



DR. ELISA BILIOTTI (Orcid ID : 0000-0002-4540-1815)

Article type : Short Communication

VITAMIN D DEFICIENCY AND HEALTH-RELATED QUALITY OF LIFE IN CHRONIC HEPATITIS C

Palazzo Donatella¹, Biliotti Elisa¹, Esvan Rozenn¹, Volpicelli Lorenzo¹, Franchi Cristiana¹,
Fontanelli Sulekova Lucia¹, Spaziante Martina¹, Santori Marta¹, Rugova Alban¹, Rucci
Paola², Taliani Gloria¹

1. Hepatology Unit, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy.
2. Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy.

Corresponding Author: Dr. Elisa Biliotti

Department of Clinical Medicine

Sapienza University of Rome, Viale dell'Università 37, 00185

Rome, Italy

Email: elisabiliotti@yahoo.it

Telephone: +39 3474425063 Fax: +39 0649970491

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jvh.13076

This article is protected by copyright. All rights reserved.

Running Title: Vitamin D, HRQOL and HCV

List of Abbreviations: CHC, chronic hepatitis C; 25-OH-D, 25-hydroxy-vitamin-D; HRQoL, health-related-quality-of-life; SF-36, Health-Survey-Short-Form-36; HCC, hepatocellular carcinoma; BMI, body mass index; e-GFR, estimated glomerular filtration rate; PF, physical function; BP, bodily pain; RP, role physical; GH, general health; VT, vitality; SF, social function; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary;

Conflict of interest: All authors have no conflicts of interests to disclose

The present research did not receive a financial support.

Abstract

Vitamin D deficiency is common in patients with chronic liver disease, including chronic hepatitis C (CHC). However, the interplay between serum 25-hydroxy-vitamin-D (25-OH-D) and health-related-quality-of-life (HRQoL) in CHC subjects has never been investigated. The study aimed to analyze the relationship between vitamin D deficiency and HRQoL in CHC patients. One-hundred-fifty-five consecutive CHC patients completed the Health-Survey-Short-Form-36 (SF-36) and their serum 25-OH-D levels were evaluated. Vitamin D deficiency was defined as a 25-OH-D level lower than 20 ng/mL. We identified 53 patients (34.2%) with vitamin D deficiency, who showed a mean 25-OH-D serum level of 12.5 ± 3.7 ng/mL. Vitamin D deficient patients had significantly higher liver stiffness values compared to those with normal levels (20.8 ± 14 vs 14.9 ± 9.7 KPa, $p=0.003$). In a multivariate linear regression analysis, vitamin D deficiency was independently associated with a lower SF-36 physical-component summary score ($p=0.034$) and SF-36 mental-component summary score

($p=0.042$) after controlling for age, gender and liver stiffness. Specifically, vitamin D deficiency was associated with 3 out of 4 physical domains of the SF-36 [physical-function ($p=0.016$), role-physical ($p=0.016$) and general-health ($p=0.002$)] and 3 out of 4 mental domains [vitality ($p=0.020$), role-emotional ($p=0.005$) and mental-health ($p=0.025$)]. In conclusion, the present study provides novel evidence demonstrating that vitamin D deficiency can contribute to a decreased physical and mental HRQoL in CHC patients. Given that serum vitamin D levels are easy to evaluate and deficiency treatment is simple and inexpensive, clinicians should be aware of the potential multiple benefits of vitamin D supplementation in CHC patients.

Introduction

Vitamin D deficiency is an important health problem in the general population and in patients with chronic hepatitis C (CHC), in which the prevalence of vitamin D deficit ranges between 46% and 92%¹. In addition to its crucial role in the regulation of bone homeostasis, vitamin D has a broad range of non-skeletal effects including cardiovascular, immunomodulatory, metabolic, neuro-muscular and brain functions². Recently, several studies showed that vitamin D deficiency is associated to worsening of physical and mental functions², thus affecting negatively quality of life in patients with chronic diseases such as chronic kidney disease³ and rheumatoid arthritis⁴.

Health related quality of life (HRQoL) measures the effects of a pathological condition on quality of life including physical and mental health, work productivity, fatigue and various aspects of daily functioning. One of the most commonly employed HRQoL measurement tools, the Health Survey Short Form-36 (SF-36), explores the physical and mental aspects of general health⁵.

HCV has been widely reported to have a profound negative impact on HRQoL. In addition, older age, severity of liver fibrosis and the presence of decompensated cirrhosis are well recognized factors which correlate with a lower HRQoL in CHC patients⁵. To date, the impact of vitamin D deficiency on quality of life in CHC patients has never been investigated, although its deficiency contributes to liver damage accelerating fibrosis progression and leading to unfavourable clinical outcomes⁶.

The aim of this cross-sectional study was to evaluate the prevalence of vitamin D deficiency in CHC patients and to analyze the relationship between vitamin D deficiency and HRQoL.

Materials and methods

One-hundred fifty-five consecutive CHC patients without vitamin D supplementation were enrolled at the Liver Diseases Unit, Policlinico Umberto I in Rome, from January 2015 to June 2016. The study protocol was approved by the Institutional Review Board and each patient provided a written informed consent to participate.

Patients were excluded when liver diseases of different or mixed etiology (autoimmune hepatitis, alcoholic liver disease, hepatitis B, haemochromatosis, Wilson's disease, α 1-antitrypsin deficiency), hepatocellular carcinoma (HCC), HIV co-infection, malignancies, psychiatric disorders, active injecting drug use were ascertained.

Age, gender, body-mass-index (BMI), comorbidities (diabetes mellitus and arterial hypertension), severity of liver fibrosis, liver function tests, estimated glomerular filtration rate (e-GFR), serum 25-hydroxy-vitamin-D (25-OH-D) levels, HCV genotype and HCV-RNA viral load were assessed in all patients. A hepato-splenic-ultrasound and a transient-elastography (Fibroscan) were also performed.

The presence of cirrhosis was defined as a liver stiffness value higher than 12.5 KPa. E-GFR was evaluated using CKD-EPI-2009 formula. Vitamin D deficiency was defined as a level of 25-OH-D lower than 20 ng/mL.

The SF-36 was used to assess HRQoL. It consists of 36 questions arranged into eight scales corresponding to eight aspects of HRQoL: physical function (PF), bodily pain (BP), role physical (RP), general health (GH), vitality (VT), social function (SF), role emotional (RE) and mental health (MH). The eight scales can be summarized into two scores: SF-36 physical component summary (PCS) and SF-36 mental component summary (MCS). The scale scores range from 0 to 100, with higher scores indicating better health. The Italian version of the SF-36 was self-administered on the same day of vitamin D evaluation.

Statistical analysis

Continuous variables were summarized as mean \pm standard deviation and categorical data as counts and percentages. Comparisons between groups were performed using χ^2 test for categorical variables and Mann-Whitney test for continuous variables. Multivariate linear regression was performed to analyze the relationship of vitamin D with HRQoL scales, controlling for the effect of gender, age and liver stiffness. Age and liver stiffness were used as continuous variables in the models, while vitamin D was used as a dichotomous variable because it has a non-linear relationship with quality of life. Data were analyzed using IBM SPSS, version 21.0 (SPSS Inc, Chicago, USA).

Results

Clinical characteristics

A total of 155 CHC patients were included in the study. The mean age was 59.2 ± 12.3 years, most of the patients were male (88/155, 56.8%) and mean BMI was 24.2 ± 3.6 kg/m². The

prevalence of diabetes mellitus and arterial hypertension was 7.1% (11/155) and 32.3% (50/155), respectively. Mean liver stiffness was 16.8 ± 11.6 KPa and half of the patients (77/155, 49.6%) had compensated cirrhosis (Child-Pugh A 5 or 6). HCV genotype 1 was the most frequent (110/155, 71%) and mean baseline HCV-RNA was 6.5 ± 6.7 Log₁₀ IU/ml.

The prevalence of vitamin D deficiency was 34.2 % (53/155). The level of serum 25-OH-D was 12.5 ± 3.7 ng/ml and 39.6 ± 16.5 ng/ml in patients with and without vitamin D deficiency, respectively. Patients with vitamin D deficiency did not differ on age, gender and prevalence of diabetes or arterial hypertension from those with normal levels, but they showed significantly higher liver stiffness values (20.8 ± 14 vs 14.9 ± 9.7 KPa, $p=0.003$) (Table).

Association between HRQoL and vitamin D levels in CHC patients

SF-36 PCS, SF-36 MCS and each physical and mental domain were compared between CHC patients with and without vitamin D deficiency. Overall, both PCS score (41.6 ± 11.1 vs 45.7 ± 8.8 , $p=0.033$) and MCS score (40.0 ± 11.1 vs 44.1 ± 12.8 , $p=0.042$) were significantly lower in CHC patients with vitamin D deficiency compared to those with normal levels.

Vitamin D deficient patients showed significantly lower scores in the physical domains (PF [69.3 ± 26.7 vs 79.4 ± 21 , $p=0.029$], RP [40.1 ± 38.7 vs 59.2 ± 39.8 , $p=0.006$] and GH [43.9 ± 22.0 vs 56.2 ± 20.8 , $p =0.002$]) and in the mental domains (VT [46.5 ± 21.8 vs 55.6 ± 22.8 , $p=0.025$], RE [43.7 ± 38.0 vs 61.9 ± 40.9 , $p=0.008$] and MH [57.2 ± 21.3 vs 66.6 ± 22.1 , $p=0.018$]) (Table).

Vitamin D deficiency as an independent risk factor for impaired HRQoL

We first examined the possible confounding role of the time of recruitment by comparing the prevalence of patients with vitamin D deficiency between the recruitment periods October-

March and April-September. Results indicate that the prevalence is similar between the two periods (36% in October-March vs. 31.9% in April-September, $\chi^2=0.295$, $p=0.587$).

Moreover, mean SF-36 scale scores did not differ between the two recruitment periods (data not shown), suggesting that the time of the year in which patients were assessed does not confound the relationship between vitamin D deficiency and HRQoL.

Then we analyzed the relationship between vitamin D deficiency and SF-36 scales adjusting for age, gender and liver stiffness using 3 multivariate linear regression models. In the first model, including the 2 summary scores of SF-36 as dependent variables, vitamin D deficiency (coded as present/absent) was independently associated with lower PCS score ($\beta=-3.660$, $p=0.034$) and with MCS score ($\beta=-4.664$; $p=0.042$). In the second model, in which the SF-36 physical scale scores were regressed on vitamin D deficiency, age, gender and liver stiffness, vitamin D deficiency was associated with 3 out of 4 physical domains [PF ($\beta=-9.844$; $p=0.016$), RP ($\beta=-17.213$; $p=0.016$), GH ($\beta=-12.582$; $p=0.002$)]. In the third model, in which the SF-36 mental health scales were regressed on vitamin D deficiency, age, gender and liver stiffness, vitamin D deficiency was associated with 3 out of 4 mental domains [VT ($\beta=-9.610$; $p=0.02$)], RE ($\beta=-20.373$; $p=0.005$), MH ($\beta=-8.898$; $p=0.025$)] (Supplementary Table 1).

Lastly, liver stiffness, an indirect parameter of the severity of liver disease, was associated with a lower PCS score ($\beta=-0.156$, $p=0.035$) but no correlation was found with MCS score ($\beta=-0.101$, $p=0.302$) (Supplementary Table 1).

We carried out three additional multivariate linear regression models in which we replaced vitamin D (coded as deficient or not) with vitamin D as a continuous variable and added a quadratic term (vitamin D squared) to take into account the non-linear relationship between SF-36 scale scores and vitamin D. These analyses confirmed the significant associations of

vitamin D with the PCS score and the PF, RP and GH scales. Moreover, vitamin D was significantly associated with all the mental health scales (Supplementary Table 2).

Discussion

This cross-sectional study demonstrated a significant and negative relationship between vitamin D deficiency and several physical and emotional domains of quality of life in patients with CHC.

The negative association with the PCS score of HRQoL and almost all its domains, including PF, RP and GH, held even after adjusting for age, gender and liver stiffness. Several studies demonstrated that normal vitamin D levels maintain muscle trophism and contractile efficiency, promote muscular protein synthesis and activate calcium uptake in the sarcoplasmic reticulum^{2,7}. Therefore, one possible explanation of the association between vitamin D deficiency and impairment of physical domains of HRQoL is that low vitamin D levels cause muscle weakness, sarcopenia, reduction of mobility and usual activities performance, thus affecting quality of life.

As expected, liver stiffness, a reliable surrogate marker of liver fibrosis severity in CHC patients, is associated with a significant impairment of the PCS score in the multivariate analysis. This finding is supported by other published studies which demonstrate that the degree of both physical and mental HRQoL impairment increases continuously from advanced fibrosis, to compensated cirrhosis and decompensation⁵. Interestingly, in the present study, liver stiffness was not associated with MCS score or mental domains of SF-36. This result may be due to the relatively small number of enrolled patients or to an unrecognized role of vitamin D deficiency as a potential factor affecting mental HRQoL in CHC patients, especially if we consider that its low levels are independently related to the

presence of advanced liver disease⁶. Thus, our data has shed light on the potential important effect of vitamin D status on the physical and mental components of HRQoL in these patients.

Finally, vitamin D deficiency is significantly associated with the impairment of 3 mental domains of HRQoL, including VT, RE and MH, after adjusting for age, gender and liver stiffness. Converging evidence suggests that vitamin D acts like a neurosteroid and modulates multiple brain functions including neurotransmission, neuroprotection and immunomodulation⁸. Accordingly, hypovitaminosis D is a risk factor for the development of depressive symptoms and its supplementation improves depression². Therefore, vitamin D deficiency may contribute to the impairment of mental health in CHC patients.

The results of the present study should be interpreted keeping in mind the cross-sectional study design, which does not allow to draw conclusions about a causal mechanism linking vitamin D deficiency with HRQoL. Despite this limitation, the study provides novel evidence on the importance of vitamin D deficiency in the impairment of several physical and emotional domains of quality of life in CHC patients. Given that serum vitamin D levels are easy to evaluate and its deficiency treatment is simple and inexpensive, clinicians should be aware of the potential multiple benefits of vitamin D supplementation in CHC patients.

References

1. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci*. 2010; 55(9):2624-8.
2. Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol*. 2018; 175:60-81.

- Accepted Article
3. Oh TR, Kim CS, Bae EH, et al. Association between vitamin D deficiency and health-related quality of life in patients with chronic kidney disease from the KNOW-CKD study. *PLoS One*. 2017; 12(4):e0174282.
 4. Raczkiwicz A, Kisiel B, Kulig M, Tlustochowicz W. Vitamin D status and its association with quality of life, physical activity, and disease activity in rheumatoid arthritis patients. *J Clin Rheumatol*. 2015; 21(3):126-30.
 5. Younossi Z, Henry L. Systematic review: patient-reported outcomes in chronic hepatitis C—the impact of liver disease and new treatment regimens. *Aliment Pharmacol Ther*. 2015; 41:497-520.
 6. Dadabhai AS, Saberi B, Lobner K, Shinohara RT, Mullin GE. Influence of vitamin D on liver fibrosis in chronic hepatitis C: a systematic review and meta-analysis of the pooled clinical trials data. *World J Hepatol*. 2017; 9:278–287.
 7. Caprio M, Infante M, Calanchini M, Mammi C, Fabbri A. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. *Eat Weight Disord*. 2017; 22(1):27-41.
 8. Cui X, Gooch H, Petty A, McGrath JJ, Eyles DW. Vitamin D and the brain: Genomic and non-genomic actions. *Mol Cell Endocrinol*. 2017; 15;453:131-143.

Table: Comparison of 155 HCV patients according to Vitamin D status.

	Vitamin D \geq 20 ng/ml (n 102)	Vitamin D < 20 ng/ml (n 53)	<i>p</i>
Age, yr – mean \pm SD	58.8 \pm 13.0	60.1 \pm 11.0	0.674
Male gender – n (%)	56 (54.9%)	32 (60.3%)	0.514
Diabetes mellitus – n(%)	6 (5.9%)	5 (9.4%)	0.414
Arterial hypertension – n(%)	32 (31.3%)	18 (33.9%)	0.744
BMI, kg/m ² - mean \pm SD	24.1 \pm 3.5	24.6 \pm 3.7	0.483
AST, U/L – mean \pm SD	75.8 \pm 45.2	85.0 \pm 56.5	0.382
ALT, U/L – mean \pm SD	93.4 \pm 74.3	86.6 \pm 54.4	0.919
eGFR, ml/min/1.73m ² – mean \pm SD	90.6 \pm 15.5	94.2 \pm 17.8	0.061
Liver stiffness, KPa – mean \pm SD	14.9 \pm 9.7	20.8 \pm 14	0.003
HCV-RNA, Log10 UI/ml – mean \pm SD	6.3 \pm 6.4	6.4 \pm 6.9	0.145
PF	79.4 \pm 21.2	69.3 \pm 26.7	0.029
RP	59.2 \pm 39.8	40.1 \pm 38.7	0.006
BP	65.1 \pm 25.5	60.2 \pm 28.3	0.221
GH	56.2 \pm 20.8	43.9 \pm 22.0	0.002
VT	55.6 \pm 22.8	46.5 \pm 21.8	0.025
SF	66.6 \pm 27.5	62.0 \pm 24.8	0.196
RE	61.9 \pm 40.9	43.7 \pm 38.0	0.008
MH	66.6 \pm 22.1	57.2 \pm 21.3	0.018
PCS	45.7 \pm 8.8	41.6 \pm 11.1	0.033
MCS	44.1 \pm 12.8	40.0 \pm 11.1	0.042

PF: physical function; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: role-emotional; MH: mental health; PCS: physical scores; MCS: mental scores.