



Osteoporosis in Hemophilia

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Author's contribution

This whole work was carried out by the author ECRM.

Review Article

Received 25th September 2013
Accepted 11th December 2013
Published 10th January 2014

ABSTRACT

Aim: The aim of this paper is to review the pathophysiology, risk factors, prevention and treatment of osteoporosis in persons with hemophilia (PWH).

Study Design and Methodology: In a search of PubMed up to September 24, 2013 using as keywords "osteoporosis" and "hemophilia" the author found 61 references, of which only the 22 focused on the aim of this study were revised.

Results: Prevention of osteoporosis in PWH is crucial. Risk factors are lack of hematological prophylaxis and development of an inhibitor (antibody) against the deficient coagulation factor, lack of exercise due to chronic pain and loss of joint function (hemophilic arthropathy), low body mass index and abnormal liver function because of viral infection (HIV, HCV). It has not been demonstrated that hemophilia has any effect on osteoclast development and/or osteoblast loss. Hemophilia does not impair mineral Ca/P/K mobilizations and metabolisms. Hemophilia does not have any general effects on the endocrine system. Substitution treatment with clotting factors does not interfere with the treatment of osteoporosis.

Conclusion: Continuous primary hematological prophylaxis and rehabilitation and exercise are paramount in PWH. PWH over the age of 50 should have routine screening for detection of osteoporosis. In PWH prevention should encourage good habits (such as a diet adequate in calcium and vitamin D) and discourage harmful habits (such as tobacco, alcohol and immobilization). Osteoporosis is multi-facial. Osteoporosis ought to be promptly treated regardless of the underlying cause.

Keywords: Osteoporosis; hemophilia; prevention; treatment.

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1. INTRODUCTION

Osteoporosis is a systemic disease characterized by low bone mass, which increases bone fragility, leading to greater ease of fracture. Typical osteoporotic fractures include vertebral fractures, inter-trochanteric fractures, fractures of proximal and distal humerus and fractures of the distal end of the radius [1].

When a patient of advanced age suffers one osteoporotic fracture, the probability of suffering another one in the future is high. An adequate fracture prevention strategy would be effective for prevention of a first fracture as well as of subsequent fractures. Therefore, it is very important to prevent and properly treat osteoporosis.

The aim of this paper is to review the pathophysiology, risk factors, prevention and treatment of osteoporosis in persons with hemophilia (PWH).

2. METHODS

In a search of PubMed up to September 24, 2013 using as keywords "osteoporosis" and "hemophilia" we found 61 references, of which only 22 were within the scope of this study. The author has reviewed the pathophysiology, risk factors, prevention and treatment of osteoporosis in PWH based on the literature search previously mentioned (22 reports) and on what is known today about the management of osteoporosis (10 important reports published in PubMed).

3. RESULTS

3.1 General Concepts on Osteoporosis

The risk of hip fracture throughout life is 5% in men. Furthermore, hip fractures increase exponentially after the age of 50. People with hip fractures occupy 20% of the beds in the Departments of Orthopaedic Surgery [1]. Bone densitometry (DXA, dual-energy X-ray absorptiometry) performed at the lumbar spine and hip for two years is the best way to diagnose osteoporosis. In fact, for every standard deviation below normal is double the risk of fracture [2]. DXA is the gold standard for diagnosis of osteoporosis [3]. It is minimally invasive (ionizing radiation received is one tenth of the received conventional radiography). One can diagnose osteoporosis and osteopenia, as well as monitor the response to treatment with the help of DXA [4]. Ultrasonography (QUS, quantitative ultrasound sonography) has emerged as a useful technique for predicting fracture risk with the advantage of being minimally invasive, inexpensive. It can also be performed on an outpatient basis. However, the results obtained with this test have poor reproducibility, with only 70% of correspondence with the results of DXA [5].

Prevention is the best way to manage osteoporosis, since there are no safe and effective methods to completely restore osteoporotic bone. Therefore, prevention of osteoporosis is far preferable to treatment, among other things, because prevention is more cost-effective. Three areas are recommended in the prevention of osteoporosis: primary, secondary and tertiary prevention [6-10].

Primary prevention involves all acts intended to lower the frequency of osteoporosis in the population, reducing its risk of occurrence. Logically, it should act on the factors that affect

the normal development of bone mass. It should encourage good habits (such as a diet adequate in calcium and vitamin D and exercise) and discourage harmful ones (such as tobacco, alcohol and immobilization).

A proper diet should contain no more than 1.5grams of protein per kilogram of weight, calcium (more than 1gram daily) and vitamin D (400-800 international units). Such a diet is effective in reducing the risk of fractures. Finally, exercise is essential.

Secondary prevention seeks to change the factors that accelerate bone loss. Tertiary prevention seeks to prevent people who have a decrease in bone density from suffering fractures. It avoids falls and uses methods to protect against them (side of hip protectors).

Currently available drugs that prevent osteoporosis are anti-resorptive agents (bisphosphonates, raloxifene) and bone-forming agents (strontium ranelate and parathyroid hormone - PTH). Among the bisphosphonates, the most important are etidronate disodium, alendronate, risedronate, ibandronate and zoledronic acid. Disodium etidronate has an anti-fracture effect, which may be due to maintenance of bone structure mediated by a decrease in bone resorption [6-10].

3.2 Osteoporosis in Hemophilia

Twenty-seven per cent of PWH have osteoporosis and 43% have osteopenia [11]. Significant osteopenia has been associated with hemophilia A [12]. Children with severe hemophilia have reduced BMD (bone mineral density) [13]. In a study published by Nair et al., the incidence of osteoporosis (T score: -2.5 or more) was significantly higher in PWH [14]. The incidence of fractures in adult life was also significantly higher in PWH compared to controls (12% vs. 0%).

Only a small number of children and young adults with hemophilia have impaired bone properties as assessed both by DXA and QUS [15]. A systematic review of the literature evaluated BMD reduction in severe hemophilia patients and its correlation with patients' characteristics. The meta-analysis confirmed the association between severe hemophilia and low BMD [16]. Ranta et al found that BMD was lower in children with hemophilia, although there was no evidence of significantly increased fracture rate [17].

3.3 Pathophysiology

Osteopenia in PWH may be partly due to liver dysfunction, but other factors, e.g. relative immobilization, may also be relevant [13]. It has been suggested that overexertion of the hematopoietic system resulting from constant excessive need for blood cell production, plays an important role in the etiology of osteoporosis [18]. For Wallny et al., the main cause for reduced bone mass in the individual with hemophilia is most probably the hemophilic arthropathy being typically associated with chronic pain and loss of joint function subsequently leading to inactivity [19].

It has not been demonstrated that hemophilia has any effect on osteoclast development and/or osteoblast loss. Hemophilia does not impair mineral Ca/P/K mobilizations and metabolisms. Hemophilia does not have any general effects on the endocrine system. Substitution treatment with clotting factors does not interfere with the treatment of osteoporosis.

3.4 Risk Factors

Children at risk are those with signs of hemophilic arthropathy [13]. Because osteoporosis may complicate the future treatment of PWH, screening of young patients for reduced BMD has been recommended by Barnes et al. [13].

Patients with hemophilia have reduced physical activity, and have other factors (hepatitis C and HIV seropositivity) which predict lower peak bone mass [20]. Some of these factors may accelerate loss of bone mass between the ages of 20 and 50 when bone mass should otherwise be stable. The results published by Tlacuilo-Parra et al suggested that low-physical activity is a risk factor for reduced lumbar bone mass in individuals with hemophilia [21]. This factor must be monitored to avoid a significant reduction in BMD that might contribute to further skeletal fragility.

Variables associated with increased bone loss included a history of HCV and HIV infections, decreased joint range-of-motion, decreased activity levels, history of an inhibitor and low body weight predict bone loss and suggest a population to target for screening [11].

According to Katsarou et al., osteoporosis among PWH is related to the severity of arthropathy and is enhanced by HIV infection [22]. In PWH, Khawaji et al., showed a significant correlation between joint evaluation score and BMD at total hip, femoral neck and trochanter [23]. Physical activity did not correlate to disease severity. The authors did not observe a correlation between BMD and severity of hemophilia. Their results indicated that the use of factor prophylaxis since early childhood may preserve normal BMD in severe hemophilia. The study of Mansouritorghabeh revealed that individuals with severe haemophilia B are prone to reduced BMD similar to individuals with severe hemophilia A [24].

Khawaji et al proposed that the responsiveness to mechanical strain is probably more important for bone mass development in children and during adolescence than in adults and underscores the importance of early onset prophylaxis [23]. According to Christoforidis et al., more studies are needed to identify the most accurate densitometric method for assessing bone status in individuals with hemophilia [25].

Ranta et al found that children with hemophilia had significantly higher urinary calcium excretion and higher serum calcium concentration as well as reduced bone resorption as compared with the controls [17]. Their findings suggested primary skeletal pathology, resulting in increased urinary calcium loss and altered bone metabolism, which may over time contribute to the development of osteoporosis in PWH.

Tlacuilo-Parra et al. [26] compared serum markers of bone turnover in children with haemophilia and normal bone mineral density (BMD) vs. those with low BMD. Their results showed that low osteocalcin levels predominated in the group with low BMD, which indicates a diminished osteoblastic bone formation activity while there were no differences with regard to bone resorption markers. Moreover, osteocalcin levels explain 10% of the variation of lumbar spine Z-score.

Naderi et al. [27] reported a cross-sectional study of bone density among PWH. Forty-two per cent of patients had normal BMD, 50% were osteopenic and the rest were osteoporotic. The results of this study suggested that men with severe hemophilia have reduced BMD. Patients at risk were those with signs of hemophilic arthropathy. Because osteoporosis may

complicate the future treatment of PWH, screening of patients with hemophilic arthropathy for reduction of BMD and preventive therapies was highly recommended.

According to Ghosh and Shetty, secondary effects in hemophilia that could lead to osteoporosis are abnormal liver function because of viral infection, bleeding and inflammation, lack of physical and athletic activities, and low body weight [28]. Franco [29] stated that the continuous improvement of substitution and antiviral treatments available to date allow better treatment to prevent osteoporosis in PWH. Moreover, for this author rehabilitation plays a vital role in helping to tackle risk factors for osteoporosis in young hemophilia patients.

Kempton et al. [30] evaluated the relationship between BMD and hemophilic arthropathy. Risk factors for low BMD in men with hemophilia under 50 included hemophilic arthropathy, low or normal BMI and HIV. According to Kempton et al., men with hemophilia over age 50 years should have routine screening for detection of osteoporosis.

Table 1 lists “secondary” effects/association in hemophilia that could lead to osteoporosis. Such temporary links/relationships deserve attentions but certainly not a mechanistic issue.

Table 1. “Secondary” effects/association in hemophilia that could lead to osteoporosis

Lack of primary hematological prophylaxis and/or development of an inhibitor
Lack of exercise (hemophilic arthropathy resulting in lack of physical activity due to loss of joint function)
Low body weight
Abnormal liver function because of viral infection (HIV, HCV)

3.5 Prevention

Appropriate preventive measures such as early treatment (primary hematological prophylaxis) and adequate mobilization, exercises, encouragement to participate in sporting activities, early assessment of BMD and administration of anti-osteoporotic therapy has been recommended in PWH [19]. A regular exercise program is recommended to prevent osteoporosis in PWH (aerobics, strength training, balance and flexibility activities) [30].

3.6 Treatment

In non-hemophilia adults, of the available bisphosphonates for osteoporosis (alendronate, risendronate, ibandronate, etidronate, zoledronic acid), zoledronic acid has the highest probability of offering the best overall fracture protection [1-10]. The evidence does not support the use of bisphosphonates as standard therapy in non-hemophilia children [1-10].

In PWH physical activity, physiotherapy, surgery to remobilize diseased joints and calcium and vitamin D supplementation, for anyone at any age, have been recommended [31,32].

Treatment with an anti-resorptive medication (usually a bisphosphonate) is not indicated for low peak bone mass that will otherwise be maintained by the patient between the ages of 20 and 50. On the other hand, on an individualized basis, treatment with an anti-resorptive may be indicated for some patients in whom rapid loss of bone mass has been confirmed by

sequential BMD measurements or who have already suffered osteoporotic fractures or who have reached an age and BMD value that places them into a high-risk category for estimated 10-year fracture risk [1-10].

4. CONCLUSIONS

It is paramount to prevent and diagnose osteoporosis in persons with hemophilia. Prevention should encourage good habits (such as a diet adequate in calcium and vitamin D and exercise) and discourage harmful ones (such as tobacco, alcohol and immobilization). Continuous improvement of hematological prophylaxis and antiviral treatments available to date allow better prevention and treatment of osteoporosis in persons with hemophilia. Rehabilitation and exercise play a vital role in helping to avoid risk factors for osteoporosis in young hemophilia patients. Osteoporosis is multi-facial. Osteoporosis ought to be promptly treated regardless of the underlying cause.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

The author has declared that no competing interests exist.

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