 	<ul style="list-style-type: none"> - Adequate intake: 5-10 µg/day.⁶⁵ - Recommended dietary allowances: 0.7 mg/day RAE for men, 0.9 mg/day RAE for women.⁶⁵ - Replacement: 60 mg/day RAE (200,000 IU/day) in 3 doses. 	<ul style="list-style-type: none"> - Recommended dietary allowances: 11 mg/day for men, 8 mg/day for women.⁶⁷ - Replacement: 50 mg/day of elemental zinc (220 mg zinc sulfate).
Comments	Higher daily maintenance doses (3,000-6,000 IU/day) may be required for patients with risk factors for vitamin D deficiency, including malabsorption syndromes. ⁶⁶	In patients not responding to vitamin A replacement, consider replacing zinc as well.	Replacing zinc itself might lead to normalization of vitamin A metabolism. ^{68,69}

RAE: retinol activity equivalents.

Vitamin D Toxicity

Vitamin D toxicity is rare, but can occur from excess supplementation as a fat soluble vitamin. Toxicity is generally caused by inadvertent or unintentional ingestion of excessively high doses. Doses greater than 50,000 IU/day can raise 25(OH)D levels to > 150 ng/mL, which is associated with hypercalcemia and hyperphosphatemia. Doses of 10,000 IU/day for up to 5 months generally do not cause toxicity.¹³ Hypercalcemia is generally responsible for the majority of symptoms of vitamin D toxicity. Early symptoms include gastrointestinal disturbances, such as anorexia, diarrhea, constipation, and nausea and vomiting. Symptoms occurring within days to weeks include bone, muscle, and joint pains, headaches, and arrhythmias. Other symptoms associated with hypercalcemia include frequent urination, excessive thirst, and kidney stones.⁷⁴

VITAMIN A DEFICIENCY IN CIRRHOSIS

Vitamin A deficiency is estimated to occur in up to two thirds of patients with cirrhosis.¹¹ In comparison, less than 1% of the US population are estimated at risk for vitamin A deficiency.⁷⁵ Prevalence is higher among patients with poor dietary intake and those living in endemic areas, women, alcoholics, patients with cholestatic

liver diseases (eg, primary biliary cholangitis [PBC], cystic fibrosis-related liver disease, and Alagille syndrome), and advanced or decompensated cirrhosis (Child-Pugh class C).^{11,21,76-80} In liver failure, elevated total bilirubin and higher body mass index are predictors of profound vitamin A deficiency.¹¹ Epidemiologic, clinical, and diagnostic information regarding deficiency of vitamin A are listed in table 1.

Mechanisms for Deficiency

Approximately 90% of vitamin A is stored in the liver and the remaining 10% is in adipose tissue. Specifically, 80% to 95% of retinol is stored in the small perisinusoidal cells (also known as stellate cells or Ito cells). These stores are notably depleted in patients who have alcohol abuse, advanced fibrosis, or cirrhosis. Multiple mechanisms overlap, causing vitamin A deficiency in cirrhosis:

- **Fat malabsorption.** Fat and fat-soluble vitamin malabsorption is common in cholestatic disorders due to insufficient or abnormal bile acids in the intestinal lumen. This mechanism is particularly important in cystic fibrosis-related liver disease, even in early stages with preserved exocrine pancreatic function.

- **Conversion of carotenoids.** Carotenoids and vitamin A undergo 3 main metabolic pathways in the liver: cleavage to form retinol, incorporation into and release as part of very low density lipoproteins, and storage.⁶⁵ All 3 functions are impaired with loss of hepatic parenchymal cells.
- **Transportation.** Retinol transport in the blood requires 2 specific proteins, retinol-binding protein and transthyretin (also known as prealbumin).⁶⁵ Both proteins are synthesized by hepatocytes. Serum levels of both proteins are remarkably decreased in liver cirrhosis.⁸¹ In PBC, impaired vitamin A mobilization outside the liver has been well described, despite adequate vitamin A absorption and sufficient hepatic stores.⁸²

Among all patients with cirrhosis, the severity of portal hypertension and the degree of portosystemic shunting influence the amount of vitamin A deficiency, suggesting there are additional endothelial mechanisms that have yet to be elucidated.⁶⁸

Clinical Assessment and Laboratory Testing

Clinical findings and adaptation tests are sufficient to diagnose vitamin A deficiency. Vitamin A deficiency correlates closely with the results of visual dark adaptation tests.⁸³ Deficiency has also been associated with decreased taste (bitter or salt) and olfaction (pyridine recognition), but the mechanism whereby vitamin A affects taste and smell remains unknown.⁸⁴ Vitamin replacement improves taste, olfaction, and generally normalizes dark adaptation testing.^{79,84} In nonresponders to vitamin A supplementation, adding zinc replacement leads to normalization of the visual adaptation tests. Clinical diagnosis can be supported by measurement of serum retinol levels, with low levels ($< 20 \mu\text{g/dL}$) or a decreased ratio of retinol to retinol binding protein (molar ratio < 0.8) suggesting deficiency.⁸⁵ Fasting specimens are preferred.

Earlier studies suggested that the retinol levels 5 h after a standard dose of oral vitamin A (called relative dose response) were appropriate to diagnose vitamin A deficiency.⁸⁶ Recent data show that both random serum retinol and relative dose response levels have significant variability and do not correlate well with vitamin A hepatic levels in patients with cirrhosis.^{18,21,87} Hepatic vitamin A stores are the ideal indicator of vitamin A status in cirrhosis, but currently there is no test available for clinical use. Serum carotene levels are typically low in patients with advanced liver disease, and decreased serum carotene is a surrogate marker for fat-soluble vitamin depletion.

Cellular Changes and Clinical Outcomes

Vitamin A deficiency promotes inflammation and can accelerate liver fibrogenesis. All-trans retinoic acid, a vitamin A active metabolite, has anti-inflammatory effects, and when deficient, exacerbates a proinflammatory pathway in the liver.⁸⁸

In alcoholic cirrhosis, vitamin A deficiency increases the expression of cytokeratin antigen in hepatocytes (with or without Mallory bodies) and cholangiocytes. Overexpression of the cytokeratin antigen correlates directly with the histologic and clinical severity of alcoholic liver disease.⁸⁹

In animal studies, vitamin A deprivation alters hepatocyte cord disposition, leading to an irregular parenchymal organization, and causes deposition of fat droplets in the cytoplasm of the hepatocytes. In addition, cytoplasmic changes in myofibroblastic-like cells at the perisinusoidal space and activation of hepatic stellate cells are seen. Once stellate cells are activated, they increase synthesis of extracellular components, specifically expression of hepatic fibronectin, laminin, and collagen type IV. These findings suggest that vitamin A deficiency promotes or accelerates hepatic fibrosis.⁹⁰

At a clinical level, vitamin A deficiency is associated with progression to cirrhosis and clinical decompensation. Increased total bilirubin, liver transaminases and prothrombin time, and presence of hepatic encephalopathy (HE) and ascites were related to lower serum retinol levels. Serum retinol values of $0.78 \mu\text{mol/l}$ or less were associated with increased liver-related death.²¹ Other reports did not show a significant association between vitamin A hepatic reserves and the occurrence of ascites or HE.¹⁸

Vitamin A Replacement

Oral vitamin replacement is safe and more efficient than intramuscular alternatives.⁹¹ For patients with ocular symptoms, 200,000 IU of vitamin A is given in 3 doses (Table 1). The first dose is given immediately on diagnosis, the second on the following day, and the third dose at least 2 weeks later. It is unclear if patients with liver cirrhosis benefit from additional doses.

Animal studies of PBC suggest that adding vitamin A to ursodeoxycholic acid significantly reduces the bile acid pool size and improves liver histology.^{93,94} Currently, there is no convincing clinical evidence supporting combined therapy in humans. Patients with cystic fibrosis-related liver disease often require higher doses of fat-soluble vitamin supplements compared to other patients with cystic fibrosis.⁷⁸

Vitamin A toxicity

Vitamin A supplementation (specifically synthetic vitamin A) at ten times the recommended dietary allowance, or about 50,000 IU per day can cause hepatotoxicity, venoocclusive disease, and cirrhosis.⁹⁵

ZINC DEFICIENCY IN CIRRHOSIS

Zinc is an important micronutrient in the human body. It is an essential element for multiple metabolic and enzymatic functions and is a critical cofactor for ammonia metabolism.⁹⁶⁻¹⁰¹ The global prevalence of zinc deficiency ranges from 4% in countries rich in animal protein and up to 73% in countries with plant-based diets.^{102,103} Zinc metabolism primarily occurs in the liver, and up to 83% of cirrhotic patients have zinc deficiency. Epidemiologic, clinical, and diagnostic information regarding zinc deficiency are listed in table 1.

Mechanisms for Deficiency

Zinc is mostly absorbed in the small intestine.¹⁰⁴⁻¹⁰⁶ The body stores the majority in skeletal muscle and bone with 11% being stored in the liver and skin.¹⁰⁷ Zinc is lost in the intestine from pancreatic secretions, in the nephrons from shedding of uroepithelial cells, and through sweat, semen, hair, and menstruation.^{107,108} Malnutrition and certain diseases, including cirrhosis, can lead to zinc deficiency.

Studies dating back to the 1950s have proposed multiple mechanisms through which patients with cirrhosis develop zinc deficiency.¹⁰⁹ Cirrhotic patients have decreased zinc absorption, hyperzincuria, decreased serum zinc concentrations, and decreased zinc content within the liver when compared to control groups.^{109,110}

Cirrhotic patients with ascites have severe muscle wasting due the catabolic state associated with a substantial loss of zinc in the urine.¹¹¹ Diuretic therapy also plays a factor as it increases renal zinc excretion and reduces serum albumin and the binding capacity for zinc.¹¹¹

Clinical Assessment and Laboratory Testing

Zinc deficiency has been shown to cause poor wound healing, alopecia, diarrhea, weight loss, hypogonadism in men, impaired night vision, anorexia with altered taste and smell, skin manifestations, including bullous pustular dermatitis, acrodermatitis enteropathica and necrolytic acral erythema, and psychologic impairment, such as HE. Along with clinical findings, data have suggested that zinc defi-

ciency occurs early in the course of liver disease and can lead to fatal manifestations in cirrhosis, including HE and impaired immune function.¹¹²⁻¹¹⁴

Typically, serum and plasma zinc levels are measured to assess the degree of zinc deficiency. However, levels are falsely reduced by a multitude of factors as only 0.1% of the total body pool is contained in the circulation. Examples include acute stress such as trauma, burns, blood loss, severe ischemia, major surgery, and infections. Zinc is closely bound to albumin in the circulation, and hypoalbuminemia has been related to zinc deficiency. Serum zinc levels are also influenced by diurnal variation and fasting.¹¹⁵ Response to zinc supplementation is monitored by evaluating the clinical response or improvement in zinc level.¹¹⁶

Biochemical Changes and Clinical Outcomes

As the main organ involved in maintaining zinc homeostasis, the liver alters zinc levels and is influenced by zinc deficiency. Turnover studies using zinc⁺⁺ showed that complete exchange of zinc in hepatocytes required less than 2 days.¹¹¹

Zinc is an important antioxidant involved in protection against oxidative stress. Zinc deficiency affects the power of the liver to regenerate, leading to cell and tissue damage through signaling cascades that damage enzymes and mitochondrial and ribosomal structures.¹¹¹ The oxidative stress can induce increased gut permeability with endotoxemia, infections such as spontaneous peritonitis, or release of stress hormones.¹¹¹

Zinc deficiency may contribute to impaired glucose tolerance and diabetes mellitus among patients with cirrhosis. Normalization of plasma zinc levels after long-term zinc treatment in advanced cirrhosis has been shown to improve glucose tolerance.¹¹⁷

Zinc deficiency is a key factor in the pathogenesis of HE as zinc is a crucial enzyme in the urea cycle to lower ammonia levels. Case studies and randomized controlled trials have shown that zinc supplementation improved cognitive function in patients with HE.^{109,111,116,118} In a double-blind randomized trial by Reding, et al.,¹¹⁸ 22 cirrhotic patients with HE were given zinc acetate 600 mg/day or a placebo for 7 days. Serum zinc was improved to normal by day 8, and supplemented patients showed improvement of HE in comparison to placebo.¹¹⁸ Another trial included 39 cirrhotic patients with HE who were given zinc supplementation with 225 mg of polprezinc in addition to standard therapy of a protein-restricted diet, branched chain amino acids, and lactulose, while 38 patients were treated with standard therapy for 6 months. Zinc supplementation significantly improved HE and

health-related quality of life as measured by the SF-36 questionnaire.¹¹⁹ At a clinical level, zinc deficiency is associated with progression to cirrhosis and clinical decompensation.

Zinc Replacement

The dose of zinc used to treat zinc deficiency among cirrhotics is usually 50 mg of elemental zinc (zinc sulfate 220 mg), taken with a meal to prevent nausea. Doses > 50 mg/day of elemental zinc are not recommended due to the potential risk of impaired copper absorption and immune suppression.¹¹⁶

Zinc toxicity

Zinc is relatively harmless, and toxicity only occurs after exposure to high doses.^{120,121} In humans, the LD50 of zinc, the amount of a substance expected to cause death in 50% of test subjects, is estimated to be 27g per day.¹²² In comparison, the recommended daily allowance of elemental zinc is 11 mg/day zinc for men and 8 mg/day for women. Intake of toxic doses of zinc is difficult, as 225-400 mg zinc is associated with nausea and vomiting.¹²³ Symptoms of toxic zinc ingestion include abdominal pain and diarrhea.¹²¹ Copper deficiency is responsible for the other toxic effects of zinc. Ingestion of large doses of zinc over a prolonged period of time is associated with copper deficiency through competitive absorption between zinc and copper within enterocytes. Signs of copper deficiency include anemia, leukopenia, neutropenia, elevated cholesterol levels, and abnormal cardiac function.¹²¹

CONCLUSION

In summary, we provided a review of vitamin D, vitamin A, and zinc deficiency in cirrhosis. These deficiencies are common regardless of the etiology of liver disease. They occur by multiple mechanisms and correlate with disease severity, morbidity, and survival. Testing for vitamin D, vitamin A, and zinc is feasible, and repletion is practical. Current hepatology guidelines do not provide specific recommendations regarding the treatment of such deficiencies in cirrhosis. Given the individual associations of these micronutrient deficiencies with outcomes, we suggest that physicians consider routine monitoring of these levels in patients with cirrhosis and provide supplementation when a deficiency is documented. Future research is needed into the optimal regimens and benefit of treating vitamin and mineral deficiencies in patients with cirrhosis.

ABBREVIATIONS

- **AASLD:** American Association for the Study of Liver Diseases.
- **EASL:** European Association for the Study of the Liver.
- **ESCPG:** Endocrine Society Clinical Practice Guidelines.
- **HE:** hepatic encephalopathy.
- **PBC:** primary biliary cholangitis.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest regarding the publication of this article.

ACKNOWLEDGMENTS

Tara J. Brigham, MLS, Mayo Clinic Winn-Dixie Foundation, Ann M. Farrell, MLS, Mayo Clinic Libraries, Mayo Clinic, Rochester, MN, for literature search.

REFERENCES

1. Dick AA, Spitzer AL, Seifert CF, Deckert A, Carithers RL, Jr., Reyes JD, Perkins JD. Liver transplantation at the extremes of the body mass index. *Liver Transpl* 2009; 15: 968-77.
2. Stephenson GR, Moretti EW, El-Moalem H, Clavien PA, Tuttle-Newhall JE. Malnutrition in liver transplant patients: preoperative subjective global assessment is predictive of outcome after liver transplantation. *Transplantation* 2001; 72: 666-70.
3. Thuluvath PJ. Morbid obesity and gross malnutrition are both poor predictors of outcomes after liver transplantation: what can we do about it? *Liver Transpl* 2009; 15: 838-41.
4. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. *Clin Gastroenterol Hepatol* 2012; 10: 117-25.
5. Chaney A, Heckman MG, Diehl NN, Meek S, Keaveny AP. Effectiveness and outcomes of current practice in treating vitamin D deficiency in patients listed for liver transplantation. *Endocr Pract* 2015; 21: 761-9.
6. Finkelmeier F, Kronenberger B, Zeuzem S, Piiper A, Waidmann O. Low 25-hydroxyvitamin D levels are associated with infections and mortality in patients with cirrhosis. *PLoS One* 2015; 10: e0132119.
7. Pescovitz MD, Mehta PL, Jindal RM, Milgrom ML, Leapman SB, Filo RS. Zinc deficiency and its repletion following liver transplantation in humans. *Clin Transpl* 1996; 10: 256-60.
8. Putz-Bankuti C, Pilz S, Stojakovic T, Scharnagl H, Pieber TR, Trauner M, Obermayer-Pietsch B, et al. Association of 25-hydroxyvitamin D levels with liver dysfunction and mortality in chronic liver disease. *Liver Int* 2012; 32: 845-51.
9. Sengupta S, Wroblewski K, Aronsohn A, Reau N, Reddy KG, Jensen D, Te H. Screening for zinc deficiency in patients with cirrhosis: when should we start? *Dig Dis Sci* 2015; 60: 3130-5.
10. Stokes CS, Krawczyk M, Reichel C, Lammert F, Grunhage F. Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. *Eur J Clin Invest* 2014; 44: 176-83.

11. Venu M, Martin E, Saeian K, Gawrieh S. High prevalence of vitamin A deficiency and vitamin D deficiency in patients evaluated for liver transplantation. *Liver Transpl* 2013; 19: 627-33.
12. Martin P, DiMartini A, Feng S, Brown R, Jr., Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; 59: 1144-65.
13. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266-81.
14. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone* 2002; 30: 771-7.
15. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010; 55: 2624-8.
16. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004; 80: 1689s-96s.
17. Iruzubieta P, Teran A, Crespo J, Fabrega E. Vitamin D deficiency in chronic liver disease. *World J Hepatol* 2014; 6: 901-15.
18. Arantes Ferreira Peres W, Villaca Chaves G, Saraiva Goncalves JC, Ramalho A, Moraes Coelho HS. Assessment of the relative dose-response test as indicators of hepatic vitamin A stores in various stages of chronic liver disease. *Nutr Clin Pract* 2013; 28: 95-100.
19. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol* 2007; 5: 513-20.
20. Malham M, Jorgensen SP, Ott P, Agnholt J, Vilstrup H, Borre M, Dahlerup JF. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. *World J Gastroenterol* 2011; 17: 922-5.
21. Peres WA, Chaves GV, Goncalves JC, Ramalho A, Coelho HS. Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. *Br J Nutr* 2011; 106: 1724-31.
22. Shen YM, Wu JF, Hsu HY, Ni YH, Chang MH, Liu YW, Lai HS, et al. Oral absorbable fat-soluble vitamin formulation in pediatric patients with cholestasis. *J Pediatr Gastroenterol Nutr* 2012; 55: 587-91.
23. Sitrin MD, Bengoa JM. Intestinal absorption of cholecalciferol and 25-hydroxycholecalciferol in chronic cholestatic liver disease. *Am J Clin Nutr* 1987; 46: 1011-5.
24. Hepner GW, Roginsky M, Moo HF. Abnormal vitamin D metabolism in patients with cirrhosis. *Am J Dig Dis* 1976; 21: 527-32.
25. Konstantakis C, Tselekouni P, Kalafateli M, Triantos C. Vitamin D deficiency in patients with liver cirrhosis. *Ann Gastroenterol* 2016; 29: 297-306.
26. Agmon-Levin N, Kopilov R, Selmi C, Nussinovitch U, Sanchez-Castanon M, Lopez-Hoyos M, Amital H, et al. Vitamin D in primary biliary cirrhosis, a plausible marker of advanced disease. *Immunol Res* 2015; 61: 141-6.
27. Anty R, Canivet CM, Patouraux S, Ferrari-Panaia P, Saint-Paul MC, Huet PM, Lebeauupin C, et al. Severe vitamin D deficiency may be an additional cofactor for the occurrence of alcoholic steatohepatitis. *Alcohol Clin Exp Res* 2015; 39: 1027-33.
28. Backstedt D, Pedersen M, Choi M, Seetharam A. 25-Vitamin D levels in chronic hepatitis C infection: association with cirrhosis and sustained virologic response. *Ann Gastroenterol* 2017; 30: 344-8.
29. Barchetta I, Angelico F, Del Ben M, Baroni MG, Pozzilli P, Morini S, Cavallo MG. Strong association between non alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. *BMC Med* 2011; 9: 85.
30. Bitetto D, Fabris C, Falletti E, Fornasiere E, Fumolo E, Fontanini E, Cussigh A, et al. Vitamin D and the risk of acute allograft rejection following human liver transplantation. *Liver Int* 2010; 30: 417-44.
31. Dasarathy J, Periyalwar P, Allampati S, Bhinder V, Hawkins C, Brandt P, Khiyami A, et al. Hypovitaminosis D is associated with increased whole body fat mass and greater severity of non-alcoholic fatty liver disease. *Liver Int* 2014; 34: e118-27.
32. Efe C, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, Smyk DS, et al. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. *Dig Dis Sci* 2014; 59: 3035-42.
33. Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, Koteish AA, et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2013; 38: 246-54.
34. El-Sherbiny M, Eldosoky M, El-Shafey M, Othman G, Elkattawy HA, Bedir T, Elsherbiny NM. Vitamin D nanoemulsion enhances hepatoprotective effect of conventional vitamin D in rats fed with a high-fat diet. *Chem Biol Interact* 2018; 288: 65-75.
35. Fang F, Wang J, Pan J, Su GH, Xu LX, Li G. Relationship between vitamin D (1,25-dihydroxyvitamin D3) receptor gene polymorphisms and primary biliary cirrhosis risk: a meta-analysis. *Genet Mol Res* 2015; 14: 981-8.
36. Farnik H, Bojunga J, Berger A, Allwinn R, Waidmann O, Kronenberger B, Keppler OT, et al. Low vitamin D serum concentration is associated with high levels of hepatitis B virus replication in chronically infected patients. *Hepatology* 2013; 58: 1270-6.
37. Finkelmeier F, Kronenberger B, Koberle V, Bojunga J, Zeuzem S, Trojan J, Piiper A, et al. Severe 25-hydroxyvitamin D deficiency identifies a poor prognosis in patients with hepatocellular carcinoma - a prospective cohort study. *Aliment Pharmacol Ther* 2014; 39: 1204-12.
38. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care* 2005; 28: 1228-30.
39. Gal-Tanamy M, Bachmetov L, Ravid A, Koren R, Erman A, Tur-Kaspa R, Zemel R. Vitamin D: an innate antiviral agent suppressing hepatitis C virus in human hepatocytes. *Hepatology* 2011; 54: 1570-9.
40. Gentile I, Scarano F, Celotti A, E DEI, Scarano R, Granata V, Pinchera B, et al. Low vitamin D levels are associated with the presence of serum cryoglobulins in patients with chronic HCV infection. *In Vivo* 2015; 29: 399-404.
41. Gossard AA, Talwalkar JA. Cholestatic liver disease. *Med Clin North Am* 2014; 98: 73-85.
42. Guo GY, Shi YQ, Wang L, Ren X, Han ZY, Guo CC, Cui LN, et al. Serum vitamin D level is associated with disease severity and response to ursodeoxycholic acid in primary biliary cirrhosis. *Aliment Pharmacol Ther* 2015; 42: 221-30.
43. Hypponen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes*. 2008; 57: 298-305.
44. Jorgensen RA, Lindor KD, Sartin JS, LaRusso NF, Wiesner RH. Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. *J Clin Gastroenterol* 1995; 20: 215-9.

45. Kong J, Ding Y, Zhang C, Fu Y, Du J, Lu C, Dou X, et al. Severe vitamin D-deficiency and increased bone turnover in patients with hepatitis B from northeastern China. *Endocr Res* 2013; 38: 215-22.
46. Li YJ, Tang YW, Shi YQ, Han S, Wang JB, Zhou XM, Chen Y, et al. Polymorphisms in the vitamin D receptor gene and risk of primary biliary cirrhosis: a meta-analysis. *J Gastroenterol Hepatol* 2014; 29: 706-15.
47. Luong KV, Nguyen LT. The role of vitamin D in primary biliary cirrhosis: possible genetic and cell signaling mechanisms. *Gastroenterol Res Pract* 2013; 2013: 602321.
48. Maggi P, Montinaro V, Leone A, Fasano M, Volpe A, Bellacosa C, Grattagliano V, et al. Bone and kidney toxicity induced by nucleotide analogues in patients affected by HBV-related chronic hepatitis: a longitudinal study. *J Antimicrob Chemother* 2015; 70: 1150-4.
49. Matsumura T, Kato T, Sugiyama N, Tasaka-Fujita M, Murayama A, Masaki T, Wakita T, et al. 25-Hydroxyvitamin D3 suppresses hepatitis C virus production. *Hepatology* 2012; 56: 1231-9.
50. Savic Z, Vracaric V, Milic N, Niciforovic D, Damjanov D, Pellicano R, Medic-Stojanoska M, et al. Vitamin D supplementation in patients with alcoholic liver cirrhosis: a prospective study. *Minerva Med* 2018. doi: 10.23736/S0026-4806.18.05723-3.
51. Targher G, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, Arcaro G. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis* 2007; 17: 517-24.
52. Terrier B, Jehan F, Munteanu M, Geri G, Saadoun D, Sene D, Poynard T, et al. Low 25-hydroxyvitamin D serum levels correlate with the presence of extra-hepatic manifestations in chronic hepatitis C virus infection. *Rheumatology (Oxford)* 2012; 51: 2083-90.
53. Wong GL, Chan HL, Chan HY, Tse CH, Chim AM, Lo AO, Wong VW. Adverse effects of vitamin D deficiency on outcomes of patients with chronic hepatitis B. *Clin Gastroenterol Hepatol* 2015; 13: 783-90.e1.
54. Anty R, Tonohouan M, Ferrari-Panaia P, Piche T, Pariente A, Anstee QM, Gual P, et al. Low levels of 25-hydroxy vitamin D are independently associated with the risk of bacterial infection in cirrhotic patients. *Clin Transl Gastroenterol* 2014; 5: e56.
55. Lange CM, Bojunga J, Ramos-Lopez E, von Wagner M, Hasler A, Vermehren J, Herrmann E, et al. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. *J Hepatol* 2011; 54: 887-93.
56. Petta S, Camma C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010; 51: 1158-67.
57. Silva M, Gomes S, Peixoto A, Torres-Ramalho P, Cardoso H, Azevedo R, Cunha C, et al. Nutrition in chronic liver disease. *GE Port J Gastroenterol* 2015; 22: 268-76.
58. Bouillon R, Norman AW, Lips P. Vitamin D deficiency. *N Engl J Med* 2007; 357: 1980-1; author reply 1-2.
59. Costa Silva M, Erotides Silva T, de Alentar ML, Honorio Coelho MS, Wildner LM, Bazzo ML, Gonzalez-Chica DA, et al. Factors associated with 25-hydroxyvitamin D levels in patients with liver cirrhosis. *Ann Hepatol* 2015; 14: 99-107.
60. Arvold DS, Odean MJ, Dornfeld MP, Regal RR, Arvold JG, Karwoski GC, Mast DJ, et al. Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial. *Endocr Pract* 2009; 15: 203-12.
61. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997; 7: 439-43.
62. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003; 22: 142-6.
63. Jamil Z, Arif S, Khan A, Durrani AA, Yaqoob N. Vitamin D Deficiency and Its Relationship with Child-Pugh Class in Patients with Chronic Liver Disease. *J Clin Transl Hepatol* 2018; 6: 135-40.
64. Rode A, Fournalos S, Nicoll A. Oral vitamin D replacement is effective in chronic liver disease. *Gastroenterol Clin Biol* 2010; 34: 618-20.
65. Gropper SS, Smith JL, Groff JL. Advanced nutrition and human metabolism. 4th ed. Belmont, CA: Thomas Wadsworth; 2005.
66. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; 96: 1911-30.
67. Russell R, Beard JL, Cousins RJ, et al. Zinc. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, zinc: The National Academies Press; 2002, p. 442-501.
68. Scholmerich J, Becher MS, Kottgen E, Rauch N, Haussinger D, Lohle E, Vuilleumier JP, et al. The influence of portosystemic shunting on zinc and vitamin A metabolism in liver cirrhosis. *Hepatogastroenterology* 1983; 30: 143-7.
69. Scholmerich J, Lohle E, Kottgen E, Gerok W. Zinc and vitamin A deficiency in liver cirrhosis. *Hepatogastroenterology* 1983;30:119-25.
70. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. *J Hepatol* 2009; 51: 237-67.
71. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology* 2009; 50: 291-308.
72. Bjelakovic G, Nikolova D, Bjelakovic M, Gluud C. Vitamin D supplementation for chronic liver diseases in adults. *Cochrane Database Syst Rev* 2017; 11: CD011564.
73. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; 51: 660-78.
74. Alshahrani F, Aljohani N. Vitamin D: deficiency, sufficiency and toxicity. *Nutrients* 2013; 5: 3605-16.
75. Bird JK, Murphy RA, Ciappio ED, McBurney MI. Risk of Deficiency in Multiple Concurrent Micronutrients in Children and Adults in the United States. *Nutrients* 2017; 9.
76. Atukorala TM, Herath CA, Ramachandran S. Zinc and vitamin A status of alcoholics in a medical unit in Sri Lanka. *Alcohol Alcohol* 1986; 21: 269-75.
77. Clugston RD, Blaner WS. The adverse effects of alcohol on vitamin A metabolism. *Nutrients* 2012; 4: 356-71.
78. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros* 2011;10 Suppl 2: S29-36.
79. Herlong HF, Russell RM, Maddrey WC. Vitamin A and zinc therapy in primary biliary cirrhosis. *Hepatology* 1981; 1: 348-51.
80. Moisseiev E, Cohen S, Dotan G. Alagille syndrome associated with xerophthalmia. *Case Rep Ophthalmol* 2013; 4: 311-5.

81. Morley JE, Russell RM, Reed A, Carney EA, Hershman JM. The interrelationship of thyroid hormones with vitamin A and zinc nutritional status in patients with chronic hepatic and gastrointestinal disorders. *Am J Clin Nutr* 1981; 34: 1489-95.
82. Nyberg A, Berne B, Nordlinder H, Busch C, Eriksson U, Loof L, Vahlquist A. Impaired release of vitamin A from liver in primary biliary cirrhosis. *Hepatology* 1988;8:136-41.
83. Carney EA, Russell RM. Correlation of dark adaptation test results with serum vitamin A levels in diseased adults. *J Nutr* 1980; 110: 552-7.
84. Garrett-Laster M, Russell RM, Jacques PF. Impairment of taste and olfaction in patients with cirrhosis: the role of vitamin A. *Hum Nutr Clin Nutr* 1984; 38: 203-14.
85. de Pee S, Dary O. Biochemical indicators of vitamin A deficiency: serum retinol and serum retinol binding protein. *J Nutr* 2002; 132: 2895S-901S.
86. Mobarhan S, Russell RM, Underwood BA, Wallingford J, Mathieson RD, Al-Midani H. Evaluation of the relative dose response test for vitamin A nutriture in cirrhotics. *Am J Clin Nutr* 1981; 34: 2264-70.
87. Ukleja A, Scolapio JS, McConnell JP, Spivey JR, Dickson RC, Nguyen JH, O'Brien PC. Nutritional assessment of serum and hepatic vitamin A levels in patients with cirrhosis. *JPEN J Parenter Enteral Nutr* 2002; 26: 184-8.
88. Ouziel R, Trepo E, Cremer A, Moreno C, Degre D, Chaouni M, Vercruysse V, et al. Correction of all-trans retinoic acid deficiency in alcoholic cirrhosis lessens the excessive inflammatory monocyte response: a translational study. *Liver Int* 2014; 34: 343-52.
89. Ray MB, Mendenhall CL, French SW, Gartside PS. Serum vitamin A deficiency and increased intrahepatic expression of cytokeratin antigen in alcoholic liver disease. *Hepatology* 1988; 8: 1019-26.
90. Aguilar RP, Genta S, Oliveros L, Anzulovich A, Gimenez MS, Sanchez SS. Vitamin A deficiency injures liver parenchyma and alters the expression of hepatic extracellular matrix. *J Appl Toxicol* 2009; 29: 214-22.
91. Walt RP, Kemp CM, Lyness L, Bird AC, Sherlock S. Vitamin A treatment for night blindness in primary biliary cirrhosis. *Br Med J (Clin Res Ed)* 1984; 288: 1030-1.
92. Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. *Acta Derm Venereol* 2011; 91: 115-24.
93. Cai SY, Mennone A, Soroka CJ, Boyer JL. All-trans-retinoic acid improves cholestasis in alpha-naphthylisothiocyanate-treated rats and Mdr2-/- mice. *J Pharmacol Exp Ther* 2014; 349: 94-8.
94. He H, Mennone A, Boyer JL, Cai SY. Combination of retinoic acid and ursodeoxycholic acid attenuates liver injury in bile duct-ligated rats and human hepatic cells. *Hepatology* 2011; 53: 548-57.
95. Geubel AP, De Galocsy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. *Gastroenterology* 1991; 100: 1701-9.
96. Bartholomay AF, Robin ED, Vallee RL, Wacker WE. Zinc metabolism in hepatic dysfunction. I. Serum zinc concentrations in Laennec's cirrhosis and their validation by sequential analysis. *N Engl J Med* 1956; 255: 403-8.
97. Leoni G, Rosato A, Perozzi G, Murgia C. Zinc proteome interaction network as a model to identify nutrient-affected pathways in human pathologies. *Genes Nutr* 2014; 9: 436.
98. Maret W. Zinc and human disease. *Met Ions Life Sci* 2013; 13: 389-414.
99. Rink L, Haase H. Zinc homeostasis and immunity. *Trends Immunol* 2007; 28: 1-4.
100. Schliess F, Gorg B, Haussinger D. RNA oxidation and zinc in hepatic encephalopathy and hyperammonemia. *Metab Brain Dis* 2009; 24: 119-34.
101. Vallee BL, Wacker WE, Bartholomay AF, Hoch FL. Zinc metabolism in hepatic dysfunction, II: correction of metabolic patterns with biochemical findings. 257:1056-1065. *N Engl J Med* 1956; 257: 1055-65.
102. Caulfield LE, Black RE. Zinc Deficiency In: Ezzati M, Lopez AD, Rodgers A, Murray CJL (Eds.). *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. 1. Geneva: World Health Organization; 2004, p. 257-9.
103. Guilbert JJ. The world health report 2002 - reducing risks, promoting healthy life. *Educ Health (Abingdon)* 2003; 16: 230.
104. Cousins RJ. Theoretical and practical aspects of zinc uptake and absorption. *Adv Exp Med Biol* 1989; 249: 3-12.
105. Lee HH, Prasad AS, Brewer GJ, Owyang C. Zinc absorption in human small intestine. *Am J Physiol* 1989; 256: G87-G91.
106. Tuerk MJ, Fazel N. Zinc deficiency. *Curr Opin Gastroenterol* 2009; 25: 136-43.
107. Lonnerdal B. Intestinal Absorption of Zinc. In: Mills CF, (ed.). *Zinc in Human Biology*. New York, NY: Springer-Verlag; 1989, p. 33-56.
108. King JC, Shames DM, Woodhouse LR. Zinc homeostasis in humans. *J Nutr* 2000; 130: 1360S-6S.
109. Hanje AJ, Fortune B, Song M, Hill D, McClain C. The use of selected nutrition supplements and complementary and alternative medicine in liver disease. *Nutr Clin Pract* 2006; 21: 255-72.
110. Solis-Herruzo J, De Cuenca B, Munoz-Rivero MC. Intestinal zinc absorption in cirrhotic patients. *Z Gastroenterol* 1989; 27: 335-8.
111. Grungreff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. *Ann Hepatol* 2016; 15: 7-16.
112. Ilchyshyn A, Mendelsohn S. Zinc deficiency due to alcoholic cirrhosis mimicking acrodermatitis enteropathica. *Br Med J (Clin Res Ed)* 1982; 284: 1676.
113. Mangray S, Zweit J, Puri P. Zinc deficiency in cirrhosis: micronutrient for thought? *Dig Dis Sci* 2015; 60: 2868-70.
114. McClain C, Vatsalya V, Cave M. Role of zinc in the development/progression of alcoholic liver disease. *Curr Treat Options Gastroenterol* 2017; 15: 285-95.
115. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. *J Res Med Sci* 2013; 18: 144-57.
116. Van der Rijt CC, Schalm SW, Schat H, Foeken K, De Jong G. Overt hepatic encephalopathy precipitated by zinc deficiency. *Gastroenterology* 1991; 100: 1114-8.
117. Marchesini G, Bugianesi E, Ronchi M, Flaminia R, Thomaseth K, Pacini G. Zinc supplementation improves glucose disposal in patients with cirrhosis. *Metabolism* 1998; 47: 792-8.
118. Reding P, Duchateau J, Bataille C. Oral zinc supplementation improves hepatic encephalopathy. Results of a randomised controlled trial. *Lancet* 1984; 2: 493-5.
119. Takuma Y, Nouse K, Makino Y, Hayashi M, Takahashi H. Clinical trial: oral zinc in hepatic encephalopathy. *Aliment Pharmacol Ther* 2010; 32: 1080-90.
120. Fosmire GJ. Zinc toxicity. *Am J Clin Nutr* 1990; 51: 225-7.
121. Plum LM, Rink L, Haase H. The essential toxin: impact of zinc on human health. *Int J Environ Res Public Health* 2010; 7: 1342-65.

-
122. Maita K, Hirano M, Mitsumori K, Takahashi K, Shirasu Y. Subacute toxicity studies with zinc sulfate in mice and rats. *Nippon Nôyaku Gakkaishi* 1981; 6: 327-36.
123. Brown MA, Thom JV, Orth GL, Cova P, Juarez J. Food poisoning involving zinc contamination. *Arch Environ Health* 1964; 8: 657-60.

Correspondence and reprint request:

Andrew P. Keaveny, M.D.
Department of Transplantation, Mayo Clinic, 4500 San Pablo
Rd, Jacksonville, FL 32224. USA
Tel.: 904-956-3256. Fax: 904-956-3359
E-mail: Keaveny.Andrew@mayo.edu