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Evidence supporting a beneficial role of vitamin D in chronic hepatitis C

To the Editor:

We read with interest the recent meta-analysis by Kitson *et al.* [1]. The authors show that baseline vitamin D level is not associated with sustained virologic response (SVR) to pegylated interferon (PegIFN) plus ribavirin therapy in patients with chronic hepatitis C (CHC). Based on this finding, they question [1] the non-skeletal benefits of vitamin D supplements, an essential determinant in regulating bone metabolism in chronic liver disease [2], on CHC. However, as vitamin D deficiency has been identified as a main risk factor for CHC development, we believe that the non-skeletal benefits of this kind of vitamin on patients with CHC cannot be negligible and the conclusions of this meta-analysis [1] needs to be further discussed and researched.

First, the studies included in the meta-analysis by Kitson *et al.* [1] were performed in patients from America, Europe, Australia, or Israel, all of whom were predominantly white in skin color. Interestingly, a community-based cross-sectional study showed that, compared with white people, blacks had lower levels of vitamin D and vitamin D-binding protein [3]. In addition, potential differences were also observed between whites and blacks in relation to the influence of vitamin D status in the degree of hepatic fibrosis in CHC patients [4]. As a consequence, levels of vitamin D and its benefits may vary in individuals with different ethnicity, therefore the irrelevance between vitamin D and SVR, and the ineffectiveness of vitamin D in CHC shown in this study, needs to be also confirmed in other races.

Second, this meta-analysis only summarized eleven studies, seven of which, with 1951 patients, were published articles and the other four were conference abstracts with less convincing evidence. Among the eleven studies, the sole outlier, identified by funnel and forest plots, belonged to a conference abstract. Another coexisting meta-analysis with eleven full-text studies demonstrated that a lower level of vitamin D was significantly associated with a lower probability of SVR in CHC patients receiving Peg-IFNα/ribavirin therapy, especially when a cut-off value of 20 ng/ml for vitamin D deficiency was adopted [5]. Furthermore, a low vitamin D status was also found to be associated with a higher risk of advanced liver fibrosis in these patients [5]. Numerous clinical evidence also suggested that vitamin D supplementation might protect against disease progression and elevate the SVR rate following treatment for CHC [6,7]. Recurrence of hepatitis C after liver transplantation is universal worldwide [8]. In addition to its association with primary CHC, vitamin D insufficiency could also result in a low SVR in patients with recurrent hepatitis C following antiviral therapy while vitamin D supplementation significantly improves the probability of achieving a SVR [8].

Potential mechanisms that link vitamin D and CHC are complex and varied. Treatment with vitamin D reduces the extra- and intracellular levels of hepatitis C virus (HCV) core antigen in a dose-dependent manner [9] and produces calcitriol which could markably inhibit HCV productions [10], suggesting that vitamin D plays a natural antiviral role. In addition, the anti-inflammatory effects by reducing several pro-inflammatory factors like TNF-α, IFN-γ, and IL-17, as well as the anti-fibrotic role of vitamin D [7], might also partly explain the benefits of this vitamin supplementation in CHC.

As there is a global high prevalence of hypovitaminosis D among CHC patients, it is crucial to determine the association between vitamin D status/vitamin D supplementation and outcomes of CHC. Larger, random clinical trials are still required to confirm the important non-skeletal effects of vitamin D in patients with CHC.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Evidence supporting a beneficial role of vitamin D in chronic hepatitis C"

To the Editor:

We thank Pang *et al.* for their interest in our recently published systematic review and meta-analysis involving 2605 patients which found no association between baseline 25-hydroxyvitamin D level and sustained virologic response (SVR) to interferon-based antiviral therapy in chronic hepatitis C infection [1]. They are correct to highlight the influence of ethnicity on both vitamin D status and genetic polymorphisms in key proteins involved in vitamin D synthesis. The studies included in our meta-analysis contained only a small number of participants of Asian [2] or African-American [3] ethnicity, leading us to highlight the study's inability to adjust for ethnicity as one of its limitations.

With regards to the recently published meta-analysis by García-Álvarez *et al.* [4] evaluating vitamin D status and response to hepatitis C therapy, this study differs from ours in that it includes those with HCV-HIV co-infection. Furthermore, we believe this study has significant methodological issues such as the inclusion of three studies involving the same Italian cohort of approximately 200 patients, and the exclusion of five large studies [2,5–8] from Europe and Australia involving 1569 patients that were readily identifiable using the stated search strategy. Our concerns about this study have recently been published [9] and the validity of the study's findings should be viewed with caution.

Our meta-analysis only evaluates the relationship between baseline vitamin D status and SVR. The impact of vitamin D supplementation on outcomes to interferon-based antiviral therapy, although interesting, is a different clinical question that has not been definitively assessed in prospective, randomized controlled trials. We agree that vitamin D has potential anti-viral, anti-inflammatory, anti-fibrotic and immunomodulatory actions relevant to liver disease, which have been highlighted in a number of pre-clinical studies [10]. However high quality prospective clinical research studies are needed to support the hypothesis that vitamin D deficiency may be responsible for the worse outcomes in HCV related liver disease.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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