Bone Mineral Density in Hemophilia Patients

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Abstract Patients with hemophilia suffer from low bone mineral density (BMD) due to several risk factors including arthropathy and resulting immobility. Recent studies have shown variable frequency of low BMD in this group of patients. This study attempts to assess the prevalence of low BMD (osteoporosis and osteopenia) and the associated risk factors in a group of Iranian hemophilia patients. Patients with moderate or severe hemophilia underwent BMD measurement by dual energy X-ray absorptiometry. The results were correlated with other variables including physical activity, calcium intake and demographic data. Forty two patients with the mean age of 31 years (range

18–72) completed the study. The prevalence of osteoporosis in the spine and the left femoral neck was 23.8 and 14.6 %, respectively, and osteopenia in the spine and femoral neck was seen in 45.2 and 31.7 % of the patients, respectively based on the WHO T-score criteria. We found only cigarette smoking to be significantly related to low BMD ($P < 0.001$). There were two cases of pathologic fracture at femoral neck and forearm (4.8 %). Low BMD is very common in patients with hemophilia. Appropriate assessment of BMD and control of predisposing factors such as prophylactic factor replacement (to prevent hemarthrosis) and cessation of cigarette smoking are warranted.

Keywords Hemophilia · Bone mineral density · Osteopenia · Osteoporosis

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Introduction

Osteoporosis is a chronic progressive bone disease characterized by low bone mineral density (BMD), bone weakening and risk of fracture [1].

It is a major health problem worldwide; and increases the risk of fracture, disability and even death [2, 3].

As osteoporosis is asymptomatic, it is diagnosed only when fracture occurs or after screening densitometry, which is usually done in postmenopausal women [4].

It is less frequently suspected and diagnosed in men, in large part, because it is less prevalent and less of a public health problem for men than for women. This is not inconsistent with the observation that men who have osteoporosis are often at higher risk of death than women with osteoporosis [3, 5].

Chronic steroid use, alcohol consumption, smoking, hypogonadism, low intake of calcium, vitamin D

deficiency and immobility have been suggested as risk factors for osteoporosis in men [3, 5].

Hemophilia A is a hereditary sex-linked bleeding disorder that affects 1 in 5,000–10,000 male births. It is due to coagulation factor VIII deficiency, characterized by spontaneous bleeding or bleeding after trivial trauma [6, 7].

Hemarthrosis (bleeding in joint) is common in hemophilia patients. Recurrent hemarthrosis causes joint destruction and thus results in arthropathy and disability that are common prior to adulthood [6, 7]. In our center, like most other centers in Iran, factor VIII replacement is done on-demand after bleeding; this strategy, unlike the prophylactic factor replacement that is popular in the developed countries, predisposes to recurrent bleeding [8, 9].

Frequent immobility for treatment of hemarthrosis and the resulting disability due to arthropathy are among the main risk factors for osteoporosis.

In addition, chronic hepatitis C (HCV) and HIV infection, common in hemophilia patients, have been suggested as risk factors for osteoporosis [3, 10].

There is a growing global insight regarding osteoporosis in hemophilia patients, though its prevalence has variably been reported between 7.5 and 84 % in some studies [3, 9]. There are few studies in the Middle East and Iran in this regard. As care of hemophilia and other risk factors may differ in Iran, we conducted this study to assess the prevalence of osteoporosis and associated factors in a major hemophilia center in Iran.

Materials and Methods

Inclusion and Exclusion Criteria

The total of 42 patients with moderate or severe hemophilia A, who were followed by the Hemophilia Center of Imam Khomeini Hospital (Tehran, Iran) were included in this study. Moderate and severe hemophilia A are defined by the plasma coagulation factor VIII level of 1–5 and <1 %, respectively. All of the patients provided informed consent after being informed of the nature of the study. Patients with known diseases affecting BMD were excluded from the study; these include any hypercorticosteroid state (Cushing's syndrome or iatrogenic), thyrotoxicosis, hyperparathyroidism, and severe liver, renal or lung diseases.

Study Design

Data were collected by two experienced interviewers using a researcher-made questionnaire containing questions on demographic data [including age, weight, height and body mass index (BMI)], hemophilia related characteristics,

calcium intake and physical activity. We checked serology for hepatitis B, C and HIV.

Calcium intake was calculated by estimating milk, yoghurt, cheese and ice cream consumption as the major sources of calcium intake using a food frequency questionnaire consisting of 11 questions [1, 11, 12]. Each one cup of milk, and yoghurt or 45 g of cheese was considered to have 330 mg of elemental calcium [13, 14]. All nondairy sources were estimated to have 250 mg per day of calcium [1], which were added to the total daily intake; any supplemental calcium was also included. Adequate daily calcium intake for under 50 years old participants was considered as 1,000 and 1,200 mg for those over 50 [6, 15].

Physical activity was estimated by the short international physical activity questionnaire (IPAQ) [16]. This questionnaire asks about weekly walking time, as well as some moderate and heavy activities, and through an algorithm, divides the participants' activities into vigorous, moderate or low.

Habits including smoking (measured as packs/year) and alcohol intake were also questioned.

BMD was assessed using dual energy X-ray absorptiometry (DEXA) by Lexxos (DMS, Digital 2D Densitometer, France). Based on the our centre's reference database, the patients were assigned BMD values and T-scores at the spine and the left and right femurs. At the spine, the mean 2nd to 4th lumbar vertebrae (L2–L4) BMD, and at the femur, BMD of the neck and total hip were measured. Normal BMD, osteopenia and osteoporosis were defined using the World Health Organization (WHO) criteria as T-scores ≥ -1 , -1 till -2.5 and ≤ -2.5 , respectively. The study was approved by the Ethical Review Board of Tehran University of Medical Sciences (Tehran, Iran).

Statistical Methods

Data analysis was performed using the SPSS software, version 16.0. Mean and standard deviation (SD) were used for describing the numeric variables and percentages with 95 % confidence interval were used for the categorical variables. *T* test and the one way ANOVA were used for assessing the relationship of numeric variables with categorical variables, and correlation coefficient was applied for determining the correlation of the numeric variables with each other. Chi square test was used for assessing the relationships among categorical variables. Statistical significance was considered as a *P* value <0.05.

Results

Forty two male patients (aged 18–72 years) participated in the study. The patients' characteristics are presented in

Table 1 Demographic and bone mineral density (BMD) data of 42 hemophilia patients

Variables	Mean $\pm$ SD (range)
Age (year)	31.1 $\pm$ 12.4 (18–72)
Weight (kg)	64.9 $\pm$ 9.84 (45–85)
Height (m)	170.36 $\pm$ 8.57 (150–187)
BMI (kg/m ²)	22.4 $\pm$ 2.9 (17.2–27.1)
BMD total spine (g/cm ²)	0.90 $\pm$ 0.17 (0.45–1.20)
BMD left femoral neck	0.83 $\pm$ 0.20 (0.38–1.44)
BMD left femoral total	0.89 $\pm$ 0.16 (0.53–1.14)
BMD right femoral neck	0.83 $\pm$ 0.19 (0.52–1.26)

Table 1. They were suffering from hemophilia A and 92.9 % (39/42) had severe hemophilia. All the patients have had the history of lower limb joints bleeding that was first occurred in their initial 11 years of life. The most common joint in the first bleeding was knee joint in 58.5 % (24/42) of the patients.

The most common infectious disease among the patients was chronic hepatitis C (32/42, 76.2 %); six had chronic hepatitis B (6/40, 14.3 %) and 2.4 % (1/42) had HIV. None of the patients had the history or stigmata of cirrhosis. There was no correlation between any of the previous infections and low BMD (T-score <-1).

Mean daily calcium intake was 955 $\pm$ 394 mg (range 360–2,131); 26 patients (61.9 %) had inadequate calcium intake. There was no statistical relationship between inadequate calcium intake and low BMD ($P = 0.407$); even in the groups with the calcium intake of <800 , 600, 400 and 200, we did not find any statistical relationship between osteoporosis or low BMD and calcium intake (data not shown).

According to the IPAQ, estimation of the patients' physical activity was vigorous (9/42, 21.5 %), moderate (13/42, 31 %) and low (20/42, 47.6 %). Mean T-scores and 95 % confidence interval for the patients with vigorous, moderate and low physical activity were -1.7 (-2.2 to -1.2), -2.2 (-3 to -1.4), and -1.6 (-2.2 to -1.1), respectively. No statistical relationship was found between physical activity and low BMD ($P = 0.355$).

Twelve patients were smokers (28.6 %), of which 6 (14.4 %) were heavy smokers (>10 packs/year). There was a statistical relationship between cigarette smoking and BMD ($P < 0.000$). Age, weight and calcium intake had no effect on this relationship ($P = 0.225$, 0.253, 0.326, respectively). The mean T-score in the light and heavy smokers (<10 or ≥ 10 packs/year) was -1.6 and -2.9 , respectively; this difference was statistically significant on T test ($P = 0.011$). On the other hand, there was a clinically significant difference among the osteoporotic, osteopenic and normal patients in the mean of the number of

Table 2 Relation of cigarette smoking and bone mineral density in 42 hemophilia patients

	Mean $\pm$ SD	P value
Number of smokers (%)	12 (28.6 %)	
Number of heavy smokers (%)	6 (14.4 %)	
Mean T-score ($\pm$ SD) in <10 packs/year smokers	-1.6 (± 1)	0.011*
Mean T-score ($\pm$ SD) in ≥ 10 packs/year smokers	-2.9 (± 1.3)	
Mean ($\pm$ SD) of cigarette smoking in osteoporotic patients	8.3 (± 15.1)	0.088**
Mean ($\pm$ SD) of cigarette smoking in osteopenic patients	2.1 (± 4.6)	
Mean ($\pm$ SD) of cigarette smoking in normal patients	0.8 (± 2.7)	

* Independent samples t test

** ANOVA

Table 3 Prevalence of osteopenia and osteoporosis at different locations among 42 hemophilia patients (based on T-scores according to the WHO criteria)

Status	Location	Number (%) (CI 95 %)
Osteopenia	Total spine	19 (45.2) (30.2–60.3)
	Left femoral neck	13 (31) (17–44.9)
	Right femoral neck	15 (35.7) (21.2–50.2)
Osteoporosis	Total spine	10 (23.8) (10.9–36.7)
	Left femoral neck	6 (14.3) (3.7–24.9)
	Right femoral neck	5 (11.9) (2.1–21.7)

smoked cigarettes on the one way ANOVA test; probably due to small sample size or wide variation in the amount of smoking, this last relation was not statistically significant ($P = 0.088$). Table 2 summarizes the data about cigarette smoking and BMD.

Five patients (5/42, 11.9 %) had significant alcohol intake regarding BMD (>2 drink/day). Since 66.7 % (28) of the responders had selected “I don't like to answer this question” in response to a question on their status regarding the consumption of alcohol, therefore, this variable could not be further interpreted.

BMD values are shown in Table 1. Overall, according to the current WHO criteria, 45.2 % (19/42) (95 % CI 30.2–60.3 %) of the patients in this study had osteopenia and 28.6 % (12/42) (95 % CI 14.9–42.2 %) had osteoporosis in the spine and/or femur (Table 3).

Two patients had a history of fracture with minimal trauma; one patient (21 years old) at the left femur with low BMD (T-scores -1.7 at the spine and the right femoral neck) and the other (45 years old) at the forearm with normal T-scores at the spine and the femurs.

Discussion

As measurement of BMD by DEXA is a powerful predictor of fracture [5], therefore we used it in the present study. Overall, 73.8 % (31/42) of the patients had low BMD at their spine and/or femur.

Larijani et al. [2] reported the first study about normative BMD in Iran in 553 randomly selected normal people. They categorized the participants according to their sex and decade of age. They reported 9.4 and 3.1 % osteoporosis in the spine and the left femur of male participants aged 20–69 years, respectively, which are lower than those of our patients (23.8 and 14.6 %, respectively; both used WHO T-score criteria). Comparison of the BMD of our participants in each decade with the above normal population showed that our patients' mean BMDs were lower in the third and fourth decades of life and the same in older ages in both spine and femur. Although the means of height of our patients were comparable with those of the mentioned normal population, their weights were lower. This low BMD in young patients implies some risk factors other than general population and raises significant concern in active age group.

Karimi et al. [17] found significant low BMD at spine and femur in a group of 55 (16–35 years-old) hemophilia patients in a case–control study in Southern Iran. They also found correlation between severity of arthropathy and low BMD.

Studies have shown that age, physical activity, serum level of sex hormones, height and weight, BMI, corticosteroid use, calcium intake, serum vitamin D level, alcohol consumption and cigarette smoking are related to BMD in general population [2, 4, 6, 10]; low physical activity, height, weight, and BMI, as well as the positivity of HCV and HIV have been correlated to low BMD in hemophilia patients [3, 8–10].

We found only cigarette smoking to be significantly related to low BMD, and more importantly, there was a correlation between the amount of smoking and severity of bone mineral loss and vice versa.

There was not any correlation between HIV or HCV seropositivity and low BMD, despite previous studies [3, 10]. In the only study in Iranian hemophilic patients, Karimi et al. [17] also did not find any correlation between HCV and low BMD.

We could not find any correlation between physical activity and low BMD ($P = 0.35$), probably due to our patients' misinterpretation of their activities [3, 10, 18].

Khawaji et al. [19] found that only intensity and duration of vigorous physical activity in young patients were significantly related to bone mass development and that this relation is minor in adulthood.

Our study showed low weight and low BMI in hemophilia patients as compared to normal population. However, we did not find any statistically significant correlation of weight, BMI or age with low BMD [2, 8–10]. In a recent meta-analysis, Iorio et al. [20] did not find any correlation between low BMD and BMI or HCV in severe hemophilia patients.

Abdelrazik et al. in a study of young severe hemophilia patients in Egypt found a significant difference in their BMD compared to the matched controls. Age and body size had no effect on this difference; however, the patients with more established hemophilic arthropathy had the lowest BMD [21].

The lifetime risk of osteoporotic fracture in men is 13 %, which increases dramatically after 75 years of age [4]. Ghosh et al. [22] in a large study on 500 hemophilia patients in India, reported 4.4 % fracture rate. Similarly we found 4.8 % (2/42) fracture rate in 21 and 45 years old men.

As hemarthrosis is the initiating event for arthropathy, immobility and consequent osteoporosis, it appears that prophylactic factor replacement and control of risk factors such as smoking are good preventive measures against osteoporosis.

On the other hand, fracture in hemophilia patients is troublesome due to the need for close cooperation of orthopedist, hematologist and physiotherapist in the patient management [3]; therefore, further inquiry about the risk factors in any patient and even surveillance of bone mineral densitometry are warranted.

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