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Full Length Research Paper

Assessment of Bone Mineral Density and Functional status in Children with Hemophilic Arthropathy

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Haemophilia and osteoporosis accompanied by chronic pain, loss of independence and increased mortality. Functional Independence Score in Hemophilia (FISH) has been developed as a measure of disability in hemophilic patients. To assess bone mineral density, and functional status in children with hemophilic arthropathy and study possible relation to articular affection. This study included twenty haemophilic male patients, assessed for body mass index, hemophilia joint health score (HJHS), functional independence score in hemophilia (FISH), and bone mineral density (BMD). 8 patients (40%) hadlow BMD, 12 patients (60%) had average BMD. A highly significant negative correlation between HJHS total and DXA were found, while a highly significant positive correlation between total functional score and DXA. A significant negative correlation between number of attacks and DXA. A positive significant correlation between age, degree of factor deficiency and number of attacks with HJHS score, while a negative significant correlation was detected of total function score and HJHS. A highly significant negative correlation between each of number of attacks and degree of factor deficiency with total functional score. A highly significant relation between degree of deficiency and a significant correlation between type of treatment and total functional score. Bone mineral density positively correlated with functional score and negatively correlated with HJHS score total and number of attacks of bleeding, which is the main contributor to arthropathy and reduced bone mass in the hemophiliacs. Decrease in total functional score affected mainly by increase in HJHS.

Keywords: Haemophilic arthropathy, Functional status, Bone density.

INTRODUCTION

Hemophilia is an uncommon genetic disorder, inherited in a recessive trait, X-linked (Franco, 2012). Hemophilia is traditionally classified as mild, moderate and severe depending on the degree of clotting factor deficit compared with that found in general population (White et al., 2001).

The definition of target joint varies, but a common definition is four bleeds into the same joint in a six-month

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time period. The most common target joints are the knees, ankles, and elbows, although patients can develop targets in other joints including the hip, wrist, and shoulder (Gilbert and Wiedel, 1996). The Hemosiderin-laden synovium produces inflammatory mediators, thus creating an intra-articular cytokine storm that further damages cartilage and then bone (Ishiguro et al., 2002).

The Hemophilia joint health score (HJHS) measures joint health in the domain of body structure and function, of the joints most commonly affected by bleeding in hemophilia: knees, ankles and elbows, its primarily designed for children with hemophilia aged 4-18 years with mild joint impairment, it can be used when there is need for orthopedic intervention or as an outcome measure of physiotherapy intervention (Hilliard et al., 2006).

FISH (Functional Independence Score in Hemophilia) has been developed as a measure of disability in patients with hemophilia. It is intended to measure what the person with disability actually does. It can be used to evaluate change in functional independence over time, or after a therapeutic intervention (Poonnoose et al., 2007).

Osteoporosis is a systemic skeletal disorder characterized in adults by low bone mass and micro architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture (National Osteoporosis Society, 2004). In the pediatric population, a somewhat different definition exists, requiring both a history of pathologic fractures and low bone mineral content or density (Gordon et al., 2007).

Low bone mineral content or bone mineral density is defined as a BMC or areal BMD Z-score that is less than or equal to -2.0, adjusted for age, gender and body size, as appropriate (The international society for clinical densitometry, 2007). Bone density varies greatly with age. This is the reason the densitometry Z-score is used in the pediatric population and not the T-score usually used in adults. Z scores of -2 SD define osteoporosis (Bishop et al., 2008). In pre-pubertal children the lumbar spine is the most useful site to scan in clinical practice (National Osteoporosis Society, 2004).

Haemophilia and osteoporosis have a number of parallels: both diseases may be accompanied by chronic pain, invalidity, loss of independence and increased mortality (Lin and Lane, 2004). Bone and hematopoietic tissues are closely inter linked by mutual regulating impact. It has been shown that hematopoietic microenvironment, being of stromal origin, plays a crucial role in supporting and regulating early hematopoietic progenitor cells (Visnjic et al., 2004).

According to this hypothesis, require mental pressure resulting in intensified proliferation of progenitor cells, when applied to either of the interacting bone or hematopoietic tissues, brings its counterpart into a stimulated state as well, leading over time to gradual exhaustion of osteogenic progenitor cells, bone depletion, and progression of osteoporosis. In the hematopoietic system, the exhausting effect of continuous, intensified proliferation is less noticeable because of the enormous proliferative potential of hematopoietic stem cells (HSC) (Krause and Theise, 2001). Finally, extensive osteoclasticresorption of bone together with exhaustion of the osteogenic cell population constitutes the conditions for the gradual development of osteoporosis (Gurevitch and Slavin, 2006).

Aim of The Work

To assess bone mineral density, and functional status in children with hemophilic arthropathy and study possible relation to articular affection.

METHODS

This study was conducted on twenty male patients suffering from hemophilia who were attending the outpatient clinic of Pediatric Physical Medicine, Rheumatology, and Rehabilitation department of Ain Shams University Hospitals. Their ages ranged from 4-18years.

Exclusion criteria

1- Patients with endocrine diseases (e.g. Hyperthyroidism, hyperparathyroidism)
2- Patients with GIT diseases (e.g. parasitic infestation, mal absorption syndrome)
3- Patients with renal diseases (chronic renal failure)
4- Congenital bone diseases (e.g. Osteogenesis imperfect, Achondroplasia) that may cause osteoporosis
5- Patients taking regular medications (e.g. some types of cancer treatment, anti-epileptics, and steroids).

All patients were subjected to:

1) Full medical history: stress on type of factor deficiency, degree of factor deficiency, frequency of bleeding and type of treatment.
2) Anthropometric measure: The weight and height of all patients were measured. Body mass index (BMI) was calculated using the standard formula [weight (kg)/height squared (M^2)
3) Clinical assessment of joint involvement: Using Hemophilia joint health score(HJHS), assessing (right knee, left knee, right ankle, left ankle, right elbow, left elbow), then global gait score assessing (walking, stair climbing, running, hopping on one leg) (Hilliard et al., 2006).
4) Functional assessment using functional independence score in hemophilia (FISH): Functional Independence Score in Hemophilia (FISH) has been

developed as a measure of disability in patients with hemophilia. It is intended to measure what the person with disability actually does, and not what he ought to be able to do, or might be able to do if circumstances were different. It can be used to evaluate change in functional independence over time, or after a therapeutic intervention (Poonnoose et al., 2007). Functional assessment include (eating and grooming, bathing, dressing, chair transfer, squatting, walking pattern, running) each item of functional assessment were scored from 1-4 as follow.

- Levels of Function and their Scores:

1- The subject is able to perform the activity without any difficulty like other healthy peers (score 4).
2- The subject is able to perform the activity without aids or assistance, but with slight discomfort. He is unable to perform the activity like his healthy peers (score 3).
3- The subject needs partial assistance/ aids/ modified instruments/ modified environment to perform the activity (score 2).
4- The subject is unable to perform the activity, or needs complete assistance to perform the activity (score 1). The maximum possible score is 32
4) Bone mineral density

Measurement of BMD was performed using a DXA scan. To assess BMD scanning was done for all patients on lumbar spine region focusing on L2 to L4. It is the most preferable site in the spine (Gordon et al., 2007). Bone mass, as measured by DXA, is reported as areal BMD (g/cm^2). In the present study, the bone mineral density is expressed in the form of Z score, BMD *z*score of more than 2 SDs below expected (less than -2) should be labeled "low for age (Gordon et al., 2007). This was performed by GE LUNAR dual energy x-ray Absorptiometry (DXA) apparatus made in (Madison, USA).

Data Management and Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

P- value: level of significance,- P>0.05: Non significant (NS)., P< 0.05: Significant (S), P<0.01: Highly significant (HS).

RESULTS

This study was conducted on 20 patients, 19 patients had hemophilia type A and a single patient had type B hemophilia.The age of patient group showed a range of 5.0 -17.0 years with a mean of (11.1± 4.1). While their body mass index (BMI) showed a range of 10.2 to 31.2 kg/m^2 with a mean of (19.5± 5.4). The number of bleeding attacks per month had a range from 1.0 - 8.0 attack/ month with a mean of (3.7±1.6). Family history was positive in 11 patients (55%), and negative in 9 (45%), 5 patients (25%) had mild haemophilia, 10 (50%) had moderate and 5 (25%) had severe haemophilia.17 (85%) were on demand treatment while 3 (15%) were on regular Treatment.HJHS and Functional score data are shown in table (1) and (2).

Table 1. The Hemophilia Joint Health Score (HJHS) of patient group.

HJHS	Range	Mean ± SD
Sum of Joints	11.0 - 69.0	36.8 ± 16.6
Gait Score	0.0 - 4.0	2.7 ± 1.8
Total score	11.0 - 73.0	39.5 ± 18.0

*Interquartile range

Table 2. Functional score among patient group

Functional score	Range	Mean ± SD
Eating and grooming	2.0 - 4.0	3.3 ± 0.7
Bathing	2.0 - 4.0	3.3 ± 0.7
Dressing	1.0 - 4.0	3.0± 0.9
Chair transfer	1.0 - 4.0	3.0 ± 0.9
Squatting	0.0 - 4.0	2.0 ± 1.2
Walking	1.0 - 4.0	2.8 ± 1.0
Stair Climbing	1.0 - 4.0	2.5 ± 0.9
Running	0.0 - 4.0	1.9 ± 1.2
Total Functional score	8.0 -32.0	24.8 ± 7.0

*Interquartile range

Using Dual Energy X-ray Absorptiometry (DXA); 8 patients (40%) showed low bone mineral density (BMD), while12 patients (60%) had average BMD.DXA results using Z score and BMD (gm/cm^2). Low bone mineral content or bone mineral density is defined as a BMC or areal BMD Z-score that is less than or equal to -2.0, adjusted for age, gender and body size (The international society for clinical densitometry, 2007) (Table 3).

Table 3. Description of DEXA results of patient group

DEXA	Range	Mean ±SD
Z score	-4.2 - 0.0	-2.0 ±1.5
BMD	1.421 - 0.485	0.7037±0.181

*Interquartile range

Table 4. Comparison between low BMD and normal BMD as regard clinical data.

Clinical data	LOW BMD Mean ±SD	normal BMD Mean ± SD	P	sig
Number of attacks	4.0 ± 1.1	3.4±1.8	0.381	NS
HJHS Total	55.1 ±10.7	29.0±13.7	0.0001	HS
Total Functional score	19.9 ± 1.9	28.1±7.2	0.002	HS

*Student t test
-P>0.05: Non significant (NS).
-P< 0.05: Significant (S).
-P<0.01: Highly significant (HS).

Table 5. Correlations between personal and medical data and DEXA.

Personal and medical data		DXA
	r	-0.383
Age	P	0.096
	Sig	NS
	r	0.334
BMI	P	0.150
	Sig	NS
	Rho	-0.393
Degree of deficiency	P	0.087
	Sig	NS
	r	**-0.473**
Number of attacks	**P**	**0.035**
	Sig	**S**

*Spearman correlation*r=correlation coeffecient

Comparing two groups low and normal BMD; patients with low BMD showed significant deterioration in both total HJHS and total functional score, while no effect on number of bleeding attacks (Table 4).

Lower and normal BMD were compared as regard degree of factor deficiency, family history and treatment however all did not reach the statistical significance (P>0.05).

There was a significant negative correlation between number of attacks and DXA while relation between age, BMI and degree of factor deficiency with DXA did not reach statistical significance (Table 5).

A highly significant negative correlation between HJHS total and DXA were found, however a highly significant positive correlation between total functional score and DXA. Table (6).

Among hemophilic patients, no significant relation was found between degree of factor deficiency, type of treatment and family history on one hand with BMD (z score) on the other hand (P>0.05).

A positive significant correlation between each of age, degree of factor deficiency and number of attacks with HJHS score, while a negative significant correlation was detected of total function score and HJHS, however BMI did not reach the statistical significance. Table (7). A highly significant negative correlation between each of number of attacks and degree of deficiency with total functional score, while relation between age and BMI with total functional score did not reach the statistical significance. Table (8).

A highly significant relation between degree of deficiency and a significant correlation between type of

Table 6. Correlations between each of HJHS Total, Total Functional score and DEXA.

Clinical data		DEXA
HJHS Total	r	-0.734
	P	0.0001
	Sig	HS
Total Functional score	r	0.646
	P	0.002
	Sig	HS

*Spearman correlation
*r=correlation coefficient
-P>0.05: Non significant (NS).
-P< 0.05: Significant (S).
-P<0.01: Highly significant (HS).

Table 7. Correlations between personal and medical data and HJHS total.

Personal and Clinical data		HJHS Total
Age	**r***	**0.486**
	P	**0.030**
	Sig	**S**
BMI	r*	-0.250
	P	0.289
	Sig	NS
Degree of deficiency	**Rho****	**0.500**
	P	**0.025**
	Sig	**S**
Number of attacks	**r***	**0.531**
	P	**0.016**
	Sig	**S**
Total Functional score	**r***	**-0.864**
	P	**0.0001**
	Sig	**HS**

*Pearson correlation *spearman correlation

Table 8. Correlations between personal and clinical data and total functional score.

Personal and clinical data		Total Functional score
Age	r*	-0.435
	P	0.055
	Sig	NS
BMI	r*	0.045
	P	0.849
	Sig	NS
Degree of deficiency	**Rho****	**-0.646**
	P	**0.002**
	Sig	**HS**
Number of attacks	**r***	**-0.717**
	P	**0.0001**
	Sig	**HS**

*Pearson correlation **spearman correlation*r= correlation coefficient for parametric data**Rho= correlation coefficient for non parametricdat

Table 9. Relation between each of family history, degree of factor deficiency and type of treatment with Total Functional score.

Clinical data		Total Functional score		
		Mean ± SD	P	sig
Family history	Positive	25.1± 7.9	0.8438	NS
	Negative	24.4± 6.0		
Degree of deficiency	Mild	30.4 ± 6.7	0.009**	HS
	Moderate	25.4 ± 5.4		
	Severe	18.0 ± 4.7		
Treatment	On demand	23.3 ± 6.4	0.017*	S
	regular	33.3 ± 2.5		

*Student t test **ANOVAA mild Vs Moderate (NS), mild Vs severe (HS), Moderate Vs severe(S)

treatment and total functional score, while no correlation between family history and total functional score. Table (9).

DISCUSSION

We aim to assess bone mineral density in children with hemophilic arthropathy**.**We found that Z score of L2-L4 values ranged from 0 to -4.2with a mean of (-2.0). 8 patients (40%) showed low bone mineral density (BMD), while12 patients (60%) had average BMD.

This in agreement with *Mostafa et al. (2012)* but they studied only severe and moderate hemophilia A, they found mean of the Z score (0.475±0.9) (Mostafa et al., 2011). *Alioglu et al. (2012)* in their study found BMD Z-score was -1.2 ± 1.24 (Alioglu et al., 2012). *Abdelrazek et al. (2007)* found significant difference between thirty hemophiliac patients with ages ranged from 4.97±3.64 years and, thirty control healthy individuals as regard BMD Z-score (Abdelrazik et al., 2007). *Barnes et al. (2004)* estimated the bone mineral density in 19 severe hemophilic patients, the difference in BMD between patients and control subjects was significant (Barnes et al., 2004).

In our study The 20 patients were subjected to clinical assessment using HJHS, the sum of joint scores =120 and the maximum gait score=4, so the total joint score =124. In our study, we found the sum of joint score ranges between (11- 69), the mean of sum of joints (36.8). Gait score ranges between (0- 4) the mean of gait score (2.7). The HJHS total score ranges between (11-73) the mean of HJHS total (39.5±18.0). The Previous results indicate an increase in clinical score among hemophiliac children due to repeated joint bleeding, which result in hemophilic arthropathy in target joints. Those in agreement with *Trakymiene et al. (2010)* in their study of 20 patients, their ages ranged from 4-17years, the HJHS score ranged from (5 - 50) (Trakymiene et al., 2010).

In our study there was significant negative correlation between HJHS total and BMD Z score (r=-0.734, p=0.001).This in agreement with previous researches (Mostafa et al., 2011; Alioglu et al., 2012; Abdelrazik et al., 2007; Barnes et al., 2004).

In our study, there was a positive significant correlation between each of age, degree of factor deficiency and number of attacks with HJHS score, while a significant negative correlation was detected with total function score and HJHS. These results indicate that increase in age of hemophiliac children means increase in HJHS total as it means long term hemoarthrosis and arthropathy.

Khanum et al. (2014), they found that HJHS was significantly lower in younger compared to older patients, HJHS and Gilbert score found to be higher in severe hemophilia than in non severe hemophiliacs (Khanum et al., 2014). *Bladen et al. (2013),* and *Trakymiene et al. (2010)* they found higher HJHS in older children (Trakymiene et al., 2010; Bladen et al., 2013).

In our study there was significant negative correlation between number of bleeding attacks and DXA (p=0.035, r=-0.473).Those in agreement with results of *Mostafa et al. (2011)* their study showed strong negative the correlation between the frequency of joint bleeding and Z score, diminished bone density. *Abdelrazek et al. (2007)* found in most patients, the frequency of joint bleeding is inversely proportional to severity of hemophilia (Mostafa et al., 2011; Abdelrazik et al., 2007).

Our study is one of few studies used FISH score assessment specially in children, in our study, we found that the total functional score ranges from (8.0 - 32.0) the mean of total functional score (24.8±7.0), and a highly significant positive correlation between total functional score and DEXA (p=0.002, r=0.646). This indicates that better BMD associated with better functional score, but we could not find other studies explain the correlation between FISH score and DXA. There was a highly significant negative correlation between number of attacks and degree of deficiency with the total functional

score. This means an increase in number of bleeding attacks and degree of factor deficiency causes decrease in total functional score (FISH).

This is in agreeing with *Tlacuilo et al. (2009)* in their study on 60 children with hemophilia, FISH score ranged (15-28) with a mean of (25.8 ± 3.6), ranging from (15 to 28), *Kashooei et al. (2014)*, (their study was mainly on adult age) they found that increase age can deteriorate the functional level, each 1 year increase in age can increase 1.07 fold of possibility of being placed in disordered group (FISH 8-24), and severe hemophilia can increase 7.34 folds the possibility of being placed in disordered function (Tlacuilo-Parra et al., 2009; Kashooei et al., 2014).

We conclude that bone mineral density positively correlated with functional score and negatively correlated with HJHS score total and number of attacks of bleeding. In patients with hemophilia number of attacks of joint bleeding is the main contributor to arthropathy which is main cause for reduced bone mass in the hemophiliacs.Decrease in total functional score (FISH score) affected mainly by increase in HJHS.

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