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Original Article

A Single-Center Study of Bone Mineral Density in Adult Patients with Severe Hemophilia A in Correlation with Markers of Bone Metabolism

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Abstract

Introduction: Osteopenia and osteoporosis are well-known hemophilia A comorbidities. The pathogenesis of bone turnover alteration resulting in reduced bone mass includes impaired osteoblastic differentiation and disinhibition of RANKL-induced osteoclastogenesis as a result of a low FVIII level.

Aim: To evaluate the bone mineral density (BMD) in adult patients with severe hemophilia A and assess a possible correlation with the bone remodeling biomarkers OPG/RANKL, CTX-1, osteocalcin, and Vit D.

Materials and methods: 28 male subjects with severe hemophilia A and 33 age-matched controls were recruited. The biomarkers were tested with the ELISA assay and BMD with DEXA of the lumbar spine (LS) and total hip (TH).

Results: The patients had lower LS-BMD (−0.955±0.145 vs. 1.118±0.079, p=0.05) and TH-BMD (−0.840±0.147 vs. 0.951±0.075, p=0.05) than those of the controls. The TH T-scores were −1.41±0.91 vs. 0.4±0.49 (p=0.05) and the LS T-scores −1.16±1.046 vs. 0.14±0.72 (p=0.05). 66.6% of patients under 50 years had osteopenia and 8.3% had osteoporosis. Fifty percent of those over 50 years old had osteopenia and 20% had osteoporosis. We found significantly higher OPG levels (123.69±107.05 vs. 41.98±18.95, p=0.05) than that in controls and lower sRANKL levels (23.49±29.39 vs. 131.32±201.27, p=0.05) and sRANKL/OPG ratio (0.27±0.35 vs. 5.28±10.01, p=0.05) than those in controls. A positive correlation was found between sRANKL and the BMD T-score of lumbar spine (p=0.001) in the patient group.

Conclusions: sRANKL level and ratio can be used as predictors of low BMD.

Keywords

FVIII deficiency, osteoporosis, RANKL, OPG

INTRODUCTION

Severe hemophilia is a rare X-linked inherited coagulation disorder characterized by spontaneous bleeding into the weight-bearing joints. The condition is caused by mutations in factor VIII gene leading to complete deficiency of the related clotting protein. Patients usually acquire extensive hemophilic arthropathy early in their life following recurrent bleeds into the joints. As the population of patients with hemophilia (PWH) ages, healthcare providers must pay more attention to age-related comorbidities. Low bone mineral density (BMD) is one such co-morbidity.[1] It is considered a metabolic disease characterized by low bone density, impaired bone architecture, increase in bone fragility, and risk of fractures. Gerstner et al.[2] have found that 27% of hemophilia patients have osteoporosis while 43% of them have low BMD.

The meta-analysis of Iorio et al.[3] in 2010 and the systematic review and meta-analysis published by Paschou et al.[4] in 2014 confirmed the association between severe hemophilia and low BMD.

Men with hemophilia A exhibit a significant reduction in both lumbar spine (LS) and total hip (TH) BMD, which appears to begin in childhood. However, the relevant pathophysiology is not exactly known and both processes of bone resorption and bone formation could be hypothesized to be altered. Immobility due to hemophilic arthropathy and a lack of weight-bearing exercises, as well as HCV, HIV, low BMI, alcohol and tobacco use, have all been blamed for the decreased bone mass in those patients.[5]

Over the last few years, clinical and experimental evidence has indicated that the deficiency of FVIII leads to decreased BMD independent of hemarthroses, physical activity, and medical comorbidities, suggesting a novel effect for FVIII outside the coagulation system.[6] Liel et al.[7] found that FVIII knockout male mice had lower BMD and cortical bone mass than the wild-type controls. Recht et al.[8] similarly showed that FVIII knockout mice decreased cancellous bone fractional area and trabecular density. Aronovitch et al.[9] noted that thrombin exerted multiple effects on osteoblasts including induction of differentiation and inhibition of apoptosis as they express thrombin receptors. They hypothesized that the complete absence of factor VIII leads to deficient thrombin generation, resulting in ineffective thrombin-mediated signaling through protease-activated receptor 1 (PAR1) expressing endothelial cells. Lack of thrombin generation secondary to FVIII deficiency could be a cause of increased osteoclast activity.

There are several bone biomarkers found to be associated with specific bone processes and overall skeletal health – carboxy-terminal telopeptide of type I collagen (CTX-1) is a marker of bone matrix resorption and osteocalcin of bone formation, additionally receptor activator of nuclear factor-κB ligand (RANKL/osteoprotegerin (OPG) axis regulates osteoclast formation.[10] In 2009, Baud'Huin et al.[11] demonstrated in a murine model that the FVIII-vWF complex inhibited RANKL-induced osteoclastogenesis and enhanced the inhibitory effect of OPG leading to bone resorption. Recent papers[12-14] revealed the physical interaction between vWF and OPG, a powerful inhibitor of osteoclastogenesis and, therefore, of bone resorption. Thus, the two main mechanisms for low FVIII involved in bone turnover are direct mitogen effect on osteoblast and disinhibition of RANKL-induced osteoclastogenesis.

AIM

The aim of this study was to evaluate BMD in severe hemophilia A adult patients and to assess a possible correlation with the circulating remodeling biomarkers OPG/RANKL, CTX-1, osteocalcin, and Vit D levels.

MATERIALS AND METHODS

Patient's characteristics

The study was conducted on 28 male patients with severe hemophilia A They were followed up at the Bleeding Disorders Center, the Hematology Department at St George University Hospital in Plovdiv, Bulgaria. The patients were consecutively enrolled in the study. Their median age was 42.88 (range 18–71) years. The patient subgroups consisted of those <50 years - 16 patients in our cohort (11 PWH on-demand treatment and 5 on primary/secondary prophylaxis) and those above 50 years - 12 patients all of them receiving on-demand replacement therapy with FVIII products. In addition, 33 male age-matched (median age 38.69 years) healthy controls were recruited on a voluntary basis. Prior to midday, samples of fresh, frozen, citrated plasma were collected from 61 male participants, and the plasma was separated within 1 hour of collection. To eliminate the confounding effects of comorbidities, participants with the presence of an FVIII inhibitor, HIV infection, chronic hepatitis C or cirrhosis, renal dysfunction, and those on antiepileptic drugs were excluded. All subjects previously provided written informed consent and all procedures were approved by the local review board.

Measurement of plasma biomarkers

Levels of bone turnover markers were assessed using original ELISA Kits Immunodiagnostic. Those included RANKL, OPG, osteocalcin, CTX-1, and Vit D levels. They were tested in the Central Clinical Laboratory of St George University Hospital in Plovdiv.

Bone densitometry (DXA)

Dual Energy X-Ray Absorptiometry (DXA) is considered the gold standard for the diagnosis of osteoporosis worldwide and it is also recommended to assess BMD for men

at risk of osteoporosis. According to the World Health Organization classification system, for people over the age of 50 a T-score of less than −2.5 SD is defined as osteoporosis, between −1 and −2.5 SD as osteopenia, and >−1 SD is considered normal. For patients under the age of 50, a Z-score which is defined by comparing the expected BMD level in the age-matched healthy group is used of −2 SD or below is defined as osteoporosis, between −2 SD and −1 SD - osteopenia and above −1 SD is "normal".[15] In our study, a DXA scan of the lumbar spine (LS), and total hip (TH) was performed by a Hologic Discovery C (S/N 47070) scanner. Although BMD values (g/cm^2) were also collected, T- and Z-scores were primarily preferred in this study as they better reflect the comparisons related to age. Thus, patients were categorized into three groups – patients with normal BMD, patients with osteopenia, and patients with osteoporosis.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows v. 22. Values were expressed as mean ± standard deviation (SD) or median as appropriate. The student's *t*-test was used to compare two independent groups for normally distributed parameters, while Mann-Whitney U-test was used to compare two independent groups for non-normally distributed parameters. Spearman's rank correlation coefficient (*r*) was used to analyze the relationship between two continuous variables. $P<0.05$ was considered statistically significant.

RESULTS

The study population included 28 patients with severe hemophilia A. Their mean body mass index was 24.86±3.59 and no correlation was observed between BMI and BMD. Still, the mean weight of patients with normal BMD was 84.8 kg, which was found to be significantly higher than the mean weight (73 kg) of patients with low BMD. The control group included 33 male individuals with a mean BMI of 22.61±2.84.

The PWH had lower LS-BMD (−0.955±0.145 g/cm^2 vs. 1.118±0.79 g/cm^2, p=0.05) **(Fig. 1)** and TH-BMD (−0.840±0.147 g/cm^2 vs. 0.951±0.075 g/cm^2, p=0.05) than the controls .

The TH T-score in the group of patients was −1.41±0.91 vs. 0.4±0.49 (p=0.05) and the LS-T-score was −1.16±1.046 vs. 0.14±0.72 (p=0.05) **(Fig. 2)**.

These results show that 66.6% of the patients <50 years had osteopenia and 8.3% had osteoporosis **(Fig. 3)**. There was no statistically significant difference in the PWH subgroup of those <50 years between subjects on-demand vs. prophylaxis LS-BMD 0.894 g/cm^2 vs. 0.972 g/cm^2, TH BMD 0.882 g/cm^2 vs. 0.856 g/cm^2 at $p<0.05$.

Among those >50 years 50% had osteopenia and 20% had osteoporosis **(Fig. 4)**.

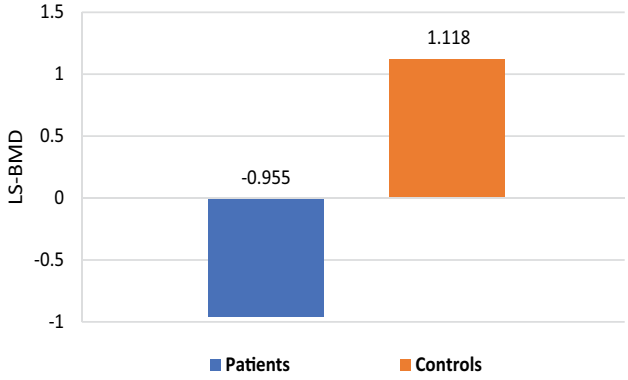

Figure 1. LS-BMD difference between the two groups.

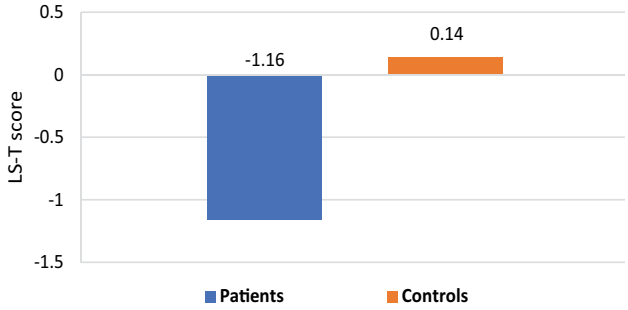

Figure 2. LS-T score difference between patient and control group.

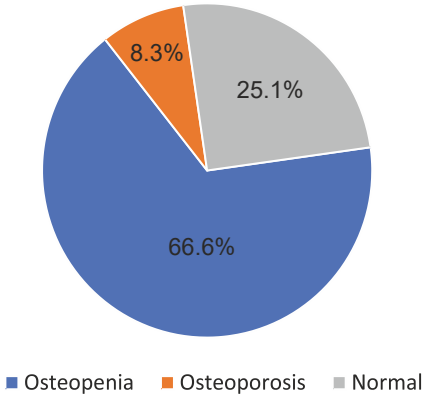

Figure 3. Distribution of patients <50 years by Z-score.

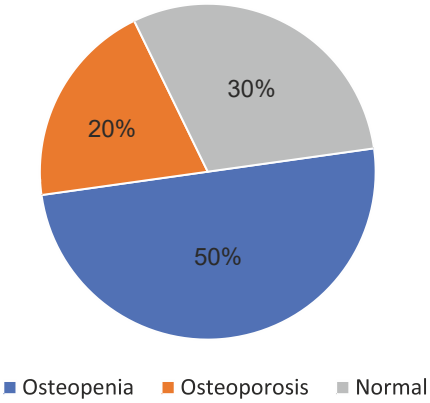

Figure 4. Distribution of patients >50 years by T-score.

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PWH showed significantly higher OPG levels (123.69±107.05 pg/ml vs. 41.98±18.95 pg/ml, p=0.05) **(Fig. 5)** and lower sRANKL levels (23.49±29.39 pg/ml vs. 131.32±201.27 pg/ml, p=0.05) **(Fig. 6)** than healthy male subjects. There was no difference in OPG and sRANKL values between patients on-demand vs. prophylaxis. sRANKL/OPG ratio was 0.27±0.35 vs. 5.28±10.01 (p=0.05).We found a strong positive correlation between sRANKL and LS-BMD as well as T-score of lumbar spine (p=0.001).

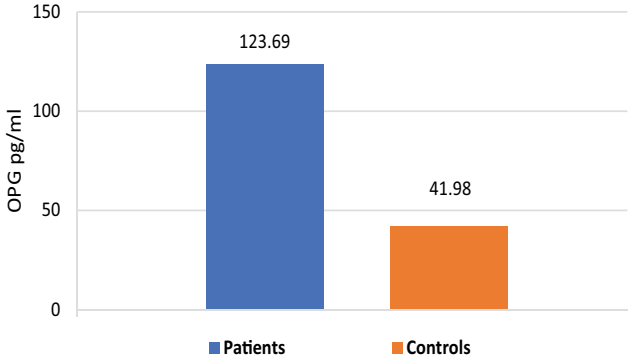

Figure 5. OPG levels in the two groups of subjects.

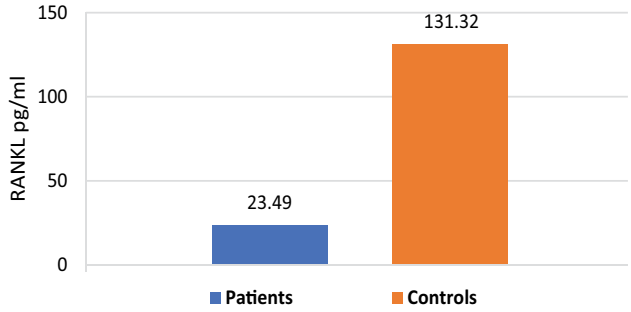

Figure 6. Difference in plasma levels of RANKL.

No statistically significant correlation could be demonstrated between BMD and Vit D for levels above and below 20 ng/mL, defined as deficiency (p=0.329).[16] Vitamin D levels were found to be low (<20 ng/mL) in 12 patients (42.86%) and in 8 (24.24%) healthy controls but almost equal number of those patients had normal and low BMD. There was no statistically significant difference between osteocalcin (1.45 ng/ml vs. 1.31 ng/ml) and CTX-1 levels (7170.29 vs. 6844.32 pg/ml) between the two groups and no correlation with BMD (p=0.432 and p=0.534).

DISCUSSION

The first study assessing bone density in patients with hemophilia was published by Gallacher et al.[17] in 1994, indicating that PWH had lower BMD (mean 0.19 g/cm^2 in LS and 0.13 g/cm^2 in FN) than the healthy population. Liver dysfunction and immobilization were defined to be the primary relevant factors leading to low BMD. From 1994 to 2007, there was not enough published data about bone health until Wallny et al.[18] shed light on osteoporosis in hemophilia as an underestimated comorbidity. Osteopenia and osteoporosis rates were 25.8% and 43.5%, respectively, confirming the high prevalence of the complication in this disease. According to a recent comprehensive report, osteoporosis in men over 50 years old in the European Union is 6.6%. Our study was the first in this country to confirm that patients with severe hemophilia A experience decreased BMD even in the young patient group <50 years – 74.9% .

In 2014, a systematic review and a meta-analysis including ten studies suggested that patients with hemophilia present a significant reduction in BMD of both LS and TH. However, there was no evidence that age, BMI, physical activity degree, or serologic status affected the BMD of LS.[4] In our study, we did not find any significant correlation between BMI and low BMD, still, PWH and low BMD display lower weight than patients with normal BMD. The observation is probably related to more affected joints and lack of exercise. Other mechanisms include increased mechanical load on the bone induced by high body weight. Adipocytes, on the other hand, enhance the peripheral conversion of androstenedione to estrogen, which helps to maintain the bone health. Furthermore, hormones like leptin promote bone development.[19]

Our results are consistent with some previous reports[19,20] and could not demonstrate a significant correlation between vitamin D levels and BMD (p=0.329), CTX-1, and osteocalcin.

Increased OPG levels (123.69±107.05 pg/ml vs. 41.98±18.95 pg/ml, p=0.05) found in patients from our center are most probably associated with compensatory response to increased bone resorption and excessive osteoclastic activity as stated before in a recent study conducted by Goldscheitter and Recht.[21] Another reason for the higher levels observed in our cohort is the fact that the vast majority received factor replacement therapy within 48 hours of sample collection which is in line with the results of a prospective study by Goldscheitter et al. in 2019 who found 6-fold increase of OPG and higher levels of OPG/RANKL ratio between day 1 and day 5 after administration of FVIII product.[22] These results confirm that FVIII interferes with this pathway and has a direct effect on bone turnover.

A strong positive correlation exists between sRANKL and BMD as well as T-score of lumbar spines (p=0.001). Our results confirm previous observations from Merchan E and Valentino L[23] who concluded that increased bone resorption is the leading mechanism for reduced bone mineral density in severe hemophilia A patients.

Limitations of the study are the absence of Hemophilia Activities List (HAL) self-reported physical activity, The International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT), HJHS scores, the small number of PWH on primary/secondary prophylaxis not enough to draw a comparison between the two groups and type of product. It is well known that prophylaxis is

not totally successful in preventing joint bleeding including microhemorrhage which may play a role in the inflammatory reaction leading to reduced BMD and osteoporosis. The evidence was supported by the observation that children with hemophilia also experience low BMD.[24] Further research is needed to fully understand the biological basis of reduced BMD in severe hemophilia A patients, to confirm the results, and to conduct larger studies including thrombin generation assays. Some of the novel non-factor replacement therapies claim to reach a level of 30% for thrombin generation and there are several studies for prophylaxis in children, which may prevent this complication in the future.

CONCLUSIONS

Our results confirm the importance of regular screening of the bone health of adult patients with hemophilia A and suggest using sRANKL level and ratio as predictors of low BMD.

Acknowledgments

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Одноцентровое исследование минеральной плотности костной ткани у взрослых пациентов с тяжёлой формой гемофилии А в корреляции с маркерами костного метаболизма

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Резюме

Введение: Остеопения и остеопороз являются хорошо известными сопутствующими заболеваниями гемофилии А. Патогенез изменения костного метаболизма, приводящего к уменьшению костной массы, включает нарушение дифференцировки остеобластов и растормаживание RANKL-индуцированного остеокластогенеза в результате низкого уровня FVIII.

Цель: Оценить минеральную плотность костной ткани (МПКТ) у пожилых пациентов с тяжёлой формой гемофилии А и оценить возможную корреляцию с биомаркерами костного ремоделирования OPG/RANKL, CTX-1, остеокальцином и витамином D.

Материалы и методы: Было набрано 28 лиц мужского пола с тяжёлой формой гемофилии А и 33 лица соответствоваших по возрасту в качестве контрольной группы. Биомаркеры были проверены с помощью анализа ELISA и BMD с DEXA поясничного отдела позвоночника (LS) и всего бедра (TH).

Результаты: У больных была более низкая LS-BMD (–0.955±0.145 против 1.118±0.079, p=0.05) и TH-BMD (-0.840 ± 0.147 против 0.951 ± 0.075, p=0.05), чем у контрольной группы. T-показатели TH были -1.41 ± 0.91 против 0.4 ± 0.49 (p=0.05), а T-показатели LS -1.16 ± 1.046 против 0.14 ± 0.72 (p=0.05). У 66.6 % больных до 50 лет была остеопения, у 8.3% — остеопороз. У 50% лиц старше 50 лет была остеопения, а у 20% – остеопороз. Мы обнаружили значительно более высокие уровни OPG (123.69±107.05 против 41.98±18.95, p=0.05), чем в контрольной группе, и более низкие уровни sRANKL (23.49±29.39 против 131.32±201.27, p=0.05) и отношение sRANKL/OPG (0.27±0.05). 0.35 против 5.28±10.01, p=0.05), чем в контроле. Выявлена положительная корреляция между sRANKL и T-баллом BMD поясничного отдела позвоночника (p=0.001) в группе больных.

Заключение: Уровень и соотношение sRANKL можно использовать в качестве предикторов низкой BMD

Ключевые слова

дефицит FVIII, остеопороз, RANKL, OPG