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Effects of Treatment Model on Bone Metabolism in Patients with Severe Hemophilia A

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Abstract

Improving bone health and preventing osteoporosis is an essential approach for hemophilia patients. Regarding precautions, the treatment model may affect bone health. To detect the effect of a treatment model (prophylaxis/on-demand treatment) on bone metabolism in patients with severe hemophilia A was the primary aim of this study. The biochemical markers of bone metabolism and bone mineral density were obtained from the patients enrolled in the study. No statistically significant differences were found between the groups due to the limitations of the prophylaxis group, such as adaptation problems, personal differences, and type of prophylaxis.

Keywords: Hemophilia, bone health, osteoporosis in hemophilia

Introduction

Hemophilia A (HA) is a rare coagulation disorder caused by factor VIII (FVIII) deficiency owing to an X-linked recessive inheritance in the genes encoding FVIII. Approximately, 85% of hemophilia patients are diagnosed with HA, while the remaining is hemophilia B, which is caused by factor IX deficiency. Hemophilias can be categorized into three groups according to factor levels: Mild for factor levels >5-40 IU/dL, moderate for 1-5 IU/dL; and severe for factor levels <1 IU/dL.[1-3]

Regarding the developed treatment options, the estimated lifespan is similar to that of the normal population. Therefore, comorbidities and prevention are increasing challenges in the management of hemophilia. Ensuring normal bone metabolism and bone mineral density (BMD) is the most pivotal of all. Low BMD can culminate in impaired bone strength and an increased risk of fracture due to fragility. In the literature, 27% of patients with hemophilia were reported to have osteoporosis, whereas 43% had osteopenia.[4]

This study aimed to evaluate the effect of prophylactic treatment on bone metabolism and osteoporosis by

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comparing biochemical bone markers and BMD in patients with severe HA who were on prophylaxis and on-demand treatment.

Material and Method

A total of 36 hemophilia patients who were being followed-up by the department of pediatric hematology in Ege University Faculty of Medicine, were enrolled in this study. Ethical approval was obtained from the Clinical Research Ethics Committee of Ege University Faculty of Medicine (decision no: 15-7/20 date: 27.07.2015). In addition, the family and/or patients signed an informed consent form. Of these patients, 24 were on prophylaxis and 12 were on on-demand treatment. Age, height, and body weight of the patients were recorded, and body mass index (BMI) was calculated using these data. Biochemical parameters related to bone metabolism [calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), calcitonin, and 25(OH) vitamin D3] were evaluated in blood samples, and BMD was measured using the dual-energy X-ray absorptiometry method. The biochemical values of the patients were evaluated based on the normal values established in the literature according to their ages.[5]

Statistical Analysis

Statistical Package for Social Sciences v.20 was used to evaluate the laboratory results. Descriptive methods were used to calculate demographic data. The results are presented as mean ± standard deviation within 95% confidence interval. The lower and upper limits of the data in the study groups were calculated using the Student t-test for a single group. Pearson and Spearman correlation analysis were used to examine the relationship between variables, while p values <0.05 were considered statistically significant.

Highlights

- Patients with hemophilia are at increased risk of impaired bone metabolism and the development of osteopenia and/or osteoporosis.
- The reasons beyond impaired bone health and precautions are still highly studied. Regarding precautions, the treatment model may affect bone health. Patients receiving prophylaxis are expected to have higher bone mineral density and better bone health.

Results

Of the 36 male patients enrolled in the current study, 24 were on prophylaxis and 12 were on-demand treatment. The mean age of whole study group was 16.5±7.1 years, whereas the mean age of the prophylaxis group was 17.46±6.1 years (8-30 years), and that of the on-demand therapy group was 16±8.6 years (9-30 years).

The mean body weight of the prophylaxis group was 63.2±18.7 kg (29-100 kg) whilst of the on-demand group was 48±19.2 kg (22-72 kg). The difference between the groups was statistically significant (p=0.047). Likewise, the mean BMIs was 22.4±4.1 kg/m^2 (14.8-29.2) and 18.4±2.6 (14.7-23.1) for prophylaxis and on-demand groups, respectively. BMI was significantly higher in the prophylaxis group (p=0.004). A comparison of the laboratory results between the two groups is presented in **Table 1**. No statistically significant differences were observed between groups in terms of laboratory results.

Regarding the L1-L4 Z-scores in the prophylaxis group; osteoporosis was detected in 5 cases (20.8%), osteopenia in 6 cases (25%), and 13 cases (54.2%) patients had normal L1-L4 BMD values. Considering the femoral neck Z-scores, osteoporosis was detected in 4 cases (16.7%) patients, osteopenia in 11 cases (45.8%) patients, and normal BMD values in 9 (37.5%) patients. In the on-demand treatment group, assessing the L1-L4 Z-scores, osteoporosis was detected in 3 cases (25%), osteopenia in 3 cases (25%), and normal BMD was observed in 6 cases (50%). By evaluating the femoral neck BMD Z-scores, osteoporosis was detected in 1 case (8.3%) patient, osteopenia was detected in 3 cases (25%), and 8 cases (66.7%) patients had normal BMD values. Vitamin D levels were found to be “deficient or insufficient” in ≥50% of patients in both groups; only 8 (33.3%) patients in the prophylaxis group and 6 cases

Table 1. *Comparison of laboratory findings between groups receiving prophylaxis and on-demand treatment*

	Prophylaxis group (n=24)			On-demand group (n=12)			P value
	N	D	I	N	D	I	
Ca	N=21 (87.5%)	N=2 (8.3%)	N=1 (4.2%)	N=12 (100%)	0	0	0.67
P	N=21 (87.5%)	N=2 (8.3%)	N=1 (4.2%)	N=12 (100%)	0	0	0.53
ALP	N=20 (83.3%)	N=2 (8.3%)	N=2 (8.3%)	N=12 (100%)	0	0	0.42
PTH	N=20 (83.3%)	0	N=4 (16.7%)	N=12 (100%)	0	0	0.14
Calcitonin	N=22 (91.7%)	0	N=2 (8.3%)	N=9 (75%)	0	N=3 (25%)	0.21
	Prophylaxis group (n=24)			**On-demand group (n=12)**			
	Deficient	**Insufficient**	**Normal**	**Deficient**	**Insufficient**	**Normal**	
25 (OH) Vit. D3	N=7 (29.2%)	N=9 (37.5%)	N=8 (33.3%)	N=2 (16.7%)	N=4 (33.3%)	N=6 (50%)	0.09

Ca; Calcium, P; Phosphorus, ALP; Alkaline phosphatase, PTH; Parathormone, 25(OH) Vit. D3; Vitamin D, N; Normal, D; Decreased, I; Increased

(50%) in the on-demand group had normal vitamin D levels according to age. In the remaining cases, vitamin D levels were found to be "deficient or insufficient" in 16 cases (66.7%) patients in the prophylaxis and 6 cases (50%) patients in the on-demand group. In **Table 2**, data on BMD measurements is presented comparatively between the two groups.

Discussion

Survival has increased significantly in patients with hemophilia due to advanced treatment modalities, such as the initiation of primary prophylaxis at an early age and accessibility to factor preparations. In addition to survival, improvements in lifestyle and quality have been achieved. Consequently, preventing comorbidities and improving quality of life are hot research topics. Protecting bone health is the most essential task.

Soft tissue synthesis, epiphyseal bone growth, and bone remodeling occur simultaneously in childhood. BMD increases throughout childhood and adolescence, reaching a plateau on average in the twenties and reaching peak bone mass.[6] Low BMD is related to increased resorption and decreased formation of bone, resulting in impaired bone mass. The worldwide prevalence of osteoporosis among men is 11.7%; thus, research is needed on this issue.[7]

Osteopenia and osteoporosis are reported to be detected in patients with hemophilia at early ages before adolescence, at 12 years of age.[6] In a recently published meta-analysis, regardless of age, region, or economic status, hemophilia patients have been demonstrated to have low BMD, about four times higher than healthy controls.[7] Many factors have an impact on peak bone mineral mass, including normal body weight and weight-related physical activity as the strongest predictors found in studies conducted in healthy children and adolescents.[6-8] Certain predictors of low BMD should be determined, and precautions should be taken.

In this study, body weight and BMI in the prophylaxis group were significantly higher than the on-demand group. However, no significant difference was detected between the two groups in terms of BMD, vitamin D level, and other laboratory markers. The mean BMI of the on-demand group was 18.4 kg/m^2, which is classified as underweight. An increased risk of fracture has been reported in previous studies.[9,10] Nevertheless, the mean BMI of the prophylaxis group was normal. Based on this finding, the estimated low BMD and related fracture risk can be considered to be decreased in the prophylaxis group.

Regarding the laboratory markers evaluated in this study; Ca, P, ALP, and PTH levels were within normal ranges according to age in the on-demand group. Comparing the two groups, no statistically significant difference was detected in terms of laboratory results. Elevated ALP levels were detected in 2 cases (8.3%) in the prophylaxis group. One of these cases presented with osteoporosis at L1-L4 BMD and osteopenia at the femoral neck, whereas he had normal laboratory results except for ALP level. Similarly, another patient had osteopenia in the femoral neck, despite normal laboratory results. Elevated PTH levels were detected in 4 cases (%16.7) in the prophylaxis group. Regarding PTH acting as a stimulator of osteoclast differentiation via osteoblasts and causing bone destruction, elevated PTH levels suggest that the balance between bone formation and resorption is disturbed in favor of bone destruction. Osteoporosis was detected in one of these patients, osteopenia in 2 cases, and normal BMD in one patient. Cases with normal BMD results can be detected early by PTH elevation.

The primary function of vitamin D is not only to ensure Ca absorption from the intestines but also to stimulate osteoclastogenesis and increase osteocalcin production by osteoblasts *in vivo*. In our study, no statistically significant difference was observed between the two groups regarding 25(OH) vitamin D3 levels. Nonetheless, recent studies showed that patients with hemophilia tend to have significantly lower vitamin D and BMD levels compared with healthy controls.[11,12] Low vitamin D levels can be associated with sustained immobilization and reduced sun exposure due to recurrent and frequent joint bleeding. Supporting this notion, Gamal Andrawes et al.[11] demonstrated a significant negative correlation between the vitamin D levels of children with severe HA and the Hemophilia Joint Health score. Although no significant difference was observed between the two groups, 61% (n=22) of our patients were found to have vitamin D deficiency and/or insufficiency, which is consistent with the literature. In the current study, no scale that assesses physical activity and joint health was used, which would be helpful in understanding the mechanism. Because vitamin D level is critical, patients with hemophilia should be tested for vitamin D deficiency regularly.

In the present study, contrary to expectations, no significant difference was identified between the groups in terms of BMD Z-scores. However, previous studies have revealed that the development of hemophilic arthropathy, which has been accused as the main cause of impaired bone health for a long time, can be prevented by prophylaxis initiated at an early age so that the factor concentration does not fall below 1%.[10] Therefore, the prophylaxis group is expected to have better BMD results. The reasons beyond these results can be attributed to differences in patients' personal characteristics and compliance with treatment. Apart from these issues, there can be problems regarding

Table 2. *Comparison of bone mineral density results in groups receiving prophylaxis and on-demand treatment*

	Prophylaxis group (n=24)			On-demand group (n=12)			P value
	Osteoporosis	Osteopenia	Normal	Osteoporosis	Osteopenia	Normal	
L1-L4	N=5 (20.8%)	N=6 (25%)	N=13 (54.2%)	N=3 (25%)	N=3 (25%)	N=6 (50%)	0.86
Femur neck	N=4 (16.7%)	N=11 (45.8%)	N=9 (37.5%)	N=1 (8.3%)	N=3 (25%)	N=8 (66.7%)	0.88

factor supply and regular use in prophylactic treatment. Although improvements have been made recently in this regard, many of the subjects developed a target joint before regular prophylaxis. Another finding in this regard was the mean prophylaxis time of our patients, which was 8.3±1.4 years (5-10), whereas the mean age of the patients was 17.46±6.1 years (8-30). From this perspective, none of the patients in the prophylaxis group were receiving “primary prophylaxis”. All patients were receiving “secondary prophylaxis” or even “tertiary prophylaxis” according to the new definition.[13]

Studies in the literature evaluating bone metabolism are increasing day after day.[2,4,6,14,15] Nonetheless, research in the pediatric era is still scarce. The primary objective is not only to define the mechanism but also to invent cures. The degree of arthropathy, number of affected joints, avoidance of weight-bearing exercise, and early-onset prophylaxis are the most studied underlying factors.[6,16,17] The number of affected joints and degree of physical activity were not elucidated in the current study, which is a limitation of the findings. In addition to these factors, the presence of liver disease caused by the hepatitis C virus (HCV) was found to be responsible for affecting the vitamin D metabolism in the liver.[18,19] However, data about the HCV are conflicting because some studies conducted with HCV-positive and-negative patients revealed no difference in osteoporosis development.[2,20] Another infectious agent that directly elevates bone destruction via increased cytokine levels is the human immunodeficiency virus (HIV). HIV also impairs vitamin D absorption by causing chronic diarrhea.[21,22] Because our patients were not HCV or HIV-positive in our study, no evaluation was made in this regard.

Apart from the aforementioned occasions, FVIII itself has been demonstrated to play a role in bone metabolism by affecting the receptor activators of the nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) pathways. The RANKL-OPG pathway plays a key role in bone resorption via osteoclasts.[23] RANK binds to its ligand RANKL to activate osteoclast proliferation and differentiation. This pathway is controlled by OPG, which negatively regulates signaling and thus controls osteoclast activity.[23,24] FVIII and the von Willebrand factor complex downregulate the RANK-RANKL connection and promote OPG activity, resulting in inhibited osteoclastogenesis.[24,25] In addition, FVIII stimulates thrombin production, which stimulates osteoblasts via its receptors.[26,27] Another mechanism was proposed after studies in FVIII-knockout mice. The levels of trabecular bone formation and bone formation markers such as N-terminal propeptide of type 1 procollagen were decreased.[28]

Study Limitation

The current study has some limitations, as mentioned in the text prior. First, none of the patients received primary prophylaxis. The mean prophylaxis time was only 8.3±1.4 years, whereas the mean age was 17.46±6.1 years (8-30). This is a major limitation of our study. In addition, compliance with prophylaxis treatment is another issue affecting bone health. The Hemophilia Joint Health score was not evaluated in this study, which could have provided information about the arthropathy status of the patients and led to a better analysis.

Conclusion

Patients with hemophilia have an increased risk of impaired bone metabolism and the development of osteopenia and/or osteoporosis. The reasons beyond this and precautions are hot research topics. In this study, low BMD values were detected, consistent with the literature. Larger-scale studies are needed to evaluate the effects of treatment type on bone health.

Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Ege University Faculty of Medicine (decision no: 15-7/20 date: 27.07.2015).

Informed Consent: In addition, the family and/or patients signed an informed consent form.

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Conflict of Interest: The authors declare no conflicts of interest.

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