

Montaño Jaramillo D, Díaz Curiel M

Unidad de Enfermedades Metabólicas Óseas - Servicio de Medicina Interna - Fundación Jiménez Díaz/Quirón Salud Madrid - Madrid (España)

Hemochromatosis and osteoporosis, in reference to 4 cases

Correspondence: Manuel Díaz Curiel - Fundación Jiménez Díaz - Avda. Reyes Católicos, 2 - 28040 Madrid (Spain)
e-mail: mdcuriel@fjd.es

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Summary

Although most people's osteoporotic conditions treated in clinical practice may be categorized in the postmenopausal osteoporosis group or related to aging, there are some osteoporosis cases linked to the development of some other disease or identifiable factor.

Most of these causes are associated with the taking of steroids, hypogonadism, malignant processes such as multiple myeloma, gastric surgery, alcoholism and treatment with anticonvulsant drugs. Hereditary hemochromatosis is another disorder related to the onset of osteoporosis. In this paper, we present 4 cases of patients with osteoporosis who also suffer hereditary hemochromatosis. The latter's characteristics are described and also its possible relationship with bone disease.

Key words: *hemochromatosis, osteoporosis, iron.*

Introduction

Osteoporosis (OP) is a disease characterized by decreased bone resistance with bone mass quality and quantity alteration that leads to disease fractures or fragility. The forearm, the vertebral bodies and the hip are the most common locations.

Risk factors include age, early menopause (and any case of low estrogen production), fractures due to previous personal fragility (this being the most important risk factor)² or in first-degree relatives, inadequate intake of dairy products, chronic gluco-corticoid intake (prednisone at doses ≥ 5 mg/d for 3 months), low body mass index (BMI) (< 19 mg/m²), high and chronic alcohol and caffeine, and smoking, as well as all those diseases that may cause a secondary OP (hypogonadism, hyperthyroidism, diabetes mellitus, renal failure and liver diseases, among others).

Hereditary hemochromatosis (HH), although uncommon, is one of the liver diseases described that can lead to the onset of OP. The most frequent form of presentation is related to the HFE gene (HH-HFE). Here we describe the existence of OP in 4 people suffering from HH-HFE.

Clinical Cases

At our hospital's metabolic bone disease center, 4 women were diagnosed with OP and as suffering from HH. We do not know the actual incidence of OP in patients with HH in our center as bone density DXA has not yet been carried out on all of these patients.

1st patient: She was diagnosed with HH-HFE and pituitary hypogonadism at 25 years and with OP at 51 years. Given the history of hypogonadism, hormone replacement therapy was started for amenorrhea and subsequently modified to raloxifene with supplements of calcium and vitamin D, with periodic follow-up. In the last review, DXA presented a T-score of -2.1 in the femoral neck (stable during treatment) and -3.2 in the lumbar spine (with slight deterioration since onset, since we started from -2.8). She did not present fractures during this time. When studying the risk factors of OP, it was observed that the patient presents adequate calcium intake, exercises regularly, is a non-smoker and has an adequate thyroid function. HH-HFE did not cause organic involvement, since it had been followed and controlled since its diagnosis, and 2 phlebotomies were performed during follow-up, with normalization of the analytical parameters of iron; she has always presented alkaline phosphatase within normal limits.

2nd patient: She was diagnosed with OP and HH-HFE (normal heterozygote/H63D) at age 64, although she had a history of vertebral fractures at age 55 and ribs at age 61 and 63 years. She has been treated for 4 years in our center, and the last DXA detected a T-score in the femoral neck of -2.6 (stable during follow-up) and in the lumbar spine of -2.1 (slight improvement with respect to initiation of treatment, -2.7). Initially she was treated with calcium and vitamin D. Subsequently, iban-

dronic acid was added and this was later replaced by denosumab until the present time, as the patient has not presented any new fractures. As for OP risk factors, she presents low calcium intake in the diet, is a smoker of 40 cigarettes/day and had menopause at 45 years. HH-HFE did not produce organic involvement since it was diagnosed and at no time did it require phlebotomies. In her follow up she has always presented alkaline phosphatase in the normal range. As a significant personal history, at 66 years the patient was diagnosed and surgically treated for colon carcinoma and, in addition, is a heterozygous carrier of the prothrombin mutation.

3rd patient: OP was diagnosed at 69 years of age and at 74 years of HH-HFE (heterozygote for C282Y) due to alterations in the ferric profile, which were already observed at the time of PB diagnosis. She was treated with calcium and vitamin D during the 5 year follow-up, and in the last DXA she presented a T-score at the femoral neck of -1.1 (worsening with respect to the time of diagnosis: 0.3, but slight improvement compared to the previous one: -1.5) and -2.3 in the lumbar spine (slight improvement compared to the start: -2.6). He did not suffer fractures during these years. As for her risk factors for OP, she has 2 children with whom she breastfeed and presented menopause at age 45, is an ex-smoker, has a low intake of foods rich in calcium, does not practice physical exercise routinely and does not have a history of fractures. HH-HFE is adequately controlled without organic alterations and at no time needed phlebotomies; During his follow-up he always presented alkaline phosphatase in the normal range. As an important pathological antecedent, he was diagnosed of chronic hepatitis C virus in response to antiviral treatment, which was maintained 9 years later.

4th patient: Diagnosed HH-HFE and later lumbar OP at 55 years. It has been followed in our consultation for 8 years, and in the last DXA presented a T-score at the femoral neck of -1.1 (being the initial of -1.6) and in the spine of -2.8 (maintained stable with respect to the start of treatment). At the beginning and during her evolution she was treated with calcium, vitamin D and raloxifene, without having presented fractures. As for her OP risk factors, she has 1 child and did not breastfeed, had menopause at age 51, is not a smoker, has adequate intake of calcium in the diet and exercises routinely. She has no previous history of fracture. She did not present organic alterations by HH-HFE and it was not necessary to practice phlebotomies during her follow-up. The alkaline phosphatase was always within the normal range. As an important personal antecedent, she was treated for chronic hepatitis C, with adequate response.

Discussion

Hepatic osteodystrophy refers to osseous diseases (mainly OP and osteomalacia, although the latter is very rare) secondary to chronic liver diseases^{1,2,6,12}, such as HH-HFE.

HH is a disease characterized by increased tissue deposits of iron secondary to decreased production or resistance to hepcidin, a hormone that in situations of excess iron decreases the intestinal absorption of iron by the enterocytes and the release of iron by macrophages^{1,10}. This raises blood iron and its reserves in the organism with the consequent formation of pathological deposits in various tissues (liver, heart, pancreas, joints, bones, pituitary and skin, among others), generating multiple symptoms depending on their location. Most patients are asymptomatic in the early stages of the disease as they do not yet have these deposits. It should be noted that patients with HH present an increased incidence of cirrhosis and hepatocellular carcinoma^{1,3,11}.

HH is a predominant disease in the Caucasian population and 5 types have been described. The most common is inherited genetic alteration in an autosomal recessive form related to the HFE gene, the most severe presentation being homozygous C282Y, and the least relevant H63D¹⁰. It should be noted that the fact that a patient is homozygous for the C282Y mutation is not a diagnosis of HH if there is no elevation of the iron stores¹, since the HFE gene has quite a variable penetrance and it is not possible to ascertain which patients homozygous for C282Y will develop the disease³.

Among the conditions related to iron overload, HH-HFE is the most common and the one in which most significant clinical complications occur, although we also find less common secondary causes, such as thalassemia major, sideroblastic anemia, multiple transfusions, long-term hemodialysis, chronic hepatitis B and C, alcoholic and non-alcoholic liver disease, among others.

The treatment for iron overload involves periodic phlebotomies until the normalization of the analytical parameters, which not only manage to control the levels of iron deposits in the body, but also improve and sometimes secondary complications of this disease disappear¹.

As for bone tissue, arthritis and OP have been found to be the main bone alterations related to HH-HFE, with arthritis being the most commonly associated, reaching up to 80% of patients. Treatment with phlebotomies does not manage to completely reverse this once it is already established^{1,9}. The association between OP and HH has been known since 1960 and the incidence of OP is approximately 25-45%^{5,7,9}. In a study conducted in Brazil, the presence of arthropathy, hepatocellular carcinoma, osteoporosis and diabetes was more common in HH-HFE patients compared to patients with iron overload from other causes⁵.

The mechanisms by which OP occurs in chronic liver diseases are not fully known, but in HH-HFE it is thought that increased blood iron, not cirrhosis, is the main cause of this association, although in cirrhotic patients, involving a higher incidence of hypogonadism, it is known that the number of OP cases increases compared to patients without hypogonadism or cirrhosis^{2,5,7,9}. Advanced HH may lead to cirrhosis (with or

without hypogonadism) which adds to the deleterious effect of excess iron on the bone.

In 1989, Terrence Diamond et al. considered that excess serum iron altered the function of osteoblasts by decreasing osteoid matrix synthesis⁷, which has been corroborated by two other studies, both *in vitro*, one of which concludes that elevation of serum iron decreases bone mineralization. With increasing ferritin and its ferroxidase activity, since it alters the function of osteoblasts by modifying the activity of the genes of CBF- α 1 (involved in the maturation and differentiation of osteoblasts), osteocalcin and alkaline phosphatase in dose-dependent form⁴. The other study also concluded that iron overload produces OP by inhibiting the proliferation, differentiation and mineralization of osteoblasts, as well as decreased alkaline phosphatase activity⁸.

This has also been studied by Valenti et al. who consider that OP in HH is related to hypogonadism, severity of iron overload and low weight, differing in alkaline phosphatase, since they found that high levels are also correlated with OP. This may be due to its relation to hypogonadism (in which bone resorption is increased, since it stimulates osteoclast activity)^{5,7,12}.

A suitable DXA diagnosis should be performed for all patients with chronic liver disease, including HH (especially HH-HFE)^{2,5,12}, although the timeframe determination for performance of this study in the follow-up of patients has not been determined^{2,6}. The most common location of T-score decrease in DXA in patients with HH-HFE is the lumbar spine, followed by the femoral neck^{5,9}.

Regarding the treatment of OP, following the same guidelines is recommended as in patients without hepatic disease, adjusted according to individual characteristics. Avoiding hormone replacement therapy in severe liver disease is also recommended¹². To reduce iron overload in HH-HFE patients, periodic phlebotomies have been shown to improve the ferric profile and thus improve osteoblastic function, which can sometimes be reflected in a decrease in the T-score value of the DXA^{5,7,12}.

As for the 4 patients presented here, HH-HFE was diagnosed based on analytical alterations at an early stage, and without any target organ damage in any of the cases. Taking into account that this diagnosis has preceded or been performed simultaneously with that of the OP (except for the 3rd patient, although the analytical alterations were already present at the time of OP diagnosis), we may consider it a risk factor associated with each patient's other clinical data and not as the main cause of OP, so that monitoring and analytical control have been performed to treat it and avoid complications of HH-HFE as would be done in any patient without OP.

In the first patient, hypogonadism is also an associated risk factor for presenting OP, although this pathology has always been controlled by the gynecology service since its diagnosis. The next patient has low calcium intake and is a smoker, which also

contributes to the presence of OP together with HH-HFE. Being a smoker, low intake of calcium-rich foods and lack of physical exercise are other risk factors associated with OP that the third patient presents. She also presented slight alterations of the ferric profile without needing phlebotomies to correct it. Finally, the last patient had no other associated factors except treated hepatitis C, although she did not develop cirrhosis or other complications.

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