

## The Study of Bone Turnover and Bone Markers in Children with Hypermobility Syndrome

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### Abstract

**Background:** Hypermobility syndrome is a prevalent condition that affects many people. A few researches have suggested that hypermobility syndrome is linked to osteopenia and can impact bone mineral density (BMD). The aim of the present study is to determine BMD, serum vitamin D level and biochemical markers of bone turnover in children with benign joint hypermobility syndrome (BJHS). **Methods:** This study comprised thirty-seven children diagnosed with BJHS together with thirty-nine children with similar demographic features as controls. All children were subjected to full medical history, nutritional history, clinical examination, laboratory investigations (serum vitamin D, serum osteocalcin, beta cross lap). Assessment of BMD was done by dual energy x-ray absorptiometry (DEXA) scan. **Results:** Children with BJHS had significant lower serum vitamin D level ( $P < 0.001$ ) although insignificant differences ( $p > 0.05$ ) were detected among the studied groups regarding mean serum osteocalcin and beta cross lap. Among patients with BJHS, the frequency of low BMD was 8.11 % while no patients had osteoporosis. No significant differences ( $p > 0.05$ ) were reported among the studied groups regarding BMD measurements. **Conclusion:** The current study concluded that vitamin D deficiency is more prevalent in children with BJHS. Raising awareness among rheumatologists and pediatricians of the possibility of this condition among children with BJHS is warranted to early detection and management of such cases.

**Key words:** Hypermobility syndrome, vitamin D deficiency, BMD

## Background

The hypermobility syndrome is defined by the British Society of Rheumatology (1992) as the presence of musculoskeletal pain or arthralgia accompanied with hypermobility for at least three months (1).

The hypermobility syndrome is one of the most common causes of musculoskeletal symptoms in adolescents, particularly in girls; In children, it is either a benign condition or may be associated with connective tissue hereditary diseases like Ehlers-Danlos syndrome and Marfan syndrome (2, 3 & 4). Chronic pain, weariness, low bone density, osteoporosis, and fractures have all been linked to hypermobile Ehlers-Danlos syndrome (5, 6).

Few researchers have looked at vitamin D levels in hypermobility syndrome and their relationship to musculoskeletal problems. There isn't enough information on vitamin D levels in the Ehlers-Danlos and hypermobility syndrome groups (7).

Dual energy X-ray absorptiometry (DEXA) has become a widely available and clinically beneficial technology in the assessment and therapy of adult bone disorders since its release in 1987 (8).

Biochemical indicators of bone turnover are readily available techniques for assessing

bone production (osteocalcin, procollagen type 1 propeptides aminoterminal) and resorption (crosslinking telopeptides of type 1 collagen C-terminal), however they are age and puberty dependent (9).

The purpose of this study was to determine bone mineral density (BMD), serum vitamin D level, and biochemical markers of bone turnover in children with benign hypermobility syndrome.

### Methods:

This case control study included 37 children diagnosed with benign joint hypermobility syndrome (group A) and 39 healthy children (group B) matched for age and sex as a control group. Patients were recruited from Rheumatology clinic at Jameel clinics, Jeddah; KSA between January 2018 and December 2020. The study was approved by the local ethical committee. Parents of patients and children included in this study signed a written informed consent form prior to participation.

The diagnosis of hypermobility syndrome was done based on Carter and Wilkinson's criteria, which were partly modified by Beighton and Horan (10).

Patients were excluded if age >18 years, had any chronic disease, were taking any

drugs, hormones, or calcium supplements within the previous six months.

Healthy children were chosen from the patients' peers, including the patients' brothers, sisters, and cousins.

### **Procedures**

All patients, including the control group, were given a complete medical history including nutrition history of daily food intake, drug history, and also history of daily activity. Thorough clinical examination was performed.

### **Bone mineral density measurement:**

Dual energy x-ray absorptiometry (DEXA) scan (DEXA – GE Lunar Prodigy™, Lunar Corp., USA) was used to measure BMD where measurements were made at bilateral femoral necks (FN), lumbar spine vertebra from L2 to L4 (LS2-4), and total body (TB) bone mineral density (BMD, g. Cm/2). Z scores were used to compare BMD to that of normal subjects of the same age and gender. A BMD z - score of  $< -2$  SD was used to define low bone mass according to Bianchi study (*II*).

### **Bone Metabolism**

Venipuncture was used to acquire blood samples under complete aseptic conditions.

Frozen serum samples ( $-80^{\circ}\text{C}$ ) were tested for biochemical indicators. On the automated analyzer Elecsys, the parameters of beta-Cross Laps (CTX) and N-MID osteocalcin (OC) were evaluated in serum using electrochemiluminescence immunoassays (ECLIA) according to manufacture instructions (Roche diagnostics, Rotkreuz, Switzerland).

### **Serum Measurements of Vitamin D**

A competitive binding radioimmunoassay (RIA) approach was used to test serum 25-hydroxyvitamin D (25OHD) among the included participants. Subjects were divided into four groups based on their serum vitamin D levels:

- 1) Severe vitamin D deficiency, with serum vitamin D concentration of less than 10 ng/ml.
- 2) Serum vitamin D levels varied from 10 to 19 ng/ml, indicating moderate insufficiency.
- 3) Mild deficiency, with serum vitamin D levels ranging from 20 to 29 ng/ml.

4) Normal serum vitamin D levels varied from 30-80 ng/ml.

Other minerals, such as calcium, magnesium, and phosphorus levels in the blood, were measured using normal laboratory protocols.

### Statistical analysis

For statistical analysis, statistical package for social science (SPSS) version 11.0 was utilized. The mean and standard deviation were used to present the data. The Chi-square test was used to look at the statistical differences and correlations between the two groups. A P value was smaller than 0.05, was considered significant. A P values less than 0.001 were judged highly significant.

### Results

The current study was conducted on two groups.

Group A: 37 children with benign hypermobility syndrome, 29 boys (78.38 %) and 8 girls (21.62 %); their ages ranged between 3 and 6 years old, with a mean of  $4.75 \pm 0.55$  years. The disease duration ranged from 3 and 6 years old, with a mean of  $4.75 \pm 0.55$  years.

Group B: 39 healthy children, they were, 31 boys (79.49%) and 9 girls (20.51%). Their ages ranged between 3 and 7 years old with a mean of  $4.95 \pm 0.63$  years. No statistically significant differences were reported between the studied groups regarding age and sex distribution ( $P > 0.05$ ).

In group A: 3 (8.11%) patients had osteopenia, Z-score of total body BMD  $< -1$  and  $> -2.5$  ( $-1.72 \pm 0.07$ ), no patients had osteoporosis.

In group B: 1 (2.56%) child had osteopenia with Z-score of total body BMD  $-1.5$  and no children had osteoporosis. (**Table 1**)

**Table 1:** shows no statistical significant differences between the studied groups regards bone mineral properties.

Bone biomarker levels were within normal ranges in both groups; there were no significant differences regarding mean serum level of bone biochemical markers between the studied groups (**Table 2**).

Mean serum level of vitamin D was significantly lower in group A than group B ( $P < 0.05$ ).

It was noticed that serum level of calcium, phosphorus and magnesium

were significantly decreased in group A than group B, but regarding serum level of potassium there were no significant changes between both groups (**table 3**).

with severe and moderate vitamin D deficiency, while there was no significant difference regarding patients with mild deficiency **Figure (1)**.

There was significant difference between both groups regarding number of patients

**Table 1:** Comparison between the studied groups regarding bone mineral properties

Variables	Group A	Group B	p-value
Total body BMD (g/cm-2)	0.94 ± 0.03	0.96 ± 0.04	> 0.05
Total body BMD z-score	0.10 ± 1.08	0.13 ± 1.09	> 0.05
L2-4 BMD (g/cm-2)	0.83 ± 0.02	0.86 ± 0.03	> 0.05
L2-4 BMD z-score	-0.19 ± 1.02	-0.21 ± 1.16	> 0.05
Femoral neck BMD (g/cm-2)	0.87 ± 0.02	0.89 ± 0.03	> 0.05
Femoral neck BMD z-score	-0.18 ± 1.13	-0.22 ± 1.17	> 0.05

BMD : bone mineral density, L 2-4 , lumbar vertebrae from L2 to L4

**Table 2:** Comparison between the studied groups regarding bone biomarker levels

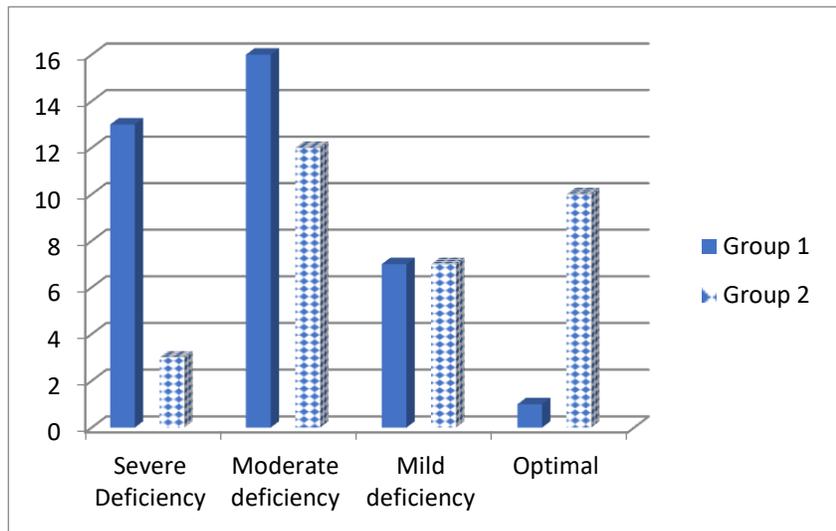
Variables	Group A	Group B	p-value
OC (ng/ml)	103.39 ± 5.27	105.32 ± 6.78	> 0.05
CTX (ng/ml)	0.99 ± 0.07	1.10 ± 0.08	> 0.05

CTX : beta-Cross Laps , OC : N-MID osteocalcin , ng/ml: nanogram/milliliter

**Table 3:** Comparison between the studied groups regarding mean serum levels of vitamin D and minerals

Variables	Group A	Group B	p-value
Vitamin D (ng/ml)	7.23 ± 1.76	27.96 ± 1.82	<0.001*
Magnesium (mmol/L)	0.75±0.13	0.89±0.21	<0.05*
Potassium (mmol/L)	4.59±0.51	4.56±0.52	> 0.05
Calcium (mmol/L)	2.09±0.13	2.41±0.14	<0.05*
Phosphorous (mmol/L)	1.36±0.31	1.68±0.34	<0.05*

P-value detected by Chi-square test, ng/ml: nanogram/milliliter , mmol/L : mill mole / litter



**Figure 1:** Comparison between the studied groups regarding grades of vitamin D deficiency

## Discussion:

BJHS is an under diagnosed heritable connective tissue disorder, with generalized joint hypermobility and a wide range of visceral, pelvic, neurologic, and cognitive dysfunctions which may be associated with deterioration of quality of life (QoL) mainly due to pain and the manifested fatigue (12).

Few studies on the benign joint hypermobility syndrome suggest that there is tendency of decrease bone density, low serum vitamin D and affect bone biomarker, but there are conflicting results. (13)

The aim of this study was to determine BMD, serum vitamin D level, and biochemical markers of bone turnover in children with BJHS.

The present study revealed that serum vitamin D level in children with hypermobility syndrome were significantly lower than in healthy children; 13 (35.14%) patients had severe vitamin D deficiency. However, no significant differences regarding BMD and bone biochemical indicators between the studied groups ( $p>0.05$ ).

With agreement to our results, it was found that serum vitamin D levels were lower in females with hypermobility syndromes when compared to healthy children, but the difference was not significant (14).

It was reported that bone mineral density of the femoral and trochanteric bones, as well as t and z scores, were significantly lower in patients with hypermobility syndrome compared to normal subjects; they also discovered that hypermobility increases the risk of low bone mass by 1.8 times (13).

It was proved that bone mineral density, both T-score and z-score, were significantly lower in children with hypermobility syndrome compared to the control group, and that hypermobility syndrome increased the risk of low bone mass by 2.6 times when compared to normal children (15).

When comparing normal children to children with joint hypermobility and children with musculoskeletal pain (independent of hypermobility), Adriana et

al., 2002, found that bone mineral density was significantly lower in children with joint hypermobility and in children with musculoskeletal pain (independent of hypermobility), which agrees with our findings (16).

Dolan et al., 2003, reported that joint hypermobility had no effect on bone mineral density, which varies from our findings; however their investigation was conducted on postmenopausal women (17).

**Conclusion:** The current study concluded that vitamin D deficiency is more prevalent in children with benign hypermobility syndrome. Raising awareness among rheumatologists and pediatricians of the possibility of this condition among children with BJHS is warranted to early detection and management of such cases.

Limitations of the current study include the relatively small sample size. In addition, the study was limited to a definite age group also the included variables should be measured in other conditions associated with hypermobility syndrome.

## List of abbreviations

Bone mineral density	BMD
BJHS	Benign joint hypermobility syndrome
Dual energy x-ray absorptiometry	DEXA
Femoral necks	FN
Total body	TB

Beta-Cross Laps	CTX
N-MID osteocalcin	OC
Electrochemiluminescence immunoassays	ECLIA

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