Published in final edited form as:
Semin Liver Dis. 2011 November ; 31(4): 387–398. doi:10.1055/s-0031-1297927.

Classical and emerging roles of vitamin D in hepatitis C virus (HCV) infection

Julio A. Gutierrez[1], **Neil Parikh**[2], and **Andrea D. Branch**[2]

[1]Division of Gastroenterology, University of California, San Diego, CA, 92093

[2]Division of Liver Diseases, the Mount Sinai School of Medicine, New York, NY, 10029

Abstract

The risk of clinically-significant vitamin D deficiency increases at 25-hydroxyvitamin D levels below 20 ng/mL, according to the Institute of Medicine. By this standard, most cirrhotic hepatitis C virus (HCV)-positive patients and many non-cirrhotic patients are vitamin D deficient. The high prevalence of vitamin D deficiency among HCV patients is a cause for concern for several specific reasons. Classic studies established the importance of vitamin D and calcium in maintaining bone. Vitamin D's beneficial effects on bone are likely to be vital for HCV-infected patients because these individuals have a high prevalence of low bone mineral density. Many pharmaceutical agents reduce bone density and exposure to these drugs may increase bone disease in HCV-positive patients. Bone loss occurs following liver transplantation and bone density is often low in patients with HIV/HCV co-infection who are on combination antiretroviral therapy. Some evidence suggests that ribavirin reduces bone density, underscoring the special need to monitor vitamin D in patients receiving HCV treatment and to prescribe supplements, as appropriate. In addition to its role in calcium metabolism, vitamin D is also an immune modulator that reduces inflammation while enhancing protective immune responses. Higher vitamin D levels are associated with less liver fibrosis and less inflammation in HCV patients. Recent studies show that low vitamin D levels are associated with treatment failure among HCV-infected patients receiving pegylated-interferon and ribavirin. If confirmed, these findings will provide an additional reason to ensure adequate levels of vitamin D. The article concludes with information about how to monitor vitamin D status and how to use vitamin D supplements most effectively in HCV-infected patients.

Keywords

Hepatitis C virus; vitamin D; hepatocellular carcinoma; bone mineral density; fracture; fibrosis; sustained virological response; interferon; ribavirin

The national debate about vitamin D requirements

Vitamin D has received tremendous attention during the past several years. This has raised awareness about the potential risks of vitamin D deficiency, but it has also generated a great

Author and Reprint Correspondence to: Dr. Andrea Branch, PhD, Division of Liver Diseases, Mount Sinai School of Medicine, Ph: 212-659-8371, andrea.branch@mssm.edu.

deal of confusion and controversy. Expert panels have reached differing conclusions about the prevalence of vitamin D deficiency in the general population and about the public health measures that need to be taken to ensure that the greatest number of people have adequate levels of vitamin D. Before examining the vitamin D requirements of HCV-infected patients, it is useful to review what the expert panels have been arguing about.

One expert panel was established by the Institute of Medicine (IOM). This group released their findings in 2010[1]. Backed by extensive published data, they determined that the most appropriate clinical indicator of vitamin D status is the serum concentration of 25-hydroxyvitamin D [25(OH)D], a vitamin D metabolite with a relatively long half-life (two to three weeks). 25-hydroxyvitamin D is produced in the liver from vitamin D, a nutrient that can either be obtained through the diet or through endogenous synthesis in sun-exposed skin. 25-hydroxyvitamin D is converted to the most active metabolite, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], in the kidney and in a number of extrarenal sites. Extrarenal synthesis of $1,25(OH)_2D$ allows high local concentrations to be produced in the exact tissues where and when they are needed. Active vitamin D is the ligand for the vitamin D receptor (VDR). The vitamin D receptor is present in many cells and tissues throughout the body. This wide-spread distribution indicates that many tissues likely depend on vitamin D for proper functioning—raising the stakes for health care officials charged with deciding what levels are optimal.

The classical functions of vitamin D are to increase calcium absorption in the intestine and to maintain bone strength. Vitamin D is now known to have many additional effects; however, the IOM panel based their nutritional recommendations solely on the amount of vitamin D needed to maintain bone. They did this because they concluded that maintaining bone is the only function of vitamin D for which there is enough high quality data to draw conclusions about the needs of the general public. The panel determined that nearly all members of the general population have met their vitamin D requirement if they have a 25(OH)D level over 20 ng/ml and they concluded that almost all healthy people 9-70 years of age can obtain an adequate supply by consuming 600 IU of vitamin D per day, even in the absence of any endogenous production of vitamin D. They also concluded that optimal 25(OH)D levels may be lower in blacks than in whites.

Almost immediately after the IOM report was released, a second expert panel, this one composed of endocrinologists, published their own recommendations about optimal 25(OH)D levels and the use of vitamin D supplements[2]. They advised that 32 ng/ml of 25(OHOD should be used as the lower limit of the target range and reported that many people will need to consume 4000 IU of vitamin D per day, or more, to achieve the desired target levels.

While it is initially startling to realize that two expert panels reached such disparate conclusions when examining the same body of data, the findings actually complement each other: IOM panel established guidelines for healthy people, and the endocrinologists establish guidelines for patients with various disease conditions who are receiving care from qualified providers. The implication is that vitamin D requirements may be greater for ill patients than for healthy individuals.

In addition to the very real possibility that people with diseases have special nutritional needs, there are other specific reasons why physicians and public health officials are unsure about vitamin D requirements. Many cross-sectional studies show an association between higher vitamin D levels and better health outcomes; however, cross-sectional studies cannot be used to establish causality. They leave open the possibility that positive associations between higher 25(OH)D levels and better health outcomes occur because healthier people exercise more and have more sunlight exposure—with higher 25(OH)D levels the *result* of better health, not the *cause*. In contrast to the large number of cross-sectional studies, relatively few well-designed randomized controlled trials of vitamin D supplements have been conducted.

Several factors contribute to the dearth of definitive clinical trials. Funding has been a problem. Vitamin D costs only about ¢15 a day, so few pharmaceutical companies have been interested in sponsoring trials. Competing research priorities have kept funding tight at NIH and other governmental agencies. These problems are compounded by the evolving understanding of vitamin D requirements. In the past, many trials used doses of vitamin D supplements that are no longer considered adequate, and they did not measure 25(OH)D levels longitudinally to determine the biological response to the supplements. Adherence was often poor, and subjects in control arms often took over-the-counter vitamin D supplements outside the trial.

More definitive studies are underway, but the results will not be available for several years. In the meantime, HCV-infected patients are probably best served by assuming that they should have 25(OH)D levels above 20 ng/mL, the cutoff for vitamin D deficiency in the general population. Without supplements many patients will have 25(OH)D levels far below this target. The amount of supplemental vitamin D needed to raise the level of 25(OH)D over 20 ng/ml is best determined empirically in individual patients. It will often be far greater than 600 IU/day. Information about how to treat vitamin D deficiency in HCV-positive patients is presented in the last section of this article.

Review of vitamin D biosynthesis and systemic effects

The term vitamin D encompasses a group of fat-soluble seco-steroids, of which vitamin D_2 and D_3 are the most abundant in humans. Unlike typical vitamins, which must be obtained from dietary sources, vitamin D can be produced by the human body when skin is exposed to UV-B irradiation. Vitamin D_3 is synthesized in humans from 7-dehydrocholesterol. It can also be obtained from dietary sources (wild salmon) and supplements. Vitamin D_2 can be obtained from UV-irradiated mushrooms. Vitamin D is hydroxylated by cytochrome P450 enzymes in hepatocytes to become 25(OH)D. A second hydroxylation produces $1,25(OH)_2D$, the ligand of the vitamin D receptor (VDR). The main effects of vitamin D are mediated by the VDR, which is widely distributed throughout the body, including in the brain, immune cells, bone, pancreas, and muscle. In the nucleus of cells, the $1,25(OH)_2D$-VDR complex combines with the retinoid-X receptor to form a transcription factor that regulates cellular gene expression. When circulating in the blood and transiting to storage and target tissues, vitamin D and its metabolites are bound to the vitamin D-binding protein (Gc-globin), which stabilizes vitamin D.

The canonical functions of vitamin D are to increase calcium absorption and to maintain healthy bones[3-6]. Active vitamin D operates in conjunction with several other hormones, including parathyroid hormone (PTH). When the serum levels of ionized calcium are low, PTH levels increase. PTH stimulates bone resorption, causing the release of calcium. This release of calcium from the skeleton maintains serum calcium levels within a narrow physiological range, but can lead to bone loss and fracture if allowed to continue unabated[7]. The PTH level is often used as an index of vitamin D repletion: Vitamin D levels are considered to be adequate when PTH levels are maximally suppressed[8-11]. Vitamin D deficiency is generally associated with PTH elevations. Further studies are needed to define the relationship between vitamin D deficiency and PTH levels in HCV-infected patients.

In addition to ensuring that the body has enough calcium, it is now known that vitamin D has many other functions. Vitamin D is a key immune modulator. It reduces levels of pro-inflammatory cytokines and inflammation[12-23], and enhances adaptive and innate immune responses[24-27]. Vitamin D supplements increase muscle strength[28-30] and they are reported reduce depression and fatigue, although improvements have not observed in all studies[31-39]. Among dialysis patients, vitamin D supplements reduce the need for erythropoiesis stimulating agents[40-43]. In one study, a vitamin D analog significantly reduced side-effects of chemotherapy[44]. Vitamin supplementation may also improve insulin resistance[45].

The impact of vitamin D on all-cause and on disease-specific mortality

Two systematic reviews of randomized controlled trials of vitamin D supplements showed a significant survival benefit[46,47]. One meta-analysis of 18 randomized controlled trials of supplementation with a trial size-adjusted mean vitamin D dose of 528 IU/day determined that the relative risk of mortality in treated patients was 0.93 (95% confidence interval, 0.87-0.99), a 7% reduction[47]. The second study reached a similar conclusion, demonstrating that vitamin D_3 supplements reduced all-cause mortality by about 6%[46]. If supplements do, indeed, confer a survival advantage of this magnitude, they may offer a cost-effective way to improve public health. Because all-cause mortality in HCV-positive adults is nearly twice that of non-HCV infected individuals[48], the survival benefits of vitamin D supplements might be especially beneficial for them. Vitamin D supplements are inexpensive and cause virtually no side-effects if used appropriately.

In keeping with the results of randomized clinical trials, many observational studies have demonstrated an association between higher 25(OH)D levels and reduced all-cause mortality and reduced disease-specific mortality, including mortality due to renal disease, cardiovascular disease, and cancer[49-51]. A recent analysis of NHANES III data showed that adults over the age of 65 years with serum 25(OH)D levels greater than 40 ng/mL had a 45% lower risk of death than those with 25(OH)D less than 10 ng/mL (hazard ratio = 0.55; 95% confidence interval, 0.34-0.88)[52]. The same study showed striking reductions in cardiovascular mortality using the same comparison groups (hazard ratio for the higher vitamin D group = 0.42; 95% confidence interval, 0.21-0.85)[52].

Vitamin D deficiency is common in HCV-positive patients and is associated with more advanced liver disease

Over the past decade, numerous studies have assessed vitamin D status in patients with non-cholestatic chronic liver diseases (Table 1). The majority of the subjects had chronic HCV infection. Arteh et al. evaluated 118 patients with chronic liver disease wherein 85% had HCV infection and 36% had HCV cirrhosis[53]. None of the patients were taking vitamin D or calcium supplements. More than 90% of the patients had 25(OH)D levels less than 32 ng/mL, the level many vitamin D experts consider to be the lower limit of the optimal range. Almost 70% of the non-cirrhotic HCV-positive patients had 25(OH)D levels below 20 ng/ml, indicating deficiency, and 14% had levels below 7 ng/mL, indicating severe deficiency. Vitamin D status was worse in patients with cirrhosis: 80% had levels below 20 ng/ml and 30% had levels below 7 ng/mL.

Another cross-sectional study found that more than 90% patients had 25(OH)D levels below 32 ng/mL[54]. In this study, 38% of the patients were HCV positive. Similar to Arteh et al., patients with cirrhosis had significantly lower levels of 25(OH)D (13.0 ng/mL) than non-cirrhotics (21.4 ng/mL). As assessed by Child-Pugh and MELD scores, the severity of liver disease correlated inversely with vitamin D levels: 65% of Child's class C cirrhotics had 25(OH)D levels below 25 ng/mL, while only 7% Child's A cirrhotics had such low levels. Vitamin D status was inversely related to INR and bilirubin. Lower vitamin D status was associated with hypoalbuminemia, anemia, and thrombocytopenia.

These findings were substantially confirmed in an analysis of 90 patients with chronic liver disease and 40 controls[55]. HCV was the leading etiology and about half of the patients had cirrhosis: 70% of the patients had vitamin D levels less than 32 ng/mL and 50% had levels less than 20 ng/mL, indicating deficiency. Almost 80% of patients with cirrhosis had vitamin D deficiency. The average 25(OH)D levels for cirrhotics, non-cirrhotics, and healthy controls were 16.3 ng/mL, 32.5 ng/mL, and 38.1 ng/mL, respectively. Lower vitamin D levels were associated with worse Child-Pugh and MELD scores, INR, bilirubin, albumin, and hemoglobin levels, and lower platelet counts.

Lange et al recently published the largest study of non-cirrhosis patients with chronic HCV infection[56]. Vitamin D status was assessed in a cohort of 468 patients who were eligible for treatment with pegylated-interferon and ribavirin. The average 25(OH)D level was 17 ng/ml and 25% of the patients had levels below 10 ng/ml. The prevalence of vitamin D deficiency was greater in patients with more advanced fibrosis.

While not as well studied, vitamin D deficiency is prevalent in liver diseases other than HCV. Targher et al. enrolled 60 non-alcoholic fatty liver disease (NAFLD) patients and 60 healthy controls and evaluated the relationship between 25(OH)D levels and hepatic steatosis, inflammation, and fibrosis[57]. Patients with HCV or HBV were excluded. Liver biopsies were scored by a single pathologist using the Brunt criteria. Patients with NAFLD had significantly lower levels of vitamin D than healthy controls (20.4 ng/mL versus 29.8 ng/mL).

In NAFLD patients, there was an inverse relationship between 25(OH)D levels and biopsy scores. Patients with simple steatosis had an average 25(OH)D level of 23.7 ng/mL while those with non-alcoholic steatohepatitis (NASH) had an average level of 14.8 ng/mL. Vitamin D levels correlated inversely with grades of steatosis, necroinflammation, and fibrosis. Although this study was cross-sectional in design, it suggested that there is a strong inverse relationship between 25(OH)D levels and hepatic steatosis, inflammation, and fibrosis in patients with NAFLD.

Studies that included patients with chronic hepatitis B and alcoholic hepatitis yielded similar results, and showed an association between lower vitamin D status and more advanced liver disease[54,58]. A recent cross-sectional study from India that evaluated patients with HBV and alcoholic hepatitis revealed a high prevalence of vitamin D deficiency[59], calling attention to the risk of this condition even in locations with high sun exposure.

In summary, a large number of studies establish that patients with chronic liver disease, especially HCV-positive patients, have decreased 25(OH)D levels compared to healthy individuals. These levels are even lower in patients with cirrhosis. Low levels of vitamin D are associated with more advanced liver disease. Regardless of the geographic location, patients with HCV infection are likely to suffer from vitamin D deficiency.

The causes of vitamin D deficiency in liver disease patients have not yet been defined and are likely to be multifactorial. Decreased endogenous production of vitamin D is likely to be a factor, especially for dark-skinned people, individuals living at high latitudes, and those who spend minimal time outdoors. The complications of liver disease may also contribute to vitamin D deficiency. Chronic inflammation can shorten the half-life of 25(OH)D by accelerating conversion to $1,25(OH)_2D$. Hepatic production of vitamin D-binding protein is reduced in patients with advanced liver disease [60] and this may also accelerate vitamin D turnover. Advanced liver disease and cholestasis can reduce the absorption of fat soluble vitamins, including vitamin D. The liver's ability to produce 25(OH)D may be reduced in some patients; although, this capability is generally well-preserved even in patients with advanced liver disease[53,61]. Interestingly, HCV infection may reduce vitamin D levels. Among patients who achieved a sustained virological response (SVR), there was a non-significant trend toward a decrease in the prevalence of vitamin D deficiency. [56]

Vitamin D and hepatocellular carcinoma

No population-based studies have investigated the relationship between hepatocellular carcinoma (HCC) and vitamin D levels; however, *in vitro*, animal, genetic, and pilot clinical trial data all suggest that vitamin D may be important in preventing and treating liver cancer. Many studies have shown that vitamin D analogues inhibit proliferation of malignant cells[62,63] and they have demonstrated that hepatoma cells are sensitive to $1,25(OH)_2D$ *in vitro* [64,65]. Seocalcitol is a synthetic analogue of vitamin D with less calcemic effects. In a descriptive study, Seocalcitol was well tolerated in patients with HCC and appeared to slow progression in some[66]. There are intriguing data suggesting that single nucleotide polymorphisms in the VDR receptor may predispose to liver cancer; however, it is important to keep in mind that human gene analysis is evolving rapidly and initial results may be

revised[67]. Falleti et al. compared VDR gene polymorphisms in patients who underwent liver transplantation for all causes with and without HCC. They found that the *BAT* A-T-C haplotype was inversely related to the occurrence of HCC, whereas the *BAT* G-T-T haplotype was directly associated with this cancer[68]. This association was independent of other risk factors for HCC. The incidence of HCC is increasing rapidly in HCV-positive patients, as discussed in the article by Ahmad and Branch in this issue. Vitamin D research in the HCC field is thus timely and important for HCV-positive patients.

Low bone density in patients with HCV and other liver diseases

Given the high prevalence of vitamin D deficiency in HCV-infected patients, it is not surprising to find bone abnormalities in this population. Over the past decade, numerous studies have measured the prevalence of osteoporosis and osteopenia by assessing bone mineral density (Table 2). In all of these studies, osteoporosis and osteopenia were defined using the WHO criteria of *T*–score < -2.5 indicating osteoporosis and *T*–score between -1.0 and -2.5 indicating osteopenia. The *T*-score represents a patient's bone mineral density (BMD) relative to a young and healthy population of the same sex. Caucasians are the reference population. Zero represents the mean BMD of the reference population. The difference between the patient's score and the norm is expressed in standard deviations above or below zero. For each standard deviation below zero, the relative risk of fracture increases two-fold.

The Mayo clinic conducted one of the largest studies of BMD in liver disease patients, evaluating more than 200 patients with advanced cirrhosis[69]. Of these patients, 68 had HCV without alcoholic liver disease (ALD), 66 had ALD, and 73 had HCV and ALD. Twenty-eight percent of the HCV-positive patients had osteoporosis and 37% had osteopenia. The percentage with osteoporosis was significantly greater in the HCV group than in the ALD group and in the mixed group. These findings were surprising because the ALD group had more advanced liver disease based on MELD and CTP grades, and significantly more smoking pack years than the HCV group. The authors theorized HCV has adverse effects on bone that are distinct from the effects of liver cirrhosis. Another study comparing patients with HCV cirrhosis to those with ALD cirrhosis found that 100% of the HCV group had low bone density while only 56% of the ALD group did [59].

Additional studies of HCV-infected patients have shown high rates of osteoporosis and osteopenia. Duarte et al. looked at 100 patients with chronic HCV and found that 17% had osteoporosis and 25% had osteopenia[70,71]. The slightly lower prevalence likely reflected the fact that only 50% of this HCV group had cirrhosis. A study of patients with HCV cirrhosis who were awaiting liver transplantation revealed hepatic osteodystrophy in 40% and osteoporosis in 14%[71]. There was no correlation between severity of liver disease and bone density. Other studies looking at patients with either HCV or HBV cirrhosis have found osteoporosis rates of 20%[72], 37%[73], and 55%[74]. The study that found 37% was one of the few to compare patients with cirrhosis to healthy controls. *T*-scores were significantly lower in the cirrhosis group than in the controls, -1.6 vs. -0.25 ($p < 0.001$). Schiefke et al examined non-cirrhotic HCV and HBV liver patients[75] and found that 53% had osteopenia, 19% had

osteoporosis in the femur, and 7% had osteoporosis in the spine. In these non-cirrhotic patients, elevated alkaline phosphatase correlated significantly with the low bone density.

Diez-Ruiz et al compared 33 patients with alcoholic cirrhosis to age-matched healthy controls and found that almost 40% of the liver disease patients had osteoporosis[76]. The prevalence of osteoporosis increased with worsening liver disease as assessed by CTP grades, in contrast to the lack of an association between osteoporosis and liver disease severity observed in patients with viral cirrhosis.

A series of studies from the Mayo clinic assessed vitamin D status and BMD in patients with PBC and PSC who were undergoing orthotopic liver transplantation (OLT)[77]. Almost 40% of the patients had osteoporosis and another 40% had osteopenia prior to OLT. During the first four months after OLT, more than 80% of patients lost bone mass. After the first four months, bone mass began to increase. Post-OLT vitamin D levels strongly correlated with bone density changes. The higher the post-OLT vitamin D levels, the greater the increase in bone mass. Over the years, the vitamin D status of patients prior to liver transplantation has improved greatly at the Mayo Clinic. The authors theorized that this occurred, in part, because of the increased use of vitamin D supplements[77]. Bone density is an important clinical concern: 30% of the study group experienced a bone fracture during the first year following OLT[78].

Effects of interferon and ribavirin on calcium and bone metabolism

Many pharmaceutical agents cause abnormalities of calcium and vitamin D metabolism. Vitamin D and calcium supplements are often used to prevent bone loss in patients receiving these medications[79]. Increasing evidence suggests that HCV treatments disrupt calcium homeostasis. In the late 1990s, case reports of bone pain and fractures in patients undergoing treatment with interferon and ribavirin prompted investigations into the possible mechanism. The first study to evaluate the impact of interferon and ribavirin on bone metabolism was conducted in 2000 by Solis-Herruzo et al[80]. This cross-sectional study looked at 32 men with chronic HCV who were under the age of 50 and who either received interferon alone or a combination of interferon and ribavirin for twelve months. Bone density was measured at the end of treatment. All patients who received interferon/ribavirin had *T*-scores below -1.0 and more than 20% had *T*-score below -2.5, indicating osteoporosis. In contrast, the patients who received interferon alone had normal *T*-scores at 12 months, not a single one had osteopenia or osteoporosis. Urinary excretion of calcium was low in patients on interferon/ribavirin, suggesting that the reduced bone density was the result of impaired intestinal absorption of calcium. Interestingly, PTH levels were not elevated. A major limitation of this study was that BMD was not assessed prior to the start of treatment and therefore, it was unclear how many patients had low bone density at baseline. Nonetheless, the results were striking. Recent data of Soumekh et al. are consistent with a negative effect of interferon/ribavirin therapy on bone. In a study of HIV/HCV co-infected patients in a retreatment trial, these investigators observed a significant decrease in serum calcium[81].

A number of studies after Solis-Herruzo did not find that HCV treatment reduced bone density[82-86]. A plausible explanation for the inconsistent results is that the effect of

treatment on bone depends on the ratio of ribavirin to interferon and on the characteristics of the patient population. Studies of cancer patients receiving interferon treatment suggest that this cytokine increases bone density[87]. It is difficult to reach firm conclusions about the impact of interferon and ribavirin on bone based on existing clinical data, as the investigations were generally small and had limited follow-up.

In vitro studies support the view that ribavirin is damaging to bone. When human osteoblasts were incubated with ribavirin, a dose-dependent decrease in cell proliferation occurred and there was a significant increase in osteoblast cell death[88]. In contrast, interferon had no effect on osteoblast cell proliferation or death. Other *in vitro* studies demonstrated that ribavirin directly enhances osteoclast formation [89], decreases intestinal calcium absorption by directly acting on intestinal mucosa cells, and interferes with $1,25(OH)_2D$ production[85]. Conversely, interferon interacts with RANK ligand and inhibits osteoclast differentiation, effects expected to increase bone density[90]. Therefore, *in vitro* studies support a protective role of interferon and a destructive role of ribavirin on bone. With new antiviral agents for HCV now on the market, questions about their effect on bone metabolism are pressing and will need to be answered through prospective trials.

Lessons from HIV-positive patients with low vitamin D status

HIV and the antiretroviral drugs used to control it are clearly detrimental to bone. Almost 50% of HIV-seropositive patients on combination antiretroviral therapy have low BMD[99]. Low vitamin D levels are a risk factor for low BMD and for elevated PTH[100]. Not surprisingly, low bone density is also a frequent occurrence in HIV-positive patients with chronic hepatitis virus infections.

One of the original studies that evaluated BMD in the HIV/viral hepatitis co-infected population was a cross-sectional study looking at more than 1200 HIV patients, half with viral hepatitis [101]. More than 90% of the co-infected patients were HCV antibody positive. Z-scores were used to assess bone density. The Z-score of a patient represents the BMD compared to that of a population matched for sex, age, and ethnicity/race. Defining a low BMD as a *Z*-score less than -2.0, 16% of the co-infected patients had a low BMD compared to 11% of the HIV mono-infected patients. Co-infected females had a lower BMD than the HIV mono-infected females, but there was no difference in BMD between HIV mono-infected and HIV/HCV co-infected males.

A more recent cross-sectional study evaluated a predominantly African American male population with HIV and HCV[102]. This study analyzed *T*-scores. They determined that an alarming 28% of the HIV/HCV co-infected patients had osteoporosis—higher than in HIV mono-infected or in HCV mono-infected patients[103]. In agreement with the aforementioned studies in HCV, no correlation was found between low BMD and liver disease severity. Interestingly, worsening BMD scores were seen in patients with well-controlled HIV, implicating antiretroviral drugs in the bone loss.

To maintain bone and prevent fractures, recent recommendations for HIV care providers state that the “goal should be to achieve 25(OH)D level > 32 mg/mL, although some experts recommend levels in the 40-50 ng/mL range[104].”

Evidence that vitamin D may influence HCV treatment outcomes

In addition to protecting the skeleton, vitamin D supplements may benefit HCV-positive patients by improving treatment responses. A growing body of evidence suggests that vitamin D deficiency may be a *modifiable* risk factor for HCV treatment failure. Petta and colleagues demonstrated that low baseline 25(OH)D levels were independently associated with a poor response to interferon/ribavirin-based therapy, and also showed that low 25(OH)D levels were associated with more severe fibrosis and necroinflammation[105]. Bitetto and colleagues found that patients whose 25(OH)D levels were greater than 20 ng/mL had an increased odds ratio for achieving an SVR of 2.07 (95% confidence interval, 1.02 - 4.17). In a stepwise logistic regression analysis, these investigators found that an unfavorable IL28B genotype (C/T or T/T) and 25(OH)D levels < 20 ng/mL were associated with treatment failure compared to the C/C allele and higher 25(OH)D levels[106]. Lange and colleagues also found that vitamin D deficiency was a risk factor for HCV treatment failure[56]. In a retreatment trial of HIV/HCV co-infected patients, Soumekh et al. found that a baseline 25(OH)D level ≥ 18 ng/ml was significantly associated with SVR in a multivariable model[81]. In contrast, a trial of treatment-naïve HIV/HCV co-infected patients did not find an association between 25(OH)D levels and SVR, although it demonstrated an inverse relationship between low 25(OH)D levels and more advanced fibrosis[107].

Intriguingly, two groups have reported that vitamin D supplements raise SVR rates. In 2009, Abu-Mouch and colleagues reported the interim results of a trial in which patients were randomly assigned to receive vitamin D supplementation prior to and during interferon/ribavirin therapy. A tiered dose of vitamin D_3 (1000-4000 IU/day) was used, with the dose determined by the baseline serum 25(OH)D level. Subjects in the vitamin D arm had a higher SVR rate[108]. Similarly, a retrospective review of post-liver transplant patients with recurrent HCV showed higher SVR rates in patients who had been concurrently treated for metabolic bone disease with vitamin D compared to controls (8/15 vs. 5/27 respectively; $p < 0.02$)[109].

Cell culture and animal studies add experimental support to the clinical data showing that vitamin D might benefit HCV patients, either by increasing treatment responses and/or by mitigating liver injury. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats, suggesting that vitamin D supplements may have an anti-fibrotic effect in patients[110]. Vitamin D may also reduce HCV replication, according to three *in vitro* studies. Using a full-length genotype 1b replicon system, Yano et al. investigated the effects of micronutrients, including vitamin D. Their data suggested that vitamin D_2 (but not vitamin D_3) inhibited HCV RNA replication with an EC_{50} of 3.8 μM (1600 ng/mL) [111]. A subsequent study showed that a MEK1/2 inhibitor abolished the anti-HCV effect [112]. Gutierrez et al. found that vitamin D_2, vitamin D_3 and 1,25$(OH)_2$D inhibited HCV replication in both genotype 1b and 2a replicons and demonstrated that cell-culture adapted, infectious genotype 2a (J6/JFH) HCV was susceptible to inhibition by vitamin D metabolites [113]. Recently, Gal-Tanamy et al. found similar results using the inter-genotypic HJ3-5 chimeric HCV virus and also demonstrated a synergy when combining vitamin D_3 or 1,25$(OH)_2$D with interferon-α[114].

How to correct low vitamin D status in HCV patients

Given the extraordinary prevalence of vitamin D deficiency, all HCV-positive patients should be checked for this abnormality, preferably during the late fall and winter months when 25(OH)D levels tend to be at their nadir. A number of reliable 25(OH)D assays are currently available: high-pressure liquid chromatography (HPLC), radioimmunoassay, and chemiluminescent assays. No consensus exists as to which is the best, although some argue in favor of HPLC [115].

Vitamin D_3 has a longer half-life than vitamin D_2. Thus, it is easier to reach target 25(OH)D levels by prescribing vitamin D_3. A simple rule of thumb for healthy adults is that individuals should receive 100 IU/daily of vitamin D_3 for every 1 ng/mL that they are below the target level of 25(OH)D. Our experience, however, indicates that HCV-positive patients often require higher doses of vitamin D supplements than this thumb rule indicated.

Although research is needed to obtain pharmacokinetic data in HCV-positive patients, a reasonable approach to correcting vitamin D deficiency is to measure the 25(OH)D level in late fall and to base the initial dose of vitamin D_3 supplements on that value: 4000 IU/day for patients with 25(OH)D below 10 ng/ml; 2000 IU/day for patients with 25(OH)D between 10 and 20 ng/ml; and 1000 IU/day for patients with 25(OH)D between 20 and 30 ng/ml. A repeat 25(OH)D measurement three months later is advised to allow the patient's response to the initial dose to be assessed. The dose can then be adjusted to achieve the desired 25(OH) level. The tolerable upper intake level (i.e. the highest average daily intake that is likely to pose no risk of adverse effects to almost all individuals in the general population) 4000 IU per day of vitamin D_3 for adults, according to the the IOM[1]. If dietary calcium intake is less than 1 gm per day, calcium citrate supplements should also be considered.

Available data suggest that the optimal level of 25(OH) for good health in the general population is about 35 ng/ml. As discussed in the opening section of this article, some experts advise higher levels, but none considers 35 ng/mL to exceed the optimal range. In the absence of outcomes data in HCV-positive patients, 35 ng/mL of 25(OH)D is the best target level to aim for. This can be achieved in almost all liver disease patients through the use of oral supplements. Injectable forms of vitamin D are available and can be used in patients with severe malabsorption. Time spent outdoors is also a very pleasurable way to increase vitamin D reserves and can be recommended to patients if they are also cautioned to avoid levels of UV exposure that might increase the risk of skin cancer.

Conclusions

Vitamin D has well known classical functions that are important for maintaining bone. Emerging data indicate that it may also increase longevity. In HCV-positive patients, there is evidence that vitamin D deficiency is a risk factor for fibrosis, necroinflammation, bone disease, and interferon/ribavirin treatment failure. The possibility that vitamin D supplements might reduce liver injury, inhibit HCV replication, raise SVR rates, and reduce liver disease progression creates an urgent need for clinical trials of vitamin D supplements in HCV-positive patients. Research is also needed to understand the mechanisms of vitamin

D action and to determine optimal 25(OH)D levels in HCV-positive patients. In the meantime, to preserve bone, serum 25(OH)D levels should be checked in HCV-positive patients and patients with vitamin D deficiency should be treated with appropriate doses of vitamin D and calcium supplements.

Acknowledgments

This work was supported, in part, by DA031095, DK090317, and CA152514 to ADB. JAG was supported, in part, by DK00720236 and AI07655803.

References

1. Ross, A Catherine; Taylor, Christine L.; Yaktine, Ann L.; Del Valle, Heather B., editors. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. the National Academic Press; Washington, D.C.: 2011.
2. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin d deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96:1911–30. [PubMed: 21646368]
3. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007; 370:657–66. [PubMed: 17720017]
4. Melhus H, Snellman G, Gedeborg R, et al. Plasma 25-hydroxyvitamin D levels and fracture risk in a community-based cohort of elderly men in Sweden. J Clin Endocrinol Metab. 2010; 95:2637–45. [PubMed: 20332246]
5. Ensrud KE, Taylor BC, Paudel ML, et al. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab. 2009; 94:2773–80. [PubMed: 19454586]
6. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med. 2004; 116:634–9. [PubMed: 15093761]
7. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001; 22:477–501. [PubMed: 11493580]
8. McKenna MJ, Freaney R. Secondary hyperparathyroidism in the elderly: means to defining hypovitaminosis D. Osteoporos Int. 1998; 8(Suppl 2):S3–6. [PubMed: 10197175]
9. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. N Engl J Med. 1989; 321:1777–83. [PubMed: 2594036]
10. Thomas SD, Need AG, Tucker G, Slobodian P, O'Loughlin PD, Nordin BE. Suppression of parathyroid hormone and bone resorption by calcium carbonate and calcium citrate in postmenopausal women. Calcif Tissue Int. 2008; 83:81–4. [PubMed: 18553042]
11. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998; 351:805–6. [PubMed: 9519960]
12. Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J. 2001; 15:2579–85. [PubMed: 11726533]
13. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006; 83:754–9. [PubMed: 16600924]
14. Cantorna MT, Yu S, Bruce D. The paradoxical effects of vitamin D on type 1 mediated immunity. Mol Aspects Med. 2008; 29:369–75. [PubMed: 18561994]
15. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab. 2008; 4:80–90. [PubMed: 18212810]

16. Giulietti A, van Etten E, Overbergh L, Stoffels K, Bouillon R, Mathieu C. Monocytes from type 2 diabetic patients have a pro-inflammatory profile. 1,25-Dihydroxyvitamin D(3) works as anti-inflammatory. Diabetes Res Clin Pract. 2007; 77:47–57. [PubMed: 17112620]
17. Cohen ML, Douvdevani A, Chaimovitz C, Shany S. Regulation of TNF-alpha by 1alpha,25-dihydroxyvitamin D3 in human macrophages from CAPD patients. Kidney Int. 2001; 59:69–75. [PubMed: 11135059]
18. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266–81. [PubMed: 17634462]
19. Bitetto D, Fabris C, Falleti E, et al. Vitamin D and the risk of acute allograft rejection following human liver transplantation. Liver Int. 2010; 30:417–44. [PubMed: 19849776]
20. Cohen-Lahav M, Douvdevani A, Chaimovitz C, Shany S. The anti-inflammatory activity of 1,25-dihydroxyvitamin D3 in macrophages. J Steroid Biochem Mol Biol. 2007; 103:558–62. [PubMed: 17267205]
21. Sun J, Kong J, Duan Y, et al. Increased NF-kappaB activity in fibroblasts lacking the vitamin D receptor. Am J Physiol Endocrinol Metab. 2006; 291:E315–22. [PubMed: 16507601]
22. Evans KN, Nguyen L, Chan J, et al. Effects of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 on cytokine production by human decidual cells. Biol Reprod. 2006; 75:816–22. [PubMed: 16957024]
23. Gysemans CA, Cardozo AK, Callewaert H, et al. 1,25-Dihydroxyvitamin D3 modulates expression of chemokines and cytokines in pancreatic islets: implications for prevention of diabetes in nonobese diabetic mice. Endocrinology. 2005; 146:1956–64. [PubMed: 15637289]
24. Enioutina EY, Bareyan D, Daynes RA. TLR-induced local metabolism of vitamin D3 plays an important role in the diversification of adaptive immune responses. J Immunol. 2009; 182:4296–305. [PubMed: 19299729]
25. Enioutina EY, Bareyan D, Daynes RA. Vitamin D3-mediated alterations to myeloid dendritic cell trafficking in vivo expand the scope of their antigen presenting properties. Vaccine. 2007; 25:1236–49. [PubMed: 17092617]
26. Ivanov AP, Dragunsky EM, Chumakov KM. 1,25-Dihydroxyvitamin D3 Enhances Systemic and Mucosal Immune Responses to Inactivated Poliovirus Vaccine in Mice. J Infect Dis. 2006; 193:598–600. [PubMed: 16425140]
27. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006; 311:1770–3. [PubMed: 16497887]
28. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009; 20:315–22. [PubMed: 18629569]
29. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis. 2005; 20:187–92. [PubMed: 16088114]
30. Dhesi JK, Jackson SH, Bearne LM, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing. 2004; 33:589–95. [PubMed: 15501836]
31. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008; 65:508–12. [PubMed: 18458202]
32. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009; 65:732–41. [PubMed: 19150053]
33. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27:24–31. [PubMed: 16316783]
34. McCann JC, Ames BN. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J. 2008; 22:982–1001. [PubMed: 18056830]
35. Wilkins CH, Birge SJ, Sheline YI, Morris JC. Vitamin D deficiency is associated with worse cognitive performance and lower bone density in older African Americans. J Natl Med Assoc. 2009; 101:349–54. [PubMed: 19397226]
36. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med. 2008; 264:599–609. [PubMed: 18793245]

37. Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J. 2004; 3:8. [PubMed: 15260882]
38. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology (Berl). 1998; 135:319–23. [PubMed: 9539254]
39. Dumville JC, Miles JN, Porthouse J, Cockayne S, Saxon L, King C. Can vitamin D supplementation prevent winter-time blues? A randomised trial among older women. J Nutr Health Aging. 2006; 10:151–3. [PubMed: 16554952]
40. Patel NM, Gutierrez OM, Andress DL, Coyne DW, Levin A, Wolf M. Vitamin D deficiency and anemia in early chronic kidney disease. Kidney Int. 2010; 77:715–20. [PubMed: 20130525]
41. Matias PJ, Jorge C, Ferreira C, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am Soc Nephrol. 2010; 5:905–11. [PubMed: 20203163]
42. Kumar VA, Kujubu DA, Sim JJ, Rasgon SA, Yang PS. Vitamin D supplementation and recombinant human erythropoietin utilization in vitamin D-deficient hemodialysis patients. J Nephrol. 2011; 24:98–105. [PubMed: 20563998]
43. Kiss Z, Ambrus C, Almasi C, et al. Serum 25(OH)-cholecalciferol concentration is associated with hemoglobin level and erythropoietin resistance in patients on maintenance hemodialysis. Nephron Clin Pract. 2011; 117:c373–8. [PubMed: 21071961]
44. Beer TM, Ryan CW, Venner PM, et al. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. J Clin Oncol. 2007; 25:669–74. [PubMed: 17308271]
45. von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. Br J Nutr. 2010; 103:549–55. [PubMed: 19781131]
46. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev. 2011; 7 CD007470.
47. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007; 167:1730–7. [PubMed: 17846391]
48. El-Kamary SS, Jhaveri R, Shardell MD. All-Cause, Liver-Related, and Non-Liver-Related Mortality Among HCV-Infected Individuals in the General US Population. Clin Infect Dis. 2011; 53:150–7. [PubMed: 21665867]
49. Elamin MB, Abu Elnour NO, Elamin KB, et al. Vitamin d and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011; 96:1931–42. [PubMed: 21677037]
50. Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D Status and Mortality Risk in CKD: A Meta-analysis of Prospective Studies. Am J Kidney Dis. 2011 Epub.
51. Scragg R. Vitamin D and public health: an overview of recent research on common diseases and mortality in adulthood. Public Health Nutr. 2011:1–18. [PubMed: 21211099]
52. Ginde AA, Scragg R, Schwartz RS, Camargo CA Jr. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. J Am Geriatr Soc. 2009; 57:1595–603. [PubMed: 19549021]
53. Arteh J, Narra S, Nair S. Prevalence of Vitamin D Deficiency in Chronic Liver Disease. Dig Dis Sci. 2009; 55(9):2624–8. [PubMed: 19960254]
54. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. Clin Gastroenterol Hepatol. 2007; 5:513–20. [PubMed: 17222588]
55. Miroliaee A, Nasiri-Toosi M, Khalilzadeh O, Esteghamati A, Abdollahi A, Mazloumi M. Disturbances of parathyroid hormone-vitamin D axis in non-cholestatic chronic liver disease: a cross-sectional study. Hepatol Int. 2010; 4:634–40. [PubMed: 21063488]
56. Lange CM, Bojunga J, Ramos-Lopez 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. [PubMed: 21145801]

57. Targher G, Bertolini L, Scala L, et al. 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. [PubMed: 16928437]
58. Miroliaee A, Nasiri-Toosi M, Khalilzadeh O, Esteghamati A, Abdollahi A, Mazloumi M. Disturbances of parathyroid hormone-vitamin D axis in non-cholestatic chronic liver disease: a cross-sectional study. Hepatol Int. 2010; 4:634–40. [PubMed: 21063488]
59. George J, Ganesh HK, Acharya S, et al. Bone mineral density and disorders of mineral metabolism in chronic liver disease. World J Gastroenterol. 2009; 15:3516–22. [PubMed: 19630107]
60. Masuda S, Okano T, Osawa K, Shinjo M, Suematsu T, Kobayashi T. Concentrations of vitamin D-binding protein and vitamin D metabolites in plasma of patients with liver cirrhosis. J Nutr Sci Vitaminol (Tokyo). 1989; 35:225–34. [PubMed: 2585144]
61. Hepner GW, Roginsky M, Moo HF. Abnormal vitamin D metabolism in patients with cirrhosis. Am J Dig Dis. 1976; 21:527–32. [PubMed: 181983]
62. Chakraborti CK. Vitamin D as a promising anticancer agent. Indian J Pharmacol. 2011; 43:113–20. [PubMed: 21572642]
63. Wu FS, Zheng SS, Wu LJ, et al. Calcitriol inhibits the growth of MHCC97 heptocellular cell lines by down-modulating c-met and ERK expressions. Liver Int. 2007; 27:700–7. [PubMed: 17498257]
64. Pourgholami MH, Akhter J, Lu Y, Morris DL. In vitro and in vivo inhibition of liver cancer cells by 1,25-dihydroxyvitamin D3. Cancer Lett. 2000; 151:97–102. [PubMed: 10766428]
65. Ghous Z, Akhter J, Pourgholami MH, Morris DL. Inhibition of hepatocellular cancer by EB1089: in vitro and in vive study. Anticancer Res. 2008; 28:3757–61. [PubMed: 19189661]
66. Dalhoff K, Dancey J, Astrup L, et al. A phase II study of the vitamin D analogue Seocalcitol in patients with inoperable hepatocellular carcinoma. Br J Cancer. 2003; 89:252–7. [PubMed: 12865912]
67. Kostner K, Denzer N, Muller CS, Klein R, Tilgen W, Reichrath J. The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. Anticancer Res. 2009; 29:3511–36. [PubMed: 19667145]
68. Falleti E, Bitetto D, Fabris C, et al. Vitamin D receptor gene polymorphisms and hepatocellular carcinoma in alcoholic cirrhosis. World J Gastroenterol. 2010; 16:3016–24. [PubMed: 20572305]
69. Carey EJ, Balan V, Kremers WK, Hay JE. Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. Liver Transpl. 2003; 9:1166–73. [PubMed: 14586877]
70. Duarte MP, Farias ML, Coelho HS, et al. Calcium-parathyroid hormone-vitamin D axis and metabolic bone disease in chronic viral liver disease. J Gastroenterol Hepatol. 2001; 16:1022–7. [PubMed: 11595067]
71. Loria I, Albanese C, Giusto M, et al. Bone disorders in patients with chronic liver disease awaiting liver transplantation. Transplant Proc. 2010; 42:1191–3. [PubMed: 20534258]
72. Chen CC, Wang SS, Jeng FS, Lee SD. Metabolic bone disease of liver cirrhosis: is it parallel to the clinical severity of cirrhosis? J Gastroenterol Hepatol. 1996; 11:417–21. [PubMed: 8743912]
73. Goral V, Simsek M, Mete N. Hepatic osteodystrophy and liver cirrhosis. World J Gastroenterol. 2010; 16:1639–43. [PubMed: 20355242]
74. Gallego-Rojo FJ, Gonzalez-Calvin JL, Munoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D. Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. Hepatology. 1998; 28:695–9. [PubMed: 9731561]
75. Schiefke I, Fach A, Wiedmann M, et al. Reduced bone mineral density and altered bone turnover markers in patients with non-cirrhotic chronic hepatitis B or C infection. World J Gastroenterol. 2005; 11:1843–7. [PubMed: 15793878]
76. Diez-Ruiz A, Garcia-Saura PL, Garcia-Ruiz P, Gonzalez-Calvin JL, Gallego-Rojo F, Fuchs D. Bone mineral density, bone turnover markers and cytokines in alcohol-induced cirrhosis. Alcohol Alcohol. 2010; 45:427–30. [PubMed: 20807717]
77. Guichelaar MM, Kendall R, Malinchoc M, Hay JE. Bone mineral density before and after OLT: long-term follow-up and predictive factors. Liver Transpl. 2006; 12:1390–402. [PubMed: 16933236]

78. Guichelaar MM, Schmoll J, Malinchoc M, Hay JE. Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors. Hepatology. 2007; 46:1198–207. [PubMed: 17654700]
79. Pack AM, Gidal B, Vazquez B. Bone disease associated with antiepileptic drugs. Cleve Clin J Med. 2004; 71(Suppl 2):S42–8. [PubMed: 15379299]
80. Solis-Herruzo JA, Castellano G, Fernandez I, Munoz R, Hawkins F. Decreased bone mineral density after therapy with alpha interferon in combination with ribavirin for chronic hepatitis C. J Hepatol. 2000; 33:812–7. [PubMed: 11097491]
81. Soumekh A, Bichoupan K, Constable C, et al. Two novel findings about interferon/ribavirin treatment: Serum calcium falls and 25-hydroxyvitamin increases. AASLD. 2011 Pending assigned number.
82. Trombetti A, Giostra E, Mentha G, Negro F, Rizzoli R. Lack of evidence for ribavirin-induced bone loss. Hepatology. 2002; 36:255–7. [PubMed: 12085375]
83. Nishida N, Komatsu Y, Komeda T, Fukuda Y. Interferon-alpha improves bone resorption and osteopenia in patients with chronic hepatitis C. Hepatol Res. 2006; 34:222–7. [PubMed: 16516539]
84. Hofmann WP, Kronenberger B, Bojunga J, et al. Prospective study of bone mineral density and metabolism in patients with chronic hepatitis C during pegylated interferon alpha and ribavirin therapy. J Viral Hepat. 2008; 15:790–6. [PubMed: 18673425]
85. Framarin L, Avataneo T, Salzedo E, Badalamenti S, Tappero G, Rosina F. Vertebral osteopenia due to bone marrow hyperplasia during interferon-alpha and ribavirin therapy for chronic hepatitis C. Dig Liver Dis. 2003; 35:732–4. [PubMed: 14620624]
86. Urganci N, Gulec SG, Arapoglu M, Vural S, Nuhog A. The effect of ribavirin on bone density in patients with chronic hepatitis C treated with interferon-ribavirin therapy. J Pediatr Gastroenterol Nutr. 2005; 41:650–2. [PubMed: 16254525]
87. Weide R, Ehlenz K, Lorenz W, Walthers E, Klausmann M, Pfluger KH. Successful treatment of osteoporosis in systemic mastocytosis with interferon alpha-2b. Ann Hematol. 1996; 72:41–3. [PubMed: 8605279]
88. Moreira RO, Balduino A, Martins HS, et al. Ribavirin, but not interferon alpha-2b, is associated with impaired osteoblast proliferation and differentiation in vitro. Calcif Tissue Int. 2004; 75:160–8. [PubMed: 15148560]
89. Lee J, Kim JH, Kim K, et al. Ribavirin enhances osteoclast formation through osteoblasts via up-regulation of TRANCE/RANKL. Mol Cell Biochem. 2007; 296:17–24. [PubMed: 16909305]
90. Takayanagi H, Kim S, Matsuo K, et al. RANKL maintains bone homeostasis through c-Fos-dependent induction of interferon-beta. Nature. 2002; 416:744–9. [PubMed: 11961557]
91. Choudhary NS, Tomar M, Chawla YK, et al. Hepatic Osteodystrophy Is Common in Patients with Noncholestatic Liver Disease. Dig Dis Sci. 2011 Epub.
92. Angulo P, Therneau TM, Jorgensen A, et al. Bone disease in patients with primary sclerosing cholangitis: prevalence, severity and prediction of progression. J Hepatol. 1998; 29:729–35. [PubMed: 9833910]
93. Guanabens N, Pares A, Ros I, et al. Severity of cholestasis and advanced histological stage but not menopausal status are the major risk factors for osteoporosis in primary biliary cirrhosis. J Hepatol. 2005; 42:573–7. [PubMed: 15763344]
94. Guanabens N, Cerda D, Monegal A, et al. Low bone mass and severity of cholestasis affect fracture risk in patients with primary biliary cirrhosis. Gastroenterology. 2010; 138:2348–56. [PubMed: 20178794]
95. Diamond T, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. Gut. 1990; 31:82–7. [PubMed: 2318434]
96. Monegal A, Navasa M, Guanabens N, et al. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. Calcif Tissue Int. 1997; 60:148–54. [PubMed: 9056162]
97. Ninkovic M, Skingle SJ, Bearcroft PW, Bishop N, Alexander GJ, Compston JE. Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. Eur J Gastroenterol Hepatol. 2000; 12:931–5. [PubMed: 10958221]

98. Sokhi RP, Anantharaju A, Kondaveeti R, Creech SD, Islam KK, Van Thiel DH. Bone mineral density among cirrhotic patients awaiting liver transplantation. Liver Transpl. 2004; 10:648–53. [PubMed: 15108256]

99. Brown TT. Bone and Vitamin D. Conference on Retroviruses and Opportunistic Infections. 2011 Conference proceedings.

100. Childs KE, Fishman SL, Constable C, et al. Short communication: Inadequate vitamin D exacerbates parathyroid hormone elevations in tenofovir users. AIDS Res Hum Retroviruses. 2010; 26:855–9. [PubMed: 20672993]

101. Lo Re V 3rd, Guaraldi G, Leonard MB, et al. Viral hepatitis is associated with reduced bone mineral density in HIV-infected women but not men. AIDS. 2009; 23:2191–8. [PubMed: 19779322]

102. El-Maouche D, Mehta SH, Sutcliffe C, et al. Controlled HIV viral replication, not liver disease severity associated with low bone mineral density in HIV/HCV co-infection. J Hepatol. 2011 Epub.

103. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006; 20:2165–74. [PubMed: 17086056]

104. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010; 51:937–46. [PubMed: 20839968]

105. Petta S, Camma 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; 51:1158–67. [PubMed: 20162613]

106. Bitetto D, Fattovich G, Fabris C, et al. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. Hepatology. 2011; 53:1118–26. [PubMed: 21480318]

107. Terrier B, Carrat F, Geri G, et al. Low 25-OH vitamin D serum levels correlate with severe fibrosis in HIV-HCV co-infected patients with chronic hepatitis. J Hepatol. 2011 Epub.

108. Abu-Mouch SM, Fireman Z, Jarchovsky J, Assy N. The Beneficial Effect of Vitamin D with Combined Peg Interferon for Chronic HCV Infection. AASLD. 2009; 50:12A–13A.

109. Bitetto D, Fabris C, Fornasiere E, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. Transpl Int. 2011; 24:43–50. [PubMed: 20649944]

110. Abramovitch S, Dahan-Bachar L, Sharvit E, et al. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. Gut. 2011 Epub.

111. Yano M, Ikeda M, Abe K, et al. Comprehensive analysis of the effects of ordinary nutrients on hepatitis C virus RNA replication in cell culture. Antimicrob Agents Chemother. 2007; 51:2016–27. [PubMed: 17420205]

112. Yano M, Ikeda M, Abe K, et al. Oxidative stress induces anti-hepatitis C virus status via the activation of extracellular signal-regulated kinase. Hepatology. 2009; 50:678–88. [PubMed: 19492433]

113. Gutierrez JA, Jones KA, Fitzgerald RL, et al. Vitamin D Metabolites Inhibit Replication of the Hepatitis C Virus. AASLD. 2010:A803.

114. Gal-Tanamy M, Bachmetov L, Ravid A, et al. Vitamin-D: An innate antiviral agent suppressing Hepatitis C virus in human hepatocytes. Hepatology. 2011 Epub.

115. Snellman G, Melhus H, Gedeborg R, et al. Determining vitamin D status: a comparison between commercially available assays. PLoS One. 2010; 5:e11555. [PubMed: 20644628]

Abbreviations

[25(OH)D]	25-hydroxyvitamin D
BMD	Bone mineral density

CTP	Child-Turcotte-Pugh
HPLC	High-pressure liquid chromatography
HCV	Hepatitis c virus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus type-1
IOM	Institute of Medicine
IFN/RBV	Interferon/Ribavirin
MELD	Model for End-stage Liver Disease
OLT	Orthotopic liver transplantation
PTH	Parathyroid hormone
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis
SVR	Sustained virological response
Gc-globin	Vitamin D-binding protein
VDR	Vitamin D receptor

Table 1
25-hydroxyvitamin D levels in chronic liver disease patients with and without cirrhosis

Etiology	N	25(OH)D < 20 ng/mL	25(OH)D < 32 ng/mL	Reference
HCV cirrhosis	43	79%	95%	Arteh et al.[53]
HCV non-cirrhosis	57	67%	89%	Arteh et al.[53]
HCV non-cirrhosis	468	66%	n/a	Lange et al[56]
NAFLD	60	48%	n/a	Targher et al.[57]
Mixed cirrhosis	51	86%	n/a	Fisher et al.[54]
Mixed non-cirrhosis	49	49%	n/a	Fisher et al.[54]
Mixed cirrhosis + non-cirrhosis	90	51.1%	67.8%	Miroliaee et al.[55]
Mixed cirrhosis	51	76.5%	86%	Miroliaee et al.[55]
Mixed non-cirrhosis	39	17.9%	56.4%	Miroliaee et al.[55]
Mixed cirrhosis	72	92%	n/a	George et al.[59]

Table 2
Low bone mineral density in chronic liver disease patients

Etiology	N	Osteoporosis %	Osteopenia %	Reference
HCV	35	14	26	Loria et al.[71]
HCV	68	28.1	36.8	Carey et al.[69]
HCV/HBV	74	20	n/a	Chen et al.[72]
HCV/HBV	43	19	53	Schiefke et al.[75]
HCV/HBV	32	55	n/a	Gallejo-Rojo et al.[74]
HBV	55	37	n/a	Goral et al.[73]
ALD	66	18.3	26.7	Carey et al.[69]
ALD	33	39.4	n/a	Diez-Ruiz et al.[76]
ALD	115	38.2	57.3	Choudhary et al.[91]
PSC	81	16	n/a	Angulo et al.[92]
PSC	204	35.2	42.4	Guichelaar et al.[77]
PBC	156	43.7	33.1	Guichelaar et al.[77]
PBC	142	32.4	n/a	Guanabens et al.[93]
PBC	185	37	n/a	Guanabens et al.[94]
Mixed	60	47	n/a	Diamond et al.[95]
Mixed	58	43	n/a	Monegal et al.[96]
Mixed	243	37	n/a	Ninkovic et al.[97]
Mixed	104	12	n/a	Sokhi et al.[98]