Association Between Low Bone Mineral Density in Hemophilia Patients and Musculoskeletal Function Impairments

Rasha Ibrahim Salman [1*], Khalid Mahdi Salih [1], Nidal Karim Al-Rahal [2]

Abstract

Background: Hemophilia A (HA) and B (HB) are inherited bleeding disorders due to the partial or total deficiency of coagulation factor (F) VIII or FIX, respectively. It is associated with low bone mineral density (BMD). **Method:** The current study was conducted on sixty-eight Iraqi patients with hemophilia to assess BMD using a DEXA scan enrolled from the National Center of Hematology, Mustansiriyah University from July 2020 to September 2021. Various medical history characteristics were recorded as (age, type of hemophilia, severity, number and site of bleeding, smoking, and alcohol intake) as well as Functional Independence Score in Haemophilia (FISH) was used to assess musculoskeletal functions and Hepatitis C virus (HCV)/Human immunodeficiency virus (HIV) seropositivity were recorded. **Results:** The results found that only 39.7% of patients have positive DEXA scans characterized by low BMD (abbreviated as DX+) and 60.3 % with normal BMD (abbreviated as DX0). The average Functional Independence (FISH) score in DX+ patients is significantly lower than those in the DX0 group, and about 33.3% of patients in the DX+ group have limitation of movement (LOM), which is significantly higher than of patients in DX0 group and 70.4% of patients in DX+ group are presented with seropositive viral infection, which is significantly higher than 39% of patients in DX0 group. **Conclusion:** It can be concluded that hemophilic patients with seropositive viral infection and severe LOM may be at higher risk of developing low BMD.

Keywords: Hemophilia, Bone Mineral Density, DEXA Scan, Functional Independence Score, Musculoskeletal Function

Significance | *Hemophilia patients with low bone density (BMD) face higher risk with severe limitation of movement (LOM) and viral infections.*

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1. Introduction

Inherited bleeding disorders (IBDs) are a collection of inherited coagulopathies caused by protein deficiencies in the coagulation, platelet function, or fibrinolysis pathways (Alli *et al.*, 2018). The prevalence of all types of hemophilia in four hemophilia centers in Baghdad is 8.1/100 000 population, which is higher than that estimated in some neighboring and regional countries (WFH, 2017; Kadhim *et al.*, 2019). Hemarthrosis (i.e. the joint bleeding) is another critical complication of hemophilia due to inflammation in the synovial membrane of the joint (synovitis) that results in severe pain, enlargement, organ overheating, and restriction of movement (Hermans *et al.*, 2011). Acute hemarthrosis affects patients with severe HA in adulthood, which is frequently caused by intensive physical activity, thus its occurrence decreases after puberty and becomes less common in middle life (Valentino *et al.*, 2007). The knee, elbow, ankle, and wrist represent the most

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commonly bled joints, while the hip joint is less damaged, which could be because a large and substantial muscular mass protects it. Similarly, small hand and vertebral joints are rarely impacted because extravasated blood produces quinine and cytokines, joint capsule swelling due to hematoma is a common source of discomfort (De Kleijn et al., 2014). Moreover, hematoma accounts for 10 to 25% of bleeding episodes in people with severe hemophilia led to hypertrophy of muscles (Bayer et al., 2010). One of the most common muscles bleeding is Iliopsoas hematoma, which is life-threatening bleeding and can lead to death in circumstances where the patient is not on a prophylactic regimen (Balkan et al., 2005), because femoral nerve in iliopsoas muscle is compressed, leaving the patient unable to extend the hip and having visible lameness (Dauty et al., 2007). Osteoporosis is a systemic bone disease characterized by low bone mineral density (BMD) and microarchitecture deterioration of bone tissue, leading to increased bone fragility and fracture risk (Adler,2011). Some studies found that the main underlying reasons for lowering bone density in patients with hemophilia include immobilization, lack of regular exercise, the elevation of bone-related turnover following secretion of pro-inflammatory cytokines, and recurrent hemarthrosis (Gerstner et al., 2009; Katsarou et al., 2010; Roushan et al., 2014; Mansouritorghabeh, 2015). Other studies identified many risk factors for developing osteoporosis in hemophilia include small body size, poor diet, tobacco smoking, high alcohol consumption and vitamin D deficiency (Anagnostis et al., 2015; Kempton et al., 2015; Eldash et al., 2017).

Materials And Methods

Participants:

The study included 68 hemophilia patients from the National Center of Hematology/Mustansiriyah University and 18 normal subjects matched in gender and age for comparison.

Data Collection:

Medical history characteristics were collected, including the type of hemophilia (type A versus type B), bleeding tendency (mild, moderate, or severe), site and frequency of hemarthrosis, therapy with deficient factor (prophylaxis or on-demand), viral infections (HIV, HBV, HCV), alcohol intake, and smoking habits.

Bone Mineral Density (BMD) Measurement:

BMD was measured using DEXA scans from GE-Lunar, USA, conducted on approximately 50% of patients at Al-Andalus National Hospital. DEXA data included BMD (g/cm2), Z-score, and T-score for classification into low BMD-Osteopenia (T score between -1 and -2.50), normal BMD (T score > -1), or osteoporosis (T score < -2.5).

Musculoskeletal Function Assessment:

The degree of limitation of movement (LOM) was assessed using FISH, with values below 18 indicating mild-moderate arthropathy (severe LOM) and scores ≥ 18 indicating severe arthropathy (mild-moderate LOM).

Ethics Approval:

The study protocol was approved by the National Center of Hematology, Mustansiriyah University, and written informed consent was obtained from all subjects.

Statistical Analysis:

Statistical analysis was performed using the Vassar Stats Web Site for Statistical Computation. Categorical variables were reported as percentages, and differences between groups were examined using the chi-square test. Differences between two independent samples were analyzed with the t-test, while differences between three independent samples were analyzed with the Tukey HSD and ANOVA tests. Numerical values were expressed as mean ± standard deviation (M ± SD), and correlation between variables was examined using the Pearson correlation test. Significance of differences was determined with a two-tail P value < 0.05.

Results

In order to evaluate a patient's BMD and T score in the lumbar spine (L1-L4) and in both femur bones (trochanter, neck, and shaft for each side), a DEXA scan is utilized. T score and BMD values in lumbar spine L1-L4 are shown in Table -1 to be -1.3 ± 1.93 and 1.001 ± 0.126 g/cm2, respectively. However, these values in dual femur (neck, trochanter, and shaft) are -0.51 ± 0.69 and 0.906 ± 0.155 g/cm2 respectively.

According to T score, only 27 patients have positive DEXA scan characterized by osteopenia in their lumbar spine and/or femur bones because their T score is between -1 and – 2.5, and represented the first group of patients (abbreviated as DX+). However, the other 41 patients involved in the second group (abbreviated as DX0), which consists of patient who have negative DEXA scan and normal BMD in femur bones and lumbar spine (T score is above -1) plus those, DEXA scan is not recommended by specialists as shown in Figure-1.

According to Age and Type of hemophilia, Table -2 show non-significant differences in the age of patients between DX+ group (28.5 ± 7.5 year) and DX0 group (27.9 ± 9.8 year). Moreover, there are no significant differences in the frequency of hemophilia type between (DX+) and (DX0) group.

Furthermore, the assessment of musculoskeletal function in patients and degree of limitation of their movement (LOM) are determined by using Functional independence score in hemophilia (FISH). Table-3 shows that FISH score in DX+ patients (20 ± 3.9) is significantly (P= 0.019) lower than those in DX0 group (23.2 ± 4.4). Furthermore, about 33.3% of patients in DX+ group are presented with severe limitation of movement (their FISH score < 18), which is significantly (P= 0.034) higher than 12.2% of patients in DX0 group.

Table 1. T-score and BMD of dual femur bones and lumbar spine based on DEXA scan

Bone Type		DEXA parameter	
		BMD (g/cm2)	T-score
Lumbar spine (L1-L4)	Range	0.814 → 1.374	-2.5 → 1.3
	M±SD	1.001 ± 0.126	- 1.3 ± 1.93
Dual femur (left & right)	Range	0.726 → 1.209	-1.8 → 2.75
	M±SD	0.902 ± 0.159	-0.62 ± 1.23

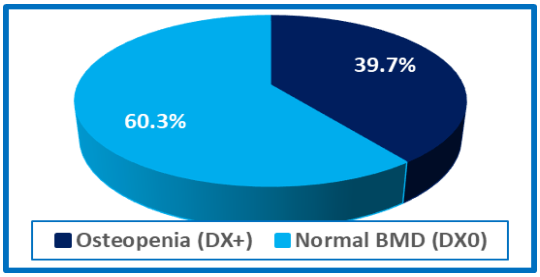

Figure 1. Patient's groups according to DEXA scan outcome.

Table 2. Comparison of age and hemophilia type between groups of patients

Feature		Patients' groups (N=68)		P value
		DX+ (n=27)	DX0 (n=41)	
Age (year)	M±SD	28.5 ± 7.5	27.9 ± 9.8	0.778
Hemophilia type (n, %)	HA	21 (77.8%)	35 (85.4%)	0.421
	HB	6 (22.2%)	6 (14.6%)	

Table 3. Distribution of patients according to the degree of their limitation of movement (LOM)

Feature		Patients' groups (N=68)		P value
		DX+ (n=27)	DX0 (n=41)	
FISH score	M±SD	20 ± 3.9	23.2 ± 4.4	0.019
LOM category (n, %)	Severe	9 (33.3%)	5 (12.2%)	0.034
	Mild	18 (66.7%)	36 (87.8%)	

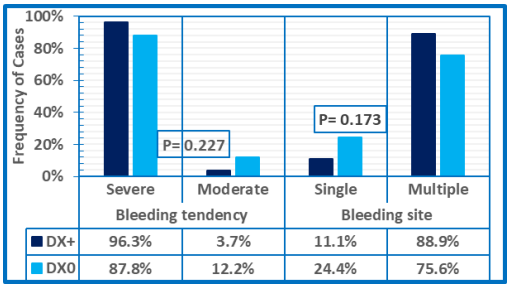

Figure 2. Frequency of cases based on severity and site of bleeding tendency

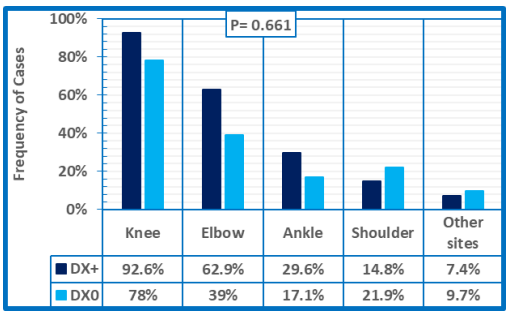

Figure 3. Frequency of cases based on the main sites of bleeding

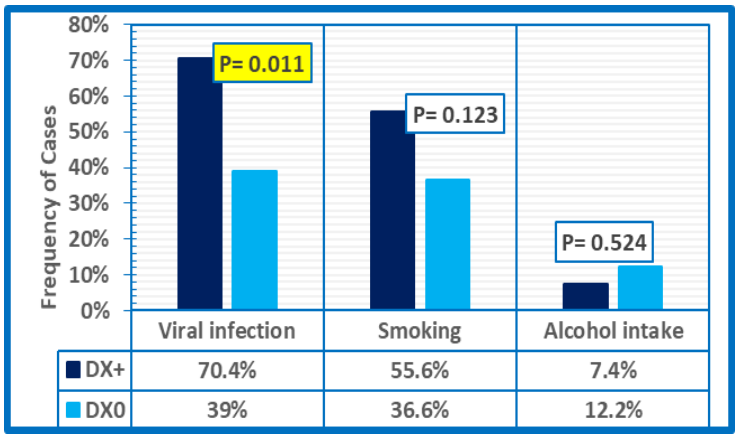

Figure 4. Frequency of cases with viral infection, smoking and alcohol intake

Moreover, according to Severity and site of bleeding tendency figure -2, show non-significant differences in the frequency of bleeding tendency and number of the affected sites between patients of DX+ and DX0 groups, since 88.9% and 75.6% of their patients respectively have experience of bleeding in multiple sites (two or more sites), while 11.1% and 24.4% respectively have experience of bleeding in single site.

On the other hand, Figure- 3, shows that 96.6%, 62.9%, 29.6%, 14.8%, and 7.4% of patients in DX+ group have bleeding sites knee, elbow, ankle, shoulder and other sites (gum, wrist, and hip) respectively which are not significantly different from those in DX0 group (78%, 39%, 17.1%, 21.9%, and 9.7% respectively.

In this study, Three factors were recorded in hemophilia patients; viral infection that may be acquired during previous therapy with deficient factor, in addition to smoking, and alcohol intake that may exacerbate the severity of disease. Figure-4 shows that the frequency of seropositive viral infection cases with hepatitis B, hepatitis C, or HIV constitutes about 70.4% of patients in DX+ group, which is significantly (P= 0.011) higher than 39% of patients in DX0 group. However, there is no significant difference in the frequency of smokers and alcohol intake habit between patients of DX+ group (55.6% and 7.4% respectively) and DX0 group (36.6% and 12.2% respectively.

Discussions

Through calculating divided by the area of bone scanned, DEXA is considered the primary clinical method utilized to evaluate skeletal health (Martineau, et al., 2021). Study has shown that hemophiliacs are more likely to have reduced BMD as a result of repeated bleeding into joints (Kovacs, 2008). About 70% of young adult hemophilia patients had reduced BMD, with 43% showing osteopenia and 27% showing osteoporosis (Gerstner et al., 2009). Furthermore, meta-analyses investigations validated the the amount of bone mineral association between secondary osteoporosis and hemophilia since severe hemophilia patients had significantly lower femoral neck BMD and lumbar spine BMD in comparison with controls, but not significantly lower total hip BMD (Iorio et al., 2010; Paschou et al., 2014). Several studies demonstrate that hemophilic patients experience more fractures than the general population (Gay et al., 2015; Tuan et al., 2019). Lately studies, revealed decreased BMD at several skeletal locations (Sossa et al., 2018; Ekinci et al., 2019; Linari et al., 2020). Yet, severe hemophilia patients who have had prophylactic factor medication since childhood could still have normal BMD (Gamal Andrawes et al., 2020). Whether the low BMD in hemophilia is directly brought on by the coagulation malfunction, or whether it develops owing to comorbidities or lifestyle factors, the underlying pathogenetic pathways and etiology are still up for debate (Ashritha et al., 2019; Gebetsberger et al., 2022). The likelihood of spontaneous joint bleeding often rises with age (Mehta and Reddivari, 2022). In addition, hemophilic arthropathies are frequently brought on by the repeated joint bleeding. Hemarthroses typically increase in frequency with physical activity and age (Peyvandi et al., 2016).The results of present study showed there were no significant differences in the age of patients between the age and hemophilia type and this agrees with Dagli and et al (2018) when he found in no colleration between age and hemophilia type. However, a study by Unal et al. (2017) found that hemophilia patients had low BMD, even within the group of young patients under the age of 50. Yet in the EU, osteoporosis has become more common among males over 50. In contrast to earlier studies that indicated a negative link between BMD and age, Anagnostis et al. (2012) found no correlation between BMD and age (Wallny et al., 2007; Gerstner et al., 2009). This is perhaps due to the fact that most patients in our study were less than fifty years, and therefore difference in BMD was less possibly emerges. In one study in which data on the association between age of patients with hemophilia and BMD was available, the largest proportion of patients had decreased BMD because they were over fifty years of age (Gerstner et al., 2009), whereas in current study the percentage was lower due to the age adopted is less than the stated age. The Functional Independence Score in Hemophilia (FISH) can be defined as one of the tools for evaluating the musculoskeletal function regarding hemophilia patients as well as the degree of their movement limitation (LOM) by gauging their independence in seven activities divided into three categories: self-care (bathing, eating, dressing and grooming), transfers (floor and chair), and mobility (step climbing and walking) (Poonnoose et al., 2007). According to Gurcay et al. (2006), 50% of patients with severe hemophilia get joint abnormalities with a substantial risk of functional disability if immediate therapy is either insufficient or unavailable. According to Tlacuilo Parra et al. (2010), the most affected activities were walking, squatting, and step climbing. Patients with mild hemophilia had a FISH score of 28, which is considerably higher compared to patients with moderate 26.2 or severe hemophilia 24. According to a recent movement, patients with functional mobility impairments had lower obesity densities than people with good functional mobility (Ekinci, 2019). In Iraq, the degree of LOM in Iraqi hemophilic patients is higher comparing to figures reported from developed countries where better treatment and care is provided; however, it is quite similar to results reported from developing part of the world, whereas, hemophiliacs receive only on demand therapy (Hassan et al., 2011). Shamoon also noted in 2017 that there was a strong positive link between the FISH score and the degree of clotting factor deficiency. The FISH score and is a highly effective tool in evaluating patients with hemophilic arthropathy since the score was lowest in patients who have a severe degree of the hemophilia

level and highest in patients with moderate hemophilia (Shamoon, 2017). In Iraq, recent study found that the overall incidence of hemarthrosis was more than 75%, and knees were most frequently affected either alone or together with other joints, followed by elbows then ankles, wrists and shoulders (Shamoon, 2017), followed by elbows then ankles, wrists, and shoulders. Recently, it was discovered that 56.3% of patients with hemophilia had at least two target joints, with elbow joints and wrist joints being the least impacted. Of all the target joints, knee joints made up roughly half of the patients' joint. Additionally, the researcher noted in his work that almost all hemophilia types were severe in terms of their severity (Kadhim et al., 2019). According to these data, numerous earlier researches did not discover any evidence of a connection between smoking behavior and BMD in hemophiliac patients (Roushan et al., 2015; Ekinci et al., 2019; Ayyash et al., 2020). With regard to viral infection, given that infections of HIV and chronic viral hepatitis can both result in chronic liver disease with numerous shortages of the coagulation factor, they can both adversely impact bleeding rates and clinical phenotypes of the infected hemophiliacs (Preston and Makris, 1993). Blood borne illnesses including HIV and hepatitis (B & C) are at risk for transmission when blood or blood products are transfused (Ahmed et al., 2007). Thus, hemophiliacs are more likely to contract such illnesses, and liver disease may result in poor bone mass (Barnes et al., 2004; Nassiri et al., 2008). Schiefke et al.(2005) found there was an increased level of bone resorption markers, which had an inverse relationship with BMD. Lately, Serdar et al. (2019) and Bordbar et al. (2020) discovered that patients with low BMD had significantly higher incidences of HCV and HBV. Recent research suggests that HCV infection affects bone microstructure and trabecular volumetric BMD in hemophilia patients, which may be due to the detrimental effects of chronic inflammation on bone metabolism (Klintman et al., 2022). Nair et al. (2007); Iorio et al. (2010) stated that, in contrast to such results, there were no connection between BMD and hepatitis C status at any site, Additionally, Unal et al. (2017), who found no connection between BMD status and HCV status, were quite similar to findings. From all findings of this study, it can be concluded that hemophilic patients with seropositive viral infection and sever LOM may be at higher risk to developed low BMD. There were no statistically significant differences between the DX+ and DX0 patient groups based on their medical history characteristics, including age, type of hemophilia, severity, number and site of bleeding, smoking, and alcohol intake.

Conclusion

In conclsuion, hemophilia patients with low bone mineral density (BMD) face a higher risk when experiencing severe limitation of movement (LOM) and seropositive viral infections. This study underscores the association between these factors, revealing that patients with low BMD often exhibit lower Functional Independence Scores in Hemophilia (FISH) and a higher incidence of LOM. Moreover, a substantial proportion of patients with low BMD are seropositive for viral infections, particularly hepatitis C virus (HCV) and human immunodeficiency virus (HIV). These findings emphasize the importance of considering both musculoskeletal function and viral infection status in assessing the risk of low BMD among hemophilia patients, guiding comprehensive management strategies.

Author contribution

R.I.S., K.M.S., N.K.A. conceptualized, reviewed, edited and wrote the article. All authors read and approved the article before publication.

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Competing financial interests

The authors have no conflict of interest.

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