IJBC 2012;1: 13-17

Frequency of Decreased Bone Mineral Density and Its Risk Factors during Childhood among Iranian Hemophilia Patients

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Submitted: 03-05-2011 , Accepted: 10-08-2011

Abstract

This study was undertaken to assess the frequency of decreased bone mineral density and its risk factors as well as its impact on the quality of life during childhood among hemophiliac patients.

Materials and Methods: Thirty seven children with severe hemophilia A and B, referred to Mofid Children's Hospital during 2010, were selected. For all patients the joint score, body mass indexes, bone mineral density, the level of inhibitor antibodies were measured. Short forms of Haeamo-QoL questionnaire were used to assess their quality of life. Data were statistically analyzed using Kolmogorov-Smirnov Z, Mann-Whitney, T-test, Fisher's eact test, and χ^2 test.

Results: In this study the overall prevalence of low bone density was 35%. Factors that were significantly associated with the frequency and severity of decreased bone density were age, presence of inhibitor antibodies, and reduced joint range of motion. Total quality of life score, and the sub scores of "viewpoint" and "others" as well as the "attitude" were decreased significantly in patients with decreased bone density.

Conclusion: According to our findings there is a high prevalence of low bone density among hemophiliac patients. The body mass index should be maintained by appropriate nutrition and exercise to prevent loss of bone density in patients with hemophilia. Prophylaxis regimen in early childhood and regular monitoring of inhibitor antibody development are advised for early detection and management of this complication.

Key words: Hemophilia, antibody, body mass index, bone mineral density, quality of life

Introduction

Hemophilia is one of the most common x-linked inherited bleeding disorders, with an incidence of 1 in every 5000 males [1]. The etiology in about 85% of cases is deficiency in factor 8 (hemophilia A) and in 10-15% of cases factor 9 deficiency is the cause (hemophilia B). Clinical findings in hemophilia A and B are almost similar. [1]

The survival rate has significantly increased among these patients due to performing prophylaxis for patients and improved therapeutic options for hemophiliac patients, so the skeletal system health is of great importance to improve life quality. [2]

In the first decade of life, the bone density increases as the child ages and reaches its maximum at around age 20-25.[6] The most important period of life for a hemophiliac in terms of increasing the bone density is the childhood and adolescence. Loss of activity due to chronic pain, excessive parental care and poor nutrition might gradually lead to decreased bone density. [3]

Considering the fact that osteopenia and osteoporosis can increase the incidence of fractures, bone pain, inactivity and their consequences in patients with hemophilia, it is of great importance to determine the frequency of reduced bone density and risk factors. [3, 4]

The measure for determining osteopenia and osteoporosis among these children is the Z-score determined through dual energy X-ray absorptiometry (DXA) of the lumbar spine, and femoral neck. . A Z score between -1 and -2.5 is considered as osteopenia and a score of less than

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-2.5 is considered as osteoporosis. [5, 6]

Due to the lack of studies on the frequency of osteopenia and osteoporosis in hemophiliac patients, particularly in children, and its risk factors in Iran, this study was undertaken to assess the frequency of decreased bone mineral density and its risk factors as well as its impact on the quality of life during childhood among hemophiliac patients.

Materials and Methods

This was a cross-sectional study on patients older than 3 years, referred to Mofid Children's Hospital during 2010, in which a diagnosis of severe hemophilia A or B had been made using clinical manifestations and serum levels of their Coagulation factors. Thirty seven children were included in this study. Demographic information such as age, sex, height, and weight (body mass index or BMI) of patients were all recorded. Venous blood samples were obtained to determine hepatitis C, HIV, and the level of inhibitor antibodies for all patients.

In addition, the activity questionnaire, by USA department of health and human services, was used to assess the range of motion of elbows, knees, and ankle. The Short form of Haeamo-QoL questionnaire was used to assess the quality of life among patients.

All patients underwent bone mineral density (BMD) measurement using dual energy X-ray absorptiometry using Lunar Dpxmd 7164 device. BMD-Z score between -1 and -2.5 was defined as osteopenia and that of less than -2.5 was considered as osteoporosis. Investigation of bone density was based on the lower Z score in femoral neck and lumbar spine in each patient. For example, if the femoral neck density was in the osteopenia range and that of the lumbar spine was in osteoporosis range, the patient was defined as having osteoporosis. This classification was performed due to the clinical significance of the lower density in clinical approach towards each patient. Also due to relatively small number of participants in this study, if we had categorized them into more groups, it would decrease the reliability of statistical analyses.

Kolmogorov-Smirnov Z-test was used to assess the normality of the data distribution.

Kolmogorov-Smirnov Z, Mann-Whitney, T-test, Fisher's exact test, and χ^2 test, were used to analyze the data. The level of significance was determined as P-value less than 0.05.

Results

This study was performed on 37 consecutive male children suffering from severe hemophilia A (36 or 97.3% of patients) or B (1 or 2.7% of patients), referring to Mofid Children's Hospital during 2010. The average age was 8.6 ± 3.8 years (range, 4-15 years) and the average BMI was 15.9 ± 2.1 (range, 13-23). The average joints range of motion was 3.2 ± 4.3 (range, 0-19) and the average Z-score was -0.55 ± 0.5 and -0.95 ± 0.72 for lumbar spine and hip, respectively (Table 1).

Bone density of 24 children (64.9%) was normal, 8 children (21.6%) were in osteopenia range and 5 children (13.5%) had osteoporosis; in other words, the prevalence of bone problems in hemophilia patients was 35.1%. The average age of hemophiliac children without bone problems was 7.6 ± 3.7 years (range, 4-15 years); among patients with osteopenia and osteoporosis this was 9.1 ± 2.4 years (range, 7-13 years) and 12.6 ± 3.7 years (range, 6-15 years), respectively. There was a

Table1: Age, BMI, Joints Range of Motion and BMD of the hip and femur in children with hemophilia, referred to Mofid Children's Hospital in 2010.

Variable	Mean	SD	Minimum	Maximum
Age	8.6	3.8	4.0	15.0
BMI	15.9	2.1	13.0	23.0
Joints Range of Motion	3.2	4.3	0.0	19.0
Hip BMD	-0.55	0.5	-2.01	0.5
Femur BMD	-0.95	0.72	-0.12	-1.2

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statistically significant association between the age of children with hemophilia and their bone status (p=0.024).

In 32 patients (86.5%) BMI was below the 5% percentile for age and sex. They were classified as low-weight patients. No patient was overweight or obese. Of these patients, 8 (25%) had osteopenia and 5 (15.6%) had osteoporosis. No hemophiliac with normal weight had bone problems. However, we did not found a statistically significant association between bone problems and weight of hemophiliacs.

In children without inhibitor antibodies, 21 (77.8%) were without bone density problems, 3 (11.1%) had osteopenia and, 3 (11.1%) had osteoporosis. In the group with inhibitor antibodies, 3 children (30%) had no bone problems, 5 children (50%) were osteopenic and 2 (20%) had osteoporosis. There was a statistically significant association between the level inhibitor antibodies among children with hemophilia and their bone status (p =0.017).

All hemophiliacs with normal range of motion in joints had normal bone density. In hemophiliacs with abnormal range of motion, 9 children (40.9%) did not have bone density problems, 8 children (36.4%) had osteopenia and 5 (22.7%) had osteoporosis. There was a statistically significant association between the range of motion of joints in hemophiliacs and their bone status (p =0/001).

In children treated on demand, 17 (58.6%) did not have bone density problems, 7 children (24.1%) suffered from osteopenia and 5 (17.2%) had osteoporosis. In prophylactic treatment group, 7 children (87.5%) had no bone density problems and only one child (12.5%) had osteopenia. No statistically significant association was found between treatment groups of patients and their bone status (p =0/216). There was a statistically significant association between total quality of life score (p=0.001) and sub scores of "viewpoint" and "others" (p <0.001), as well as "attitude" (p <0.001) dimension and hemophiliacs' bone density status.

No statistically significant association was observed between the physical condition (p = 0.442), emotional status (p = 0.096), family status (p = 0.395), friends relationships (p = 0.296), school condition (p = 0.077), treatment (p = 0.267), exercise (p = 0.388) and behavior (p = 0.442) with the bone status of hemophiliacs (Table 2).

Discussion

In this study, the overall prevalence of low bone density was 35.1%. The prevalence of low bone density in a study by Gerstner et al. at Phonix Arizona Hospital in US [7] was 70%. In another study by Katsarou et al. [8] in Greece, the prevalence of osteoporosis was 86% and 65% in the femoral and lumbar areas, respectively. In a study by Nair et al. at KEM Hospital in India [9], prevalence of osteoporosis was 50% and 32% in the lumbar and

Table2: Simultaneous prevalence of observed alleles

Bone Status	Normal BMD		Osteopenia or Osteoporosis		P Value
Quality of Life	Mean	SD	Mean	SD	
Physical	27.6	23	35.1	32.1	0.442
Emotional	55.7	26.7	38.5	29.2	0.096
Viewpoint	82.1	26.2	33.3	29.6	< 0.001
Family	27.4	22.2	21.0	16.7	0.395
Friends	67.3	27.5	56.2	30.5	0.296
Others	80.1	16.1	42.7	25.1	< 0.001
School	61.5	29.4	28.1	32.9	0.077
Treatment	51.8	28.7	41.1	20.1	0.267
Exercise	34.7	24.8	24.2	23.7	0.388
Behavior	67.4	20.9	51.6	21.1	0.142
Total	53.6	12.4	37.5	10.7	0.001

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pelvic regions, respectively. The higher prevalence of bone density reduction in these studies might be due to older age of their patients compared to our study patients. In a study by Tlacuilo-Parra et al. [10] in Mexico, on children between the age of 6 to 16 years (with an age range similar to our study), the prevalence of low bone density was 38%, which is similar to ours.

In our study, 86.5% of patients had lower than normal BMIs. No statistically significant relationship was observed between patients' BMIs and bone problems. This observation is in line with findings of studies by Iorio et al. [11] and Nair et al. [9], though it is contrary to a study from Australia [12], which found an association between increasing BMI and reduced bone density. In explaining the relationship between BMI and bone density loss, it cannot be clearly stated whether the reduced bone density is secondary to changes in BMI, or is one of its causes.

In our study, there was a statistically significant relationship between the average age of children with hemophilia and their bone status (p = 0.024), suggesting that bone density reduction increases with increasing age. This finding is in line with studies by Gerstner et al., Katsarou et al. and Nair et al. [7, 8, 9]

In our study there was a statistically significant relationship between inhibitor antibodies and the bone density (P =0.017). This finding is similar to findings of a study by Gerstner et al. [7]

There was a statistically significant relationship in children with hemophilia; between the average joint score and the bone density. Also, all patients without a reduction in bone density had normal joint scores. This association can be justified when the role of joint activity in preventing the bone mass reduction is considered. This finding is in line with findings from the studies by Gerstner et al. [7] and Nair et al. [9] , but dissimilar to the a study from Australia [12].

No statistically significant relationship was found between treatment groups and the bone density status (p = 0.216). Despite the fact that there must be a larger number of patients for an accurate judgment on this absence of relationship, the findings are in line with the results of a study from Sweden [13]. There was associations between total quality of life score (p = 0.001), and its aspects including the scores of "others" viewpoints (p<0.001) and "attitude" (p<0.001), and their decreased bone density.

Conclusion

According to our findings there is a high prevalence of low bone density among hemophiliac patients. The body mass index should be maintained by appropriate nutrition and exercise to prevent loss of bone density in patients with hemophilia. Prophylaxis regimen in early childhood and regular monitoring of inhibitor antibody development are advised for early detection and management of this complication.

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