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ORIGINAL ARTICLE

# Vitamin D Status and Risk of Osteoporosis in Hemophilia Patients

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## ABSTRACT

**Aim:** Assessment of vitamin D status in Hemophilia patients at Zagazig University Children Hospitals.

**Subjects& Methods:** The study was carried out at the Pediatrics and Clinical Pathology Departments/ Zagazig University Children Hospitals (ZUCH) during the period from February 2018 to August 2018. The study was performed on 30 Hemophilia A male children aged from 6 to 18 years old. Participants were registered in and were followed up regularly, at the Pediatric Hematology Outpatient Clinics. Participants were subjected to medical history taking, assessment of the body mass index (BMI) and investigations that included Ca, Ph, ALP, vitamin D. Statistical analysis for obtained data using suitable significance tests was performed.

**Results:** 53.3 % of Hemophilia patients showed marked factor VIII deficiency compared to 33.3% who showed moderated deficiency. 26.7% of all patients showed deficiency of vitamin D (10-19.99 ng/dl) compared to 40% who had severe deficiency of vitamin D (level <10 ng/dl).

**Conclusion:** There was a statistically significant direct proportion between both factor VIII and vitamin D deficiencies as the severer factor VIII deficiency, the lower vitamin D level.

**Keywords:** Hemophilia, Vitamin D, ZUCH.

## INTRODUCTION

Hemophilia is an inherited disorder caused by a deficiency of coagulation factor VIII that results in musculoskeletal bleeding including hemarthrosis and musculoskeletal complications. This joint arthropathy has many longstanding consequences on bone health that is usually accompanied by inactivity and chronic bone pain **[1].**

Lack of exposure to sunlight in Hemophilia patients due to restriction of movement caused by arthropathy may lead to deficiency of vitamin D as sunlight is regarded the principal source of vitamin D production **[2].**

Vitamin D has an essential role in calcium (Ca) absorption and bone mineralization. Osteoclasts, osteocytes, and hematopoietic cells are the main receptors in which vitamin D is expressed. They affect bone development, resorption, and hematopoiesis. Vitamin D deficiency leads to reduced bone density and osteoporosis **[3].**

## STUDY DESIGN

The current study is a cross sectional study that was carried out at the Zagazig University Children Hospital during the period from February 2018 to August 2018.

The study was performed on 30 Hemophilia A male children aged from 6 to 18 years old. Participants were registered in and were followed up regularly, at Pediatric Hematology Outpatient Clinics. Ethical approval for the study was obtained from the Institutional Review Board (IRB) at the faculty of medicine, Zagazig University. Written informed consent was obtained from all participants' parents, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the

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Volume 28, Issue 3, May 2022, Page 534 -541

World Medical Association (Declaration of Helsinki) for studies involving humans.

## METHODS

After detailed history taking and general examination, assessment of the body mass index (BMI) was done **[4].** In addition, the following investigations were done:

i. Serum Ca, phosphorus (Ph) and alkaline phosphatase (ALP) levels.
ii. Serum vitamin D (25(OH)D) and Parathormone levels; using Vitamin D ELISA KIT, Cayman Chemicals, USA [5].
iii. The collected data were tabulated and analysed using SPSS version 24 software (SPSS Inc, Chicago, ILL Company). distributed. Categorical data were presented as number and percentages. Chi square test (X2), or Fisher's exact test (FET) were used to analyze categorical variables. Quantitative data were tested for normality using Kolomogrov Smirnove test assuming normality at P>0.05. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was used to analyze normally distributed variables among 2 independent groups, or Man Whitney U test for nonparametric ones. Difference among 3 independent means was analyzed using ANOVA for parametric variables or Kruskal Wallis test (KWT) for nonparametric ones. Spearman's correlation coefficient (rho) was used to assess correlation between non parametric variables. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant, P≤0.001 is highly significant (HS), P value >0.05 is non-significant (N-S) [6].

## RESULTS

Table (1): Demographic data of the studied Hemophilia Patients: the current study included (30 male) Hemophilia Patients, their age ranged from 6 to 22 years old and mean age was 12.17± 4.1 years old.

Table (2): Clinical presentation of Patients:13.3% of the studied patients complained of lt knee joint Hemarthrosis while Both Knee joints Hemarthrosis is found in 36.7% of the studied patients, regarding muscle hematoma, iliopsoas is the most prominent muscle hematoma followed by quadriceps and calf muscles (13.3%, 6.7% & 6.7%) respectively, Epistaxis and Bleeding per gum are found in (16.7% & 6.7%) respectively.

Table (3): Orthopedic manifestation of studied patients: 16.7 % of the studied patients has no bone pain, while about 1/3 of the studied hemophilia patients complained of bone pain (30%), and Bone pain is accompanied with chronic arthropathy in 40% of the studied patients, regarding fracture it is found on top off Bone pain and chronic arthropathy in 13.3% of the studied patients.

Figure (1): Pie diagram showing the degree of severity in factor VIII deficiency among participants (Mild (> 5%); Moderate (1- 5%); Severe (< 1%)), showing that 16.7 % of the studied patients has no bone pain, while about 1/3 of the studied hemophilia patients complained of bone pain (30%), and Bone pain is accompanied with chronic arthropathy in 40% of the studied patients, regarding fracture it is found on top off Bone pain and chronic arthropathy in 13.3% of the studied patients.

Table (4): Serum levels of Ca+, Ph and ALP among patients: the mean of serum Ca+ among the studied group is 9.04±1.26 (mg/dL), with a range from (7-11.2 mg/dL). And mean of serum ALP among the studied group is 235.43±73.54 (IU/L), with a range from (108-400 IU/L).

Table (5): Vitamin D level, status and parathyroid hormone level among participants: the mean of vitamin D level among the studied group is 18.13±10.56 (ng/ml), with a range from (4.53-27.10) (ng/ml) and 40% of the studied group had sever deficiency of vitamin D.

Table (6): Body mass index (BMI) among patients: the mean of body mass index among the studied Hemophilia patients was 20.98±8.29 kg/ ht2, with a range from 11 to 47

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Volume 28, Issue 3, May 2022, Page 534 -541

kg/ ht2, and half of the studied patients were healthy weight (50%) and 13.3% of were obese.

Table (7): Severity of Hemophilia in relation to Vitamin D level and status among patients: there was highly statistically significant difference between mean vitamin D level, vitamin D status and severity of hemophilia.

**Table (1):** Demographic data of the studied Hemophilia Patients

| Demographic data | Studied patients (N=30) | |
|---|---|---|
| | No. | % |
| **Age (years)** | | |
| Mean ± SD | 12.17± 4.1 | |
| Median (Range) | 11.5 (6-18) | |

N: number of patients included.

**Table (2**): Clinical presentation of Patients**.**

| Item | Studied patients (N=30) | |
|---|---|---|
| | No. | % |
| **Joint bleeding** | | |
| • Rt knee joint | 3 | 10.0 |
| • Lt knee joint | 4 | 13.3 |
| • Both Knee joints | 11 | 36.7 |
| **Muscle bleeding (hematoma)** | | |
| • Iliopsoas | 4 | 13.3 |
| • Quadriceps | 2 | 6.7 |
| • Calf muscle | 2 | 6.7 |
| **Mucous membrane bleeding** | | |
| • Bleeding per gum | 2 | 6.7 |
| • Epistaxis | 5 | 16.7 |

N: number of patients included.

**Table (3):** Orthopedic manifestation of studied patients

| Item | Studied patients (N=30) | |
|---|---|---|
| | No. | % |
| **Orthopedic manifestation** | | |
| • No bone pain | 5 | 16.7 |
| • Bone pain | 9 | 30.0 |
| • Bone pain + chronic arthropathy | 12 | 40.0 |
| • Bone pain + fracture + chronic arthropathy | 4 | 13.3 |

N: number of patients included.

**Table (4):** Serum levels of Ca+, Ph and ALP among patients

| Item | Studied patients (N=30) |
|---|---|
| **Serum Ca+ (mg/dL)** | |
| ▪ Mean ± SD | 9.04±1.26 |
| ▪ Median (Range) | 9.3(7-11.2) |
| **Serum Ph (mg/dL)** | |

https://dx.doi.org/10.21608/zumj.2020.16685.1703
Volume 28, Issue 3, May 2022, Page 534 -541

| Item | Studied patients (N=30) |
|---|---|
| ▪ Mean ± SD | 4.05±1.11 |
| ▪ Median (Range) | 4.0(2.4-7) |
| **Serum ALP (IU/L)** | |
| ▪ Mean ± SD | 235.43±73.54 |
| ▪ Median (Range) | 230.5(108-400) |

Ca: Calcium, Ph: Phosphate, AlP: Alkaline Phosphatase

**Table (5):** Vitamin D level, status and parathyroid hormone level among participants

| Item | Studied patients (N=30) | |
|---|---|---|
| | **No** | **%** |
| **Vitamin D status** | | |
| • Severe Deficiency (< 10 ng/ml) | 12 | 40.0 |
| • Deficiency (10-19.99 ng/ml) | 8 | 26.7 |
| • Insufficiency (20-29.99 ng/ml) | 10 | 33.3 |
| • Normal (>30 ng/ml) | 0 | 0.0 |
| **Vitamin D level(ng/ml)** | | |
| ▪ Mean ± SD | 18.13±10.56 | |
| ▪ Median (Range) | 16(4.53-29.10) | |
| **Parathyroid Hormone (pg/mL)** | | |
| ▪ Mean ± SD | 43.6±19.47 | |
| ▪ Median (Range) | 38.1(10.8-98.9) | |

**Table (6):** Body mass index (BMI) among patients.

| Item | Studied patients (N=30) | |
|---|---|---|
| | **No** | **%** |
| **BMI (Kg/ht$^2$)** | | |
| ▪ Mean ± SD | 20.98±8.29 | |
| ▪ Median (Range) | 20(11-47) | |
| **Body mass index** | | |
| Underweight: BMI (< 18.5 Kg/ht$^2$) | 10 | 33.3 |
| Healthy weight: BMI (18.5 -24.9 Kg/ht$^2$) | 15 | 50.0 |
| Overweight: BMI (25 - 29.9 Kg/ht$^2$) | 1 | 3.3 |
| Obese: BMI (≥ 30 Kg/ht$^2$) | 4 | 13.3 |

BMI: Body mass index

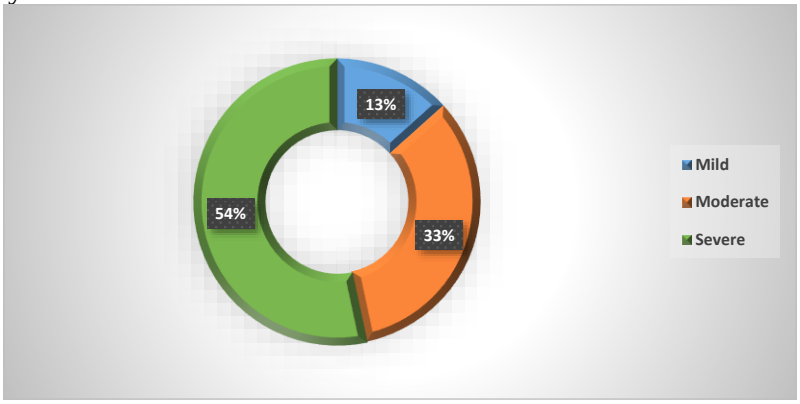


**Figure (1):** Pie diagram showing the degree of severity in factor VIII deficiency among participants (Mild (> 5%); Moderate (1- 5%); Severe (< 1%)).

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Volume 28, Issue 3, May 2022, Page 534 -541

## DISCUSSION

Hemophilia A is an x-linked recessive inherited bleeding disorder which distributed worldwide. The clinical manifestations of bleeding vary from superficial ecchymosis to lethal hemorrhage in central nervous system that occurs either spontaneously or after trauma and surgery **[7].** Hemarthrosis (bleeding in joint) is common in Hemophilia patients. Recurrent hemarthrosis causes joint destruction and thus results in arthropathy and disability that are common prior to adulthood **[8].**

The current study included 30 male Patients with Hemophilia A, with mean age of 12.17± 4.1 years old. According to clinical presentations of the studied patients our results revealed that about 60% of patients had hemarthrosis mainly in both knee joints, (36.7 %), and 83.3% of studied patients complained of bone pain which was accompanied with chronic arthropathy in 40% of them and fracture in (13.3%). These results are in consistence with **Rodriguez-Merchan [9]** who reported that hemarthrosis tends to recur despite the synovial membrane's capacity to reabsorb the blood. So, patients with chronic Hemophilia arthropathy will tend to have local disuse, muscular atrophy and pain. Muscle hematomas can occur in any part of the body although the most common sites are the iliopsoas muscle and the flexor compartment of the forearm **[10].**

Similarly, we found Muscle hematoma in 26.7% mainly in iliopsoas muscle (13.3%) followed by quadriceps as well as calf muscles each (6.7%). **Palatucci et al. [11]** showed that intramuscular hematomas were a common acute bleeding episode in persons with hematoma because of trauma, especially from intramuscular injections otherwise, in iliopsoas mainly which agreed with our results.

Our results showed that the mean of body mass index among the studied Hemophilia patients was 20.98±8.29 kg/ ht2, and half of them had healthy weight and only 13.3% of them are obese, but with no significant difference. In the contrary, **Tlacuilo-Parra et al. [12]** reported in their study that the mean body mass index among patients was high 22.65 ±8.28 kg/ ht2 in severe Hemophilia patients with normal BMD versus 19.48 ±4.29 kg/ ht2 p-0.039.

The current study showed that the mean serum Ca+ among the studied group was 9.04±1.26 mg/dl and mean serum phosphorus was 4.05±1.11 mg/dl, and the mean serum alkaline phosphatase was 235.43±73.54 IU\L. **Kriemler et al. [13]** agreed with the current results concerning serum calcium and phosphorus that were within normal reference range, however they disageed with the present work concerning alkaline phosphatase which as they reported normal alkaline phosphatase serum level. This could be explained by severe bone morbidity and lack of adherence for calcium and vitamin D supplementations. Also, **Albayrak and Albayrak et al. [14]** reported in their study that mean serum Ca+, PH and alkaline phosphatase were 9.68 ± 0.4 mg/dl, 4.51 ±0.68 mg/dl and 191.25± 65.69 IU\L respectively. Similarly, **Eldash et al. [15]** and **Kiper-Unal et al. [16]** reported that the means of serum Ca+ among their studied Hemophilia patients were 9.3±1.1 mg/dl and 9.7±0.4 mg/dl and the mean serum phosphorus was 4.1±1.7 mg/dl and 3.1±0.6 mg/dl, respectively which were slightly higher in both studies in serum calcium level than the results of current study and slightly lower in serum phosphorus.

In our study we found that the mean vitamin D level among the studied group was 18.13±10.56 (ng/ml), 40% of the patients had severe vitamin D deficiency, 26.7% had vitamin D deficiency and 33.3% had insufficient vitamin D level. Similarly, **Albayrak and Albayrak et al. [14]** reported in their study that the mean vitamin D level among his study Hemophilia patients was 16.35±7.49 ng/ml, and they found a high degree (96%) of vitamin D deficiency among Hemophilia children and they reported that Hemophilia patients are prone to vitamin D deficiency countrywide and perhaps worldwide and this deficiency results from both Hemophilia-related factors and is a reflection of the prevalence of vitamin D deficiency in healthy children.

Studies have published data about vitamin D levels in adult Hemophilia patients. Three of them report a high prevalence of vitamin D deficiency and two report no difference and reported percentage deficiencies of 67, 47, and 87%, respectively **(Gerstner et al. [17], Paschou et al. [3] and Linari et al. [18].** On the contrary, **Katsarou et al. [2]** reported no difference from controls.

In a Pediatric osteoporosis study from Turkey, mean 25-OH vitamin D levels were lower in Hemophilia children compared with their healthy age-matched controls (9.1± 4.9 vs. 42.2± 6.8ng/ml) **[19].** That study did not supply the ratio of deficient to healthy patients; this study is from a sunny country but shows low mean levels in Hemophilia children. In the other study, **Ranta et al. [20]** reported normal mean values (47± 17ng/ml) in Hemophilia children with 50% insufficiency. The study is from Finland, a country having vitamin D supplementation and fish-rich nutrition. In an Egyptian study conducted by **Eldash et al. [15],** they reported that 43.2 and 35.1% of children with Hemophilia had moderate and mild vitamin D deficiency, respectively, with significant difference between cases and controls. These differences may be partially attributed to the high prevalence of vitamin D deficiency worldwide **[21]** and small sample size **[3].** The variances in vitamin D deficiency ratios among children with Hemophilia advocate that vitamin D levels should be tested in each geographic area and repeated over time.

Regarding relation between severity of Hemophilia and level of vitamin D, our results revealed that there was a significant association between severity in Hemophilia A and level of vitamin D, where mean vitamin D level in patients with severe Hemophilia A was 10.04±4.12 ng/ ml versus 23.29±7.23ng/ ml and 17.66±9.07 ng/ ml in mild and moderate Hemophilia respectively. p value=0.003. also, 87.5% of patients with severe Hemophilia A showed severe deficiency of vitamin D versus 25% and 20% in patients with mild and moderate Hemophilia respectively p value=0.041. Similarly, **Sanadhya and Singh [22]** found a statistically significant correlation between serum Vitamin D levels and severity of Hemophilia. Where 97.14% of patient with sever Hemophilia had insufficient vitamin D level and they concluded that as the severity of Hemophilia increases, the severity of vitamin D deficiency also increases. Similar results were reported by **Linari et al. [18]** in their study conducted in Greece. **Albayrak and Albayrak et al. [14]** that a high degree of vitamin D deficiency among Hemophilia children and this high degree of deficiency in children with Hemophilia suggested that Hemophilia patients were prone to vitamin D deficiency.

**Eldash et al. [15]** proposed that Hemophilia-related elements may increase the liability for vitamin D deficiency among children with Hemophilia. In their study, 43.2 and 35.1% of children with Hemophilia had moderate and mild vitamin D deficiency, respectively with significant difference between Hemophilia patients and healthy control and they suggested that this deficiency resulted from several factors. Some factors may be due to reduced exposure time to sun, area exposed, and depth of penetration, Immobilization due to arthropathy and frequent hospitalizations also may result in a degree of sun light deprivation. In addition, rapid changes in calcium metabolism caused by immobilization and inactivity can decrease vitamin D levels.

The current study showed that the mean of body mass indexes among the studied Hemophilia patients was 20.98±8.29 kg/ ht2, and half of the studied patients were healthy weight (50%), only 13.3% of them are obese. The mean among the studied severe Hemophilia patients is 20.44 ±9.02 kg/ ht2. **Tlacuilo-parra et al. [23]** reported in their study that the proportion of obese and overweight patients according to the severity of Hemophilia was as follows: 28% in mild, 20% in moderate and 33% in sever Hemophilia A; however, the difference between groups wasn't significant (P=0.620).

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Volume 28, Issue 3, May 2022, Page 534 -541

## SUPPLEMENTARY DATA

**Table (7):** Severity of Hemophilia in relation to Vitamin D level and status among patients.

| variable | Severity according to factor level | | | | | | Test | p- value |
|---|---|---|---|---|---|---|---|---|
| | Mild (N=4) | | Moderate (N=10) | | Severe (N=16) | | | |
| | No | % | No | % | No | % | | |
| **Vitamin D level(ng/ml)** | | | | | | | **KWT** | |
| Mean ± SD | 23.29±7.23 | | 17.66±9.07 | | 10.04±4.12 | | 11.730 | 0.003* (S) |
| Median (Range) | 20.5 (5.3-29.1) | | 16.15 (9.8-26.26) | | 8.86 (4.53-16.28) | | | |
| **Vitamin D status** | | | | | | | **$X^2$** | |
| • Severe Deficiency | 0 | 0.0 | 2 | 20.0 | 8 | 50.0 | 9.503 | 0.041* (S) |
| • Deficiency | 1 | 25.0 | 2 | 20.0 | 6 | 37.5 | | |
| • Insufficient | 3 | 75.0 | 6 | 60.0 | 2 | 12.5 | | |

*N: number of patients, KWT: Kruskal-Wallis test; $X^2$: Chi-square test; P- value < 0.05 is significant; S: significant*