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CORRESPONDENCE

Oxidative Stress Might Play a Role in Low Serum Vitamin D Associated Liver Fibrosis Among Patients with Autoimmune Hepatitis

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Dear Editor

We have read with great interest the promising article by Efe et al. [1] recently published in your journal. The authors successfully demonstrated the role of Vitamin D in the hepatic fibrotic process and severe inflammation in patients with autoimmune hepatitis (AIH). Moreover, they stated that Vitamin D might be a potential biomarker for predicting treatment response and histological features in AIH. Although the authors discussed comprehensively possible links in this association, we would like to suggest an alternative mechanism relating Vitamin D to liver fibrosis, which we think may be important for a better understanding of the results presented in this study.

In their study, the authors give a detailed discussion relating Vitamin D and hepatic fibrosis in AIH. But it seems that the authors mainly attribute the possible connection between these two entities to immunological mechanisms, namely to T cell-mediated hepatic inflammation and liver damage. Although there is growing evidence that low Vitamin D is related to advanced liver fibrosis, the pathophysiological mechanisms still need to be defined. In this context, we think that oxidative stress mechanisms, by directly inducing fibrotic processes, could possibly play a significant role in the eventual outcome.

Several studies have reported that low vitamin D levels are associated with increased markers of oxidative/nitrosative stress [2]. Experimental studies also demonstrated that Vitamin D, via interaction with the Vitamin D receptor, protects against oxidative stress and can influence migration, gene expression and proliferation of fibroblasts, and diminishes the inflammatory and fibrogenic activity of hepatic stellate cells [3]. Moreover, it has been shown that Vitamin D has antiproliferative effects in liver fibrosis and that Vitamin D supplementation provides significant protection against oxidative stress-mediated complications and strengthens antioxidant defenses [4–6].

Interface hepatitis is the histological hallmark of AIH, consisting of infiltration of CD4 and CD8 T lymphocytes, plasma cells, and macrophages into the liver parenchyma [7]. There is accumulating evidence that suggests interface hepatitis to be an example of apoptosis rather than a necrosis [8]. Nitric oxide (NO)-dependent modifications may contribute to the activation of intrinsic apoptotic pathways that induce cell death. However, the mechanism by which this pathway is activated in cells exposed to NO is not known [9]. The factors that affect cell-specific sensitivity to NO-mediated apoptosis can be related to several influences, including the redox state within the cells, apoptotic signaling cascade activation, regulation of cell survival, and apoptotic gene expression [10]. Based on these findings, it is reasonable to consider that elevated oxidative stress levels contribute to enhanced inflammation and liver damage in AIH by inducing apoptotic pathways.

As discussed above, in addition to the other mechanisms mentioned by the authors, it is reasonable to suggest a potential link between low Vitamin D levels and liver fibrosis via oxidative stress pathways. Understanding the intricacies of

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this pathway may also provide new avenues for therapeutic intervention with antioxidant supplementation.

Reply

We thank to Dr Beyazit and co-workers for their interesting comments regarding our study [1, 11]. The possible role of serum vitamin D has been better described in patients with other etiologies of chronic liver disease, while its influence on AIH has not been thoroughly investigated. In our study, we focused on the immunomodulatory properties of vitamin D and we hypothesized that its low levels may be the cause of increased inflammatory activity, the consequence of which could lead to advance fibrosis. This association was prominent even at the early stage of fibrosis or in patients with mild histological activity. This is of interest in view of the fact that at the same time point, other markers of liver function such as prothrombin time and albumin levels were within the normal ranges.

This is of interest in view of the fact that levels of "free" 25-hydroxyvitamin D are dependent on the concentration of not only vitamin D binding P but also alternative serum binding proteins such as albumin. Thus, while alteration of albumin levels could account for changes of free vitamin D, the reverse is not always likely *per se*. Thus, neither decreased production of albumin nor of vitamin D protein is a prerequisite for diminished vitamin D levels.

In particular, archetypical autoimmune diseases such as multiple sclerosis have been linked to vitamin D deficiency, independently of any liver involvement. Thus, several studies have shown that over-expression of vitamin D prevents the occurrence of multiple sclerosis or at least reduces the rate of relapses in these patients [12]. Elegant studies in animal models of the studies have profoundly shown similar effects.

These findings suggest that the inverse relationship between vitamin D levels and histological features cannot be fully explained by histological activity and synthetic dysfunction of the liver. In fact, most studies reporting on the association between low levels of vitamin D and disease severity have not taken into account that low levels of vitamin D in severely ill patients may relate to dietary factors, adiposity, skin pigmentation, and renal dysfunction. Hence, some other mechanisms may account for the association between low levels of vitamin D and the induction of autoimmune destruction of the hepatocytes.

Oxidative stress can inflict damage on hepatocyte DNA, induce apoptosis, and increase production of inflammatory cytokines [13]. Importantly, oxidative stress is not disease specific and it is responsible for fibrosis progression in various causes of chronic liver diseases. The data regarding the role of oxidative stress in AIH are limited. Sanz-Cameno et al. [14] showed an enhanced intrahepatic inducible nitric oxide synthase expression and nitrotyrosine accumulation, which correlated significantly to the severity of hepatic inflammation in AIH. In other studies [8, 15], wide range of prooxidant and antioxidant markers were detected in blood and urine of patients with AIH. In an in vitro study [3], vitamin D reduced inflammation and prevented fibrosis progression by inhibiting stellate cells activity. However, importantly, Kupffer cells and myofibroblasts can also promote hepatic inflammation and fibrogenesis by increasing oxidative stress, and the antioxidant properties of vitamin D have not been shown on these pathways [13]. Finally, several of the effects mediated by vitamin D are tightly linked with the role played by vitamin D receptor, which is expressed on many immune populations (T lymphocytes, natural Killer cells) and can illicit transcriptional responses that may account for the immune-mediated destruction of tissues, including the liver [12]. Needless to say that vitamin D exerts a prominent effect on immunoregulatory cells and that vitamin D deficiency is strongly associated with numerical and functional impairment of the suppressor activity of immunoregulatory cells, thus further enhancing the auto-destructive potential of self-targeting immune cells.

In conclusion, the development of AIH is the read out of complex, multi-factorial immunoregulatory mechanisms. Hence, the exact role of oxidative stress and vitamin D in the pathogenesis of AIH needs to be further investigated in animal models. If this association is to be externally validated, controlled and prospective clinical trials that determine the efficacy of vitamin D and antioxidants as supplemental therapies must be encouraged in AIH.

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Conflict of interest None.

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