The Analysis of Hematological Parameters CBC, ABO, NLR, and APTT and Its Implications on Haemophilic Patients with Low Bone Mineral Density

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

Abstract

Background: Haemophilia is a rare X-linked recessive genetic disorder characterized by the absence or deficiency of factor VIII (haemophilia A) or factor IX (haemophilia B). The current study aimed to assess some hematological factors in hemophilic patients with low bone mineral density (BMD). **Objective:** The study was carried out on Iraqi patients with hemophilia at the National Center of Hematology, Mustansiriyah University. **Method:** Sixty-eight male patients were involved in this study, with ages ranging from (14 to 53) years. Along with the patient group, 18 healthy subjects with matched age and gender were involved as the control group. Various hematological parameters were determined in the samples of healthy and patient subjects. **Results:** The results found that; only 39.7% of patients have positive DEXA scan characterized by low BMD (abbreviated as DX+) and 60.3 % with normal BMD (abbreviated as DX0), and reveal non-significant in ABO system distribution; all RBCs indices, WBC, prothrombin time, and platelets count (PLT) in patients (DX+, DX0) and control groups, higher NLR ratio was greater in patients in the DX+ group than in the DX0 and control groups; furthermore Activated-partial thromboplastin time (APTT) in DX+ and DX0 groups of patients are significantly ($P < 0.0001$) higher than in control group. **Conclusion:** the increase in neutrophils-lymphocytes ratio (NLR) and prolonged of APTT may be a marker that increases the risk of low bone density development in hemophilic patients.

Keywords: Hemophilia, DEXA scan, BMD, NLR, APTT

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

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Introduction

IInherited 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).Recent studies have shown a reduction in bone mass in patients with hemophilia (Anagnostis *et al.,* 2012; Katsarou *et al.*, 2010). Due to recurrent hemorrhage and decreased mobility, hemophilic patients are unable to maintain bone mineral density (BMD). 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 (Katsarou *et al.,* 2010;

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Roushan et al., 2014; Mansouritorghabeh, 2015).

Moreover, dual-energy X-ray absorptiometry (DXA) is advised for determining osteoporosis severity (DXA) (Watts, et al., 2012). DXA scans of the hip and lumbar (central area) are used to diagnose, and the results are displayed as the region's bone mineral content (BMC, gr/cm2). Previous studies on Iraqi patients with hemophilia reported that group O constitutes more than one third of patients with hemophilia, while the rest have non-O blood groups but without significant differences between hemophilia types (Kadhim et al., 2019; Hameed et al., 2020). Furthermore, Sagir et al. (2017) showed that the corresponding relative frequencies of each type of bleed (hemarthrosis, muscle hematomas, epistaxis, gum bleeds, gastrointestinal hemorrhage and hematuria) were statistically similar between the two patient's categories of the ABO blood group categories (O and non-O).On the other hand, neutrophil–lymphocyte ratio (NLR) as an inflammatory marker is associated with the pathophysiological mechanism regarding inflammation and prothrombotic factors, characterized by an increased number of circulating leukocytes and cytokines. Neutrophils play a crucial role in innate immune responses, whereas lymphocytes play a significant role in inflammatory responses (Orfanu et al., 2017).

Furthermore, the APTT is a coagulometric assay in which platelet-poor plasma is stimulated by a reagent containing phospholipids, an activator (eg, ellagic acid, silica), and calcium chloride.the concentration and functionality of coagulation factors of the intrinsic and final pathways of the coagulation cascade, as well as the presence of specific (i.e., inhibitors against discrete coagulation factors) or nonspecific (i.e. inhibitors against antiphospholipids) inhibitors to reaction components, all affect the time to fibrin formation as measured by optical or mechanical methods (Paula et al., 2013;Rogers et al., 2007). Additionally, APTT is used to track the effects of the parenteral direct thrombin inhibitor argatroban, which is given to patients with thrombosis and thrombocytopenia brought on by heparin (Rasmussen et al., 2020). Moreover, evaluating hemostasis using screening tests like thrombin time (TT), APTT, and prothrombin time (PT) tests is rational. Typical results include extended APTT or PTT with normal PT and bleeding time (Bain et al., 2012). Studying coagulation factors must come after a prolonged screening test to establish the final diagnosis and gauge the severity of the condition and track the effectiveness of replacement therapy (Lippi et al., 2012).

Materials and Methods

Participants

The study was conducted between July 2020 and September 2021 in hemophilic patients who had been followed up at the National Center of Hematology, Mustansiriyah University. We included 68 men with hemophilia patients and 18 of control, and BMD measurement was performed only in the patients with hemophilia.

Bone Mineral Density (BMD) Measurement

The BMD of lumbar spin and fem¬oral neck was measured with a DXA (GE-Lunar, USA). A DEXA scan was performed on about 50% of patients under the supervision of a hematologist at the Center to measure BMD in lumbar spine (L1-L4) and femur bones (trochanter, shaft and neck). The functional independence score in hemophilia (FISH) was used to determine the limitation of movement (LOM).

Blood biochemistry analysis

All participants underwent (patients and control) the following laboratory assessments: blood group, complete blood count (CBC), activated partial thromboplastin time (APTT) and prothrombin time. According to ABO and Rh systems, blood groups in all subjects (patients and control) were determined by using blood groups typing kit from AFCO, Jordan.

CBC was determined on a full automated hematology analyzer DxH 500 from (Beckman Coulter, USA). APTT and pt. were analyzed with a coagulation analyzer. The study protocol was approved by in the National Center of Hematology, Mustansiriyah University. All subjects gave written informed consent.

Statistical Analysis

Vassar Stats Web Site for Statistical Computation is used to apply statistical analysis (Lowry, 2013). Categorical variables are reported as percentages, and the Chi-square test examines differences between several groups. The differences between two independent samples are analyzed using the t-test, while those between three independent samples are analyzed using the Tukey HSD and ANOVA tests. On the other hand, numerical values are expressed as mean ± standard deviation (M ± SD). The Pearson calculator test also examines the correlation between two variables. A two-tailed P value less than 0.05 is used to measure the significance of differences.

Results

According to T score, only 27 (39.7%) 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 (60.3%) patients were involved in the second group (abbreviated as DX0), as previously published (Rasha Ibrahim Salman et al., 2024).

The mean age of patients with hemophilia was (28.1 ± 8.9 years) and it was (30.6 ± 11 years) in the control group. Table -1 shows non-significant (P=0.308) difference in the average age between patients and control group. Also, there were no significant differences (P=0.422) in the frequency of adolescents and adult cases between two groups.

Table 1. The matched age between patients and control groups

Age (years)		Patients (N=68)	Control (N=18)	P value
Range		14 - 53	17 – 52	0.308
M ± SD		28.1 ± 8.9	30.6 ± 11	
Category (n, %)	Adolescents	10 (14.7%)	4 (22.2%)	0.442
	Adults	58 (85.3%)	14 (77.8%)	

Table 2. RBCs indices in patients and control groups

RBCs indices	Normal range	Patients' groups		Control	P value
		DX+ (n=27)	DX0 (n=41)		
Count (x 10^6/µl)	4.06 – 5.63	5.4 ± 0.5	5.1 ± 0.6	5.2 ± 0.4	0.148
Hb (g/dl)	12.5 – 16.3	14.7 ± 1.9	14.5 ± 2	14.1 ± 1.5	0.584
Hct (%)	36.7 – 47.1	44.8 ± 4.8	42.9 ± 4.7	45.4 ± 4.2	0.121
MCV (fl)	73 – 96.2	83.1 ± 11.5	85.8 ± 9.7	87.9 ± 7.4	0.259
MCH (pg)	23.9 – 33.4	27.3 ± 4.6	29.1 ± 3.8	27.4 ± 2.9	0.112
MCHC (g/dl)	30 – 36	33.1 ± 1.5	33.6 ± 1.4	32.9 ± 1.3	0.082
RDW-CV (%)	10.5 – 14.5	14.1 ± 2.5	14.1 ± 1.8	13.2 ± 1.7	0.074

Table 3. Totals and differential count of WBCs in patients and control group. NLR= neutrophil-lymphocyte ratio; Different small letters indicate significant difference between columns.

WBCs (x10^3/ µl)	Normal range	Patients' groups (n=68)		Control (n=18)	P value
		DX+ (n=27)	DX0 (n=41)		
Total count	3.6 – 10.2	7.6 ± 1.9	6.7 ± 1.7	6.9 ± 1.1	0.105
Neutrophil	1.7 – 7.6	4.3 ± 1.5	3.6 ± 1.6	3.3 ± 1	0.053
Lymphocyte	1 – 3.2	2.5 ± 0.7	2.4 ± 0.8	2.7 ± 0.6	0.324
Monocyte	0.3 – 1.1	0.49 ± 0.19	0.51 ± 0.21	0.53 ± 0.14	0.869
NLR	NA	1.9 ± 0.5 [a]	1.3 ± 0.4 [b]	1.1 ± 0.3 [b]	< 0.0001

Table 4. Hemostasis-related parameters in patients and control groups. PLT= platelets; PT=prothrombin time; APTT=activated-thromboplastin time; different small letters indicate significant difference between columns.

Parameter (M±SD)	Normal range	Patients (n=68)		Control (n=18)	P value
		DX+ (n=27)	DX0 (n=41)		
PLT (x10^3/ µl)	150 - 450	267 ± 108	256 ± 78	275 ± 77	0.741
PT (second)	14 – 17	14.1 ± 1.7	14 ± 2.4	14.1 ± 1.4	0.970
APTT (second)	21 - 35	69.2 ± 21.2 [a]	78.9 ± 24.5 [a]	25.6 ± 2.6 [b]	< 0.0001

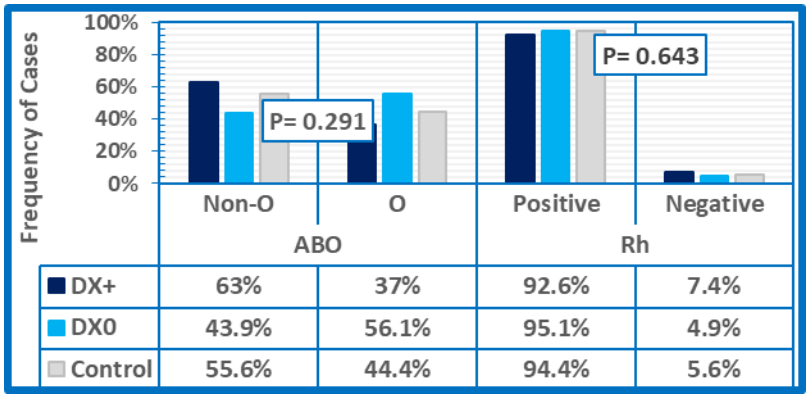

Figure 1. Frequency of ABO and Rh blood groups in control and patients.

Figure 1, which shows the distribution of blood groups B, A, AB, and O across patients of hemophilia and control groups, complies with the ABO system. The distribution regarding Rh blood groups across the control and patient groups shows no appreciable differences, and the Rh positive blood type predominates in all groups.

All RBCs indices [hemoglobin (Hb) concentration, RBCs count, hematocrit (Hct), and mean cell volume (MCV)] as determined by CBC. In both the control and patient groups, mean cell hemoglobin concentration (MCHC) and red cell distribution width-coefficient variation (RDW-CV)] are within the normal physiological range with no significant differences (Table -2).

Moreover, Table 3 shows that all values of the total and differential counts of WBCs are within physiologically normal values and without significant differences between patients and control groups. However, the neutrophil-lymphocyte ratio (NLR) in patients of DX+ group (1.9 ± 0.5) is significantly ($P < 0.0001$) higher than in its value in patients of DX0 and control groups (1.3 ± 0.4 and 1.1 ± 0.3 respectively).

On the other hand, Table 4 shows the non-significant difference in the platelets count (PLT) between patient's groups DX+, DX0 and control group (267 ± 108, 256 ± 78, and 275 ± 77 x103/ µl, respectively) and their values are within the normal range in all groups. Also, this table reveals non-significant differences in prothrombin time (PT) between all groups (14.1 ± 1.7s, 14 ± 2.4s, and 14.1 ± 1.4s, respectively) and their values are within normal range. However, activated-partial thromboplastin time (APTT) in DX+ and DX0 groups of patients (69.2 ± 21.2s, and 78.9 ± 24.5s, respectively) are significantly ($P < 0.0001$) higher than 25.6 ± 2.6s in the control group.

Discussions

According to Figure 1, results shows that the major clinical approach used to assess skeletal health is DEXA, which measures the amount of bone mineral divided by the area of bone scanned (Martineau et al., 2021). After observing femoral neck fractures and non-traumatic lumbar injuries in two adult males with severe hemophilia A, Gallacher and colleagues first evaluated BMD in patients with hemophilia. According to a study, frequent joint bleeding makes hemophiliacs more likely to have lower bone mineral density (Kovacs, 2008).In young adult hemophilia patients, BMD was reduced in about 70% of cases, with 43% exhibiting osteopenia and 27% exhibiting osteoporosis (Gerstner et al., 2009) Numerous studies show that hemophilic patients fracture more frequently than the normal population (Gay et al., 2015; Tuan et al., 2019) Recent case-control studies showed reduced BMD at various bone sites (Sossa et al., 2018; Ekinci et al., 2019; Linari et al., 2020). However, persons with severe hemophilia who have taken preventive factor treatment since childhood may nonetheless have normal BMD (Gamal Andrawes et al., 2020). The underlying pathogenetic mechanisms and etiology of hemophilia remain unclear, and it is unclear whether the coagulation dysfunction directly causes the low BMD or whether it develops due to comorbidities or lifestyle factors (Ashritha et al.,2019 ; Gebetsberger et al., 2022). Moreover, ABO blood group is the most significant blood group system in transfusion medicine and by employing the classical serological agglutination test (Daniels, 2009). The associations between ABO blood groups and certain diseases have been described. According to earlier research on hemophiliacs in Iraq, group O accounts for more than one third of cases, with the remaining cases having non-O blood groups but showing no appreciable variations in hemophilia types (Kadhim et al., 2019; Hameed et al., 2020).

Furthermore, a cohort study of 209 Italian individuals with severe hemophilia showed that the distribution of ABO blood groups was similar to that in the generally healthy general population (Franchini et al., 2017). The matching proportionate frequency of each form of hemorrhage (hemarthrosis, muscular bleeding, etc.) were also demonstrated by Sagir et al. (2017).

Furthermore, Sagir et al. (2017) showed that the corresponding relative frequencies of each type of bleed (hemarthrosis, muscle hematomas, epistaxis, gum bleeds, gastrointestinal hemorrhage and hematuria) were statistically similar between the two patient's categories of the ABO blood group categories (O and non-O). ABO blood types, on the other hand, were demonstrated to play a role in the inter-individual half-life variations of the infused FVIII and its in vivo immunogenicity in the recipient hemophiliacs, according to other studies (Vlot et al., 2000; Franchini et al., 2017). It was shown that hemophiliacs with O blood type have lower von Willi brand factor (vWf) antigen levels than hemophiliacs with blood groups other than O, which results in a shorter half-life of the infused FVIII and a correspondingly higher annual consumption of the clotting factors, which suggests higher bleeding rates (Vlot et al., 2000; Fischer et al., 2009). The present results show a normal blood picture of hemophilic patients, consistent with most studies dealing with hemophiliacs. It was observed that iron deficiency is highly common in patients with HA; out of the 39 patients studied, 19 were iron deficient, giving a total frequency of iron deficiency of 48.7%. Yet, other studies have documented an aberrant blood picture, for example. Compared to patients with non-severe HA (20%), those with severe HA (66.7%) exhibited a considerably higher prevalence of iron deficiency (Ahmed et al., 2015).

Additionally, a recent work discovered that 36 out of 50 hemophilic individuals (72%) had hemoglobin levels below 13 g/dl, which could be related to occult blood loss in the urine or stool or iron deposition in the synovial membrane during recurrent bleeding episodes. Because of this, iron deficiency is

common in haemophilia patients, and all patients' mean ferritin levels (21/ng) were within the lower range of normal (Poongavanam et al., 2017). However, the moderating effects of functional platelet variation on hemorrhagic diseases have received little attention. By utilizing early techniques for measuring platelet coagulant activity, the first study that looked at factors underlying phenotypic diversity in severe hemophilia was published in 1973 and showed that the mild group displayed higher levels of platelet coagulant activity than the severe group (Walsh et al., 1973). More specialized assay techniques were developed since this significant study was first published; these techniques centered on platelet-derived microparticles, which are acknowledged as crucial mediators of hemostasis and thrombosis with at least a fourfold variation of procoagulant microparticles in healthy individuals and even greater heterogeneity among hemophilia patients (Proulle et al., 2005; Yee, 2006). The effects of changes in platelet function in hemophilia remain to be more clearly identified, since recent research suggested that platelet function may contribute in part to variances in bleeding tendency in hemophilic patients with comparable factor levels (Zhou et al., 2015; Riedl et al., 2017).

Table 3 shows that patients in the DX+ group have a significantly higher neutrophil-lymphocyte ratio (NLR) than those in the DX0 and control groups. The importance of NLR as an inflammatory marker is connected to the pathophysiological pathway involving prothrombotic factors and inflammation, which is defined by an increase in circulating leukocytes and cytokines. While lymphocytes are important in inflammatory responses, neutrophils are essential in innate immune responses (Orfanu et al., 2017). Consequently, an elevated NLR shows an out-of-balance inflammatory response and can be employed as a prognostic marker in individuals with osteopenia as well as a potential indication of malignancies, infections, intestinal inflammatory illnesses, cardiovascular diseases, and other diseases (Omar et al., 2018; Farah et al., 2020; Önder et al., 2021; Song et al., 2021). The current study's findings, which are congruent with those of Dagli et al.,(2018) show that low BMD and NLR in patients with hemophilia do not significantly correlate. However, numerous studies have shown this connection in several illnesses. Examples include the finding that NLR is a single marker for osteoporosis by Öztürk et al. (2013) and that inflammation is present during bone remodeling. Huang and Li (2016), also found a significant association between NLR and BMD in osteoporotic postmenopausal women. Activated partial thromboplastin time is a crucial examination when a patient tends to bleed, for monitoring hemophilia or unfractionated heparin therapy, or when there is a specific suspicion. It serves as a broad measure regarding coagulation's intrinsic and common pathway.

Additionally, APTT is used to track the effects of the parenteral direct thrombin inhibitor argatroban, which is given to patients with thrombosis and thrombocytopenia brought on by heparin (Rasmussen et al., 2020). It was established that a prolonged APTT is suggestive of hemophilia in the presence of a normal prothrombin time and platelet count, which is consistent with the present study's findings (Srivastava et al., 2013). The increase in neutrophils-lymphocytes ratio (NLR) and prolonged APTT may be a marker that increases the risk of developing low bone density in hemophilic patients.

Conclusion

In conclusion, this study showed a concerning prevalence of low bone mineral density (BMD) among hemophilic patients, indicating a potential link to elevated neutrophil-lymphocyte ratio (NLR) and prolonged activated partial thromboplastin time (APTT). The findings determined the importance of vigilance for bone health in hemophilia management, as recurrent hemorrhages and decreased mobility contribute to BMD reduction. While the study elucidates hematological parameters and their association with BMD, further research is warranted to elucidate the underlying mechanisms and optimize preventative strategies. Enhanced awareness and tailored interventions may mitigate the risk of low BMD and associated complications in this vulnerable population.

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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