which a drug is prescribed somehow lessens its effect. Although this statement may have been made tongue-in-cheek, we do not believe that it is an unreasonable policy to promote when the outcome can only increase patient safety. We therefore stand by our recommendation that when the patient is an individual whose job performance has the potential to adversely affect others, it is reasonable to make sure he/she is not impaired before returning to work.

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Why Vitamin D Status Should Be Checked in Patients With Nonalcoholic Fatty Liver Disease

To the Editor: In an excellent clinical vignette in the January 2012 issue of *Mayo Clinic Proceedings*, Nelsen et al[1] discussed the diagnosis and management of patients with nonalcoholic fatty liver disease (NAFLD). We suggest that in patients with this hepatic manifestation of the metabolic syndrome, vitamin D status should also be considered.

In addition to its traditional calcium-related effects on the skeleton, vitamin D deficiency has now been recognized to exert nonskeletal adverse effects on several other organ systems. Hypovitaminosis D is highly prevalent in the United States and around the world. In particular, it reaches a peak of 75% in patients with metabolic syndrome.[2] In this setting, it has been found that patients with biopsy-proven NAFLD had a significantly higher prevalence of hypovitaminosis D (defined as a serum vitamin D concentration of ≤37.5 nmol/L) and markedly lower 25-hydroxyvitamin D (25[OH]D) levels (the best estimates of overall vitamin D status level) than matched controls.[3] The 25(OH)D concentrations were lower in individuals with nonalcoholic steatohepatitis than in those with simple steatosis and inversely associated with the severity of liver histology among NAFLD patients, after adjustment for a broad spectrum of potential confounders. Interestingly, a strong independent association between low 25(OH)D levels and NAFLD has also been found in a population of adults without signs of severe liver damage.[4] This association was independent of diabetes, dyslipidemia, and insulin resistance.

Although the cross-sectional design of these studies[3,4] does not allow establishment of a causative nature of the associations between hypovitaminosis D and NAFLD, the linear inverse correlation between serum 25(OH)D levels and the degree of NAFLD suggests that vitamin D may exert a dose-dependent effect of fat accumulation in hepatocytes. Several mechanisms may explain a causal role of vitamin D deficiency in the development of NAFLD and nonalcoholic steatohepatitis. In fact, vitamin D is capable of reducing free fatty acid–induced insulin resistance both in peripheral tissues and in hepatocytes.[4] Moreover, vitamin D exerts an immunomodulatory action by suppressing fibroblast proliferation and collagen production,[5] which may be particularly important in the evolution to cirrhosis.

Therefore, although intervention trials are warranted to evaluate whether vitamin D supplementation may be a means to prevent and/or treat patients with NAFLD, we believe that vitamin D status should be checked in individuals with liver steatosis.

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In reply: Vitamin D and its relationship to nonalcoholic fatty liver disease (NAFLD) has become of recent interest as studies have linked low serum 25(OH)D levels with NAFLD. The potential therapeutic role of vitamin D supplementation in NAFLD is an intriguing concept given its

safety profile, its important role in modifying cardiometabolic outcomes, and the fact that many NAFLD patients have hypovitaminosis D. Mascitelli et al recommend that serum vitamin D levels should be assessed in all patients with NAFLD and metabolic syndrome. We agree that assessment of serum 25(OH)D levels should be performed in NAFLD patients. A study by Targher et al[1] evaluated serum 25(OH)D levels in 60 patients with biopsy-proven NAFLD and showed that serum 25(OH)D concentrations were significantly lower in patients with NAFLD than in controls. In addition, serum vitamin D concentrations were lower in individuals with more severe liver histology after adjustment for many potential confounders. The authors caution about making a causal inference because low serum concentrations of vitamin D may only be a reflection of an unhealthy lifestyle, since NAFLD is often accompanied by the metabolic syndrome.[2] However, it is possible that low vitamin D levels are driving the progression of NAFLD, since this study found an inverse association with vitamin D levels and worsening histological features of NAFLD.[1] No other study to date has looked specifically at vitamin D levels in biopsy-proven NAFLD. In a larger cohort study aimed at investigating the relationship between NAFLD and hypovitaminosis D in patients with different stages of insulin resistance and no previously diagnosed liver disease, an association was found between low levels of vitamin D and early ultrasonography-diagnosed NAFLD.[3] This study further supports the association between low serum vitamin D levels and NAFLD.

The role of vitamin D in NAFLD may be associated with its known anti-inflammatory actions. It has been shown to dose-dependently suppress the release of tumor necrosis factor α and interleukin 6 and also up-regulate synthesis of the anti-inflammatory cytokine interleukin 10.[4,5] A group of investigators have also shown that the addition of vitamin D to differentiated mesenchymal multipotent cells displayed a decreased profibrotic signaling pathway and gene expression, leading to decrease in collagen deposition.[6] This pathway may provide the mechanism by which vitamin D can improve fibrosis in NAFLD. In addition, it may have a potential role in other liver diseases. Recently, it was found that vitamin D deficiency predicted an unfavorable response to antiviral treatment of recurrent hepatitis C. Vitamin D supplementation improved the probability of achieving a sustained viral response following antiviral treatment.[7] However, another more recent case-control study spanning more than 4 years found no difference in vitamin D levels between patients with and without progression of hepatitis C liver disease; hence, the authors concluded that there was no role for vitamin D supplementation in patients with advanced chronic hepatitis C.[8]

Although therapeutic trials related to vitamin D in other disease states have been disappointing,[9,10] a recent randomized study showed that improving vitamin D status in insulin-resistant women resulted in decreased insulin resistance and improved insulin sensitivity; however, these changes were not evident until higher serum levels of vitamin D were reached.[11] Interventional studies are necessary to determine whether vitamin D deficiency predicts incident NAFLD, whether vitamin D supplementation will be protective against NAFLD, and what mechanisms might account for such protection. In the interim, it is reasonable to recommend that patients with NAFLD receive 1000 IU of vitamin D_3 per day.[12]

We agree that the serum vitamin D level should have been assessed in our patient[13] given the prevalence of hypovitaminosis in NAFLD. We have contacted the patient and are arranging testing and clinic visitation for discussion of the potential benefit of vitamin D supplementation.

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