

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Could Vitamin D Supplementation Benefit Patients with Chronic Liver Disease?



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G&H Do vitamin D levels affect the progression of fibrosis or the development of cirrhosis in patients with chronic liver disease?

IB In a recent study, my coauthors and I found that patients with nonalcoholic fatty liver disease (NAFLD) had reduced serum levels of 25-hydroxy vitamin D—the biologically active form of vitamin D—compared to subjects without NAFLD (14.8±9.2 ng/mL vs 20.5±9.7 ng/mL, respectively; $P<.001$). Other research has shown that vitamin D levels correlate with the severity of non-alcoholic steatohepatitis (NASH) and NAFLD in a dose-dependent manner.

In general, patients who have a vitamin D deficiency have a greater degree of hepatic inflammation and fibrosis, and they likely have more rapid progression of fibrosis. In hepatitis C virus (HCV)-infected patients with related cirrhosis, the presence of vitamin D deficiency increases as the severity of liver dysfunction increases. In contrast, sufficient vitamin D levels (>50 nmol/L) decrease the occurrence of rapid fibrosis progression in patients with chronic hepatitis C (CHC).

G&H How does vitamin D alter disease progression in patients with chronic liver disease?

IB There are several potential mechanisms through which vitamin D may influence the degree of hepatic inflammation and/or the progression of fibrosis in patients with liver disease. First, studies have shown

that vitamin D acts as an immunomodulator, affecting both innate and adaptive immunity. Experimental data demonstrate that rats with severe vitamin D deficiency have higher levels of hepatic messenger RNA for several inflammatory markers—such as Toll-like receptor (TLR) 2, TLR 4, TLR 9, resistin, interleukin (IL)-1 β , IL-4, and IL-6—and for the oxidative stress marker heme oxygenase-1, compared to vitamin D-replete rodents. Moreover, the di-hydroxylated active form of vitamin D—denoted as 1 α ,25(OH) $_2$ D—has an anti-proliferative effect on adaptive immunity. It inhibits proliferation of T helper type 1 (Th1) lymphocytes, thus reducing the production of both interferon- γ and IL-2, reducing macrophage activation, and shifting the balance to a T helper type 2 phenotype, which is associated with increased production of IL-4, IL-5, and IL-10. In addition, 1 α ,25(OH) $_2$ D increases regulatory T cells, enhances the secretion of IL-10, and decreases the release from dendritic cells of IL-12 (a cytokine that is critical in Th1 development).

Second, several studies have shown that vitamin D inhibits HCV replication in a dose-dependent manner, which may explain the improvement in sustained virologic response (SVR) rates that has been observed when vitamin D is added to antiviral therapy.

Finally, low serum levels of vitamin D are associated with higher hepatic resistin gene expression, upregulation of hepatic inflammatory and oxidative stress genes, and insulin resistance, the latter of which is a key component in the pathogenesis and progression of both NASH and NAFLD.

G&H Could you briefly comment on some of the key studies that have shown an association between vitamin D levels and chronic liver disease?

IB The literature on vitamin D and chronic liver diseases is extensive. The first findings in this area regarded the high prevalence of vitamin D deficiency among individuals with different types of autoimmune liver disease, such as autoimmune hepatitis. Subsequently, studies demonstrated that vitamin D deficiency is present in approximately one third of individuals with chronic liver disease. Furthermore, baseline vitamin D status was found to influence the incidence of rejection after liver transplantation.

More recently, an association between vitamin D levels and NASH was observed in both adults and children. Finally, my coauthors and I recently demonstrated that expression of the vitamin D receptor (VDR) on liver cells was significantly reduced in patients with either NASH or CHC compared to subjects without liver disease. We also found that VDR expression in the liver is inversely correlated with the severity of liver inflammation and fibrosis.

G&H How do polymorphisms in the VDR impact the efficacy of vitamin D supplementation in patients with chronic liver disease?

IB The AA genotype of the CYP27B1 polymorphism is associated with higher SVR rates and higher serum levels of vitamin D in patients who are infected with HCV genotype 1. As CYP27B1 encodes 1 α -hydroxylase, the enzyme required for the bioactivation of 25(OH)D₃ to 1,25(OH)₂D₃ (calcitriol), this finding highlights how the active form of vitamin D is directly involved in influencing the response to therapy with pegylated interferon and ribavirin in patients with CHC. In contrast, the VDR bAt[CAA] haplotype and the CC genotype of the Apal allele are associated with rapid fibrosis progression and cirrhosis. These data suggest that the genetic predisposition to worse progression and prognosis of chronic liver disease may be mediated by vitamin D activity, among other things, as expressed by the presence and/or function of a specific VDR.

Despite the lack of data about the effect of vitamin D supplementation on the prognosis of liver diseases, evidence shows that different single nucleotide polymorphisms in the gene encoding the VDR may influence clinical responses to vitamin D supplementation in different settings. In particular, a recent study by Jain and colleagues demonstrated that vitamin D supplementa-

tion yielded greater improvements in insulin sensitivity among women with the FokI Ff genotype compared to those with the FokI FF genotype.

G&H What dose of vitamin D is appropriate for patients with chronic liver disease who are taking supplements?

IB There is still a lack of consensus regarding optimal vitamin D target levels and dosing strategies. Currently, I am conducting a study in which patients are receiving a dose of 2,000 units of vitamin D per day. This dose was also used in studies showing an improvement in SVR rates when vitamin D was added to interferon therapy in patients with HCV infection, as well as in studies of patients with cardiovascular disease or insulin resistance.

While I think 2,000 units per day is reasonable, liver disease patients may require higher doses in order to achieve serum levels of 25-hydroxy vitamin D above 20 ng/mL. Some studies in the literature suggest that reasonable daily doses would be 4,000 units of vitamin D per day for persons in the general population with severe vitamin D deficiency (<10 ng/mL) and 2,000 units per day for those with vitamin D insufficiency (10–20 ng/mL). The recommended dose of vitamin D for healthy adults is 800–1,000 units per day, but vitamin D may provide benefits at higher doses than have been traditionally recommended. In a 2006 study, researchers examined the association between 25-hydroxy vitamin D levels and various health outcomes, including bone mineral density, lower extremity function, dental health, risk of falls, risk of fractures, and risk of colorectal cancer; this study found that serum concentrations of vitamin D above 30 ng/mL were most beneficial. In order for at least 50% of the population to reach this level, all adults would require supplementation with at least 1,000 units of vitamin D.

G&H What are the possible adverse effects of vitamin D supplementation?

IB Vitamin D is normally relatively safe because it is stored in adipose tissue and is released in equilibrium with the concentration of vitamin D in the serum. However, adverse events can occur in rare cases. Specifically, vitamin D toxicity may increase the level of calcium in the serum and the urine, and mild vitamin D toxicity can be associated with excess thirst, a metallic taste in one's mouth, poor appetite, weight loss, itchy skin, vomiting, diarrhea, and constipation. To prevent these adverse events, dietary supplements should only be taken under the supervision of a healthcare provider.

G&H Given the potential benefit of vitamin D, is supplementation recommended for patients with chronic liver disease?

IB Although a number of studies suggest that vitamin D and its metabolites can synergize with interferon treatment to directly inhibit HCV replication in vitro, vitamin D supplementation has not yet been approved as a therapy for liver disease. Also, no randomized controlled trials of vitamin D supplementation in patients with NASH or NAFLD have been published to date, so the benefit of vitamin D in this population remains unknown.

G&H Do you think vitamin D supplementation will be recommended for patients with chronic liver disease in the future?

IB Yes, vitamin D supplementation will likely be recommended in the future, at least for certain groups of patients. For HCV-infected patients, the literature suggests that supplementation with vitamin D can help patients achieve SVR, and this benefit seems to come without risk to the patient. In addition, data have shown that vitamin D levels can predict rejection following liver transplantation in HCV-infected patients.

Because of the lack of data regarding vitamin D supplementation in patients with NAFLD or NASH, we do not know if vitamin D supplementation can ameliorate steatosis in patients with metabolic disease or whether vitamin D supplementation can halt the progression from NAFLD to NASH. Trials assessing vitamin D supplementation in this population are in progress, but the results of these studies are not yet available.

G&H Aside from its role in the treatment of chronic liver disease, might vitamin D supplementation be beneficial for patients with other conditions?

IB Yes, vitamin D has a crucial role in the regulation of calcium and bone metabolism, and it is known to pre-

vent osteoporosis, rickets, and osteomalacia. Studies are also exploring whether vitamin D may play a role both in the prevention of cardiovascular disease and in the reduction of insulin resistance; this association is being explored in conditions such as metabolic syndrome, type 2 diabetes, and obesity.

Suggested Reading

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