

Hepatitis C Virus: From Liver to Bone Disease, There are Multiple Stations

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Background

Osteoporosis is defined as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" Common fractures are vertebral compression fractures, fractures of the distal radius, and proximal femur [1].

World Health Organization defines osteoporosis as a bone mineral density (BMD) measurement of 2.5 standard deviations or more below the population mean BMD of sex-matched young adults, i.e., a t-score of ≤ -2.5 . The term "established osteoporosis" includes the presence of a fragility fracture [2].

Osteoporosis can result in spontaneous or low trauma fractures in the patients, adversely affecting morbidity, quality of life. The prevalence of osteoporosis associated fracture ranges from 5% to 20% [3].

Hepatic Osteodystrophy

Osteoporosis and osteopenia are well known complications in patients with chronic liver disease. Its prevalence varies considerably. It ranges from 12 to 55% according to many factors including patient selection, diagnostic criteria, underlying liver disease [4] and it also increases with the increased severity of the liver disease defined as advanced Child-Pugh score [5].

Osteoporosis is a risk factor for development of fractures, which may be a source of morbidity in patients already debilitated by chronic liver disease. Prevention of morbidity of hepatic osteodystrophy is to identify those patients who are predisposed to development of osteopenia and osteoporosis [5].

Hepatic bone disease is caused by a variety of causes ranging from chronic hepatitis as HCV

and HBV [6] to cirrhosis. Compensated as well as decompensated cirrhosis whatever its cause affect BMD leading to osteopenia and osteoporosis [7]. Patients awaiting for liver transplantation have different degree of osteopenia as well as osteoporosis [8]. Osteoporosis and osteopenia are alterations in BMD that frequently occur in chronic liver disease; predominantly in chronic cholestatic disease and liver cirrhosis [9].

Hepatitis C Virus and Bone affection

Chronic hepatitis C (HCV) is systemic disease rather than hepatotropic virus. HCV affects more than 170 million people worldwide [10] and is the single important cause of liver disease in Egypt [11]. It is associated with multisystemic manifestations [12]. Liver disease is the most common affection, and leads to liver cirrhosis and hepatocellular carcinoma [13].

Osteopenia and osteoporosis are common in chronic HCV patients. In most studies suggesting that HCV by itself provokes osteopenia [14]. Some of this research involved non cirrhotic patients [14], others, individuals affected by liver cirrhosis [15], or both cirrhotics and non-cirrhotics [16], and some were restricted to patients awaiting organ transplantation [17] and also in renal transplant patients infected with HCV [18].

The pathogenesis of osteoporosis in chronic liver disease including HCV is still unknown and it is most likely that multiple factors are operating simultaneously [19].

The development of osteoporosis may be related to both increase bone resorption and/ or decrease bone formation [20]. Inhibition of osteoblast (bone forming cell) by retained substances of cholestasis as unconjugated bilirubin, retained bile acids, toxic effect of alcohol, and excessive tissue iron deposition [21].

Various potential inciting factors that either directly or indirectly alter bone mass are insulin-

like growth factor 1 (IGF-1) deficiency, hyperbilirubinemia, hypogonadism, subnormal 25-hydroxyvitamin D levels, vitamin D receptor genotypes, vitamin K, osteoprotegerin (OPG) and receptor activator of nuclear factor interactions and concurrent use of drugs like cholestyramine, diuretics, glucocorticoids and immunosuppressive agents [6-22]. Lifestyle factors (smoking, alcoholism, and immobility), malnutrition and low body mass index [23].

Increase osteoclast activity is cytokine mediated mechanism of bone loss. The proinflammatory cytokines interleukin-1(IL-1) and tumor necrosis factor (TNF) increase osteoclast activity and are increased in hepatic inflammation and fibrosis. TNF increased in viral hepatitis and alcoholic liver disease as well as in patients with cirrhosis [24].

Application of therapy must consider general measures (correction of reversible risk factors, calcium intake and supplementation) and specific treatment for osteoporosis. Bisphosphonates are antiresorptive drugs that can improve BMD in other chronic liver disease, but only limited data are available for osteoporosis in HCV infection [6].

Summary and Comment on the paper

In this issue of the Afro-Egyptian Journal of Infectious and Endemic Diseases Abdelkader et al. [25], discussed the impact of HCV on BMD both in cases with chronic hepatitis and in cases with HCV cirrhosis in comparison to apparently healthy controls. The authors included 80 participants. Of them 30 patients were chronic HCV infection without cirrhosis, 30 patients were chronic HCV infection with compensated cirrhosis and 20 age and gender matched apparently healthy controls. All subjects of the study performed liver function tests, viral markers, liver biopsy, hormonal assay and BMD measurement by Dual energy X-ray absorptiometry (DEXA). They found that in patients with chronic hepatitis C the frequency of osteopenia was 36.7%, osteoporosis was 6.7%, total patients with low BMD were 43.3%. In cirrhotic patients, the frequency increased as follow: osteopenia was 43.3%, osteoporosis was 10.0%, and total patients with low BMD were 53.3% vs 5.0% in the healthy controls. There was also no significant difference between patients with low BMD and patients with normal BMD as regards age, gender, common risk

factors, liver function tests or hormonal levels. They concluded that reduced BMD is common in chronic HCV-infected patients and consequently, HCV infection is a risk factor of osteoporosis, and this risk is increased with advancement of the liver disease.

The paper looks interesting because it discuss an important issue that we commonly face in the everyday clinical practice. Liver cirrhosis is a debilitating condition and with increase in the severity it seems that BMD affection increases and more morbidity awaits the patients. We suppose that this study do have some limitations, the first of all is the small sample size. A large sample may be more presentable to the level which present of this big problem. Second, the cross sectional design of this study, a prospective study is more valuable and may address the HCV induced BMD morbidities more clearly. Third, exclusion criteria needs to be more dependable and should include for example smokers, alcohol abusers, patients under hormonal therapy affecting calcium metabolism, patients with thyroid and parathyroid disturbances, severe renal insult and associated HBV infection. Lastly, a selection bias seems to be present. It not obvious how patients were selected and how they were randomized.

Recommendations:

According to the previous discussion, it may be valuable to conduct a prospective study over a long period of time to evaluate the impact of HCV on the bone health. Implication of HCV genotyping during this study may add to our knowledge is there any impact of HCV genotype on BMD?. Likewise, little is known about the effect of antiviral agents against HCV on BMD and their potential benefit on bone impairment. Hence, impact of HCV therapy on the HCV induced BMD affection needs further investigation.

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