Dear Editor,

We submit the revised version of our manuscript re-titled **"Vitamin D deficiency and viral hepatitis-associated liver diseases: a literature review"** to be considered for publication in World Journal of Gastroenterology. We sincerely thank the editor and reviewer for considering our study and for providing valuable comments and suggestions. We have carefully considered all the comments and revised this review accordingly. We believe that the review has been improved. All changes in the text were highlighted and rebuttals to the queries are interleaved as below.

Thank you very much for your time and consideration.

With best regards

PD Dr. Thirumalaisamy P. Velavan

Rebuttals to reviewer comments

Reviewer #1: This is a very good review focused on a topic of interest and widely debated in the literature: the role of vitamin D in chronic hepatic diseases, in particular the ones associated to viral hepatitis. I just have a note to make the exposure more clear and correct. Twice in the text (lines 237-240, and lines 333-334) is reported an association between vitamin D deficiency and NAFLD: in both cases the literature cited does not directly refer to NAFLD pathogenesis but rather to the association with other pathological conditions. Despite the absence of a clear causal link, vitamin D deficiency is often associated with NAFLD. To refer this phenomenon more clearly, I suggest to add some specific citations on pathogenesis and epidemiology of NAFLD (see for example a recent review: "Cimini et al. Relationship between adipose tissue dysfunction, vitamin D deficiency and the pathogenesis of non-alcoholic fatty liver disease. World J Gastroenterol. 2017;23:3407-3417; or also "Ha Y, et al. The Association between Vitamin D Insufficiency and Nonalcoholic Fatty Liver Disease: A Population-Based Study. Nutrients. 2017;9. pii: E806").

We thank the reviewer for the suggestion. We have added an additional paragraph to describe the association between vitamin D deficiency and NAFLD as below.

Although vitamin D is associated with NAFLD, a recent study showed that vitamin D insufficiency was not associated with the presence of NAFLD[83]. Relationship between vitamin D deficiency and the pathogenesis of NAFLD has been systematically reviewed[10], and that vitamin D could be used as a supplement in the management of NAFLD. However, clinical trials concluded that vitamin D supplementation has a less impact on the NAFLD pathogenesis such as hepatic fat, injury, and hepatic steatosis[84, 85].

There are few words in the text that need to be corrected, for example: Line 54: metabolism Line 59: prevalence Line 415: substance

We have corrected the text accordingly

Reviewer #2: The manuscript is a review of the literature about the vitamin D deficiency and its association with liver diseases influenced by viral hepatitis, primarily hepatitis B and C viruses (HBV, HCV). The authors initially provide a general overview of vitamin D metabolism and function itself, and then discuss issues related to vitamin D deficiency, its prevalence around the world, and potential reasons for deficiency and the variation among different populations. Afterwards, the authors discuss the literature on vitamin D deficiency and its association and/or relevance to HBV and HCV, liver cirrhosis (viral and non-viral), and hepatocellular carcinoma (HCC). The authors then close with a brief discussion on vitamin D analogues and the potential for HCC treatment. The manuscript flows well and provides a nice narrative. I have some comments that would hopefully benefit the authors in their revision.

1) When discussing the literature in certain sections, it is helpful to note what types of studies were used to illustrate certain facts. For example, under the "Vitamin D Deficiency" section, the prevalence of vitamin D deficiency for certain countries were provided. It is noted in the subsequent paragraph that the prevalence for vitamin D deficiency in the United States was obtained from the cross-sectional analysis of the US NHANES. Yet, it is unclear, without going to the references themselves, what studies were done for the Asian countries.

We thank the reviewer for the suggestion. In this review paper, we focused on the role of vitamin D deficiency in viral hepatitis B and C and we have briefly reviewed this issue in the table 1 and 2. We have provided the types of studies in these table. In the section of "Vitamin D Deficiency", we also have provided this information for studies done in Asian countries as below

Serum levels in Asian populations were assessed in three large cross-sectional studies in China (n=3262)[56], South Korea (n=6925)[55], and in Thailand (n=2641)[54].

2) While the Tables 1 and 2 provide a great brief overview of various aspects of the different studies, it would be helpful to know whether the study participants, especially in case-control or "randomized prospective", are hospital-based or population-based. It would help orient the reader to see whether the participants are a reflection of what is seen in hospitals or medical centers, or if they reflect the general population of those countries. Also, for the prospective or nested case-control studies, is there information on the length of follow-up? This type of information could provide some idea of temporality.

We thank the reviewer for the suggestion. All study participants in "case-control" or "randomized prospective" studies presented in the table 1 and 2 were hospital-based populations. We also have added the information on the length of follow-up in both tables accordingly.

3) Minor: While acronyms are provided in the beginning, I suggest the authors provide the full words (e.g. "CHB" for chronic hepatitis B) in the text itself.

We have amended in the text accordingly

4) Minor: Though the overall English is fine, the paper could benefit from some editing and/or review for consistency in usage and spacing.

We have carefully proofread the manuscript and corrected accordingly.

Reviewer #3: The review is adequate in terms of major clinically relevant information. However, some aspects relative to the interaction of inflammation-

vitaminD deficiency-progression of viral disease, as well as vitamin D deficiency-cytokines-fibrogenesis could be expanded.

We thank the reviewer for the valuable suggestion. We have added this aspect related to the interaction of vitamin D deficiency-cytokines-fibrogenesis as follow:

Furthermore, vitamin D directly inhibits the proliferation and profibrotic phenotype of hepatic stellate cells and reduces thioacetamide-induced liver fibrosis in an animal model [109]. There are several lines of evidence to support an inverse association of vitamin D levels with liver fibrosis induced by chronic viral hepatitis[4, 100, 111, 112]. More specifically, a high expression of hepatic Toll-like receptors (TLR2 and TLR4) can result in the production of tumor necrosis factor alpha (TNFα) in chronic hepatitis C[113]. This cytokine is shown to modulate fibrosis [114, 115]. In this context, vitamin D might elicit an anti-inflammatory mechanism by downregulating the expression of TLR2 and TLR4 molecules. Recent in-vivo studies have documented on the reduced production of TNFα by monocytes, macrophages and myeloid dendritic cells treated with vitamin D [116, 117]. Corroborating the findings, a yet another study show that circulating vitamin D levels inversely correlate with TLR2 and TLR4 expression [118].

There are some typos and spelling errors.

We have proofread and corrected the text accordingly

Reviewer #4:

- HBV and VD: SNPs genetic variants are related with changes in VD function in HBV infected patients. Low levels of VD, can also influence the reply to antiviral treatment. - HCV and VD: the role of VD to improve the levels of fibrosis markers, has been studied. Please include these data in this section.

We have discussed the role of vitamin D to improve the levels of fibrosis markers in the section of "VITAMIN D AND VIRAL HEPATITIS-RELATED LIVER CIRRHOSIS".

"The association of vitamin D with LC has been more intensively discussed in chronic hepatitis C and in NAFLD patients, rather than in chronic hepatitis B. A recent meta-analysis included seven studies in order to assess vitamin D serum levels and advanced liver fibrosis in patients with chronic hepatitis C. Low vitamin D levels were related to advanced fibrosis, with two cutoff values set of either 10 ng/ml (OR=2.5, 95%CI: 1.2-4.7) or 30 ng/ml (OR=2.2, 95%CI:1.2-4.0)[86]"

We have also added the data on the role of vitamin D in the pathogenesis of liver cirrhosis in this section:

More specifically, a high expression of hepatic Toll-like receptors (TLR2 and TLR4) can result in the production of tumor necrosis factor alpha (TNFα) in chronic

hepatitis C[113]. This cytokine is shown to modulate fibrosis [114, 115]. In this context, vitamin D might elicit an anti-inflammatory mechanism by downregulating the expression of TLR2 and TLR4 molecules. Recent in-vivo studies have documented on the reduced production of TNFα by monocytes, macrophages and myeloid dendritic cells treated with vitamin D [116, 117]. Corroborating the findings, a yet another study show that circulating vitamin D levels inversely correlate with TLR2 and TLR4 expression [118].

- Viral hepatis and HIV: recently some papers are published on the VD levels in co-infected patients. I suggest to include a new section.

We thank the reviewer for the suggestion. In this review article, we discussed general aspects of vitamin D deficiency and, in particular, the significance of vitamin D hypovitaminosis in the outcome of viral hepatitis. Hence, the clinical outcomes in co-infected patients with HIV associated with vitamin D levels as well as the association between SVR rates to antiviral therapy and vitamin D in this population were already addressed/discussed in the section "Association of vitamin D deficiency with SVR to antiviral therapy in chronic hepatitis C patients" and in the table 2 (Ref No.7 and No. 95).

- Figure: i suggest also to made a figure that summarize the role of low levels of VD in HBV and HCV infection.

We thank the reviewer for the suggestion. As addressed in the review that vitamin D deficiency is involved in the pathogenesis of chronic hepatitis B and C virus infections and high prevalence of vitamin D deficiency in patients with HBV and HCV infection are found worldwide. However, the causal relations between vitamin D deficiency and the pathogenesis of chronic liver diseases caused by HBV and HCV are still not fully understood. Most of the studies included in the review as references are clinical observations, cross-sectional, prospective and clinical trial studies. Therefore, we assume that the table that summarizes the role of low levels of vitamin D in HBV and HCV infection would be an appropriate way to deliver the information. We are also afraid that the figure would create a bias due to a controversial findings related to the causal relations between vitamin D deficiency and HBV, HCV infections.

In this context, we have already summarized the role of low levels of vitamin D in HBV and HCV infection in the tables (table 1 and 2).