

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Vitamin D Deficiency and Liver Disease

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G&H What is the connection between vitamin D deficiency and liver disease?

SN The liver produces 25-hydroxy (25-OH) vitamin D, also known as calcidiol, the immediate precursor to the metabolically active 1,25 dihydroxyvitamin D 1-25 vitamin D, also known as calcitriol. 25-OH vitamin D is the most abundant circulating form of vitamin D, and its measurement is used to assess vitamin D deficiency.

In patients with liver failure, the levels of 25-OH vitamin D can be low due to impaired synthesis. However, liver function needs to be severely compromised in order for this impairment to occur. Liver disease could also lead to impaired absorption of vitamin D, which is possibly connected to impaired bile acid production or gut edema associated with portal hypertension.

Low vitamin D levels and bone disease are well-recognized complications of “cholestatic” liver disease, which decreases the production or flow of bile. More recently, studies have confirmed low vitamin D levels in noncholestatic liver disease.

G&H What is the prevalence of vitamin D deficiency, according to your most recent study findings?

SN Vitamin D deficiency is extremely common in our patient population. We conducted a study of 118 patients with liver disease, and a total of 109 (92.4%) patients had some degree of vitamin D deficiency. This finding is also reflected in other reports. The deficiency was seen even in patients without liver failure, though

the severity of deficiency—expressed as very low levels of vitamin D (<7 ng/mL)—was more common in patients with cirrhosis (29.5% vs 14.1%; $P=.05$).

G&H What health benefits are connected to vitamin D?

SN A 2007 report in *The New England Journal of Medicine* noted several health benefits associated with vitamin D. More recently, vitamin D has been shown to play an important role in reducing the risk of many chronic diseases, including type 2 diabetes mellitus, cardiovascular diseases, cancers, and autoimmune and infectious diseases. These effects may be secondary to both local production of calcitriol and its autocrine and paracrine actions on cellular proliferation and differentiation, apoptosis, insulin and renin secretion, interleukin, and bactericidal proteins production.

G&H What health risks are posed by vitamin D deficiency?

SN Vitamin D is a key player in calcium absorption, and deficiency can lead to decreased calcium absorption, which can, in turn, cause bone diseases such as rickets or osteomalacia. These diseases are associated with prolonged and severe vitamin deficiency and are not seen in the western world. However, subclinical vitamin D deficiency (or vitamin D insufficiency) is extremely common and may contribute to the development of osteoporosis by decreasing absorption of calcium.

Vitamin D deficiency also causes muscle weakness, and adequate levels are required for optimal function and strength of the muscle. Studies have found low vitamin D levels to be associated with frequent falls.

G&H Does vitamin D deficiency impact treatment decisions for liver disease? If so, how?

SN Some liver disease can be associated with osteoporosis, and vitamin D deficiency can potentially exacerbate

that. Many post-transplant patients are also prone to accelerated bone loss, which could be worsened by vitamin D deficiency. Dangerously low levels of vitamin D may also increase some side effects of interferon therapy, such as muscle aches. There are some reports of hepatitis C patients with vitamin D deficiency responding poorly to interferon therapy.

G&H What are the treatments for vitamin D deficiency?

SN Vitamin D3 (cholecalciferol) is readily available over the counter, and there are many preparations with 400 IU of vitamin D and calcium. Vitamin D is also available at higher strengths (2,000 IU, 5,000 IU). Mega doses of vitamin D at 50,000 units are available as prescription. Vitamin D2 (ergo calciferol) is also available as 400 and 50,000 units.

Calcidiol, which does not require hepatic hydroxylation, is also available in patients with liver disease as 25–50 microgram capsules. The active form of vitamin D calcitriol is also available but is associated with a higher risk of hypercalcemia, if not monitored closely.

G&H Are new treatments for vitamin D deficiency currently being explored?

SN New treatments are not necessarily what is needed for vitamin D deficiency associated with liver disease. Rather, greater recognition of the problem is the priority.

G&H Are certain populations more susceptible to vitamin D deficiency than others? If so, is there any understanding about why?

SN Vitamin D is synthesized in the skin by ultraviolet rays from the sun; ultraviolet rays convert 7-dehydrocholesterol to vitamin D. Thus, anyone with less exposure to the sun is susceptible to vitamin D deficiency. For example, people who live in higher latitudes with long winters may have difficulty. In areas located above approximately 35° north latitude, little or no vitamin D can be produced between November and February. Likewise, people who cover their skin completely when outdoors could be more likely to experience vitamin D deficiency.

As discussed above, severe liver failure impairs hydroxylation of vitamin D and causes vitamin D deficiency. Other conditions that could decrease the bioavailability of vitamin D include a reduction in fat absorption associated with cystic fibrosis, celiac disease, Whipple disease, Crohn's disease, bypass surgery, and medications that reduce cholesterol absorption.

Anticonvulsants, glucocorticoids, and highly active antiretroviral therapy medications can activate the destruction of 25-OH vitamin D and 1,25-dihydroxyvitamin D, converting them into inactive calcitric acid. Obesity can lead to the sequestration of vitamin D in body fat, reducing its bioavailability.

Other factors that have been found to be associated with vitamin D deficiency include breastfeeding (increased risk for the infant), nephrotic syndrome, chronic kidney disease, and hyperphosphatemia.

G&H Is vitamin D deficiency in people with liver disease associated with any differences in outcome compared to liver disease patients without vitamin D deficiency?

SN A recent report published in *Hepatology* found a link between low vitamin D levels and severe fibrosis in patients with genotype 1 hepatitis C. The same study also found that patients with vitamin D deficiency had a lower chance of response to interferon.

There are some reports that low 25-OH vitamin D levels are associated with the more severe histologic changes of nonalcoholic fatty liver disease.

G&H How can vitamin D deficiency be prevented?

SN The best ways to prevent vitamin D deficiency are sun exposure, fortified food, and fish oil.

G&H What research is needed with regard to vitamin D deficiency associated with liver disease?

SN As noted above, clinicians and patients need to be more aware of the potential for and risks of vitamin D deficiency. Current research needs include evaluating the role of vitamin D supplementation to enhance treatment response among patients with hepatitis C and the role of actin-free vitamin D binding protein in hepatocellular carcinoma. In addition, it is important for us to learn the optimal duration and dose of vitamin D replacement for patients with liver failure.

G&H Should patients with liver disease be monitored for vitamin D deficiency?

SN Yes. All hepatologists should monitor vitamin D levels and treat deficient patients. The goal for all patients with chronic liver disease should be a 25-OH vitamin D level of 30 ng/mL. Anything less than 15–20 ng/mL is considered deficiency.

G&H Has vitamin D deficiency always been a problem for people with liver disease, or has this been changing recently?

SN It is likely that it was always a problem, but the data from the National Health and Nutrition Examination Survey indicate that the mean serum level of 25-OH vitamin D has decreased over the last 2 decades. It may be that the more severe vitamin D deficiency is only now coming to light.

Suggested Reading

Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357:266-281.

Petta S, Cammà C, Scazzone C, 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;51:1158-1167.

Holick MF. Vitamin D status: measurement, interpretation, and clinical application. *Ann Epidemiol.* 2009;19:73-78.

Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol.* 2007;5:513-520.