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Vitamin D deficiency and HCV chronic infection: What comes first?

To the Editor:

Dear Sir, we read with great interest the paper published by Lange *et al.* [1] reporting that serum vitamin D deficiency and the *CYP27B1*-1260 promoter polymorphism are more prevalent in patients with chronic hepatitis C compared to controls, and that they are associated with a lower response rate to interferon-alfa based therapy. Comparing patients with chronic hepatitis C to a large control group, the authors found a strong association between the presence of chronic hepatitis C and severe vitamin D (25-OH D3) deficiency (serum levels <10 ng/ml in 25% of the patients *vs.* 12% of controls, p <0.00001). Furthermore, adding new observations to the recently published data [2], the authors showed that serum vitamin D deficiency is associated with a lower probability to achieve sustained viral response (SVR) after antiviral therapy in easy to treat hepatitis C virus (HCV) genotypes.

The association between vitamin D deficiency and HCV chronic infection has been previously reported by several authors [3] and different studies demonstrated that it seems to be preferentially related to the HCV etiology rather than to the severity of liver disease [4]. These observations raise the question about what comes first, vitamin deficiency or HCV infection? In other words, may vitamin D deficiency confer an enhanced susceptibility to HCV chronic infection, or can HCV chronic infection, through a still unknown mechanism, cause vitamin D deficiency?

To try to answer this question Dr. Lange *et al.* [1] examined whether the eradication of HCV infection determined a significant increase in the serum levels of vitamin D. They determined 25-OH D3 serum concentrations before and 24 weeks after the end of antiviral therapy, in 50 patients with HCV genotype 1 chronic hepatitis who achieved SVR. Although in these patients the median value of 25-OH D3 serum concentrations increased slightly 24 weeks after the end of antiviral treatment (16.2 *vs.* 18.2 ng/ml), the authors outlined that a trend for having a lower prevalence of severe vitamin D deficiency (25-OH D3 <10 ng/ml) after HCV eradication has been detected (33% *vs.* 26%, $p = 0.092$). Hence the authors speculate that HCV infection itself may affect vitamin D metabolism, providing preliminary evidence that a potential direct viral effect on vitamin D synthesis could be hypothesized.

Although this assumption may be acceptable, we are not completely convinced that this can be supported by the data presented, not only for the lack of statistically significance they have. In the analysis of vitamin D serum concentrations, the authors did not consider the season in which the serum sample was taken, that represent a very important variable able to influence vitamin D serum concentration [5]. Analyzing a cohort of 211 north-Italian patients with chronic HCV related hepatitis treated with pegylated interferon and ribavirin, we identified as independent predictors of low ($\leqslant$20 ng/ml), vitamin D serum levels the age >50 years (O.R. 2.37, 95% C.I. 1.34–4.21, $p = 0.002$) and having drawn the blood sample for vitamin D measurement during the winter or spring months (O.R. 2.06, 95% C.I. 1.15–3.67, $p = 0.016$). When the analysis was performed in the subgroup of the 144 patients who underwent a pre antiviral treatment liver biopsy, a higher histology grade (O.R. 3.42, 95% C.I. 1.37–8.54, $p = 0.004$) and having drawn the blood sample for vitamin D measurement during the winter or spring months (O.R. 2.79, 95% C.I. 1.35–5.74, $p = 0.005$) were the only independent predictors of low vitamin D serum levels [6].

As the authors evaluated vitamin D serum levels 24 weeks after the end of antiviral therapy, it is inevitable that the season in which the second assessment of the vitamin D serum levels was made can not be the same of the first determination. Thus the change in vitamin D serum levels in patients who achieved SVR, observed by Lange *et al.* [1], may be preferentially due to the season influence rather than to the eradication of HCV infection. Since the time in which antiviral therapy has been started is generally an easily recoverable data, the authors should analyze their data taking into account this important variable in order to confirm the association they found towards a lower prevalence of vitamin D deficiency in patients who achieved SVR.

In conclusion, it seems evident that a close interplay between low vitamin D serum levels and HCV chronic infection exist, but, until now, we still do not know what come first.

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.

References

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Reply to "Vitamin D deficiency and HCV chronic infection: What comes first?"

To the Editor:

We thank Dr. Bitetto *et al.* for their interest in our study recently published in the *Journal of Hepatology* [1]. In this study, we reported a high prevalence of severe vitamin D deficiency in patients with chronic hepatitis C, even in the absence of significant liver fibrosis. We found that vitamin D deficiency was associated with failure to achieve a sustained virologic response (SVR) to therapy of chronic hepatitis C with pegylated interferon-alfa and ribavirin. Bitetto *et al.* have now accentuated the important question, whether vitamin D deficiency is caused by hepatitis C virus (HCV) infection, or whether vitamin D deficiency may confer an enhanced susceptibility to chronic HCV infection. We believe that this question cannot be finally answered at the moment. In our study, we reported a slight increase of 25-hydroxyvitamin D serum levels from baseline to week 24 after completion of antiviral therapy in those patients who achieved a SVR. As highlighted by Bitetto *et al.* and others [2,3], we have made an attempt to stratify the patients included in this sub-analysis according to the season in which serum samples for vitamin D measurement were taken. In detail, 50% of patients started therapy in winter/spring and SVR was ascertained in summer/autumn, which was vice versa in the remaining 50% of patients. Meanwhile, we have also re-analyzed our complete cohort according to the season when baseline serum samples for vitamin D detection were taken. Although we observed slightly lower baseline 25-hydroxyvitamin D serum levels in patients who started therapy in winter/spring compared to summer/autumn (mean 16.6 and 18.7 ng/ml, $p = 0.054$), severe vitamin D deficiency (<10 ng/ml) was associated with chronic HCV infection during all seasons (26% *vs.* 19% in winter/spring *vs.* summer/autumn, respectively, compared to 20% *vs.* 6% in winter/spring *vs.* summer/autumn samples in our non-HCV infected control group). In addition, season had no significant influence on SVR rates. Nevertheless, we fully agree with Bitetto *et al.* that our observations do not prove that HCV infection itself can cause vitamin D deficiency. In addition to a residual season influence, factors such as changes in life-style or eating habits may contribute to the increase of vitamin D serum levels after successful HCV eradication. To resolve the "what comes first" question results of basic research on a potential interplay between HCV infection and vitamin D metabolism, as well as additional clinical data from large and well defined patient cohorts are required.

Conflict of interest

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References

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Tips for portal vein thrombosis (pvt) in cirrhosis: Not only unblocking a pipe

To the Editor:

Han *et al.* recently published a case series of patients with cirrhosis who had developed portal and splanchnic vein thrombosis at various intervals from treatment with transjugular intrahepatic portosystemic shunt (TIPS), for complications of the resulting portal hypertension [1]. We are pleased that they confirmed our published findings that TIPS is feasible and effective in patients with PVT, including those with cavernous transformation of the portal vein [2].