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Review Article

Influence of antiretroviral therapy on bone metabolism of patients with chronic hepatitis B: a review

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Abstract

Hepatitis B is a major public health problem worldwide and associated with significant mortality. To prevent or delay the deleterious effects of chronic infection by the hepatitis B virus, patients should be carefully followed, and antiviral therapy indicated according to specific recommendations. Currently, available drugs inhibit viral replication and slow or stop the progression of inflammation and fibrosis of the liver. However, the drugs for oral use in the treatment of hepatitis B, jointly referred to as nucleoside/nucleotide analogs, are indicated for prolonged use and have potential side effects. The reduction in bone mineral density was associated with the use of tenofovir, already evaluated in patients infected with HIV because the drug is also part of the therapeutic arsenal for this viral infection. There are few studies on the effects of tenofovir in patients with mono hepatitis B. Therefore, this literature review proposes to examine how hepatitis B acts in the body and the mechanisms by which antiretroviral drugs (especially tenofovir) can affect bone metabolism.

Keywords: Tenofovir. Hepatitis B. Bone metabolism. Bone health.

INTRODUCTION

Hepatitis B is the most common chronic infection and an important public health problem globally[1]. Approximately two billion individuals are already infected worldwide, and 350-400 million individuals are infected with the chronic hepatitis B virus (HBV)[2,3]. Chronic hepatitis B (CHB) has a high load, accounting for about 600,000 deaths annually due to complications related to liver diseases, such as cirrhosis and hepatocellular carcinoma[4,5]. New data from the World Health Organization showed that about 257 million individuals worldwide live with CHB, and viral hepatitis was responsible for about 887,000 deaths in 2015 due to complications, such as cirrhosis and hepatocellular carcinoma[6,7].

Currently, CHB is treated with medications belonging to two main groups as follows: immunomodulatory agents (interferons) and analogs of nucleoside/nucleotide (ANNs). The latter group includes the most frequently used medications, especially entecavir and tenofovir (TDF), which are first-line drugs. Treatment goals are to improve the quality of life, prevent the development of liver cirrhosis and its complications, and prevent the development of hepatocellular carcinoma[3,8]. To achieve these goals, oral medications (ANNs) are used over a long period, sometimes for a lifetime, depending on the patient's response to treatment parameters[9].

Data on effects of ANNs in non-HIV-infected patients with hepatitis B are scarce. Some studies have found that reduced bone mineral density (BMD) (osteopenia or osteoporosis) is frequently observed in patients with HBV using TDF. However, the effects of ANNs on bone loss are unclear[10-12].

Based on these gaps in the knowledge on changes in bone metabolism due to CHB and the use of ANNs, this review of the literature proposes to examine how HBV acts in the body and the mechanisms by which antiretroviral drugs, especially TDF, can affect bone metabolism.

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HEPATITIS B: GENERAL CONSIDERATIONS

Viral hepatitis B is caused by a DNA virus belonging to the family Hepadnaviridae. DNA viruses belonging to this family have characteristics such as incomplete double strand, and the reverse transcriptase enzyme is responsible for the replication of the viral genome. When analyzing the genome of this virus, it is possible to observe a circular and partially duplicated DNA of approximately 3,200 base pairs, and one strand is smaller compared to another. The surface antigen of hepatitis B (HBsAg) comprises spherical viral particles (42 nm) composed of an external envelope protein. HBV has 10 different genotypes and ratings from A to J and is considered an oncogenic virus. These genotypes and ratings are differentiated by the nucleotide sequence in the genome pathogenicity and geographical distribution[13-17].

Clinical manifestations of the disease will depend on each patient, and most patients with chronic infection acquire the virus early in life[18-20]. Transmissions can occur sexually or can be perinatal and bloodborne. Virus genotypes and their global distribution are associated with the mode of transmission. In Asian countries, the predominant genotypes are B and C, which are transmitted perinatally (from mother to child)[19,21].

Approximately 240 million individuals have HBV infection. Patients with chronic infection are unable to eradicate the virus due to the presence of covalently closed circular DNA (cccDNA) in the core of infected hepatocytes[22-24]. This viral feature only allows the patient to control viral replication through the use of antiretroviral drugs, and therefore, currently, the goal of treatment is reducing the risk of complications for virological suppression[22,25-27].

VIRAL REPLICATION

HBV infection begins in hepatocytes, which form cccDNA-stable mini-chromosomes in the nucleus, which is the first step of viral replication called transcription. Subsequently, five species of RNA messengers are formed as follows: main mRNA/pregenomic (3.5 kb), precore mRNA (3.5 kb), mRNA LHBs (2.4 kb), mRNA SHBs (2,1 kb), and X mRNA (0.9 kb). The pregenomic mRNA is the precursor to the synthesis of viral DNA genome reverse transcriptase. Thus, the viral genome encapsidated by the core protein of hepatitis B virus (HBcrAg) is packaged by the proteins of hepatitis B surface (HBs) in the endoplasmic reticulum, and then, new viral particles are secreted into the bloodstream, resulting in a large number of new virions[28,29]. Therefore, measurement of serum HBV DNA level can provide an estimate of viral replication and is widely used as a marker for the efficacy of antiretroviral drugs. However, ANNs are able to act only in limited stages of the viral replication cycle, and the production of intermediate viral proteins may not be significantly affected. Thus, measurement of viral proteins can be useful in monitoring the activity of HBV, especially in patients receiving drugs when HBV DNA levels are undetectable. One method of detection is quantification of HBsAg, which is found in viral particles in spherical or filamentous forms. Another indicator of viral DNA levels that may be used is HBcrAg[22,30].

ANTIRETROVIRAL THERAPY

Antiretroviral therapy for the control of viral replication is performed with medications known as immunomodulatory agents (interferon) and ANNs[3].

After initiation of the treatment for viral control with antiretroviral therapy, patients may reach a stage where viral DNA level is undetectable, but most of them will have persistent infection[31,32]. Studies show that patients using drugs such as interferon, lamivudine, entecavir, or TDF for 126 months on average had undetectable viral DNA levels but detectable intrahepatic cccDNA levels[22,33,34,35].

Regarding the decision on the initiation of antiretroviral therapy, studies suggest that it should be based on individual and family characteristics, assessing the history of liver cirrhosis, comorbidities, and pregnancy. Additionally, the clinical profile must be analyzed for increased serological (HbeAg) levels of transaminases and hepatic histology, when possible[8,13]. The primary goal of drug therapy is to reduce the progression of liver disease and consequently prevent the development of cirrhosis and hepatocellular carcinoma[6,13].

Patients may receive monotherapy or a combination of two antiretroviral drugs depending on the case. Cases of unsatisfactory suppression of viral replication may be indicative of a combination of antiretroviral drugs. The drugs TDF and entecavir are inhibitors of the enzyme reverse transcriptase and considered to be the first-line treatment for hepatitis B. The choice of TDF is based on its high-potency viral suppression and high genetic barrier against viral resistance mutations[5]. However, this drug can cause kidney toxicity and bone demineralization, and when there is either of these manifestations in the patient, we recommend the use of entecavir[36,37].

Despite being widely used in viral control, entecavir has reduced effectiveness in the presence of viral mutations in patients administered with ANNs, such as lamivudine. Therefore, it is necessary to assess the clinical history of each patient so that the best antiretroviral therapy may be selected since the antiviral drugs TDF and entecavir are excreted by the kidneys, and patients with kidney disease may require adjustments in dosing[26,38].

Based on the evidence of bone changes that chronic use of antiretroviral drugs, such as TDF, can cause serious side effects, it is necessary to understand how the bone is formed, the process of bone metabolism, and the action of antiretroviral drugs in the system.

BONE TISSUE

Bone tissue is composed of compact and cortical bone (80%). The diaphysis of long bones consists mainly of cortical bone, and the remaining 20% of the skeleton is formed by trabecular or spongy bone. Surrounded by these two types of structures is the bone marrow[39-44]. The trabecular bone has a lower density than the cortical bone and interconnects and supports the cortical bone shell of long bones. Based on bone formation, it was observed that the loss of trabecular bone during life can increase the risk of fractures[39,42,45,46].

Osteoblasts are mononuclear cells that produce osteoids and are responsible for bone formation[41]. The maturation, differentiation, and survival of these cells are connected to different kinds of growth and hormonal factors, such as bone morphogenetic protein, wingless protein, β-growth factor, parathyroid hormone (PTH), platelet-derived growth factor, and fibroblast growth factor (FGF)[42,45-47].

Osteoclasts are responsible for bone resorption, thus removing old bone[43]. These cells participate in osteoclastogenesis, and it is known that different types of mediators participate in this process, such as nuclear κ-β factor, RANKL, osteopontin, PTH, stimulating factor macrophage colony (M-CSF), and angiotensin II. Osteoclasts can affect osteoclastogenesis by three mechanisms as follows: RANKL mediation, M-CSF mediation, and tyrosine-based immunoreceptor activation. RANKL is a key factor in promoting osteoclast differentiation by binding to the cell surface receptor monocyte-macrophage lineage cells, can inhibit apoptosis induction by anti-apoptotic β-kinase enzyme, and is also responsible for the production of reactive oxygen species (ROS), potent inducer of osteoclastogenesis[42,46,48]. The dominant mediator regulating osteoclast differentiation is the RANKL/RANK/osteoprotegerin (OPG) osteoblast, which promotes osteoclast differentiation by RANKL binding to a RANK receptor in membrane mononuclear osteoclast precursors. The osteoclast differentiation by RANKL is inhibited by OPG, which is also produced by osteoblasts[45,49-51].

In bone remodeling, the process of resorption is faster than formation, which requires 3-6 months or up to 1 year (elderly) to occur. Resorption of organic and mineral components of the bone occurs initially with the formation of small cavities in bone surfaces, and subsequently the formation of a new bone occurs. This process of formation and resorption is activated by specific hormones and cytokines, and after the process is complete, the result is a new and healthy bone[42,45,52].

The remodeling process occurs in small clusters of cells called basic multicellular bone remodeling units and is characterized by coupling the functions of osteoclasts, osteoblasts, and osteocytes. Each unit is spatially and chronologically separated from other sets, suggesting that the activation sequence of cellular events responsible for remodeling is also controlled locally by factors generated in the bone microenvironment[45,49,53,54].

Bone loss is linked to the deterioration of the collagen-forming organic matrix of bone and a gradual imbalance in the remodeling process[55]. Usually, bone loss is accompanied by deterioration of the bone architecture, resulting in a reduction in the number of trabeculae in the spongy bone, increasing intertrabecular distance, and leading to loss of trabecular connectivity. Moreover, a reduction in cortical bone thickness and an increase in the porosity of the trabecular bone may result in femoral fragility[56].

Bone quality can be defined by addressing the bone characteristics of stiffness, bone capacity to withstand deformations, flexibility, ability to deform to allow energy absorption during an impact, and being light to allow movement. Bone homeostasis between stiffness and flexibility varies according to bone mineral content; therefore, the higher the mineral content, the greater the stiffness and the lesser the flexibility. Bone strength is mainly determined by bone mass, which is reflected by BMD and microarchitecture. Therefore, bone strength arises from bone quantity and quality, the latter of which encompasses the geometrical and material factors that contribute to resistance to fracture. Bone quality, which is not specifically defined, is described as a combination of all factors that determine the strength of the skeleton to resist fractures such as microarchitecture, accumulated microscopic damage, collagen quality, size of mineral crystals, and bone turnover rate. From this definition, it can be observed that BMD can account for 70-75% of the variation in bone strength, while the rest may be related to other factors, such as accumulation of microfractures, altered microarchitecture, disordered bone remodeling, and influence of additional skeletal factors[47,56,57].

BONE METABOLISM

The main minerals that comprise bone mineral content are calcium, phosphorus, and magnesium. These minerals are regulated by the PTH, calcitocin, and 1,25-dihydroxyvitamin D and absorbed by the intestine. Intestinal absorption needs to attend to the increase in bone mass during the growth phase and bone remodeling in the adult phase[58,59].

PTH is a polypeptide hormone synthesized by the parathyroid glands and has the following main functions: release of calcium in the extracellular fluid, conversion of 25-hydroxycholecalciferol to 1,25-dihydroxyvitamin D, reduction in phosphate reabsorption by renal tubules, and increased calcium reabsorption[60,61]. Additionally, vitamins and minerals are also essential in maintaining bone health. Vitamin D is a vital nutrient for the maintenance of bone mineralization and mass throughout life. The active form of this vitamin is 1,25-dihydroxyvitamin D, which is responsible for the maintenance of calcium and phosphorus homeostasis and increases the absorption of calcium in the intestine. The main function of vitamin D is to act with PTH in the maintenance of extracellular calcium levels[62,63,64].

Calcium is a major mineral that plays several essential functions, such as vasoconstriction, vasodilation, and transmission of nerve impulses, which are associated with the development and maintenance of bones[65,66]. The highest calcium levels in the body are in the bones and teeth, mainly as hydroxyapatite (99%), and 1% is in the extracellular fluid. The amount of calcium absorbed in the gastrointestinal tract is related to the bioavailability of dietary calcium and ability of intestinal absorption[65,67,68].

Therefore, proper action of hormones and adequate intestinal absorption of nutrients are essential in maintaining bone mass[61].

EFFECTS OF BONE METABOLISM AND ANTIRETROVIRUS

The third generation of ANNs, TDF, and entecavir represents the first-line treatment for CHB. Despite the success in viral control, studies show potential toxic effects of these drugs associated with indefinite antiretroviral therapy[69].

TDF is a cyclic nucleotide analog of adenosine monophosphate that has emerged as a highly effective drug in the treatment of hepatitis B[70,71]. Recommended by most medical organizations for liver diseases, it ranks first in the line of antiretroviral drugs. Most research related to this medication is conducted in HIV-positive patients. The focus of concern is based on the adverse effects of the use of this drug on BMD[72]. Randomized studies evaluating long-term use of TDF in HIV-positive patients found a reduction in BMD and increase in bone fracture risk. Another study found that HIV-positive patients had increased risk of osteoporotic fractures with TDF use under a highly active antiretroviral therapy[69,73,74]. TDF use was also associated with decreased BMD compared with the use of other medications (entecavir and lamivudine) in HIV-positive patients, but its effects on BMD in patients with CHB remain unclear and poorly investigated[3].

The mechanism of bone toxicity is unclear. We suggest three potential mechanisms that may lead to bone changes: preferential uptake by osteoclasts (altered gene expression and increased bone resorption), uptake by osteoblasts (altered gene expression and decreased bone formation), and uptake by osteoclasts and osteoblasts (altered gene expression of both cell types and finally the balance between reabsorption and bone formation, resulting in bone loss)[69].

Concerning its performance in the kidney, renal tubule dysfunction may develop, resulting in hypophosphatemia, abnormalities in vitamin D metabolism, and defects in bone mineralization, and recent studies indicate that TDF is responsible for altering gene expression and function of osteoblasts. In the kidney, TDF disoproxil fumarate is hydrolyzed into TDF and subsequently phosphorylated into TDF diphosphate (active metabolite) by cellular kinases. TDF is excreted by the kidneys through a combination of glomerular filtration and active tubular secretion, and the main renal excretion mechanism involves the absorption of TDF on the basolateral side of the proximal tubular cell through human ion carrier 1 and protein multiple drug resistance[73,75]. Studies indicate that the use of TDF for approximately 7 years is safe and effective and that adverse renal effects occur in patients with a predisposition to kidney disease or comorbidities. However, several studies have shown that prolonged use may lead to the development of Fanconi syndrome, which leads to the deregulation of calcium and phosphorus levels and acute renal failure, osteomalacia, and increased risk of fractures. Moreover, it can also lead to metabolic acidosis, glycosuria, and aminoaciduria[3,73].

In evaluating renal function and changes caused by TDF use, mainly hypophosphatemia, a hormone called FGF23 is involved in phosphate metabolism. This hormone is secreted by osteocytes and reduces the expression of sodium phosphate transporters in the proximal tubule through excessive induction of phosphate loss. FGF23 is also responsible for inhibiting the hydroxylation of 25-hydroxyvitamin D, leading to a reduction in 1,25-dihydroxyvitamin D (calcitriol) level. This mechanism leads to reduced gastrointestinal absorption of calcium and phosphate; thus, excessive FGF23 levels, typical in congenital osteomalacia, is characterized by diminished renal phosphate, hypophosphatemia, low serum calcitriol levels, bone mineral loss, and increased risk of fractures. Recent studies have evaluated cases of elevated serum FGF23 levels in HIV-positive men receiving TDF therapy. When the medication was discontinued, there was a decline in rates and reversal in the loss of phosphate. Data on TDF influence on FGF23 levels and loss of phosphate, vitamin D metabolism, and BMD in patients with CHB are still limited[3,76-78].

In patients who are HIV positive and have CHB and chronic hepatitis C without drug treatment, the presence of liver disease was associated with an increased risk of bone changes in the case of coinfection. Moreover, studies have suggested that bone loss in chronic viral infection is the result of cumulative interactions and time dependency between classical risk factors of the patient in the development of osteoporosis and viral load-associated inflammation and use of antiretroviral drugs[73,79,80].

CONCLUSION

Studies on bone metabolism and how it can be affected by factors such as chronic infection and medication use continue to evolve, and a better understanding of the physiology of bone loss is still a major challenge.

The changes caused by the antiretroviral regimen, especially by the drug TDF, should be continuously investigated so early-onset comorbidities that affect the quality of life of the patient, such as osteopenia and osteoporosis, can be diagnosed.

Therefore, new therapeutic strategies need to be studied and explored to prevent or reverse bone changes and better understand the mechanisms by which these disorders develop for a better quality of life of patients with CHB.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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