Original Article

Osteoporosis in Patients With Hemophilia: Single-Center Results From a Middle-Income Country

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Abstract

Increased number of patients with hemophilia have been identified to have osteoporosis at early ages. Low bone mineral density in the setting of hemophilia has been associated with decreased mobility, sedentary life style, on demand treatment or delayed prophylaxis, low body weight and viral infections. The aim of this study was to investigate the impact of hemophilia on bone health of adult patients living in a middle income country. A total of 61 adult patients with hemophilia who were followed at the Hematology Department of Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa were consecutively included in this study. Bone health of the patients was assessed using the bone mineral density (BMD) and vitamin D levels. Z and t scores are used for evaluation of BMD in patients with hemophilia aged < 50 and $\geq$ 50 years, respectively. Information on treatment and co-morbidities including viral diseases were obtained from the medical files of the recruited patients. Bone mineral density was found normal in 30, and low in 29 patients. Vitamin D levels were below 20 ng/ml in 46 patients. No significant relationship was found between the severity of hemophilia and bone density. Vitamin D levels were significantly lower in patients who had a history of joint intervention. Neither annual bleeding rate nor the treatment modality (on demand versus prophylaxis) were associated with the bone mineral density and vitamin D levels. Annual factor consumption was higher in patients whose bone mineral densities was low both in femoral and lumbar regions. The results of this study depicting the situation of adult hemophilia population from a middle income country show that bone mineral density and vitamin D levels were decreased in a considerable amount of patients at early ages.

Keywords

arthropathy, bone mineral density, hemophilia, hepatitis b, osteoporosis

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Introduction

Hemophilia is a rare X-linked inherited coagulation disorder mainly characterized by bleeding into the weight bearing joints (knee, elbow, and ankles).[1] It results from mutations in factor VIII (FVIII, hemophilia A) or factor IX (hemophilia B) genes leading to partial or complete deficiency of the related clotting proteins.[2] Patients with severe hemophilia defined as those having clotting factor activity levels of 1% or less tend to bleed more often. They usually acquire extensive hemophilic arthropathy early in their life following recurrent bleeds into the joints when treated with "on demand" factor replacement therapy.[3] It has been shown by randomized controlled studies both in children and in adults that development of hemophilic arthropathy can be prevented or at least be delayed by regular prophylactic factor replacement. The earlier the prophylaxis begins, the better is the outcome with regard to joint health.[4]

Osteoporosis is a metabolic bone disease characterized by low bone density, impaired bone architecture, and increase in bone fragility.[5] Recurrent intra-articular bleeds which

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frequently occur early in the childhood in patients with severe hemophilia receiving insufficient factor replacement usually results in hemophilic arthropathy. This, in turn, leads to frequent episodes of immobility and lack of weight-bearing exercises, making it difficult for the hemophilic patient to optimize his peak bone mass and cause a decline in bone mineral density (BMD).[6]

Furthermore, factors such as infections with hepatitis C virus (HCV) or human immunodeficiency virus (HIV),[7] inability to get sufficient sunlight in association with a sedentary lifestyle, and so on have also been held responsible for decreased bone mass in hemophilia.[8] In addition, development of target joints have been associated with an increased risk of falling and fracture.[9] In a study conducted by Gerstner et al, it has been found that 27% of hemophilia patients have osteoporosis while 43% of them have low BMD.[10] For the prevention of osteoporosis in hemophilia patients, prophylactic factor replacement therapy, calcium and vitamin D replacement, physical exercise, and quitting smoking and alcohol are recommended.[11] The aim of the present study was to investigate the impact of the bleeding disorder on bone health in patients with hemophilia.

Materials and Methods

Sixty-one adult patients with hemophilia A and B who were followed at the Hematology Department of Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa were consecutively included in this study. Data on the most recent calcium, parathormone, and vitamin D levels; mode of factor replacement therapy; factor levels; dose and total amount of factor concentrate consumed during the last 12 months; number of bleeding episodes in the preceding 12 months; dual-energy X-ray absorptiometry history of joint surgery and/or radioactive synovectomy therapy; comorbidities; serologic status for hepatitis B; hepatitis C; and HIV were collected from patient files.

Bone health of the patients was assessed using the BMD and vitamin D levels. *Z* and *t* scores are used for evaluation of BMD in patients with hemophilia aged < 50 and ≥ 50 years, respectively. A *Z* score of ≥ −2 indicated normal BMD, while values < −2 designated low BMD. For the *t* score normal and low values were ≥ −1 and < −1, respectively. Low BMD included both osteopenia and osteoporosis. Furthermore, patients were categorized according to the site of BMD measurement into 4 groups: those with normal BMD (group 1), patients with a low BMD both in femur and lumbar area (group 2), patients with an isolated low femur BMD (group 3), and patients with an isolated low lumbar BMD (group 4). Patients were also divided into 2 groups according to their vitamin D levels being ≥20 and <20 ng/mL.

Statistical Analysis

SPSS version 22.0 Statistical package software (SPSS, Chicago, Illinois) was used to run the statistical analysis. Pearson χ^2 test and Fisher exact test were used when comparing parametric data. Kruskal-Wallis test and Mann-Whitney *U* test were used for the evaluation and comparison of nonparametric data. Results were evaluated at the 95% confidence interval and with the significance level of $P < .05$.

Table 1. General Features of the Cohort.[a]

	n (%)
BMD	
Normal	30 (50.8)
Low BMD	29 (49.2)
Total	59 (100)
Hemophilia	
Hemophilia A	51 (83.6)
Hemophilia B	10 (16.3)
Factor level	
Factor level < 1	49 (80.3)
Factor level > 1	12 (19.6)
Hemophilia severity	
Severe 0-1	49 (80.3)
Medium 2-5	11 (18)
Light >5	1 (1.6)
Bleeding in the last 1 year	
Absent	23 (37.7)
Present	38 (62.2)
Hepatitis B	
Absent	49 (80.3)
Present	12 (19.6)
Hepatitis C	
Absent	42 (68.8)
Present	19 (31.1)
Treatment modality	
On demand	16 (26.2)
Prophylaxis	45 (73.7)
Vitamin D level	
>20 ng/mL	12 (20.6)
<20 ng/mL	46 (79.3)
Total	58 (100)
Joint replacement	
Absent	50 (81.9)
Present	11 (18.0)
Radioactive synovectomy	
Absent	50 (81.9)
Present	11 (18.0)
Any intervention to intraarticular	
Absent	42 (68.8)
Present	19 (31.1)

[a] n = 61.
Abbreviation: BMD, bone mineral density.

Results

A total of 61 male adult hemophilia patients were included in the study. Data on patient characteristics were given in Tables 1 and 2. Median age of the patients was 37.8 years (range: 20-63). Forty-nine of the 61 patients were severe hemophiliacs, while 11 were moderate hemophiliacs, and 1 had mild hemophilia. Fifty-one and 10 patients were diagnosed with hemophilia A and B, respectively. Sixteen patients were treated on

Table 2. Patient Characteristics.

	Number of Patients	Patients Lost at Follow-Up	Average	SD	Range	Lower Limit of Normal Range	Upper Limit of Normal Range
Age	61	0	37.8	11	43	20	63
BMI	54	7	25.06	3.7	18	17	35
Weight	54	7	75.4	12.8	55.0	50	105
Bleeding in the last 1 year	61	0	2.2	4.3	20	0	20
Hemoglobin	31	30	14.3	1.57	7	8,9	16
Calcium	58	3	9.58	0.9	7	9	16
Magnesium	47	14	2	0.3	2	2	4
Fosfor	33	28	3.05	0.5	3	2	4
Parathyroid hormone	50	11	43.3	17.6	91	20	111
Alkaline phosphatase	56	5	87.3	23.8	133.0	44	177
Smoking (package/year)	27	34	15.7	10.9	39.0	1	40
Initiation of prophylaxis (years)	45	0	31.3	9.9	37	16	53
Amount of units per kg	50	11	1981	941	3627	213	3840
Amount of factor taken in the last year (unit)	57	4	14 8551	57 601	208 000	16 000	224 000

Abbreviations: BMI, body mass index; SD, standard deviation.

demand, while the rest received prophylactic factor replacement therapy. The mean age for initiation of prophylaxis was 31.3 years. Twenty-three patients did not have any intra-articular and/or extra-articular bleeding in the preceding 12 months. There was a history of at least one surgical joint intervention in 19 patients, including 11 joint replacement surgeries and 11 radioisotope synovectomies. Bone mineral density was found to be normal in 30 patients (50.8%) and low in 29 patients (49.2%). Of the 29 patients, an isolated low femoral BMD was found in 18 patients, while in 5 patients, there was an isolated low lumbar BMD. Six patients had low femur and lumbar BMD. Vitamin D levels were higher than 20 ng/mL in 12 patients and below 20 ng/mL in 46 patients. Chronic hepatitis B and C infection were present in 12 and 19 patients, respectively. There were no patients with positive HIV serology.

Association of BMD with clinical and laboratory findings, as well as treatment modality, is summarized in Table 3. Based on these data, no significant correlation was found between the severity of hemophilia and the BMD ($P = 0.899$). Of those with a normal BMD, 25 (83.3%) patients had severe hemophilia and 5 (16.6%) had moderate hemophilia. Twenty-two (75.8%) patients with a low BMD were severe hemophiliacs, 6 (20.6%) had moderate, and 1 (3.4%) had mild hemophilia. No significant relation was found between BMD and the number of bleeding episodes within the 12 months prior to study enrollment ($P = .592$). There was a significant correlation between chronic hepatitis B infection and BMD ($P = .045$). Chronic hepatitis B infection was detected in 3 (9.7%) of the patients with normal BMD and in 9 (30.0%) of low BMD patients.

Bone mineral density did not change in patients receiving on-demand or prophylactic factor replacement ($P = .602$). Factor consumption (U/kg/yr) within the last 12 months, when examined according to the site of low BMD, differed in groups 2, 3, and 4 being 3396 $\pm$ 543 U/kg/yr, 2110 $\pm$ 704 U/kg/yr,

Table 3. Association Between Bone Mineral Density and Clinical Parameters.

	Normal BMD (n = 30), n (%)	Low BMD (n = 29), n (%)	*P*
Hemophilia			
Hemophilia A	25 (83.3)	24 (82.7)	.720
Hemophilia B	5 (16.6)	5 (17.2)	
Hemophilia severity			
Severe 0-1	25 (83.3)	22 (75.8)	.899
Medium 2-5	5 (16.6)	6 (20.4)	
Light >5	0 (0.0)	1 (3.3)	
Bleeding in the last 1 year			
Absent	10 (33.3)	11 (37.9)	.923
Present	20 (66.6)	18 (62.1)	
Hepatitis B			
Absent	27 (90.0)	20 (68.9)	.045
Present	3 (10)	9 (31.0)	
Hepatitis C			
Absent	23 (76.6)	18 (62.0)	.350
Present	7 (23.3)	11 (38.0)	
Treatment modality			
On-demand	9 (30.0)	6 (20.6)	.602
Prophylaxis	21 (70.0)	23 (79.3)	
Level of D vitamin			
>20 ng/mL	4 (14.2)	8 (28.5)	.329
<20 ng/mL	24 (85.7)	20 (71.4)	
Joint replacement			
Absent	24 (80.0)	25 (86.2)	.388
Present	6 (20.0)	4 (13.7)	
Radioactive synovectomy			
Absent	23 (76.6)	25 (86.2)	.544
Present	7 (23.3)	4 (13.7)	
Any intervention to intraarticular			
Absent	20 (66.6)	21 (72.4)	.844
Present	10 (33.3)	8 (27.5)	
Complication associated with nonarticular bleeding			
Absent	11 (39.2)	12 (42.8)	1.0
Present	17 (60.8)	16 (57.1)	

Abbreviation: BMD, bone mineral density.

and 1308 ± 1068 U/kg/yr, respectively. Patients with normal BMD (Group 1) had a mean factor consumption of 1691 ± 869 U/kg/yr. Group 2 stood out to have significantly higher factor consumption among all.

No significant correlation was found between a low BMD and a history of joint intervention. Age was a more important determinant of bone health. Mean age of patients with low BMD (41.1 years) significantly differed from those with normal BMD (34.4 years; $P = .019$).

Mean body mass index (BMI) of the patients with normal BMD was found to be higher than that of the patients with low BMD ($P = .027$). Similarly, a significant relation was found between the mean weights and BMD of the patients ($P = .001$). Mean weight (81.58 kg) of patients with normal BMD was found to be significantly higher than the mean weight (70.15 kg) of patients with low BMD.

No statistically significant correlation could be shown between the BMD and vitamin D at study entry for levels above and below 20 ng/mL ($P = .329$). Vitamin D levels were found to be low (<20 ng/mL) in almost equal number of patients with normal (24 patients; 85.7%) and low BMD (20 patients; 71.4%). Regarding phosphorus, mean serum phosphorus levels (3.24 mg/dL) of the patients with normal BMD were found to be significantly higher than that (2.85 mg/dL) of the patients with low BMD ($P = .04$).

We observed an association of borderline significance between having a history of surgical joint intervention (joint replacement surgery + radioactive synovectomy) and vitamin D levels ($P = .040$). Thus, the number of patients with surgical joint interventions was significantly higher in the group of patients with vitamin D levels below 20 ng/mL.

Discussion

Musculoskeletal complications, in particular joint disease, constitute the main disease burden in patients with severe hemophilia. The aim of the present study was to evaluate the impact of hemophilia on bone health. A statistically significant association was found between BMI, body weight, and BMD of the patients. Patients with decreased BMD tend to have low BMI and body weight. Our results are in line with those of Gerstner et al and Kempton et al, who similarly found a linear correlation between BMD and BMI.[10,12] In a study by Roushan et al conducted on 42 moderate and severe hemophilia patients, the BMI and weight of the patients were lower than the normal population. However, no correlation between low BMD and low body weight and low BMI could be demonstrated.[13] The association of body weight and osteoporosis has not been fully clarified. One of the suggested mechanisms include the increased mechanical load on the bone induced by high body weight leading to increased bone mass which occurs in response to this load.[14] On the other hand, adipocytes enhance peripheral conversion of androstenedione to estrogen, which help maintain bone health. Furthermore, hormones like leptin, insulin, preptin, and amylin promote bone development by interfering with osteoblast and osteoclast activity.[15]

In our cohort, BMD was normal in 30 patients and low in 29 patients. We compared the amount of factors per weight used within the past year in patients with low and normal BMDs and found that in a subgroup of patients who had a low femur and lumbar BMD, there was significantly higher factor consumption. Increased factor consumption in patients with decreased BMD can best be explained by the increased bleeding rate in those patients. In the study performed by Naderi et al, no correlation was found between factor consumption and BMD.[16] However, in that study t scores instead of Z scores were used, despite the fact that most of the recruited patients were under 50 years of age. Current guidelines on osteoporosis recommend usage of Z scores for evaluating BMD in patients under 50 years of age.[17]

The comparison of BMD scores of patients with and without a history of a joint replacement surgery and/or radioactive synovectomy did not result in any statistically significant difference. In addition, BMD was not found to be correlated with the annual joint bleeding rate. Wallny et al analyzed 62 patients with severe hemophilia in a study and reported that the BMD decreased as the number of affected joints and severity of the arthropathy increased.[18] Another study conducted by Katsarou et al found a significant correlation between the BMD and hemophilic arthropathy in 90 hemophilia patients including 80 with severe hemophiliacs.[19] Based on this finding, the authors speculated that the low BMD was a result of decreased physical activity and weight-bearing activities associated with hemophilic arthropathy. Although we found increased annual factor consumption in the subgroup of patients with low femur and lumbar BMD, we couldn't show a correlation between annual bleeding rate and BMD in general. This might be explained by the fact that 12 of 61 patients in our study were moderate hemophiliacs with a mild bleeding phenotype. Furthermore, in our study, the extend of joint disease was indirectly represented by the number of joint bleeds, while in the previous 2 studies, joint physical and radiological scores were used to evaluate the joint health. Physical joint health scoring could not be carried out in our patients due to unavailability of dedicated physiotherapists at our center at the time of study.

In our study, 45 patients received prophylactic factor replacement therapy while 16 patients were treated on demand. No statistically significant difference could be shown between the group of patients on prophylaxis and those receiving on-demand treatment with regard to BMD. Similarly, Khawajı et al compared the BMD of 26 patients with severe hemophilia who were on prophylaxis to 16 rarely bleeding patients with moderate hemophilia, who received on-demand treatment and could not identify any significant difference. These results suggest that prophylactic factor replacement therapy in severe hemophiliacs might contribute to long-term preservation of BMD.[20] In another study, Mahmoud Ghaniema et al compared 20 patients with hemophilic arthropathy to another 20 patients without hemophilic arthropathy and could not demonstrate a statistically significant difference in calcium levels and BMD between 2 groups.[21] The number of adult patients with severe

hemophilia receiving prophylaxis has been steadily increasing in Turkey after the reimbursement of prophylactic factor replacement therapy in 2005. Almost two-third of severe hemophilia patients at our center are on prophylaxis and patients who receive on-demand treatment are usually those who bleed less frequently and therefore prefer to be treated on demand. Furthermore, all patients included in this study were on tertiary prophylaxis, that is, they have established joint diseases at the time when they started prophylaxis. Therefore, our cohort did not seem to provide a useful base for the evaluation of the impact of prophylaxis on BMD. For this, large-scale, multicenter trials comparing prophylactic and on-demand treatment strategies were conducted in a homogeneous population of patients with severe hemophilia.

Although immobility, lack of weight-bearing exercises, HCV, and HIV have been held responsible for decreased BMD, some authors suggested that FVIII deficiency, itself, may directly affect the BMD. Liel et al found that FVIII knockout male mice had lower BMD and cortical bone mass compared with their wild type, independent of hemarthroses, physical activity, and medical comorbidities.[8] Recht et al similarly showed that FVIII knockout mice have decreased cancellous bone fractional area, trabecular density, and trabecular separation, but no difference in mineralization when compared with the control group.[22]

In our cohort, hepatitis B virus incidence was found to be significantly higher in the group with the low BMD ($P = .045$). In a study conducted by Schiefke et al, the BMD was significantly lower in patients with noncirrhotic hepatitis B.[7] Literature rather focuses on the correlation between the BMD and HCV and HIV in hemophilia patients. Wallny et al found a correlation between the low BMD and hepatitis C in hemophilia patients.[18] But in another study conducted by Yucel et al, we could not find a correlation between BMD and hepatitis C infection in hemodialysis patients.[23] This could be accounted for the fact that Turkey is located in the intermediate endemic region, hepatitis B surface antigen (HBsAg) prevalence is 2% to 8%, but The United States, Northern Europe, Australia, and parts of South America located in the low endemic regions, and HBsAg prevalence is less than 2%.[24]

Our study could not demonstrate any significant correlation between the vitamin D levels and the BMD ($P = .329$). These results contradict with the study conducted by Anagnostis et al who reported a correlation between low vitamin D levels and the low BMD.[25] In another study conducted by Eldash et al, on the other hand, it was found that the vitamin D level and the BMD of the hemophilia patients were significantly lower, compared to the healthy patients in the control group.[26] Given that vitamin D levels in healthy, young male Turkish population are not known, it is difficult to draw any conclusion with regard to the interaction of vitamin D levels and BMD in our cohort.

Interestingly, however, 18 of our 46 patients with a vitamin D level <20 ng/mL had a history of joint intervention, while this was the case in only 1 out of 12 patients with a vitamin D level of > 20 ng/mL ($P = .040$). Based on the literature, no data were found about the vitamin D level in the patients with a history of joint intervention (radioactive synovectomy and/or joint replacement surgery). The low vitamin D results in hemophilia patients have been associated with sedentary lifestyle, restricted exposure to sunlight, and decreased physical activity. Given that patients with a history of joint intervention usually represent hemophiliacs with severe hemophilic arthropathies, the decreased of physical activity and limited exposure to sunlight might underlie the vitamin D deficiency. Even though Turkey is situated in a location with plenty of sunlight geographically, the underlying cause of the vitamin D deficiency in the majority of patients could be associated with their sedentary lifestyle based on their lack of physical activity.

Conclusions

Our study conducted in a cohort of mainly severe hemophilia patients living in a middle-income country in which prophylactic factor replacement therapy has been introduced in 2005 demonstrates, mostly in line with the current literature, that BMD was low in a typically young male population. Increased factor consumption has been observed in patients with low BMD and decreased vitamin D levels were found to be associated with a history of joint intervention. Furthermore, hemophilia patients with chronic hepatitis B in our cohort had lower levels of BMD. These results confirm the importance of regular screening of bone health in adult people with hemophilia, especially if they have established hemophilic arthropathy restricting their daily mobility.

In the very near future, early introduction of prophylaxis utilizing new treatment alternatives, including extended half-life factor concentrates or nonfactor treatments such as emicizumab will result in higher and more stable trough levels which would allow to better control the joint bleeds and prevent hemophilic arthropathy. This would not only lead to a more flexible and "normalized" physical activity but also to more healthy bones. Hence, increased mobility and less restricted daily life might help preventing early occurrence of osteoporosis in adults with hemophilia by increasing the mechanical load on bones and exposure to daylight.

Declaration of Conflicting Interests

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