Original article   http://dx.doi.org/10.1016/j.apjtb.2016.11.027

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

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ARTICLE INFO

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.

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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

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