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Clinical correlations between chronic hepatitis C infection and decreasing bone mass density after treatment with interferon-alpha

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ABSTRACT

Objective: To compare the bone mass density in chronic hepatitis patients before and after interferon-α treatment.

Methods: A total of 70 patients with chronic hepatitis C were treated with interferon-α and were evaluated. The treatment dosage was three million IU three times a week for one year. All the patients underwent bone mass density detection at lumbar spine and femoral neck before and after the interferon-α treatment. All the necessary information such as age, sex, and laboratory test, history of occurrence of fractures, lifestyle, and menopause status was collected by interviewers face-to-face from participants at the research visit. Smoking was categorized by whether participants were nonsmokers or smokers. Menopause was designated if there had been complete cessation of menses for more than 12 months. All statistical analyses were performed by SPSS version 14 (SPSS, Inc., Chicago, IL, USA).

Results: Among 70 patients, 52% were male, 48% were female and the mean age was (57.0 ± 9.6) years (range: 24–79). Twenty-nine percent of the patients had a history of smoking. The mean body mass index was (24.4 ± 3.6) kg/m^2 (range: 18.4–35.3). Of the 70 cases, 21 had high fibrosis-4. The prevalence of overall fracture history was 2.9% (two patients).

Conclusions: Chronic hepatitis C virus infection did increase the risk of development of metabolic bone disease in this cohort. Indeed, greater reduction of bone mass density occurs in advanced liver fibrosis. The bone loss in earlier stages of chronic hepatitis C infection is likely to result from increased bone reduction rather than decreased bone formation. Overall, these observations suggest an important role for chronic hepatitis C virus infection in increased bone turnover in osteodystrophy pathogenesis.

1. Introduction

Hepatitis C virus (HCV) infects about 200 million people [1] and is considered a public health and economic problem worldwide [2]. Spontaneous natural virus clearance occurs in approximately 20%–30% of patients, while 70%–80% of patients develop acute HCV infections that become chronic, which leads to the development of cirrhosis in 20% of cases, while the same percentage of those patients will develop hepatocellular carcinoma. Approximately 70%–80% of hepatitis C cases are acute and usually occur during the first six months of HCV infection without symptoms and hence difficult to be diagnosed [3]. In the remaining 20%–30% of

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cases, HCV infection tends to produce chronic liver disease which is associated with other symptoms such as joints pain and muscle ache, poor appetite, nausea, vomiting, and fever [4]. If the infected individual cannot overcome the disease and clear the virus during its acute phase within the first few months of infection, it is converted into a chronic disease [4]. HCV is a positive, single stranded RNA virus with the size of 55–65 nm that belongs to Flaviviridae family [5,6]. HCV was first discovered to be the cause of most transfusion-associated non-A and non-B hepatitis infections [2]. There are about eleven different genotypes of HCV with various subtypes and strains [7,8]. The HCV viral genome encodes a poly-protein of 3010 amino acids including four structural (Core, E1, E2 and P7) and six non-structural (NS2, NS3, NS4A, NS4B, NS5A, NS5B) proteins [9,10]. Currently, the main treatment for hepatitis C is a combination of interferon alpha (IFN-α) or/and ribavirin administered during a period of 12–24 weeks depending on the genotype involved. Currently, IFN-α is choosed for the treatment of several diseases such as viral chronic hepatitis, multiple sclerosis and some cancers and skin disorders [11,12]. In addition to its therapeutic effects, IFN-α also shows important side effects including flu-like symptoms, weight loss, hypoalbuminemia, anemia and various psychiatric side effects such as depression, anxiety and psychosis. Moreover, some other symptoms such as fever, fatigue, headache, arthritis and myalgia might frequently appear during the treatment [13,14]. It has been reported that the symptoms caused by depression could have negative effects on the improvement of patients medical conditions and their response to medical treatments [15,16]. These unwanted symptoms and side effects occurred during the treatment with IFN-α may restrict its use or result in early discontinuation of IFN-α treatment [14,17]. It has also been shown that 23%–45% of the HCV infected patients treated with IFN-α developed depression that could lead to suicidal attempts [17,18]. However, administration of antidepressant medications could be useful to reduce the psychological side effects of IFN-α during the treatment of chronic HCV [19,20]. Therefore, it is important to identify patients who may develop depression during the course of treatment, because it is a relatively common phenomenon that may cause serious clinical issues. It has also been reported that age, female gender, basal immune activation, history of psychiatric disorder, anxiety and depression scores are associated with IFN-α induced depression [21,22] which may decrease the quality of life among these patients [23,24]. To date, many studies examining the relationship between depression and IFN-α treatment have been cross-sectionally designed or based on the depressive symptom rating scale. Therefore, it appears that it is not enough to perform studies only based on a structured clinical interview, especially in developing countries. Moreover, it seems that there is not adequate data regarding factors associated with depression as compared to the prevalence of IFN-α induced depression. Therefore, due to the lack of published information about the effects of IFN-α treatment on quality of life in patients with chronic HCV in Iran, we aimed to study the impact of IFN-α on quality of life in patients with chronic HCV and investigate the occurrence of clinical factors associated with IFN-α therapy that induces major depression in patients.

2. Materials and methods

2.1. Patients

From January 2013 to December 2014, a total of 70 patients with chronic hepatitis C infection were treated with IFN-α at a dosage of three million IU three times a week for one year. All patients underwent bone mineral densitometry (BMD) at lumbar spine and femoral neck before and after the IFN-α treatment. All the necessary information such as age, sex, history of occurrence of fractures, lifestyle, and menopause status was collected by interviewers face-to-face from participants at the research visit. Smoking was categorized by whether participants were nonsmokers or smokers. Menopause was designated if there had been complete cessation of menses for more than 12 months.

The study protocol was performed according to the Iran University of Medical Sciences regulations and approved by The Ministry of Health and Medical Studies of Iran Ethic Committee. Informed written consent was obtained from the dean of faculty of Medical Sciences.

2.2. Laboratory evaluations

Patients had standard laboratory assessments that were performed by licensed clinical laboratories, including HCV RNA, HCV genotype 1 or 3, alanine aminotransferase, bilirubin, albumin, parathyroid hormone, serum calcium, alkaline phosphatase, serum phosphate, 25-hydroxyvitamin D (25-OH vitamin D), intact parathyroid hormone, bone alkaline phosphatase (BAP), C-terminal cross-linking telopeptide of type I collagen (CTX), and international normalized ratio. BAP reflects enzymatic activity of osteoblastic cells and is widely accepted as a marker for osteoblastic activity and bone formation [25], whereas serum CTX, as a collagen-degradation product, is a marker of bone resorption [26]. HCV detection was performed using an RT-PCR technique.

2.3. Body composition and BMD

Dual-energy X-ray absorptiometry (DXA) is one of the powerful tools to measure bone mass density. However, there has always been some ambiguities in accuracy of DXA results [27,28]. Therefore, we attempted to recruit the simple method of body mass index (BMI) to assess body composition. BMI was defined as weight (kg) divided by height (m) squared. In this regards, we weighed each participant and used DXA method to determine the BMD in the lumbar spine (L2–L4) and the left femoral neck. All data obtained from DXA scans were compared with the control data obtained from the DXA manufacturer reference population. For descriptive analyses, osteoporosis was defined as a T score ≤ -2.5. Osteopenia was defined as $-2.5 <$ T score ≤ -1.0. Low BMD was defined as Z score ≤ -2.0.

2.4. Statistical analysis

To evaluate the prevalence of osteopenia, osteoporosis, and low BMD among male, premenopausal, and postmenopausal female patients a *Chi*-squared test was used. We compared the BMD, T score, and Z score between study groups and healthy

age-matched control groups using *t*-tests. One-way ANOVAs were used to compare site-specific BMD and Z scores among male, premenopausal, and postmenopausal female patients and to compare site-specific BMD and T score between different fibrosis (FIB)-4 values. $P < 0.05$ was considered to be statistically significant. The SPSS version 14 (SPSS Inc., Chicago, IL, USA) program was used for all statistical analyses.

3. Results

3.1. Characteristics of study population

The clinical characteristics of the study population are shown in Table 1. The mean age was (57.0 ± 9.6) years (range: 24–79). The patients comprised of 52% male and 48% female, of whom 29% had a history of smoking. The mean BMI was (24.4 ± 3.6) kg/m^2 (range: 18.4–35.3). Fifty seven percent of patients were infected with HCV genotype 1 and 43% were infected with HCV genotype 3. Among the 70 cases, 21 patients had high FIB-4 and two (2.9%) showed an overall fracture history, and one patient had vertebral fractures.

Table 1
Characteristics of patients with chronic hepatitis C ($n = 70$).

Characteristic	Value
Age (years)	57.0 ± 9.6
Gender (male/female)	37/33
BMI (kg/m^2)	24.4 ± 3.6
HCV RNA (IU/mL × 10^6)	4.5 ± 1.4
HCV genotype 1 or 3 (*n*/*n*)	40/30
International normalized ratio	1.08 ± 0.05
Alanine aminotransferase (IU/L)	69 ± 56
Bilirubin (mg/dL)	0.80 ± 0.25
Albumin (g/dL)	5.5 ± 0.2
Parathyroid hormone (pg/mL)	38.1 ± 11.3
Serum calcium (mg/dL)	8.5 ± 0.1
Alkaline phosphatase (IU/L)	92 ± 20
Serum phosphate (mg/dL)	2.9 ± 0.5
25-OH vitamin D (ng/mL)	22.6 ± 19.2
Thyroid-stimulating hormone (μIU/mL)	1.8 ± 0.9
Cigarette smoking (*n*)	20
Postmenopausal women (*n*)	18
FIB-4 > 3.25 (*n*)	21
Number with fractures [*n*(%)]	2 (2.9%)

Numbers are reported as mean ± SD unless indicated otherwise. Normal values ranges for: alanine aminotransferase, 0–31 IU/L; bilirubin, < 1.2 mg/dL; albumin, 3.97–4.94 g/dL; parathyroid hormone, 10–69 mg/dL; serum calcium, 8.62–10.20 mg/dL; alkaline phosphatase, 38–126 IU/L; serum phosphate, 2.7–4.5 mg/dL; 25-OH vitamin D, 20–40 ng/mL; thyroid stimulating hormone 0.25–5.00 μIU/mL.

3.2. Elevated BAP and CTX in patients with reduced BMD

The clinical and laboratory data of chronic hepatitis C infected patients with or without osteopenia/osteoporosis are summarized in Table 2. Osteopenic/osteoporotic patients had significantly higher BAP and CTX values than the non-osteopenic/nonosteoporotic group. In addition, the proportion of female patients and the prevalence of high FIB-4 (> 3.25) were higher in osteopenic/osteoporotic patients ($P < 0.05$).

Table 2
Clinical, biological, and densitometric data in patients with osteopenia/osteoporosis (T score ≤ −1) versus patients without osteopenia/osteoporosis (T score > −1).

Clinical, biological, and densitometric data	T score ≤ −1	T score > −1
Age (years)	55.7 ± 13.3	53.0 ± 11.9
Female (%)	77.2*	46.9
Menopause (%)	89.2	76.7
BMI (kg/m^2)	23.0 ± 2.5	24.0 ± 2.7
HCV RNA (IU/mL × 10^6)	6.4 ± 6.4	8.2 ± 17.6
HCV genotype 1 (%)	80	70
FIB-4 > 3.25 (%)	45*	25
International normalized ratio	1.08 ± 0.14	1.07 ± 0.11
Parathyroid hormone (pg/mL)	38.4 ± 23.6	32.2 ± 19.3
Serum calcium (mg/dL)	8.8 ± 0.7	8.8 ± 0.5
Serum phosphate (mg/dL)	3.9 ± 0.8	3.8 ± 0.4
25-OH vitamin D (ng/mL)	19.7 ± 5.4	20.8 ± 5.9
Thyroid-stimulating hormone (μIU/mL)	2.4 ± 1.1	2.2 ± 1.1
Cigarette smoking (%)	20.0	38.9
BAP (IU/L)	55.5 ± 51.5*	41.5 ± 18.3
CTX (ng/mL)	0.29 ± 0.17*	0.19 ± 0.19

Numbers are reported as mean ± SD unless indicated otherwise. *All data were considered significant where $P \leq 0.05$ as compared with patients without osteopenia/osteoporosis.

3.3. Correlations of bone measures with hepatic fibrosis

As shown in Table 2, we found a significant difference between low and high FIB-4, which is described in Table 3. BMD of the femoral neck ($P < 0.009$) or lumbar spine ($P < 0.011$) was lower in the high FIB-4 group. A similar result was observed in T scores of the femoral neck ($P < 0.008$) and lumbar spine ($P < 0.011$).

3.4. BMD comparison of study group and control group

BMD values (g/cm^2), Z scores, and the lumbar spine's T scores in patients and controls are summarized in Table 4. In postmenopausal patients with chronic HCV infection, the mean BMD values ($P < 0.001$), Z score values ($P < 0.001$) and T score values ($P < 0.001$) of the lumbar spine were significantly lower than those of the control group. In men and premenopausal women, we also found a significant difference in the mean values of lumbar spine BMD, Z score and T score, when comparing the study groups with healthy age-matched controls. In postmenopausal women, eight patients (54.0%) in the study group and eighteen (19.4%) in the control group had osteopenia and five patients (34.0%) in the study group and four (4.3%) in the control group had osteoporosis.

3.5. Increased frequency of low BMD in premenopausal women with chronic HCV infection

BMD values and prevalence of osteoporosis, osteopenia and low BMD are demonstrated in Table 5. The prevalence of osteoporosis seemed lower among postmenopausal women at each of the two sites. Mean Z scores of the lumbar spine were significantly lower for premenopausal women. The prevalence of low BMD (Z score ≤ −2.0 at either site) was higher among premenopausal women. Mean T scores of both sites were significantly lowest for postmenopausal female patients and highest for male.

Table 3
Lumbar spine and femoral neck BMD and T score by FIB-4 (n = 70).

Group by FIB-4	Number of patients	Femoral neck		Lumbar spine	
		BMD (g/cm^2)	T score	BMD (g/cm^2)	T score
FIB-4 < 1.45 (no or minimal fibrosis)	22	0.72 ± 0.09	−0.52 ± 0.01	0.91 ± 0.09	−0.65 ± 0.05
1.45 ≤ FIB-4 ≤ 3.25	26	0.62 ± 0.06	−0.83 ± 0.08	0.87 ± 0.09	−0.97 ± 0.09
FIB-4 > 3.25 (significant fibrosis)	22	0.55 ± 0.03	−1.45 ± 0.11	0.81 ± 0.08	−1.59 ± 0.11
P value		< 0.009	< 0.008	< 0.011	< 0.011

Values are presented as mean ± SD.

Table 4
Comparison of BMD, T scores, and Z scores at the lumbar spine between the study groups and healthy age-matched controls.

Group		BMD (g/cm^2)	Z score	Low BMD [n (%)]	T score	Osteopenia [n (%)]	Osteoporosis [n (%)]
Men	Controls (n = 138)	1.20 ± 0.20	1.20 ± 0.38	1 (0.7)	0.91 ± 0.38	12 (8.7)	0 (0.0)
	Patients (n = 37)	0.99 ± 0.11	−0.10 ± 0.01	0 (0.0)	−0.76 ± 0.10	12 (33.0)	0 (0.0)
Premenopausal	Controls (n = 44)	1.18 ± 0.14	0.64 ± 0.12	1 (2.3)	0.46 ± 0.15	4 (9.1)	1 (2.3)
women	Patients (n = 18)	0.98 ± 0.10	−0.69 ± 0.90	1 (0.9)	−0.86 ± 0.11	5 (28.0)	0 (0.0)
Postmenopausal	Controls (n = 93)	1.11 ± 0.15	0.98 ± 0.10	0 (0.0)	−0.14 ± 0.05	18 (19.4)	4 (4.3)
women	Patients (n = 15)	0.83 ± 0.08	0.19 ± 0.05	0 (0.0)	−1.75 ± 0.25	8 (54.0)	5 (34.0)
P value		< 0.001	< 0.001		< 0.001		

Values for BMD, Z score and T score are presented as mean ± SD.

Table 5
BMD measures.

Site–specific data		Male patients (n = 37)	Premenopausal female patients (n = 18)	Postmenopausal female patients (n = 15)
Femoral neck	BMD (g/cm^2)	0.72 ± 0.06	0.78 ± 0.07	0.63 ± 0.08
	Z score	0.110 ± 0.015	−0.540 ± 0.700	0.090 ± 0.010
	Low BMD [n (%)]	0 (0)	1 (0.7)	0 (0)
	T score	−0.76 ± 0.07	−0.96 ± 0.10	−1.55 ± 0.16*
	Osteopenia [n (%)]	14 (41.18)	7 (38.89)	8 (53.33)
	Osteoporosis [n (%)]	5 (13.51)	5 (27.78)	2 (13.33)
Lumbar spine	BMD (g/cm^2)	0.99 ± 0.10	0.98 ± 0.12	0.83 ± 0.95
	Z score	−0.100 ± 0.010	−0.690 ± 0.074*	0.187 ± 0.022
	Low BMD [n (%)]	0 (0)	1 (0.9)	0 (0)
	T score	−0.760 ± 0.066	−0.860 ± 0.091	−1.750 ± 0.190*
	Osteopenia [n (%)]	15 (40.54)	4 (22.22)	3 (20.00)
	Osteoporosis [n (%)]	3 (8.11)	2 (11.11)	2 (13.33)

Values for BMD, Z score and T score are presented as mean ± SD. *: All data were considered significant where $P \leq 0.05$.

4. Discussion

It is still controversial whether chronic HCV infection is a risk factor for the development of bone disease. It has been suggested a complex correlation between bone metabolism and choronic HCV infection [25].

In this study, we observed that the risk of development of metabolic bone disease was increased by chronic HCV infection. Indeed, greater reduction of BMD occurs in advanced liver fibrosis. The bone loss in chronic hepatitis C infection at its earlier stages is likely to be resulted from increased bone resorption rather than in decreased bone formation.

Other investigators have reported that there is no significant differences in the vitamin D status, levels of BMD, or the prevalence of either osteoporosis or osteopenia between women with chronic HCV infection and healthy age-matched controls [24].

The etiologic mechanism of osteopenia in HCV is unknown. Choronic HCV infected patients with liver cirrhosis frequently show low BMD and biological mechanism for this phenomenon is not fully known. It is suggested that the balance in bone metabolism between bone resorption and decrease of bone mass could be shifted in the course of any alteration of the vitamin D-parathyroid hormone axis. It has also been reported that the decreased concentration of 25-OH vitamin D levels in hepatitis C patients is getting worse by the level of severity of liver inflammation. Moreover, cytokines are systematically increased in chronic hepatitis which can stimulate bone resorption. In the mean time, the levels of bone resorption markers are increased in patients with viral chronic hepatitis and osteodystrophy, which indicates a decrease in BMD [25].

Patients with high bone turnover could be identified by the measurement of noninvasive markers of bone turnover in urine or serum and is predictive of fracture risk independent of BMD [26].

In summary, we examined the clinical correlations between chronic hepatitis c infection and decreasing BMD after treatment with IFN-α. We found that the risk of development of metabolic bone disease is not increased in chronic HCV infection. Indeed, greater reduction of BMD occurs in advanced liver fibrosis. The bone loss in earlier stages of chronic hepatitis C infection is

likely to be resulted from increased bone resorption rather than in decreased bone formation. Overall, these observations suggest an important role for chronic HCV infection in increased bone turnover in osteodystrophy pathogenesis. For a better assessment of the correlation between HCV infection and BMD and the mechanism linking HCV to this disorder, more studies should be performed in large scales.

Conflict of interest statement

We declare that we have no conflict of interest.

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