ORIGINAL ARTICLE

Correlation between Vitamin D3 level and extrahepatic manifestation in chronic hepatitis type-C virus patients

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Background: Chronic hepatitis type-C virus (HCV) infection is one of the most common worldwide viral disorders, which leads to various clinical complications as well as extrahepatic manifestations. Furthermore, Vitamin D3 has also been reported to have relationship with the mentioned complications. The aim is to evaluate the correlation between Vitamin D3 level and extrahepatic manifestation in chronic HCV patients. **Materials and Methods:** This cross-sectional study has been carried out on 90 patients with chronic hepatitis C. The level of Vitamin D3 was assessed in plasma of 90 patients with chronic HCV. Genotyping was done and clinical and sign and symptoms of recruited patients were gathered. Extrahepatic manifestations were evaluated and the correlation of blood, hepatic, and immunological factors and the level of Vitamin D3 were assessed. **Results:** Most of our patients were male (92% vs. 8%). Twenty-nine percent had the insufficient amount of Vitamin D3 (21–30 ng/ml), and the remains had the Vitamin D3 level between 13–20 ng/ml. Furthermore, our assessment demonstrated that deficiency of Vitamin D3 was associated with the extrahepatic manifestations such as purpura (odds radio [OR] [95% confidence interval (CI) 95%] = 8.80 [1.74–44.47], $P = 0.004$), vasculitis (OR [95% CI] = 11.70 [3.01–45.41], $P < 0.001$), arthralgia (OR [95% CI] = 20.26 [4.21–97.47], $P < 0.001$), myalgia (OR [95% CI] = 4.00 [1.01–17.27], $P = 0.048$), and glomerulonephritis ($P = 0.021$). **Conclusion:** According to our results, the extrahepatic manifestation in the patients with sufficient levels of Vitamin D3 would be less possible. In fact, it could be stated that deficiency in the Vitamin D3 can have a significant relationship with these manifestations.

Key words: 25-hydroxy Vitamin D3, extrahepatic manifestations, hepatitis type-C virus

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INTRODUCTION

Hepatitis C virus (HCV) infection is common in most of the countries; so that in the world about 170 million people are infected.[1] About 184 million people worldwide have chronic HCV, which most of HCV cases remain undetected. It has been reported that the annual incidence of HCV infection has reached to its peak in most countries.[2] Regardless of the epidemiological prevalence of HCV, hepatitis C chronic hepatitis occurs at 70%–50% of cases after acute hepatitis C.[1,2]

The most common symptoms of chronic hepatitis C are mainly lethargy and jaundice is rare. With the exception of mixed cryoglobulinemia (MC) associated with vasculitis, glomerulonephritis membranous proliferative, and lymphoproliferative disorders such as B-cell lymphoma and unjustifiable monoclonal gammopathy, extrahepatic complications of chronic hepatitis C that occur mediated immune systems, are common.[1] In many studies, HCV has also been known as a risk factor for liver complications such as cirrhosis, arthropathy, and liver cancer. Extrahepatic manifestation also has been existed in more than 70% of these patients.[3-5]

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Vitamin D is one of the most important components, which has a critical role in various body functions. It has a pivotal role in the metabolism and immune system.[6] It has been reported that Vitamin D deficiency is associated with polymorphisms of Vitamin D gene. It has been reported that common polymorphisms of Vitamin D gene is associated with the risk of breast, colon, prostate, and thyroid cancer.[7-9] It has been suggested that Vitamin D plays a critical role in the regulation of the immune system by promoting the development of regulatory T-cells and decreasing pro-inflammatory cytokines such as Th1 and Th17 cytokines and B-cell differentiation.[10] Moreover, Terrier *et al*. (2012) showed that patients with Vitamin D deficiency, are more likely to have systemic vasculitis, purpura, MC, and low C4 serum level and also they found that Vitamin D supplementation has a beneficial effect in patients with HCV and extrahepatic manifestation.[3]

As mentioned above, it is necessary to measure the Vitamin D level in patients with hepatitis C and extrahepatic manifestation and to recognize Vitamin D deficiency and extrahepatic manifestation to perform therapeutic measures through taking Vitamin D supplements, using this study, and future research on patients with a Vitamin D deficiency.

MATERIALS AND METHODS

This cross-sectional study has been carried out on 90 patients with chronic hepatitis C referred to Omid Hepatitis Research Center in Omid Hospital from February 2016 to February 2017.

Patients with positive anti-HCV antibodies and positive-HCV RNA (real-time polymerase chain reaction) were considered as chronic hepatitis C patients. Patients were excluded if they wish to not participate in the study or coinfected with HBV and HIV.

The ethical code was obtained from research deputy of Isfahan University of Medical Sciences with No IR.MUI. REC.1395.3.211. At baseline, the purpose of the study was explained to each patient, written consent of each patient was obtained and then required samples were taken for laboratory tests and were assessed in a single laboratory.

Physical examination was implemented. Their demographic and contextual factors such as age, sex, weight, liver and spleen sizes, ascites, liver function test (alanine aminotransferase, aspartate aminotransferase, bilirubin total, and direct) drug use, blood transfusions, alpha-fetoprotein, disease duration, lethargy, jaundice, itching, and dark urine were recorded.

Clinical extrahepatic manifestation such as cryoglobulinemia including purpura, vasculitis, myalgia, peripheral neuropathy, and renal involvement was investigated. Six categories of extrahepatic manifestation including (1) dermatologic (purpura and vasculitis), (2) autoimmune diseases (arthralgia and myalgia), (3) neuropathy, (4) renal (glomerulonephritis), (5) hematologic (thrombotic events, such as pulmonary thromboembolism [PTE] and deep venous thrombosis [DVT]), and (6) diabetes were evaluated among the patients. None of our patients had diabetes and coincidence of two manifestations and any known comorbidity.

Laboratory tests including P-ANCA, C-ANCA by ELISA method, FANA, ds DNA by IFA, C3 and C4 by immunoturbidimetry and cryoglobulins, and RF by immunoturbidimetry were analyzed in patients with extrahepatic manifestation. Furthermore, in patients with thrombotic events, IgG and IgM anticardiolipin antibodies by ELISA, venereal disease research laboratory (VDRL) by the serological method, activated partial thromboplastin time, and computed tomography (CT) by coagulation methods were analyzed.

Serum level of 25-hydroxy Vitamin D3 (25[OH] Vitamin D3) was assessed by 25(OH) Vitamin D kit (CALBioTech) with ELISA method. The kit is highly sensitive and is able to evaluate of Vitamin D3 with both manual and full automation ELISA instrument techniques. The incubation time of kit was 2.5 h. In patients, 25(OH) Vitamin D3 serum level of <12 ng/ml as a Vitamin D deficiency and of 13–30 ng/ml as a Vitamin D Insufficiency and of >30 ng/ml as a Vitamin D sufficiency was considered.

Statistical analysis

Finally, collected data were entered into SPSS software version 20 (SPSS, Inc., Chicago, IL, USA).

Qualitative data in the forms of frequency and frequency percentage and quantitative data in the forms of mean and standard deviation have been demonstrated. Furthermore, according to the results of Kolmogorov–Smirnov normality test indicating nonnormal distribution of variables; partial correlation by controlling confounders (sex and age) was evaluated to measure the correlation between continuous variables and Vitamin D level variable. Furthermore, we used logistic regression to identify the impact of Vitamin D levels on extrahepatic manifestation. In all analyzes, the significance level of less than 0.05 was considered.

RESULTS

In this study included 90 patients with chronic hepatitis C, (men = 83 [92.2%], women = 7 [7.85%], mean age = 42.32 ± 10.15 years). Eighty-three (92.2%) of them more than a year and 7 patients (7.8%) less than a year

infected with HCV. Genotypes of HCV were genotype I in 58 patients (64.4%) and genotype III in 32 patients (35.6%). Clinical symptoms such as lethargy and jaundice had the highest prevalence [Table 1].

The mean plasma level of Vitamin D3 (level of 25[OH] Vitamin D3 plasma) in these patients generally was equal to 36.19 ± 15.35 ng/ml, so that the Vitamin D level in 33 patients (36.7%) was insufficiently and in 57 patients (63.3%) was sufficiently. The mean plasma level of Vitamin D3, in patients with genotype 1 was equal to 35.63 ± 15.22 ng/ml and in genotype 3 was equal to 34.75 ± 13.81 ng/ml is (P = 0.428) [Figure 1].

On the other hand, laboratory tests of patients are presented in Table 2. The liver complications of these patients indicated that, arthralgia complication and vasculitis frequency were 16 cases (17.8%) as the most frequent and then purpura and myalgia frequency were 10 cases (11.1%) and 9 cases (10%) respectively, which were the most common extrahepatic manifestation [Table 2].

Furthermore, after controlling age and sex as confounding variables; hematologic, hepatitis, and immunological factors had no significant association with Vitamin D3 level (level of 25[OH] Vitamin D3 plasma) (P > 0.05), and only those who have a higher C3, also had a higher Vitamin D3 level (r = 0.251, P = 0.030) [Table 3].

Finally, the correlation between Vitamin D3 level and extrahepatic manifestation showed that, in general, patients with extrahepatic manifestation had a lower Vitamin D3 levels compared to patients without extrahepatic manifestation. So that patients with Vitamin D insufficiency versus sufficiency had the most frequently purpura (24.2% vs. 3.5%, odds radio [OR] =8.80, 95% confidence interval [CI] = 1.74–44.47; P = 0.004), vasculitis (39.4% vs. 5.3%, OR = 11.70, 95% CI = 3.01–45.41; P < 0.001), arthralgia (42.4% vs. 3.5%, OR = 20.26, 95% CI = 4.21–97.47; P < 0.001), myalgia (18.2% vs. 5.3%, OR = 4.00, 95% CI = 1.01–17.27; P = 0.048), and glomerulonephritis (9.1% vs. 0%; P = 0.021) [Table 4].

DISCUSSION

Evaluation of correlation between Vitamin D3 level and extrahepatic manifestation, which was our main objective, revealed that deficiency of Vitamin D3 is associated with purpura, vasculitis, arthralgia, myalgia, and glomerulonephritis; however, the other investigated complications such as neuropathy and thrombotic events (PTE and DVT) were not related with Vitamin D3 status. We hypothesis that it might be due to our relatively small population study, which was our limitation factor determined the precise association.

Table 1: Baseline clinical and biological characteristics of patients

Characteristics	Value
Epidemiological features	
Sex	
Male	83 (92.2)
Female	7 (7.8)
Age (year)	42.32±10.15
Drug addiction	
No addiction	42 (46.7)
Injection	48 (53.3)
Inhaler	27 (30.0)
Oral	27 (30.0)
Thalassemia	8 (8.9)
Hemophilia	13 (14.4)
Blood transition	40 (44.4)
Characteristics of HCV infection	
HCV infection duration (years)	
≤1	7 (7.8)
>1	83(92.2%)
HCV genotype	
1	58 (64.4)
3	32 (35.6)
Clinical symptoms	
Lethargy	48 (53.3)
Weight loss	30 (33.3)
Jaundice	38 (42.2)
Weight gain	11 (12.2)
Itching	30 (33.3)
Dark urine	51 (56.7)
Physical examination	
Hepatomegaly	4 (4.4)
Splenomegaly	3 (3.3)
Ascites	2 (2.2)

Data are shown *n* (%) or mean±SD. SD=Standard deviation; HCV=Hepatitis C virus

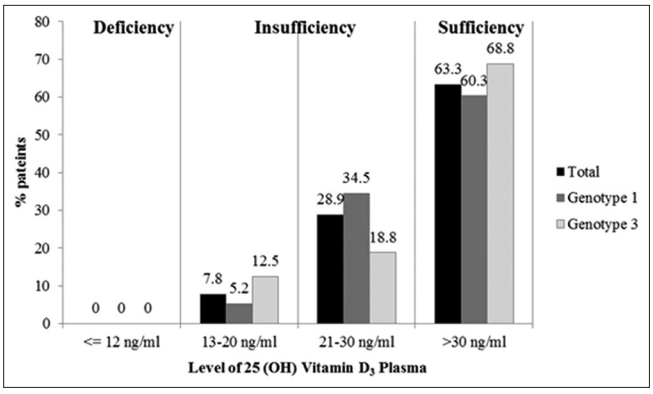

Figure 1: Frequency percentage of level of 25-hydroxyvitamin Vitamin D3 plasma in patients with chronic hepatitis C

HCV infection causes the high rate of mortality due to initiation of fatal liver disorders, such as hepatocellular carcinoma and liver cirrhosis. Furthermore, it leads to extrahepatic diseases, which have a variety of clinical manifestations.[11] The prevalence of HCV in Iranian population has been reported to <1%.[12]

Table 2: Laboratory tests and extrahepatic manifestation in patients with chronic hepatitis C

Laboratory tests	Mean±SD	95% CI
Laboratory tests		
WBC	7383.12±3988.05	6477.94-8288.29
Hb	14.87±2.19	14.37-15.36
Plt	228,493.51±1.10	203,527.72-253,459.29
ESR	11.33±22.29	8.76-13.89
BUN	12.53±4.50	11.51-13.55
Cr	1.04±0.87	0.8387-1.23
Na	139.18±1.99	138.73-139.63
K	4.44±0.52	4.33-4.56
AST	32.54±23.99	27.10-37.99
ALT	41.05±35.14	33.08-49.03
ALP	242.48±92.54	221.48-263.48
Bilirubin total	1.17±1.42	0.8472-1.49
Bilirubin direct	0.45±0.99	0.22-0.67
Bilirubin indirect	0.72±0.73	0.56-0.89
Anti-DNA	7.11±4.21	6.15-8.06
ANA	0.07±0.03	0.06-0.08
CH50	75.47±30.91	68.46-82.49
CANCA	1.63±2.09	1.16-2.11
CRP	3.80±2.50	3.23-4.37
PANCA	1.96±1.40	1.64-2.28
RF	13.26±4.98	12.13-14.40
C3	110.48±22.32	105.41-115.55
C4	24.74±8.32	22.85-26.63
AFA	2.12±0.65	1.98-2.27
Extra-hepatic manifestations	***n* (%)**	
Extra-hepatic manifestations, *n* (%)		
Purpura	10 (11.1)	
Vasculitis	16 (17.8)	
Arthralgia	16 (17.8)	
Myalgia	9 (10.0)	
Neuropathy	1 (1.1)	
Glomerulonephritis	3 (3.3)	
Thrombotic events (PTE, DVT)	2 (2.2)	

PTE=Pulmonary thromboembolism; DVT=Deep venous thrombosis; Hb=Hemoglobin; ESR=Erythrocyte sedimentation rate; WBC=White blood cell; Plt=Platelet; BUN=Blood urea nitrogen; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; ALP=Alkaline phosphatase; ANA=Antinuclear antibody; CRP=C-reactive protein; RF=Rheumatoid factor; SD=Standard deviation; CI=Confidence interval; AFP: Alpha-fetoprotein; PANCA:Perinuclear Anti-Neutrophil Cytoplasmic Antibody; CANCA: cytoplasmic anti neutrophil cytopelasmic antibody

Our results showed that most of the patients recruited to the study were male (92% vs. 8%). In the recent review about the prevalence of HCV among our population, the male/female ratio is noticeably high.[13] The study about the epidemiology of chronic HCV infection between males and females has also confirmed that HCV prevalence is existing more in males than females.[14] Furthermore, more of our investigated patients were addicted (53% vs. 47%), and all of them used drug through injection. In various studies, it has been reported that use of drug through injection can lead to the considerably higher probability of HCV infection. It has also been stated that most of the drug-injected people are serologically positive for anti-HCV.[15,16] Our patients were genotyped, and they had only two types of 1 and 3. The dominant type of HCV was type 1 and about 35% of remain had the type 2. Genotypes Distribution of HCV is different among different parts around the world. Genotype 1 is the most common worldwide genotypes, which about 70% of HCV infection in the United States is relating to type-1, and genotypes 2 and 3 forms and is responsible for the 30% of remaining. The prevalence of genotype 1 among African Americans is higher than above-reported ratio and reach to 90%. The predominant genotype in Egypt is genotype 4. Genotype 5 is existing in South Africa, and genotype 6 is seen in Hong Kong.[17]

On the other hand, extrahepatic manifestations among investigated patients were purpura (11%), vasculitis (18%), arthralgia (18%), and myalgia (10%) with highest incidence rates, and also were neuropathy (1%), glomerulonephritis (3%), and thrombotic events (such as PTE and DVT) (2%) with lowest frequency. In the study about extrahepatic manifestations in chronic HCV infection, it has been demonstrated that 17% of the patients at least one skin manifestation, in which purpura was owned the most prevalence (7%). For rheumatologic involvement, arthralgia was the most incidence factor (19%), and myalgia was the least frequently symptom (2%). Neurological involvement including sensory and motor neuropathy was positive in 14% of chronic HCV patients, and it has been reported as an important extrahepatic manifestation of chronic HCV infection.[18,19] Another study has shown that purpura and neuropathy symptoms were 10% and 7%, consequently.[20]

Vitamin D3 deficiency frequently appears in chronic HCV patients. Vitamin D3 maintains hemostasis of Ca and P (phosphorous). Moreover, Vitamin D3 is important for modulating of pro-inflammatory cytokines.[21] Our patients were divided into the three categories of Vitamin D3 status, including deficiency, insufficiency, and sufficiency and for the better overview of insufficient Vitamin D3; this group was subdivided into 13–20 ng/ml and 21–30 ng/ml. Our findings showed that about 63% of patients had the sufficient amount Vitamin D3, while 29% of the patients were placed into 21–30 ng/ml and the remains (8%) had 13–20 ng/ml Vitamin D3. We did not detect any deficiency among our chronic HCV patients. Many studies have reported the different outcomes of measurement of Vitamin D3 between groups.[3,22] The evaluation of plasma level of Vitamin D3 in 94 patients revealed that about 60% of chronic HCV patients suffered from Vitamin D3 insufficiency.[3] Another investigation showed that 75% of 260 chronic HCV patients had insufficiency in Vitamin D3 and about 25% were normal in terms of Vitamin D3 level; only one patient was in deficiency group.[22]

Table 3: Correlation between clinical factors and Vitamin D level in patients with chronic hepatitis C

Variables	Level of 25-(OH) D_3 plasma
WBC	
Correlation	0.026
P	0.824
Hb	
Correlation	−0.037
P	0.751
Plt	
Correlation	−0.011
P	0.928
ESR	
Correlation	0.027
P	0.816
BUN	
Correlation	−0.194
P	0.095
Cr	
Correlation	−0.143
P	0.222
Na	
Correlation	−0.276
P	0.017
K	
Correlation	−0.131
P	0.262
AST	
Correlation	0.176
P	0.131
ALT	
Correlation	0.088
P	0.451
ALP	
Correlation	0.152
P	0.194
Bilirubin total	
Correlation	0.119
P	0.310
Bilirubin direct	
Correlation	0.165
P	0.157
Bilirubin indirect	
Correlation	0.014
P	0.906
Anti-DNA	
Correlation	−0.089
P	0.447
ANA	
Correlation	−0.027
P	0.818
CH50	
Correlation	0.158
P	0.177
CANCA	
Correlation	−0.079
P	0.499
PANCA	
Correlation	0.122
P	0.298
CRP	
Correlation	0.132
P	0.259
RF	
Correlation	−0.074
P	0.528
C3	
Correlation	0.251
P	0.030
C4	
Correlation	0.130
P	0.265
AFA	
Correlation	−0.023
P	0.846

Controlled variables=Age and sex. Hb=Hemoglobin; ESR=Erythrocyte sedimentation rate; WBC=White blood cell; Plt=Platelet; BUN=Blood urea nitrogen; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; ALP=Alkaline phosphatase; ANA=Antinuclear antibody; CRP=C-reactive protein; RF=Rheumatoid factor; AFP: Alpha-fetoprotein; PANCA:Perinuclear Anti-Neutrophil Cytoplasmic Antibody; CANCA: cytoplasmic anti neutrophil cytopelasmic antibody 25-(OH) D3=25-hydroxyvitamin D3

The relationship between Vitamin D3 level and hematologic, hepatic, and immunology factors was assessed, and the only factor which was correlated with Vitamin D3 was C3 (r = 0.251, P = 0.030). In the study by Gentile *et al.*, the level of C3 was in adverse association with Vitamin D3 level.[22] Clinical findings have found that HCV inhibits production of C3 complement.[23] C3 has been identified as the candidate marker for fibrosis in the HCV patients.[24] It takes part in the sclerosis of renal in the glomerulonephritis. Serological assessment reveals hypocomplementemia with low level of C3.[25] GWAS study has found that Vitamin D3 has a pivotal role in the innate immune components, such as dendritic cells and complements.[26] Cryoglobulin reports were negative for all the patients. In the absence of cryoglobulin, the level of C3 was 0.86 g/l in study of Gentile *et al.*,[22] although it was 1.1 g/l in our evaluations. We could not find any correlation between Vitamin D3 with other important factors, such as C4, C-ANCA, and P-ANCA. In addition, the thrombotic events such as PTE or DVT existed in one patient only, and we did not any further evaluation of the association between plasma Vitamin D3 levels and FANA, VDRL, and CT factors.

Our final assessment of the association of deficiency of Vitamin D3 on the extrahepatic manifestation in the insufficient and sufficient groups revealed that purpura, vasculitis, arthralgia, neuropathy, and glomerulonephritis symptoms were significantly appeared in the insufficient group compared to the group with sufficient Vitamin D3

Table 4: Extrahepatic manifestations of patients, according to Vitamin D levels

Extrahepatic manifestations	Mean±SD	Insufficiency (13-30 ng/ml)	Sufficiency (>30 ng/ml)	OR (95% CI)	*P*
Purpura					
No	35.79±13.95	25 (75.8)	55 (96.5)	8.80 (1.74-44.47)	0.004
Yes	31.54±19.96	8 (24.2)	2 (3.5)		
Vasculitis					
No	36.48±14.03	20 (60.6)	54 (94.7)	11.70 (3.01-45.41)	<0.001
Yes	29.94±16.71	13 (39.4)	3 (5.3)		
Arthralgia					
No	37.36±15.17	19 (57.6)	55 (96.5)	20.26 (4.21-97.47)	<0.001
Yes	25.87±6.25	14 (42.4)	2 (3.5)		
Myalgia					
No	35.51±13.99	27 (81.8)	54 (94.7)	4.00 (1.01-17.24)	0.048
Yes	33.55±20.77	6 (18.2)	3 (5.3)		
Neuropathy					
No	35.44±14.69	32 (97)	57 (100)	-	0.186
Yes	24.00±0.0	1 (3)	-		
Glomerulonephritis					
No	35.74±14.72	30 (90.9)	57 (100)	-	0.021
Yes	22.97±3.96	3 (9.1)	-		
Thrombotic events (PTE, DVT)					
No	35.45±14.79	32 (97)	56 (98.2)	1.75 (0.11-28.94)	0.692
Yes	29.50±6.36	1 (3)	1 (1.8)		

Data are shown *n* (%) or mean±SD. OR=Odd ratio; CI=Confidence interval; PTE=Pulmonary thromboembolism; DVT=Deep venous thrombosis; SD=Standard deviation

levels. In general, the association between Vitamin D3 levels and occurrence of extrahepatic manifestation indicates that the higher levels of Vitamin D3 reduce the probability of incidence of mentioned complications. This association was strongly significant in the dermatologic complications such as purpura and vasculitis, and autoimmune diseases such as arthralgia and myalgia. For the three complications of neuropathy, glomerulonephritis, and hematologic (such as PTE and DVT), this relationship was not significant, perhaps due to the low frequency of complications in these three cases, and therefore, it cannot be spoken definitely about relationship between them and Vitamin D3 status.

Terrier *et al*., in agreement with our results, found that deficiency of Vitamin D3 in chronic HCV patients was related to the more presence of extrahepatic manifestations such as arthralgia, myalgia, vasculitis, purpura, and neuropathy.[3] Ladero *et al*. stated that Vitamin D3 deficiency in chronic HCV results in a variety of manifestation and therapy with it and improves response to therapy.[20] It is the hypothesis that due to the important role of Vitamin D in the numerous vital parts of the body, it can be a worthy prospective marker for various disorders such as different hepatitis infections.

CONCLUSIONS

Our findings demonstrated that insufficiency of Vitamin D3 was significantly associated with more occurrence of extrahepatic manifestations such as purpura, vasculitis, arthralgia, myalgia, and glomerulonephritis, but we did not find any significant association between Vitamin D3 status and thrombotic events and neuropathy. Furthermore, we could not find the positive cryoglobulin among chronic HCV patients. According to the clinical symptoms of our patients, and due to important role of Vitamin D3 on the hepatitis function as well as its other beneficial roles in the various pivotal body functions, use of Vitamin D3 as a supplement diet or as an antiviral drug therapy would be a beneficial approach for helping HCV patients to relief the extrahepatic manifestations.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Medical; 2014.
2. Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. Nat Rev Gastroenterol Hepatol 2017;14:122-32.
3. Terrier B, Jehan F, Munteanu M, Geri G, Saadoun D, Sène D, *et al.* Low 25-hydroxyvitamin D serum levels correlate with the

presence of extra-hepatic manifestations in chronic hepatitis C virus infection. Rheumatology (Oxford) 2012;51:2083-90.
4. Al-Dahshan MA, Al-Dahshan TA. Hepatitis C virus infection associated arthritis. J Egypt Soc Parasitol 2012;42:33-40.
5. Cacoub P, Gragnani L, Comarmond C, Zignego AL. Extrahepatic manifestations of chronic hepatitis C virus infection. Dig Liver Dis 2014;46 Suppl 5:S165-73.
6. Baradaran A. Beyond mineral metabolism, the bright immunomodulatory effect of Vitamin D in renal disease. J Nephropharmacol 2012;1:17-8.
7. Serrano D, Gnagnarella P, Raimondi S, Gandini S. Meta-analysis on Vitamin D receptor and cancer risk: Focus on the role of TaqI, ApaI, and Cdx2 polymorphisms. Eur J Cancer Prev 2016;25:85-96.
8. Vaughan-Shaw PG, O'Sullivan F, Farrington SM, Theodoratou E, Campbell H, Dunlop MG, *et al.* The impact of Vitamin D pathway genetic variation and circulating 25-hydroxyvitamin D on cancer outcome: Systematic review and meta-analysis. Br J Cancer 2017;116:1092-110.
9. Nasri H, Ardalan MR. Association of serum Vitamin D level with age in individuals with normal renal function. J Nephropharmacol 2012;1:7-9.
10. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients 2013;5:2502-21.
11. Ali A, Zein NN. Hepatitis C infection: A systemic disease with extrahepatic manifestations. Cleve Clin J Med 2005;72:1005-8, 1010-4, 1016.
12. Javadi A, Ataei B, Kassaian N, Nokhodian Z, Yaran M. Co-infection of human immunodeficiency virus, hepatitis C and hepatitis B virus among injection drug users in drop in centers. J Res Med Sci 2014;19:S17-21.
13. Mirminachi B, Mohammadi Z, Merat S, Neishabouri A, Sharifi AH, Alavian SH, *et al*. Update on the prevalence of hepatitis c virus infection among Iranian general population: A systematic review and meta-analysis. Hepat Mon 2017;17:e42291.
14. Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, *et al.* Higher clearance of hepatitis C virus infection in females compared with males. Gut 2006;55:1183-7.
15. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, *et al.* Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: Results of systematic reviews. Lancet 2011;378:571-83.
16. Aceijas C, Rhodes T. Global estimates of prevalence of HCV infection among injecting drug users. Int J Drug Policy 2007;18:352-8.
17. Kasper DL, Fauci AS, Hauser SL, longo DL, Jameson JL, Loscalzo J. Harrison's Parinciples of Internal Medicine. Vol. 3. 19th ed. New York: Mc Graw Hill Education; 2015.
18. Cacoub P, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, *et al.* Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'etude et de recherche en medecine interne et maladies infectieuses sur le virus de l'hepatite C. Medicine (Baltimore) 2000;79:47-56.
19. Negro F, Esmat G. Extrahepatic manifestations in hepatitis C virus infection. J Adv Res 2017;8:85-7.
20. Ladero JM, Torrejón MJ, Sánchez-Pobre P, Suárez A, Cuenca F, de la Orden V, *et al.* Vitamin D deficiency and Vitamin D therapy in chronic hepatitis C. Ann Hepatol 2013;12:199-204.
21. Petta S, Grimaudo S, Marco VD, Scazzone C, Macaluso FS, Cammà C, *et al.* Association of Vitamin D serum levels and its common genetic determinants, with severity of liver fibrosis in genotype 1 chronic hepatitis C patients. J Viral Hepat 2013;20:486-93.
22. Gentile I, Scarano F, Celotti A, DE Iuliis E, Scarano R, Granata V, *et al.* Low Vitamin D levels are associated with the presence of serum cryoglobulins in patients with chronic HCV infection. *In Vivo* 2015;29:399-404.
23. Mazumdar B, Kim H, Meyer K, Bose SK, Di Bisceglie AM, Ray RB, *et al.* Hepatitis C virus proteins inhibit C3 complement production. J Virol 2012;86:2221-8.
24. Yang L, Rudser KD, Higgins L, Rosen HR, Zaman A, Corless CL, *et al.* Novel biomarker candidates to predict hepatic fibrosis in hepatitis C identified by serum proteomics. Dig Dis Sci 2011;56:3305-15.
25. Pyrsopoulos NT, Reddy KR. Extrahepatic manifestations of chronic viral hepatitis. Curr Gastroenterol Rep 2001;3:71-8.
26. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of Vitamin D on immune function: Lessons learned from genome-wide analysis. Genome-wide view on the physiology of Vitamin D. Frontiers in physiology 2014;5:151.