Osteoporosis and Genetic Haemochromatosis (GH)

Advice for patients from the Haemochromatosis Arthropathy Research Initiative (HARI)

Introduction

Osteoporosis occurs in patients with genetic hemochromatosis (GH) more frequently than expected. Recent studies have shown that in GH there is a decrease in bone mineral density (BMD) as measured by bone densitometry (DEXA), the standard detection method used in clinical practice\[^1, 2\]. The decrease in BMD leads to an increased risk of fracture\[^3\], so-called fragility fractures occurring in the absence of significant trauma e.g. after a simple fall from standing height for peripheral bones (such as the hip or wrist), and sometimes spontaneously for vertebral fractures. These fragility or low-trauma fractures are characteristic of osteoporotic disease and differentiate this from conventional fractures caused by high impact.

Bone metabolism, iron and GH

Bone is a living tissue that is constantly renewed with a resorption phase that removes the aging bone and a bone construction phase that replaces it. In osteoporosis, this equilibrium is disturbed, so that there is an imbalance in which bone break down or resorption is not matched by bone formation. This occurs in a variety of situations such as after the menopause, when there is excess bone resorption and with increasing age or when taking therapeutic corticosteroids, when there is reduced bone formation. In the case of GH, bone loss is related to both a decrease in bone formation and also an increase in bone resorption. How GH causes this is not fully understood, but there is a link with the accumulation of iron in the bone substance or matrix, leading to a decrease in bone mass and alteration of bone microarchitecture and strength\[^4\]. Other genes that influence bone turnover and strength may also be affected by iron and contribute to bone loss and osteoporosis. There seems to be a link
between the extent of iron overload and the severity of osteoporosis, but this relationship is not absolute and significant bone loss is seen in some people with only modest iron overload. Some of the organ related severe consequences of GH have a negative effect on bone, such as liver cirrhosis and reduced sex hormone production (hypogonadism), adding to the risk of osteoporosis, in addition to non-GH related traditional risk factors such as menopause, increasing age, taking bone toxic agents (steroids, alcohol, tobacco) and endocrine disease[4]. Nonetheless, iron overload is a risk factor for osteoporosis, and even in the general population, iron metabolism seems to have an influence on the occurrence of osteoporosis. For example, postmenopausal women with relatively high ferritin values (but still in the normal range) have significantly lower bone density and a higher fracture risk[5].

Prevalence of osteoporosis and fractures in GH

The prevalence of osteoporosis (defined by a T score on DEXA less than -2.5) in GH ranges from 23.3% to 34.2% compared to 4.6% in a sex and age matched healthy comparison population in one study [1, 2]. The prevalence of fractures in GH has not been accurately determined, but is estimated to be in the order of 20%. One study showed that osteoporotic fractures in people with GH seem to preferentially affect vertebrae, and to be especially likely in those who had a peak ferritin higher than 1000 µg/L[3]. The occurrence of an osteoporotic fracture at an unexpectedly young age without traditional risk factors, such as low body mass index or in women who have been without menstruation for a prolonged time, should be a trigger for investigation of the cause, with the first diagnosis of GH being one potential explanation.

Treatment of osteoporosis

At present, the management of osteoporosis in people with GH does not differ fundamentally from that of the non-haemochromatosis population, as there are no treatments specific to osteoporosis available for people with GH [Ref of national osteoporosis guidelines of each country]. It is not yet known whether venesections have an impact on the evolution of osteoporosis-related bone loss in GH, however, studies are currently underway to determine
whether this may be so.

Standard treatment strategies to prevent fractures in people with osteoporosis are used according to country-specific recommendations, stratified according to the severity of bone loss (the T score on DEXA) and whether or not the person has had a fragility fracture, or has other traditional risk factors for osteoporosis.

Weight bearing physical exercise (see supplementary ‘Advice about Exercise’ at the end of this article), adapted where necessary to the ability of patients with co-existing arthritis, is advised for all people.

An important component of the management of osteoporosis is a multidisciplinary programme to reduce risk factors for falls, particularly for the frail and elderly. This includes reducing hazards in the home (e.g. slippery floors, obstacles, insufficient lighting, missing handrails), an assessment and correction of visual acuity and the withdrawal of psychotropic drugs which might increase the chance of falls.

**Dietary advice**

It is necessary to ensure a daily dietary intake of calcium (one of the main constituents of the bone) of about 1g/day. Milk (including semi skimmed and skimmed) and yoghurt (even low fat) are the best sources of calcium. Other foods that contain high amounts of calcium are cheese, kale, broccoli, watercress, bok choy, okra, sardines, and almonds. Some drinks, bread and cereals are fortified with calcium and calcium can also be taken as a medication (tablets or sachets) with or without vitamin D.

Vitamin D is also necessary for bone building and function and a blood concentration of at least 30ng/ml is recommended in people with osteoporosis. Vitamin D allows the absorption of calcium in the digestive tract and promotes calcium incorporation into the bone matrix (mineralization). It is made in the skin from the sun’s ultraviolet (UV) rays. In countries at the latitude of Northern Europe from October – March, UV in sunlight is not strong enough to
make Vitamin D in the skin. This means there is a risk of deficiency of vitamin D in the general population by the end of this period every year. Dietary sources rich in vitamin D are oily fish (e.g. salmon, tuna, mackerel, cod), mushrooms, ricotta cheese, egg yolk, soy milk and tofu. However, for most people, dietary sources are not sufficient to maintain adequate levels of vitamin D and supplementation by medication is required. To correct deficient states, high dose supplements are first given, such as Vitamin D3 20,000U three times per week. Once adequate levels are reached, low dose supplements are continued, such as 1000U (25micrograms) daily or the equivalent in divided doses across the week. Different forms are available and Vitamin D3 (the type made in our skin) is preferred over Vitamin D2 (from plants). It is not recommended to administer too much in one dose, and monitoring blood levels to be sure adequate and not toxic levels are maintained is important.

Care not to drink alcohol in excess is doubly important for GH patients because, not only is this toxic to the liver, but it is also a cause of bone loss.

**Medications for osteoporosis**

In addition to diet and/or supplements of calcium and vitamin D, there are a number of additional drugs available for people with osteoporosis to correct the imbalance of bone remodeling. Some of these drugs prevent bone breakdown (e.g denosumab and the bisphosphonates such as alendronic and zoledronic acid) and others increase bone formation (e.g teriparatide). They are prescribed according to country specific guidelines based on an assessment of the severity of osteoporosis, presence of risk factors, prior occurrence of fragility fractures and the likelihood of future fragility fractures.

**Conclusion and Summary**

In conclusion, osteoporosis is a recognized complication of hemochromatosis, sometimes leading to fragility fractures. The occurrence of an osteoporotic fracture at an unexpected young age should prompt investigation for iron overload. Indeed, it may lead to the early diagnosis of GH. Treatment follows the principles of management of osteoporosis in the
general population, including weight bearing exercise, maintaining adequate levels of calcium and Vitamin D and specific bone therapies where necessary.

References

Advice about Exercise

• Lifelong age-appropriate exercise is an effective way of maintaining bone health

• Regular exercise increases muscle strength, improves balance and coordination, and maintains bone strength by stimulating bone formation and decreasing bone resorption: High-impact weight-bearing exercises help build bones and keep them strong. If you have broken a bone due to osteoporosis or are at risk of breaking a bone, you may need to avoid high-impact exercises. If you’re not sure, you should check with your healthcare provider. Examples of high-impact weight-bearing exercises are:
  • Dancing
  • High-impact aerobics
  • Hiking
  • Jogging/running
  • Jumping Rope / Skipping rope
  • Stair climbing

Low-impact weight-bearing exercises can also help keep bones strong and are a safe alternative if you cannot do high-impact exercises. Examples of low-impact weight-bearing exercises are:
  • Using elliptical training machines
  • Low-impact aerobics
  • Using stair-step machines
  • Fast walking on a treadmill or outside

Muscle-Strengthening Exercises
These exercises include activities where you move your body, a weight or some other resistance against gravity. They are also known as resistance exercises and include:
  • Lifting weights
  • Using elastic exercise bands
  • Using weight machines
  • Lifting your own body weight
  • Functional movements, such as standing and rising up on your toes

• A number of systematic reviews have reported that:
  - walking alone or swimming does not prevent osteoporosis, since it only provides a modest increase in the mechanical loads applied to the skeleton.

  - the frequently promoted ‘whole-body vibration exercises’ have shown no beneficial effects on bone in postmenopausal or elderly women.

  - Yoga and Pilates can also improve strength, balance and flexibility. However, certain positions may not be safe for people with osteoporosis or those at increased risk of broken bones. For example, exercises that have you bend forward may increase the chance of breaking a bone in the spine. A physical therapist should be able to advise which exercises are safe and appropriate for you.
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