Short Review: Open Access

Non Alcoholic Fatty Liver Disease and Bone Fractures in Patients with HIV

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Abstract

Human immunodeficiency virus infection has posed a challenge for mankind and now this disease is more of a challenge for quality of life than for virus related mortality. This review aims to study two prevalent diseases that may affect this population by decreasing their quality of life. Bone fractures are much more common in the HIV-positive population and have many etiopathogenesis implicated. Non-alcoholic fatty liver disease is also common in HIV-positive patients and may even lead to cirrhosis and related complications. So it is important to search prevention and therapeutical options for these diseases and clarify the association of liver and bone as a multisystem disease and their inter-relations.

Keywords

HIV; Non-alcoholic fatty liver disease; Bone fractures; metabolic bone diseases

Introduction

The human immunodeficiency virus (HIV) infection is, nowadays, a chronic disease with relevants morbidity and life quality issues. In this sense, we propose a brief review about the interrelations of bone fractures, non alcoholic fatty liver disease (NAFLD) and this infection. The aim is to contribute with the care and prevention of this prevalent disease in HIV positive patients.

Materials and Methods

Papers were selected by search in Pubmed library with the terms HIV and bone fractures; non-alcoholic fatty liver disease and HIV; non-alcoholic fatty liver disease and bone fractures; liver disease and bone fractures; metabolic bone disease and liver disease. Two independent investigators carried out the search strategy. The studies were included if the papers were in English. The study quality was evaluated by its design, number of cases and controls.

Review

The human immunodeficiency virus (HIV) positive patient is considered at high risk for bone fractures and low bone mineral density. There are several factors involved such as chronic inflammation, the virus itself and the treatment regimens [1]. The anti-retroviral regimens although they reduce chronic inflammation they do not prevent the bone loss which occurs with a reduction of 2 to 6% of bone mineral density after the beginning of the regimens [2]. Loss of mineral bone density after initiation of antiretroviral therapy (ART) occurs independently of the antiretroviral regimen [3]. Regimens including tenofovir influence bone loss more than others and it is inferred that this effect is related to renal tubular dysfunction.

The HIV positive population is at risk for liver disease, which represents 14% of all non AIDS related deaths [4,5]. The virus itself may interfere with the sterol regulatory element binding protein 1 increasing lipogenesis and peroxisome-activated receptor gama, related to insulin signaling [6]. Although the Multicenter AIDS cohort study had shown the prevalence of 13% of computed tomography defined fatty liver in HIV infected population [7], lower than in non-infected population, this population of HIV-positive patients had a number of more pronounced metabolic disorders after introduction of antiretroviral therapy, including lipodystrophy. Lipodystrophy is defined as an increase of the abdominal fat (visceral) and loss of peripheral adipose tissue. There is also a high prevalence of metabolic syndrome and deficiency of vitamin D in this population [8]. Lipoatrophy, which is the loss of peripheral adipose tissue, is partially explained and has a multifactorial etiology including ART effect on the differentiation of adipocytes, and changes in mitochondrial functions. This is associated with adverse metabolic changes and produces a pathological phenotype with elevated triglycerides, increased HOMA index and reduced HDL cholesterol. A significant number of patients treated with stavudine and zidovudine develop changes consistent with lipodystrophy. These changes are associated with metabolic disorders such as insulin resistance, dyslipidemia and hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) [9]. The risk of fracture is greater when there is coinfection with hepatitis C virus than in mono infected individuals [8].

Non-alcoholic fatty liver disease (NAFLD) is prevalent in patients with HIV infection and may affect between 3-57% of patients with infection [5,10]. Metabolic disorders predispose patients with HIV at high risk of bone fractures. Currently, both the fracture /bone disease and NAFLD are prevalent diseases in the general population, extremely important in the HIV carrier stage, and show significant morbidity. The metabolic syndrome is a major cause of nonalcoholic hepatic steatosis and, at the same time, is correlated with low bone density. Preliminary studies have shown a higher frequency of bone fractures in patients with NAFLD [11]. The lower bone density in these patients could be related to inflammatory cytokines present

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in NAFLD, and less physical activity by the restriction imposed by body weight among other possibilities. Although the body mass index (BMI) is inversely correlated with bone fractures many other predisposing factors like cytokines are present in metabolically active fat tissue and pose a substantial risk for bone fractures [12]. In one large study, NAFLD was associated with osteoporotic fractures in men 40 years or older [13]. Surprisingly and interestingly, there is a study that also showed a relation between the degree of steatosis and its severity with bone density, pointing to the need for long-period longitudinal studies [14]. Vitamin D, involved in all processes of metabolic bone disease and found in lower plasma concentration in HIV-positive patients, also interferes with the liver disease and is associated with more advanced fibrosis and faster evolution of chronic liver disease [15]. A meta-analysis recently published demonstrated that hypovitaminosis D is not only related to NAFLD as it can contribute to the development of steatohepatitis and fibrosis through increased inflammation [16]. Moreover, vitamin D directly modulates the peroxisome proliferator activated receptor (PPAR-γ) and the metabolism of fatty free acids (FFA) [16].

Studies in animals deficient in leptin, with high circulating levels of adiponectin, and large amount of subcutaneous fat showed that there was small amount of fat in liver and skeletal muscle and lower systemic inflammatory condition of these animals. The most likely hypothesis is that besides the protective effects of adiponectin in metabolism in this animal model, the expansion of the subcutaneous fatty tissue provides a healthy storage that prevents lipotoxicity [17]. Studies in patients with lipodystrophy allowed the formulation of a hypothesis that the lack of subcutaneous fat is important in the metabolic imbalance of these patients [18]. Lipodystrophy shows that it is not necessarily the amount of adipose tissue that determines NAFLD but, above all, it is the dysfunction of adipose tissue, and these patients are also more susceptible to the development of steatohepatitis and type 2 DM [19].

Chronic liver diseases are associated with vitamin D deficiency that may reach 86% of this population, through many mechanisms [20]. The fatty liver disease may present as steatosis, steatohepatitis and cirrhosis excluding alcohol consumption and represents the most common liver disease in Western countries [21]. Metabolic syndrome is being increasingly recognized as related to vitamin D levels. NAFLD, as a liver expression of metabolic syndrome, also has been linked to hypovitaminosis D [22].

Metabolic bone disease is common in cirrhosis and osteoporosis can reach about half of the patients unrelated to vitamin D deficiency [23,24]. Anyway, the replacement of vitamin D is recommended in this population of patients with cirrhosis in order to reach levels of 25 to 30 ng/ml. Vitamin D is a pro-hormone important in this group of cirrhotic patients for its anti proliferative, immunological properties and in muscle function in those patients at risk of infection, hepatocellular carcinoma and sarcopenia [25]. A recent study demonstrated the dosage of 25 OH vitamin D is not accurate for evaluation of bone metabolism and vitamin D bioactivity in cirrhosis [24].

Non-alcoholic fatty liver disease (NAFLD) is considered, increasingly, a multisystemic disease and despite the concern related to death from liver causes, scientific knowledge demonstrates, today, that this should be extended to several other causes of mortality such as cardiovascular disease, neoplastic, among others. NAFLD is not only a marker of cardiovascular risk but is also involved in its pathogenesis. The association with various diseases is increasingly emphasized. This exists both with type 2 diabetes mellitus as with other diseases such as sleep apnea, psoriasis, osteoporosis, colorectal cancer and multiple endocrine diseases. Extrahepatic manifestations can be better understood in a complex microenvironment of inflammation and metabolic derangement [26]. Abdominal ultrasound is the imaging technique most commonly used to assess NAFLD. The detection of moderate to severe disease is adequate but the initial grades are not diagnosed with the same accuracy and features can vary interobservers. Computerized tomography is also not able to diagnose at an early stage and has the great burden of radiation for repeated and long-term use. The resonance spectroscopy and MRI may be used and allow for the detection and quantification of the liver fat [27,28]. Recently, a research showed good correlation of MRI with liver biopsy to quantify hepatic steatosis in diabetic patients [26].

Transient liver elastography by controlled vibration is used and validated for the assessment of liver fibrosis related to hepatitis C. In patients with HIV infection it is not sufficiently studied, but research conducted in patients with aminotransferase elevation in the last 6 months without viral hepatitis infection investigated elastography compared to liver biopsy and elastography cannot substitute liver biopsy yet in this context [25].

The relevance of deeper knowledge in chronic and prevalent diseases in patients with HIV is emphasized from the long survival experienced now in this population and the need to improve their quality of life.

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