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IM - COMMENTARY

Is vitamin D deficiency predictor of complications development in patients with HCV-related cirrhosis?

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Around 130–170 million people in the world, according to WHO estimates, are infected with hepatitis C virus (HCV), with a wide variability in geographical distribution [1]. HCV causes both acute and chronic hepatitis, the latter evolving to cirrhosis with impairment of liver structure and function, development of fibrosis, portal hypertension and hyperdinamic circulation [2]. During this progression, the varying degree of fibrosis can be assessed through non-invasive serological tests and/or imaging techniques, which have been proposed as reliable indicators [3]. Clinical complications of cirrhosis are esophageal varices, ascites with spontaneous bacterial peritonitis, hepato-renal syndrome, hepatopulmunary syndrome and hepatic encephalopathy [4, 5].

Vitamin D is a secosteroid hormone which is involved in several processes [6]. It has pleiotropic effects being mainly implicated in bone and calcium homeostasis, cardiovascular system function, pancreatic endocrine cells, muscle and adipose tissue [7]. The role of vitamin D on immune response has been clearly demonstrated throught in vitro and in vivo studies [8, 9]; it exerts her effect on the regulation of inflammatory pathways by binding its receptor (VDR) in the nucleus of macrophages and/or dendritic cells. Thereby, vitamin D enhances phagocytic, chemotactic and antimicrobial activity acting as a transcription factor for antimicrobial peptides, as cathelicidin and beta-defensing [10, 11]. Moreover, the complex vitamin D/VDR protects against oxidative stress production, influencing fibroblast gene expression and reducing the inflammatory and fibrogenic activity of hepatic stellate cells in the liver [12]. The hepatic expression of VDR is associated with the severity of both liver fibrosis and inflammation, being progressively lower moving from patient with low to moderate necro-inflammatory activity. The link to inflammatory mechanism was not specifically related to HCV infection, being present also in a highly inflammatory liver disease, as autoimmune hepatitis. Low hepatic VDR expression could be a factor involved in liver disease severity, also mediated by hepatocytes, cholangiocytes and other inflammatory cells promoting fibrogenic mechanisms [13]. Also patients with NAFLD had significantly lower levels of vitamin D due to mild inflammation, and this might contribute to the NAFLD progression [14]. It is noteworthy that, vitamin D promotes the switch from the Th1 (pro-inflammatory) to the Th2 (anti-inflammatory)-mediated immune pattern exerting an important role in adaptive immune response [15]. Storage and conversion of vitamin D usually happens in the liver [16]; its deficiency is prevalent in chronic liver disease and the degree of deficiency correlates with the severity of disease [17].

In this context, the paper by Yousif et al. [18] shows how vitamin D deficiency is a risk factor for hepatic encephalopathy (HE) and spontaneous bacterial peritonitis (SBP) in cirrhotic patients; further they showed as lower serum vitamin D levels are associated with increased mortality in these patients. In this study, the authors studied 135 patients suffering from HCV related cirrhosis: 45 of them without complications served as control group, 45 were complicated with hepatic encephalopathy (HE) of different degree and 45 with spontaneous bacterial peritonitis (SBP). In this last group, 12 patients have classic SBP, 5 patients presented with mononuclear bacteriascites (MNB) and finally 28 patients with culture negative neutrocytic ascites (CNNA). Further, the authors described that lower serum levels of vitamin D were associated with worse HE grade with a statistically significant difference between all grade of HE, while serum vitamin D level was lower in patients with classic SPB and MNB compared to patients CNNA. A significant correlation between severity of cirrhosis (assessed by Child–Pugh score) and low serum levels of vitamin D have been also found in patients complicated with HE and SPB. Thus, vitamin D

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may be useful as prognostic factor in HCV-related cirrhosis. A low threshold of vitamin D, less than 7.2 ng/ml, was significantly related to high mortality rates. Cut-off of levels less than 7.1 ng/ml were able to predict mortality in SBP and less than 6.6 mg/ml in patients with HE.

Literature review shows as vitamin D deficiency has been associated with increased mortality in the general population [19]. In particular, it is a risk factor for infections [20, 21], for hepatic decompensation, inflammation and increasing mortality in cirrhosis. In particular, as in the study of Yousif et al. [18], another study by Anty et al. [22] reported that low vitamin D levels inversely correlated with Child–Pugh score. In addition, it was also reported by Trepo et al. [23] that the association between lower vitamin D serum levels and liver disease complication was present in patients with alcoholic liver disease, as well.

Vitamin D deficiency is probably caused in HCV-related liver cirrhosis by several mechanisms implicated in vitamin D absorption such as activation and hydrolytazation of 25 (OH) D or malabsorption due to portal hypertension. The increased risk of infections can be caused by immunological derangements. In particular, cathelicidin belongs to a group of antimicrobial peptides with pleiotropic effect; one of this role is the protection of the epithelial barrier against infections [24]. The increased risk of SBP, as in the study of Yousif et al. [18], can be caused by immunological impairment in peritoneal macrophages response which is inhibited by low serum levels of vitamin D [25]. It is noteworthy that the most recent European and American guidelines suggest vitamin D supplementation in chronic liver disease with or without complications.

However, the role of vitamin D is relevant in many inflammatory and autoimmune conditions, not only in viral liver disease. In fact, being vitamin D a modulator of the immune system, its deficiency may be implicated in the development of autoimmune disorders, including type 1 diabetes, multiple sclerosis, lupus erythematosus, rheumatoid arthritis and Behcet disease. In all these cases, it has been shown that vitamin D supplementation can be useful [26]. A prevalence of vitamin D deficiency has been also found in patients with inflammatory bowel disease. In particular, vitamin D can promote the induction and maintenance of remission through its anti-inflammatory activity and repair of the intestinal mucosal barrier. Vitamin D supplementation can be considered an adjuvant therapy in improving disease activity, quality of life and reducing relapses [27]. Another inflammatory condition in which vitamin D plays a prognostic role is acute pancreatitis where it is associated with a severity of disease and is predictor of intensive care unit admission [28].

From a neurological point of view, little is known about vitamin D deficiency and HE; Vidot et al. [29] have recently reported that lower serum levels of vitamin D in patients with cirrhosis showed an inverse correlation with MELD and overt HE. However, in this study, the authors were not able to find a relationship between vitamin D deficiency and subjective nutritional assessment (SGA) scores. Other neurological studies [30, 31] reported that vitamin D deficiency could lead to cognitive impairment by interacting with the extracellular matrix and the peri-neuronal net, regulating brain plasticity. In addition, both neurons and glial cells exposed on their surface VDR, thus low serum levels of vitamin D could result as cognitive diseases, like overt HE in cirrhosis.

In conclusion, the study by Yousif et al. [18] added more information to the studies already existing in the literature. In fact, reporting about the prognostic role of vitamin D deficiency in patients with HCV related cirrhosis and its complications, the authors increase our knowledge about the need for supplementation in these patients at high risk of developing severe complication, as high grade HE and SPB, and overall mortality.

Moreover, it can be considered a challenge for future studies in patients with cirrhosis of all etiologies, assessing the impact of vitamin D supplementation on infections rate and severity of complications, including overall mortality. Given the role of vitamin D in many other conditions, it could be useful to investigate the pathophysiological mechanisms in various settings attempting to understand how vitamin D supplementation is able to improve outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights As Commentary this article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. WHO (2017) Global hepatitis report. http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
2. Licata A, Mazzola A, Ingrassia D et al (2014) Clinical implications of the hyperdynamic syndrome in cirrhosis. Eur J Intern Med 25:795–802
3. Soresi M, Giannitrapani L, Cervello M et al (2014) Non invasive tools for the diagnosis of liver cirrhosis. World J Gastroenterol 20:18131–18135
4. Moller S, Bendtsen F (2015) Complication of cirrhosis. A 50 years flashback. Scand J Gastroenterol 50:763–780

5. Poordad FF (2015) Presentation and complications associated with cirrhosis of the liver. Curr Med Res Opin 31:925–937
6. Perez-Lopez FR (2007) Vitamin D: the secosteroid hormone and human reproduction. Gynecol Endocrinol 23:13–24
7. Caprio M, Infante M, Calanchini M et al (2016) Vitamin D: not just bone. Evidence for pleiotropic extraskeletal effects. Eat Weight Disord 22:27–41
8. Hewison M (2011) Antibacterial effects of vitamin D. Nat Rev Endocrinol 7:337–345
9. Mangin M, Sinha R, Fincher K (2014) Inflammation and vitamin D: the infection connection. Inflamm Res 63:803–819
10. Lin R (2016) Crosstalk between vitamin D metabolism, VDR signaling and innate immunity. BioMed Res Int
11. Gombart AF (2009) The vitamin D-antimicrobial pathway and its role against infection. Future Microbiol 4:1151–1165
12. Macaluso FS, Maida M, Minissale MG, et al (2013) Metabolic factors and chronic hepatitis C: a complex interplay. Bio Med Research International, pp 564–645
13. Petta S, Grimaudo S, Tripodo C et al (2014) The hepatic expression of vitamin D receptor is inversely associated with the severity of liver damage in genotype 1 chronic hepatitis C patients. J Clin Endocrinol Metab 100:193–200
14. Hariri Mitra, Zohdi Sara (2019) Effect of vitamin D on non-alcoholic fatty liver disease: a systematic review of randomized controlled clinical trials. Int J Prev Med 10:14
15. Hoe E, Nathanielz J, Toh ZQ, Spry L, Marimia R, Balloch A et al (2016) Anti-inflammatory effects of vitamin D on human immune cells in the context of bacterial infection. Nutrients 8:806
16. Holick MF (2007) Vitamin D deficiency. N Engl J Med 57:266–281
17. Arteh J, Narra S, Nair S (2010) Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci 55:2624–2628
18. Yousif MM, Sadek AMEM, Farrag HA, Selim FO, Hamed EF, Salama RI (2019) Associated vitamin D deficiency is a risk factor for the complication of HCV-related liver cirrhosis including hepatic encephalopathy and spontaneous bacterial peritonitis. Intern Emerg Med. https://doi.org/10.1007/s11739-019-02042-2
19. Gaksch M, Jorde R, Grimnes G et al (2017) Vitamin D and mortality: individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. PLoS One 12(2):e0170791. https://doi.org/10.1371/journal.pone.0170791
20. Buonomo AR, Zappulo E, Scotto R et al (2017) Vitamin D deficiency is a risk factor for infections in patients affected by HCV related liver cirrhosis. Int J Infect Dis 63:23–29
21. Buonomo AR, Scotto R, Zappulo E, Nerilli M, Pinchera B, Perruolo G, Formisano P, Nappa S, Gentile I (2019) Severe vitamin D deficiency increases mortality among patients with liver cirrhosis regardless of the presence of HCC. In Vivo 33(1):177–182. https://doi.org/10.21873/invivo.11456
22. Anty R, Tonohouan M, Ferrari-Panaia P et al (2014) Low levels of 25-hydroxy vitamin D are independently associated with the risk of bacterial infection. Clin Transl Gastroenterol 5:e56
23. Trepo E, Ouziel R, Pradat P et al (2013) Marked 25-hydroxyvitaminD deficiency is associated with poor prognosis inpatients with alcoholic liver disease. J Hepatol 59:344–350
24. Vandamme D, Landuyt B, Luyten W et al (2012) A comprehensive summary of LL37, the factotum human cathelicidin peptide. Cell Immunol 280:22–35
25. Zhang C, Zhao L, Ding Y et al (2016) Enhanced LL-37 expression following vitamin D supplementation in patients with cirrhosis and spontaneous bacterial peritonitis. Liver Int 36:68–75
26. Pelajo CF, Lopez Benitez JM, Miller LC (2010) Vitamin D and autoimmune rheumatological disorders. Autoimmun Rev 9:507–510
27. Li J, Chen N, Wang D et al (2018) Efficacy of vitamin D in treatment of inflammatory bowel disease. A meta-analysis. Medicine (Baltimore) 97:12662
28. Hye J, Kim JW, Lee KJ (2019) Vitamin D deficiency predicts severe acute pancreatitis. UEG J 7:90–95
29. Vidot H, Potter A, Cheng R, Allman-Farinelli M, Shackel N (2017) Serum 25-hydroxyvitamin D deficiency and hepatic encephalopathy in chronic liver disease. World J Hepatol 9:510–518
30. Mayne PE, Burne THJ (2019) Vitamin D in synaptic plasticity, cognitive function, and neuropsychiatric illness. Trends Neurosci S0166-2236(19)30006-2. https://doi.org/10.1016/j.tins.2019.01.003
31. Annweiler C, Allali G, Allain P et al (2009) Vitamin D and cognitive performance in adults: a systematic review. Eur J Neurol 16:1083–1089