Musculoskeletal Manifestations and Bone Mineral Density in Chronic Hepatitis C Patients

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Abstract

Background: many extrahepatic manifestations including auto-immune, rheumatic disease and metabolic bone impairment have been stated in hepatitis C virus (HCV) infected patients. Direct antiviral agents (DAAs) are major developments in the treatment of HCV infection and were reported to have effect on the musculoskeletal manifestations. **Objectives:** to evaluate the effect of hepatitis C and direct antiviral agents (DAAs) on musculoskeletal system, bone mineral density (BMD). **Methods**: the current study involved 60 patients with hepatitis C, 30 patients with no history of anti-viral agent's treatment (group I) and the other 30 patients achieved response on DAAs within the last year (group II). All patients were subjected to history taking, physical examination, investigations including (calcium, Phosphorus, Parathormone hormone, alkaline phosphatase and vitamin D) and DEXA scan for BMD measurement. **Results**: In this study, group I showed significantly lower bone mineral density compared to group_II . The frequency of musculoskeletal manifestations caused by HCV in group I is higher than group II including: arthralgia (70%), sicca symptoms (50%), fatigue (40%), fibromyalgia (20%), arthritis and cryoglobinemic vasculitis (10%). **Conclusion:** Musculoskeletal manifestations including decreased BMD are frequent in chronic hepatitis C (CHC) patients and treatment with DAAs proved a beneficial impact.

Key words: Chronic hepatitis C, Musculoskeletal manifestations, Bone mineral density, DAAs

Introduction

Hepatitis C is an acute and chronic hepatitis, ranging from a mild illness lasting a few weeks to a serious, lifelong illness. Globally, an estimated 71 million people have chronic hepatitis C infection. Approximately 399,000 people die each year from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma. Antiviral medicines can cure more than 95% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis (1).

Hepatitis C is associated with several extrahepatic manifestations and should be considered as a systemic disease (2). Extrahepatic manifestations include mixed cryoglobulinemia, lymphoproliferative disorders, renal disease, insulin resistance, type 2 diabetes, sicca syndrome, rheumatoid arthritis-like polyarthritis, and autoantibody production (2). In addition, HCV has been implicated in metabolic bone impairment. Hepatic osteodystrophy refers to osteoporosis and osteomalacia associated with chronic liver disease (4). Osteopenia was observed in over than 50 % of subjects with CHC and approximately 30% of patients with chronic liver disease suffer from osteoporosis (3).

Interferon alfa (IFN) has long been the cornerstone of antiviral combinations in patients infected with HCV with a low rate of efficacy and poor tolerance. In addition, use of IFN was associated with high rates of severe adverse events. In patients infected by HCV and with autoimmune/inflammatory rheumatic diseases. IFN was either contraindicated or reported to induce a flare of the disease. Recently, new direct-acting antiviral (DAA) IFN-free treatments led to HCV cure in most (>90%) patients with a good safety profile (severe adverse events <5%) and a short duration (12 weeks) (5).

Cure of HCV infection is defined as the absence of detectable HCV RNA in the blood at least 12 weeks after treatment completion (sustained virologic response [SVR], is strongly associated with reduced liver-related morbidity and mortality) (6,7).

The aim of this work is to evaluate the effect of hepatitis C as well as DAAs on the musculoskeletal system and the bone mineral density.

Patients & Methods

This is a cross-sectional which was carried out on 60 patients with hepatitis C virus from the inpatients' and the outpatients' clinic of

Hepatology, Gastroenterology & Infectious Diseases, Rheumatology, Rehabilitation and Physical Medicine departments in Benha University Hospitals from February 2019 to April 2020. Informed consents from all patients were obtained in accordance with the local ethical committee 12-02-19.

All the enrolled patients were tested positive for antibodies to HCV by using an enzyme immunoassay. Thirty patients were chronically infected with HCV as determined by testing consistently positive for HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR). The other thirty patients had their HCV RT-PCR turned negative after treatment with DAAs within the last one year before the study. All patients were tested negative for HBsAg.

The exclusion criteria were: patients aged less than 18 years old, patients known to have end stage liver disease (Child C cirrhosis- Clinically manifest liver decompensation- serum albumin less than 2.8g/dl, total serum bilirubin more than 3mg/dl, INR 1.7 or more- Platelet count less than 50000/mm3), other liver diseases (e.g cholestatic, metabolic and autoimmune liver diseases), renal dysfunction, thyroid and parathyroid disorders, Cushing's syndrome, diabetes, patients who received calcium, vitamin D, medications influencing bone metabolism like (corticosteroids, hormone replacement therapy, calcitonin, bisphosphonates, cytotoxic, anti-metabolites, anticoagulants, anti-convulsant, thyroxin and interferon), and post-menopausal women.

All patients were subjected to medical history taking and complete physical examination. Laboratory investigations were done for all patients including complete blood count, Erythrocyte Sedimentation Rate (ESR), c-reactive protein (CRP), liver function tests (Serum total bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), PT, INR, serum albumin), serum urea and creatinine, serum alkaline phosphate (SAP), serum calcium , serum phosphorous, serum parathyroid hormone (PTH) , serum vitamin D, Serum cryoglobulins in patients with mixed cryoglobinemia, abdominal ultrasound and DEXA scan .

Statistical analysis: The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data were

presented and suitable analysis was done according to the type of data obtained for each parameter. Quantitative data were presented in the form of mean, standard deviation (SD), range by applying t- test for comparison between two groups of normally distributed variables and qualitative data were presented in the form numbers and percentages by applying Chi-square test to study association between two qualitative variables.

Fischer exact test used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. Correlation analysis was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. Linear regression analysis was used for prediction of risk factors. P value of <0.05 was considered statistically significant and <0.001 was considered statistically highly significant.

Results

The present study was carried out on 60 patients with hepatitis C. They were divided into two groups. Group I: 30 patients with no history of anti-viral agent's treatment. Group II: 30 patients who achieved response to DAAs within the last year.

Our data revealed that alkaline phosphatase, calcium, phosphorus, Parathyroid hormone did not differ significantly according to BMD in HCV infected patients. Vitamin D level decreased significantly in osteopenia and osteoporosis. Moreover, stratifying patients according to vitamin D level into sufficient and insufficient categories. Significant association was found between insufficient vitamin D with osteoporosis and osteopenia (table 1).

Lumbar spine BMD showed significant positive correlation with calcium (figure 2), vitamin D level (figure 3), and significant negative correlation with alkaline phosphatase (figure 1). T score showed significant positive correlation with body mass index (figure 5) and vitamin D level (figure 6), and significant negative correlation with age and parathyroid hormone (figure 4). Otherwise, no significant correlations were found regarding BMD, Z and T scores with other studied parameters (table 2).

We found that group I showed significantly lower bone mineral density (figure 9), T score (figure 8) and non-significantly lower Z score (figure7) when compared to group II. Moreover, group I was significantly associated with osteopenia and osteoporosis (table 3).

Besides, we observed that group I had significantly higher frequency of arthralgia and fibromyalgia than group II. Both groups showed no significant differences regarding arthritis, fatigue, Sjogren syndrome and Cryoglobulinemic vasculitis (table 4).

Regression analysis was conducted for prediction of BMD in HCV patients using age, gender, body mass index, alkaline phosphatase, calcium, phosphorus, parathyroid hormone, vitamin D as covariates. Higher alkaline phosphatase, lower calcium and vitamin D were associated with lower BMD in univariable analysis. Using significant covariates in univariable analysis into multivariable analysis revealed that lower calcium and vitamin D were considered independent predictors of lower BMD in HCV infected patients (table 5).

Table (1): Comparison of baseline laboratory data according to BMD in all studied patients**.**

		Normal BMD		**Osteopenia**		**Osteoporosis**		***P***
		N=18		**N=36**		**N=6**		
ALP (U/L)	**Mean ±SD**	169.3	46.7	197.8	57.5	144.0	25.2	0.158
Calcium (mg/dL)	**Mean ±SD**	8.8	0.6	8.8	0.5	8.6	0.4	0.543
Phosphorus (mg/dL)	**Mean ±SD**	4.4	0.9	4.7	0.6	4.4	0.1	0.397
PTH (pg/ml)	**Mean ±SD**	49.5	14.1	45.7	10.5	55.6	4.8	0.210
Vit D3 (ng/mL)	**Mean ±SD**	25.5	8.1	18.6	6	14.2	3.7	**<0.001**
Sufficient vit D	**N, %**	3	16.7%	0	0%	0	0%	
Insufficient vit D	**N, %**	15	83.3%	36	100%	6	100%	

P value <0.05 is significant ALP=Alkaline Phosphatase; PTH=Parathyroid Hormone Vit -D= Vitamin D; N=number SD= standard deviation BMD=Bone Mineral Density

Table (2): Correlations between BMD, Z and T score with other studied parameters.

	BMD		Z score		T score	
	R	***P***	***r***	***P***	***R***	***P***
Age	-0.235	0.071	0.145	0.270	-0.409	**0.001**
BMI	0.085	0.521	-0.003	0.979	0.365	**0.004**
ALP (U/L)	-0.335	**0.009**	-0.346	**0.007**	-0.143	0.276
Calcium (mg/dL)	0.306	**0.014**	0.125	0.342	-0.120	0.362
Phosphorus (mg/dL)	0.023	0.861	-0.189	0.148	0.146	0.267
PTH (pg/ml)	-0.109	0.408	-0.013	0.923	-0.348	**0.006**
Vit D3 (ng/mL)	0.362	**0.004**	0.109	0.407	0.443	**<0.001**

P value <0.05 is significant□ □PTH=Parathyroid Hormone□ □Vit D3= Vitamin D□ □ □BMI=Body Mass Index□ □ALP=Alkaline Phosphatase

Table (3): Comparison of bone mineral density between studied groups.

		Group I N=30		Group II N=30		***P***
BMD(*g/cm2*)	**Mean ±SD**	0.81	0.12	0.89	0.10	**0.004**
Z score	**Mean ±SD**	-1.5	0.4	-1	0.3	0.150
T score	**Mean ±SD**	-2.2	0.7	-0.6	0.1	**<0.001**
Osteopenia	**N, %**	24	80%	12	40%	
Osteoporosis	**N, %**	6	20%	0	0%	

P value <0.05 is significant□ □BMD= Bone Mineral density□ □N=number□ SD= standard deviation

Table (4): Comparison of baseline clinical manifestations between studied groups.

	Group I N=30		Group II N=30		***P***
	N	%	N	%	
Arthralgia	21	70%	9	30%	**0.002**
Arthritis	3	10%	0	0%	0.237
Fibromyalgia	6	20%	0	0%	**0.024**
Fatigue	12	40%	9	30%	0.417
Sjogren syndrome	15	50%	9	30%	0.114
Cryoglobulinemic vasculitis	3	10%	0	0%	0.237

P value <0.05 is significant; N=number

Table (5): Regression analysis for prediction of BMD in the studied patients.

	Univariable		**Multivariable**	
	B	***P***	***B***	***P***
Age	-0.002	0.153		
Gender	0.098	0.263		
BMI	0.004	0.248		
ALP	-0.002	**0.046**	-0.004	0.866
Calcium	0.067	**0.034**	0.063	**0.022**
Phosphorus	-0.018	0.433		
PTH	0.023	0.859		
Vit D3	0.005	**0.010**	0.007	**<0.001**

B, regression coefficient. P value <0.05 is significant; ALP=Alkaline Phosphatase PTH=Parathyroid Hormone Vit D3= Vitamin D BMI=Body Mass Index

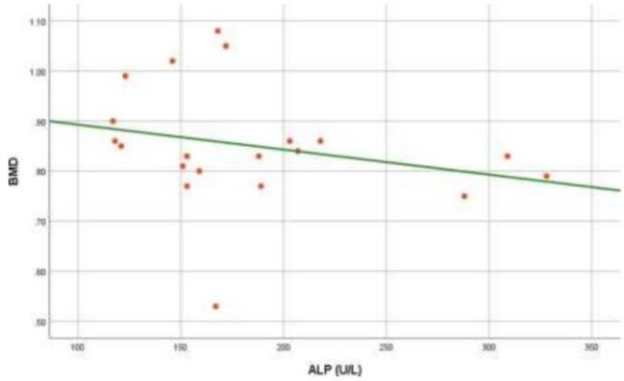

Figure (1). Correlations between BMD with ALP.

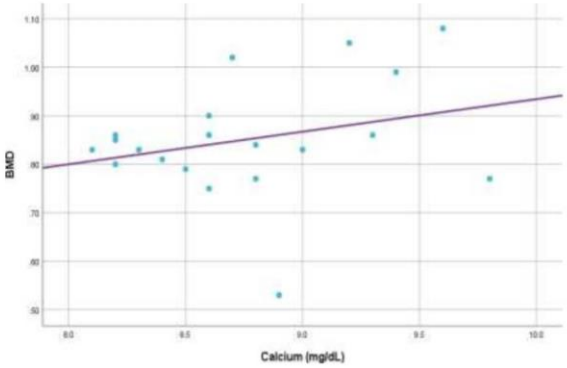

Figure (2). Correlations between BMD with calcium level.

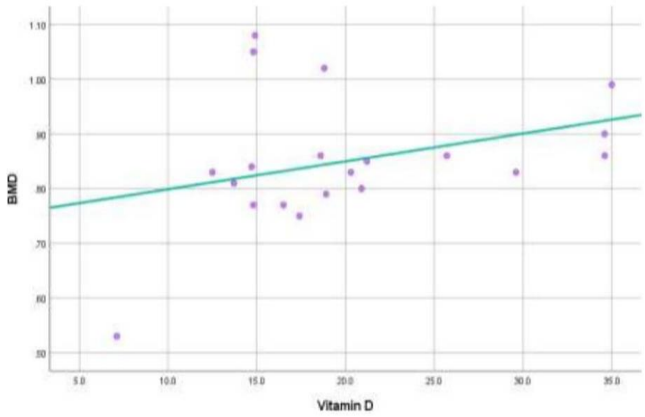

Fig. 3: correlation between BMD and vitamin D level

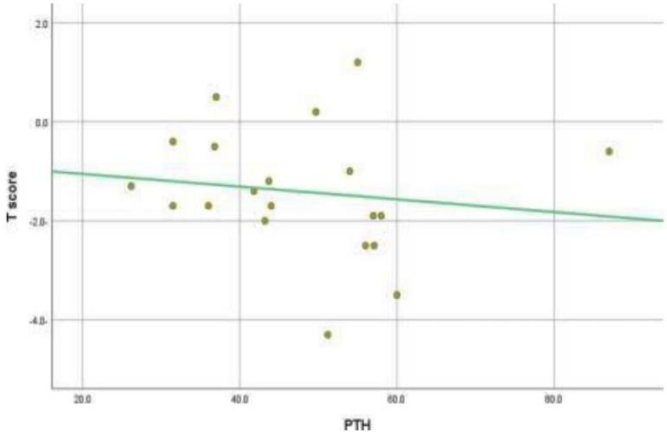

Fig. 4: correlation between T score and PTH

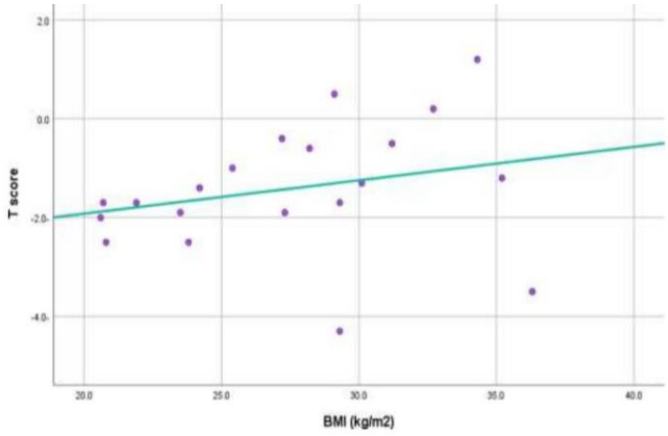

Figure (5). Correlations between T score with BMI.

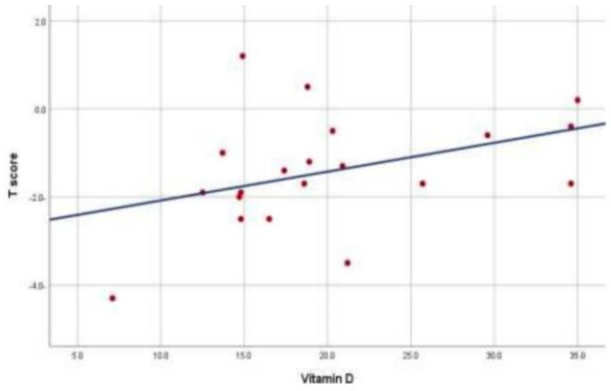

Figure (6). Correlations between T score with vitamin D.

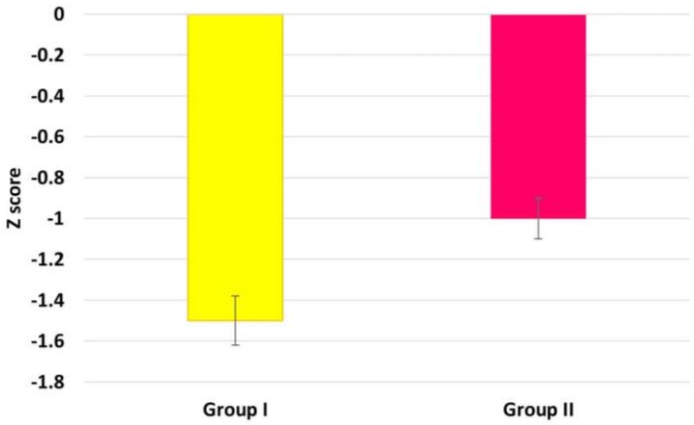

Figure (7). Baseline Z score in studied groups.

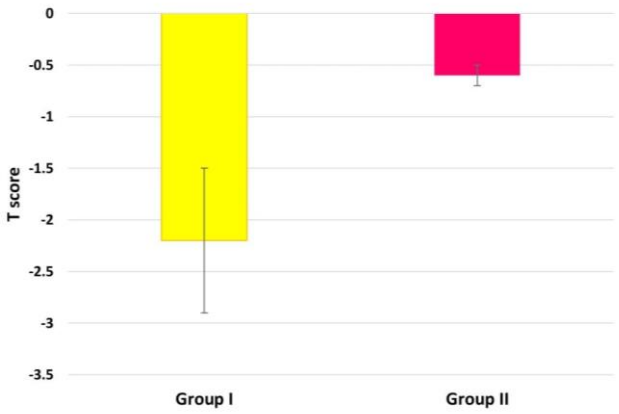

figure (8). Baseline T score in studied groups.

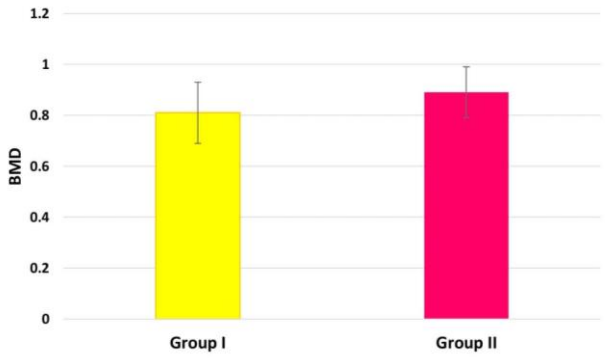

Figure (9). Baseline BMD in studied groups.

Discussion

Hepatitis C virus (HCV) infected patients are known to be exposed to major liver complications i.e. cirrhosis and hepatocellular carcinoma. In addition, many extrahepatic manifestations including rheumatologic disorders have been reported in up to two-third of these patients. These manifestations include frank auto-immune and rheumatic diseases (such as arthralgia, myalgia, arthritis, sicca syndrome and vasculitis) which may dominate the course of the disease (8).

Hepatic osteodystrophy refers to osteoporosis and osteomalacia associated with chronic liver disease. Osteoporosis is a disorder of low bone mass, microarchitectural malformation and structural weakness while osteomalacia is a disorder of decreased osteoid mineralization at sites of bone formation. Liver is involved in several metabolic mechanisms. Therefore, it is not surprising that liver disease is one of the secondary causes of osteoporosis and around one third of patients with chronic liver disease suffer from osteoporosis (9, 10).

Few data from smaller studies reporting bone loss in non-cirrhotic patients with chronic HCV infection are available. The risk for bone depletion in the earlier stages of chronic HCV infection is not yet fully elucidated and remains a matter of debate (11, 12, 13).

Direct acting antivirals (DAA) are major developments in the treatment of HCV infection with cure rates higher than 90%. These drugs were reported to improve the hepatic and extrahepatic sequelae of hepatitis C including the BMD (14).

The present study was planned to assess BMD using DEXA scan and the calcium profile (Ca, P, PTH, ALP) in non-cirrhotic chronic HCV patients and assess the musculoskeletal manifestation of this chronic infection. Also, we aimed to evaluate the benefits of DAAs on BMD. It was carried out on 60 patients with chronic hepatitis C.

Regarding chronic HCV infection in our study, lower body mass index was associated with osteopenia and osteoporosis rather than normal BMD. Vitamin D level decreased significantly in the patients with osteopenia and osteoporosis. Lumbar spine BMD correlated positively with calcium, vitamin D level and negatively with alkaline phosphatase. Z score corelated negatively with alkaline phosphatase while T score correlated positively with BMI and vitamin D level, and negatively with age and parathyroid hormone. Lower calcium and vitamin D were considered independent predictors of lower BMD in HCV infected patients.

The correlation of BMD with calcium and vitamin D was reported by Sharawat et al., (15) and Ardawi et al., (16). However, an Indian study did not show any correlation between vitamin D and hip or lumbar spine BMD (17). The association between the insufficient vitamin D and low BMD (osteoporosis and osteopenia) agrees with the theory that Vitamin D deficiency contributed to altered bone mineralization and led to low bone mass (18,19).

Also, the increased levels of alkaline phosphatase in the patient with low BMD may indicate that the bone loss in earlier stages of CHC patients is secondary to the increased bone resorption rather than the diminished bone synthesis. This was approved by many previous studies focusing this point of research (20, 21, 22, 23).

Regarding the effect of drugs, our study showed that the untreated patients had increased incidence of lower BMD (osteopenia and osteoporosis) and lower T-score than the treated ones. Also, the frequency of musculoskeletal manifestations in the former group was higher than the later

one. We demonstrated that the higher viral load and lower vitamin D were considered independent predictors of lower BMD in HCV infected patients without history of anti HCV treatment. Besides, we found that higher phosphorus, lower calcium and vitamin D were considered independent predictors of lower BMD in HCV infected patients with history of anti HCV treatment.

The decreased BMD, the lower T-score and non-significantly lower Z score in non-cirrhotic chronic HCV patients in this study agreed with several researches that reported these data in their patients (3, 24, 25, 26, 27, 28). Bedimo et al.,(28) reported the association between the HCV infection and the microarchitectural changes at the lumbar spine by using the trabecular bone score and suggests that there are microstructural abnormalities underlie the higher fracture risk in HCV infection. Controversially, Pelazas-González et al., (29), Solís-Herruzo et al., (30) and Nanda et al .,(31) showed that chronic HCV infection did not lead to discernable metabolic bone disease in postmenopausal women, but it might be a risk factor for bone fractures. Min et al.,(32) hypnotized that if the patients with hepatitis C were well treated by antiviral drugs, the bone loss would possibly be prevented and our results support this hypothesis.

Our results are linked up with Hofmann et al., (33) who reported a high prevalence of osteopenia (43%) in the absence of cirrhosis and an improvement of BMD along with therapy. On the same side, Redondo-Cerezo et al., (27) stated that their patients with chronic hepatitis C had low bone mass associated with increased bone resorption and their patients who responded to antiviral therapy tending to normalize bone mass and bone turnover in parallel with the reduction of inflammatory markers.

In this study, the frequency of musculoskeletal manifestations caused by HCV in the untreated group was higher than the patients who received DAAs treatment. Arthralgia was the most frequent followed by sicca symptoms, fatigue, fibromyalgia, arthritis and cryoglobulinemic vasculitis. Other studies regarding HCV aligned with our results as they reported, arthralgia in 6.5% to 57%, myalgia in 1.3% to 61%, and arthritis in up to 5% of their HCV patients (34,35,36,37). Another study made by Ídila and Rita (38) showed that in patients infected with HBV and HCV, arthralgia was the most prevalent rheumatic manifestation in 97.4% and 90.6%, followed by myalgia in

81.6% and 65.6%, and arthritis in 26.3% and 40.6% of patients, respectively. HCV drives clonal expansion of B cells (39,40) to generate immunoglobulin (Ig) M rheumatoid factor in susceptible people that results in immune complex deposition in small vessels and vasculitis. The mechanisms of other manifestations are multifactorial, including a direct interaction between viral proteins and intracellular signaling pathways, viral replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Immune activation may lead to a chronic inflammatory state that can affect several systems (41). With viral clearance, clinical improvement occur and cryoglobulin levels decrease (42, 44). Reversal of other immunologic abnormalities has also been documented with normalization of regulatory T-cell and other specific T- and B-cell populations (42, 43).

The limitations of our study were the small-sized study, the inability to demonstrate the actual disease duration as the hepatitis C acute infection may be asymptomatic and the patients discover it accidently. Finally, it would be better to evaluate the patients before and after the treatment in a longitudinal study to state the effect of the antiviral drugs on the musculoskeletal manifestations accurately.

We recommend further larger scaled studies to be performed to reveal the exact mechanisms of hepatic osteodystrophy in chronic hepatitis C patients especially in non-cirrhotic patients. Screening for hepatic osteodystrophy in chronic hepatitis C patients better to be done as it is usually asymptomatic. Longitudinal study is needed to study the effect of therapy on the same group of patients. Further studies should be done to show the short term and the long-term clinical benefits of DAAs.

The occurrence of rheumatological manifestations that were reported in patients with hepatitis C infections during this study emphasizes the importance of considering viral hepatitis as a differential diagnosis for patients with rheumatic symptoms. Also, hepatitis serological testing should be considered as a routine investigation in the approach of rheumatic diseases, particularly in countries with high prevalence of hepatitis C. Finally, there was a significantly reduced BMD in non-cirrhotic patients with chronic hepatitis C Infection than in patients with SVR by DAAs treatment which show a promising effect of these agents. We conclude that HCV infection is associated with many rheumatological manifestations

and these symptoms are decreased with treatment with DAAs the matter which needs further studies.

References

1. **WHO (2018) Hepatitis C**. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat .2018; 6:35–47

2.**Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M.** Extrahepatic manifestations of hepatitis C: a meta-analysis of prevalence, quality of life, and economic burden. Gastroenterology.2016; 150:1599–1608.

3. **Schiefke I, Fach A, Wiedmann M, Aretin A, Schenker E, Borte G et al.** Reduced bone mineral density and altered bone turnover markers in patients with noncirrhotic chronic hepatitis B or C infection. *World J Gastroenterol*.2005; 11:1843–7.

4. **Gabriela Handzlik-Orlik, Michał Holecki, Krzysztof Wilczyński and Jan Duława** .Osteoporosis in liver disease: pathogenesis and management. *Ther Adv Endocrinol Metab.2016* ; 7(3) 128–135.

5. **Cacoub P, Comarmond C, Domont F, Le´a Savey, Anne C. Desbois and David Saadounet.** Extrahepatic manifestations of chronic hepatitis C virus infection. Ther Adv Infect Dis .2015; 3(1):3-14.

6. **Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS , Brinkley SC,et al.** Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA .2012; 308:370-8.

7. **van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al** .Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA.2012; 308:2584–2593.

8. **Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JM, et al.** Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Arthritis Rheum.1999; 42:2204–12.

9. **Guanabens, N. and Pares, A.** Management of osteoporosis in liver disease. *Clin Res Hepatol Gastroenterol*.2011; 35: 438–445.

10. **Collier JD, Ninkovic M, Compston JE .** Guidelines on the management of osteoporosis associated with chronic liver disease. Gut , 50 Suppl. 2002 ; 1(1):i1–9.

11.**Yenice N, Gumrah M, Mehtap O, Kozan A, Turkmen S .**Assessment of bone metabolism and mineral density in chronic viral hepatitis. Turk J Gastroenterol.2006; 17: 260–266.

12. **Lo Re V 3rd, Guaraldi G, Leonard MB, Localio AR, Lin J, Orlando G, et al.** Viral hepatitis is associated with reduced bone mineral density in HIV-infected women but not men. AIDS. 2009; 23:2191–2198.

13. **El-Maouche D, Mehta SH, Sutcliffe C, Higgins Y, Torbenson MS, Moore RD, et al.** Controlled HIV viral replication, not liver disease severity associated with low bone mineral density in HIV/HCV co-infection. J Hepatol. 2011; 55:770–776.

14. **Ioannou, G. N., & Feld, J. J.** *What are the Benefits of a Sustained Virologic Response to Direct-acting Antiviral Therapy for HCV Infection? Gastroenterology*.2018.10.033.

15. **Sharawat, I. K., & Dawman, L**. *Bone mineral density and its correlation with vitamin D status in healthy school-going children of Western*

*India. Archives of Osteoporosis, 14(1).*2019; doi:10.1007/s11657-019-0568-3

16. **Ardawi MS, Sibiany AM, Bakhsh TM, Qari MH, Maimani AA .** High prevalence of vitamin D deficiency among healthy Saudi Arabian men: relationship to bone mineral density, parathyroid hormone, bone turnover markers, and lifestyle factors. Osteoporos Int.2012; 23: 675–686.

17. **Kota S, Jammula S, Kota S, Meher L, Modi K .** Correlation of vitamin D, bone mineral density and parathyroid hormone levels in adults with low bone density. Indian J Orthop.2013; 47:402–407

18.**Yoshida, T. & Stern, P. H**. How vitamin D works on bone. *Endocrinology and metabolism clinics of North America* 41, 557–569, https://doi.org/10.1016/j.ecl.2012.04.003.

19. **Lips, P. & van Schoor, N. M**. The effect of vitamin D on bone and osteoporosis. Best practice & research. *Clinical endocrinology & metabolism.2011;* 25, 585–591.

20.**Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD.** Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY . J Bone Miner Res.2000; 15:1526–1536

21. **Hsu SH, Tsai KS.** Different age-related trends of bone and nonbone forms of alkaline phosphatase in Chinese men and women. Clin Chem. 1997; 43:186–188.

22.**Iki M, Kajita E, Dohi Y, Nishino H, Kusaka Y, Tsuchida C, Yamamoto K, Ishii Y .** Age, menopause, bone turnover markers and lumbar bone loss in healthy Japanese women.Maturitas.1996; 25:59–67

23.**Melton LJ 3rd, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL .** Relationship of bone turnover to bone density and fractures. J Bone Miner Res.1997; 12:1083–1091

24. **Biver, E., Calmy, A. & Rizzoli, R**. Bone health in HIV and hepatitis B or C infections. *Therapeutic* Advances *in Musculoskeletal Disease.2017;* 9, 22–34.

25. **Gaudio, A., Pennisi, P., Muratore, F., Bertino, G., Ardiri, A., Pulvirenti, I. et al**. Reduction of volumetric bone mineral density in postmenopausal women with hepatitis C virus-correlated chronic liver disease: a peripheral quantitative computed tomography (pQCT) study. *European journal of internal medicine. 2012;*23, 656–660.

26.**Orsini, L. G., Pinheiro, M. M., Castro, C. H., Silva, A. E. & Szejnfeld, V. L.** Bone mineral density measurements, bone markers and serum vitamin D concentrations in men with chronic non-cirrhotic untreated hepatitis C. *PloS one.2013;* 8, e81652,
https://doi.org/10.1371/journal.pone.0081652.

27. **Redondo-Cerezo, E., Casado-Caballero, F., Martin-Rodriguez, J. L., Hernandez-Quero, J., Escobar-Jimenez, F., & Gonzalez-Calvin, J. L.** *Bone mineral density and bone turnover in non-cirrhotic patients with chronic hepatitis C and sustained virological response to antiviral therapy with peginterferon-alfa and ribavirin. Osteoporosis International.2014; 25(6), 1709 1715.*

28. **Bedimo, R. J., Adams-Huet, B., Poindexter, J., Brown, G., Farukhi, I., Castanon, R ,et al.** *The Differential Effects of Human Immunodeficiency Virus and Hepatitis C Virus on Bone Microarchitecture and Fracture Risk. Clinical Infectious Diseases.2017; 66(9), 1442–1447.*

29. **Pelazas-González, R., González-Reimers, E., Alemán-Valls, M. R., Santolaria-Fernández, F., López-Prieto, J., González-Díaz, A. (2013)**. *Bone*

alterations in hepatitis C virus infected patients. European Journal of Internal Medicine, 2013;24(1), 92–96.

30. **Solís-Herruzo, J. A., Castellano, G., Fernández, I., Muñoz, R., & Hawkins, F.** Decreased bone mineral density after therapy with alpha interferon in combination with ribavirin for chronic hepatitis C. J Hepatol. 2000; 33:812 7.

31. **Nanda, K. S., Ryan, E. J., Murray, B. F., Brady, J. J., McKenna, M. J., Nolan, N.,et al.** *Effect of Chronic Hepatitis C Virus Infection on Bone Disease in Postmenopausal Women. Clinical Gastroenterology and Hepatology, 2009; 7(8), 894–899.*

32. **Min, C., Bang, W. J., Kim, M., Oh, D. J., & Choi, H. G.** *The association between hepatitis and osteoporosis: a nested case-control study using a national sample cohort. Archives of Osteoporosis, 2019; 14(1).*

33.**Hofmann WP, Kronenberger B, Bojunga J, Stamm B, Herrmann E, Bücker A, et al.** Prospective study of bone mineral density and metabolism in patients with chronic hepatitis C during pegylated interferon alpha and ribavirin therapy. J Viral Hepat.2008; 15:790-6.

34.**Mohammed RH, El Makhzangy HI, Gamal A, Mekky F, El Kassas M, Mohammed N, et al.** Prevalence of rheumatologic manifestations of chronic hepatitis C virus infection among Egyptians. Clin Rheumatol.2010;29(12):1373-80.

35. **Cheng Z, Zhou B, Shi X, Zhang Y, Zhang L, Chen L, et al.** Extrahepatic manifestations of chronic hepatitis C virus infection: 297 cases from a tertiary medical center in Beijing, China. Chin Med J (Engl).2014;127(7):1206-10.

36. **El Garf A, El Zorkany B, Gheith R, Sheba VH, Moneim GA, El Garfet K**. Prevalence and clinical presentations of hepatitis C virus among patients admitted to the rheumatology ward. Rheumatol Int .2012; 32(9):2691-5.

37. **Tınazlı M, Meryem G, Aykaç A, Süer K.** Hepatitis C virus infection among patients admitted to a rheumatology ward in northern Cyprus. The Egyptian Rheumatologist.2007; 39(4):245-7.

38.**Ídila Mont'Alverne Xavier de Oliveira and Rita do Socorro Uchôa da Silva .** Rheumatological Manifestations Associated with Viral Hepatitis B or C, Revista da Sociedade Brasileira de Medicina Tropical *Journal of the Brazilian Society of Tropical Medicine*. 2019;Vol.:52:e20180407

39. Charles, E. D., Green, R. M., Marukian, S., Talal, A. H., Lake-Bakaar, G. V., Jacobson, I. M., et al. Clonal expansion of immunoglobulin MCD27 B cells in HCVassociated mixed cryoglobulinemia. Blood.2008; 111:1344–1356.

40. Carbonari M, Caprini E, Tedesco T,Mazzetta F,Tocco V,Casato M, et al. Hepatitis C virus drives the unconstrained monoclonal expansion of VH1-69-expressing memory B cells in type II cryoglobulinemia: a model of infection-driven lymphomagenesis. J Immunol .2005; 174:6532–6539.

41. Kuller LH, Tracy R, Belloso W, Wit SD, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008; 5:e203.

42. Emery JS, Kuczynski M, La D,Almarzooqi S,Kowgier M ,Shah H,et al. Efficacy and safety of direct acting antivirals for the treatment of mixed cryoglobulinemia. Am Gastroenterol .2017; 112:1298–1308.

43. Saadoun, D., Pol, S., Ferfar, Y., Alric, L., Hezode, C., Si Ahmed, S. N.,et al. Efficacy and safety of sofosbuvir plus daclatasvir for treatment of

HCVassociated cryoglobulinemia vasculitis. Gastroenterology.2017; 153:49–52.e5.

44. Comarmond C, Garrido M, Pol S. Direct-acting antiviral therapy restores immune tolerance to patients with hepatitis C virus-induced cryoglobulinemia vasculitis. Gastroenterology.2017 ;152:2052–2062.e2.

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