Assessment of Serum Vitamin D, Serum Calcium and Bone Mineral Density in Juvenile Idiopathic Arthritis Patients of Bangladesh

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ABSTRACT

Objective: To assess the serum concentrations of vitamin D and calcium and bone mineral density (BMD) in patients with juvenile idiopathic arthritis (JIA) and to compare them with those of healthy children.

Patients & Methods: A total of 75 JIA children were evaluated and compared to healthy individuals matched for age and sex in this cross-sectional case-control study. Laboratory evaluations included serum calcium and 25-hydroxyvitamin D. The normal range of serum calcium was 9-11 mg/dl; vitamin D was classified as normal (>32 ng/ml), insufficient (20-32 ng/ml), and deficient (<20 ng/ml). BMD was assessed by dual-energy X-ray absorptiometry (DXA) of the lumbar spine and both femur necks. BMD (in g/cm²) was expressed in Z score, the number of standard deviations above or below the mean value of an age- and sex-matched reference population. In children, low bone mass was defined as a Z-score equal or less than minus 2 (-2).

Results: The mean vitamin D level in both cases and controls was low, which was 18.66 ± 10.22 and 21.3 ± 4.07, respectively. Vitamin D deficiency and insufficiency in JIA patients were 69.3% and 21.3%, respectively. The mean concentration of serum calcium of cases was 9.46±0.46 mg/dl. Low bone mass in JIA patients' lumbar, right femur, and left femur was found in 97.3%, 69.3%, and 70.7%, respectively ($p < 0.001$, 0.023, 0.016). All types of JIA had low bone mass in lumbar vertebrae. BMD Z-scores in the right and left femoral necks showed a significant correlation with types of JIA ($p=0.007$ and 0.035, respectively). There was no significant association between disease duration and vitamin D or BMD at any sites in our study.

Conclusion: The study indicated that hypovitaminosis D and low bone mass are common in JIA patients and healthy controls in Bangladesh. It highlights the need to enhance dietary intake of calcium and vitamin D, along with promoting physical activities and sunlight exposure for JIA patients.

Keywords: Juvenile idiopathic arthritis, Dual energy X-ray Absorptiometry, Bone mineral density, 25-hydroxy vitamin-D

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the most common chronic illnesses of childhood. The International League of Associations for Rheumatology (ILAR) defined JIA as "definite arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks. " JIA is divided into seven subgroups: polyarticular RF-positive, polyarticular RF-negative, oligoarticular, systemic, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis (1). The worldwide incidence of JIA ranges from 0.8 to 22.6 per 100,000 children per year, with the prevalence ranging from 7 to 401 per 100,000 children (2). A pilot study conducted in a semi-urban area of Bangladesh showed that the prevalence of JIA was 60.5 per 100,000 children (3).

Both immunogenetic susceptibility & external triggers play a role in the pathogenesis of JIA. Here T lymphocytes have a central role releasing pro-inflammatory cytokines like TNF-α, IL-6 & IL-1, which induce inflammation in JIA (2). TNF-α significantly elevates bone resorption and attenuates osteoblastogenesis and bone formation (4).

There are multifactorial causes of bone loss in JIA. These include poor nutrition, decreased appetite and inadequate sun exposure from decreased outdoor activities, and glucocorticoid and methotrexate therapy (5). Vitamin D plays an important role in calcium (the major component of the collagen framework of bone along with phosphate) homeostasis. It elevates plasma calcium by increasing absorption in the intestine, calcium mobilization in bone, and calcium reabsorption in the kidney (6, 7). Vitamin D deficiency is associated with impaired intestinal calcium absorption, resulting in compensatory hyperparathyroid

ism, increased bone resorption, and decreased bone integrity. Parathormone (PTH) causes elevation of calcium but decreases phosphate by increasing its renal excretion (8). Vitamin D deficiency can also modulate the innate and adaptive immune response. Vitamin D suppresses T cell proliferation and ultimately results in decreased production of inflammatory cytokines (IL-17 & IL-21) with increased production of anti-inflammatory cytokines such as IL-10. It is assumed that vitamin D deficiency is also associated with increased autoimmune disease (9). It has been shown in several studies that a high frequency of vitamin D insufficiency or deficiency occurs in patients with rheumatoid arthritis. However, only a few studies have assessed the serum concentrations of vitamin D in children and adolescents with JIA and concluded that many children with rheumatic conditions are at risk of vitamin D deficiency. So, children with JIA are at risk for osteopenia and osteoporosis, which may result in vertebral compression and fractures of long bones (10). A study shows osteopenia and/or osteoporosis occur in all of the JIA subtypes and are most commonly found in systemic & polyarticular disease (11).

A bone mineral density (BMD) test is the best way to determine bone health. A BMD test can identify osteopenia and osteoporosis, determine the risk of fracture, assess growth retardation, and measure response to treatment. The most widely recognized BMD test is called dual energy x-ray absorptiometry (DXA). DXA is the standard study used to establish or confirm a diagnosis of osteopenia or osteoporosis (12). In JIA, a decrease in bone mass has also been described in a high percentage of children with an increased risk of osteoporosis, which correlates with the duration of active disease and the number of affected joints (13).

In this study we want to assess the serum concentration of 25-hydroxyvitamin D [25(OH)D] and calcium in JIA patients, to determine bone mineral density (BMD) in different types of JIA, to estimate the vitamin D deficiency or insufficiency associated with disease duration, and to determine the relationship of BMD with duration of JIA at diagnosis.

PATIENTS AND METHODS

This cross-sectional case-control study included 75 newly diagnosed cases of JIA attending a pediatric rheumatology clinic and admitted to the general pediatric ward of a tertiary hospital in Bangladesh. Among them, 43 (57.3%) were males and 32 (42.7%) females with an age range of 4 to 16 years. As a control group, 25 children of a similar age group (4 to 16 years) were included, and among them, 16 (64.0%) were males and 9 (36.0%) were females. All the children of cases and control groups were free from any autoimmune or chronic disease with no history of taking corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), or calcium and/or vitamin D supplementation. The cases were diagnosed, and sub-types were documented according to the International League of Associations for Rheumatology (ILAR) classification of JIA. Common subtypes like oligoarticular JIA, polyarticular JIA (rheumatoid factor positive and negative), systemic JIA (s-JIA), and enthesitis-related arthritis (ERA) were included in the study. All the patients were subjected to demographic data, detailed history, and clinical examination, including general examination and local examinations of joints.

Blood samples were collected from patients by venipuncture for serum 25(OH)D and calcium levels. Serum 25(OH)D was determined by the chemiluminescent microparticle immunoassay (CMA) technique using the SIEMENS ADVIA Centaur XPT. Serum calcium was measured by the CA method with the reagent glycine buffer OCPC/8-quinolinol and using the machine SIEMENS Dimension ExL automated biochemistry analyzer.

Bone mineral density (BMD) of the patients was measured in the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), BMU, Dhaka, which included measurements of lumbar vertebrae (L1-L4) and both femoral necks. The BMD is measured by DXA as bone density in gm/cm^2. Analysis of data from DXA was computerized and completely automated (software 3DXA, Medix DR dosimetry 2009.)

The reference value of serum calcium is 9-11 mg/dl; according to International Society for Clinical Densitometry (ISCD) 2007 criteria, a Z-score > -2 was within the expected range for age, and a Z-score ≤ -2 was defined as low bone mass. 25 (OH) vitamin D level: less than 20 ng/ml indicates deficiency, 20-32 ng/ml indicates insufficiency, and 32-100 ng/ml indicates sufficiency. For our study we considered hypovitaminosis D (vitamin D

deficiency + vitamin D insufficiency): less than 32 ng/ml and a sufficient level of vitamin D: more than 32 ng/ml.

All statistical calculations were done using the statistical software SPSS 22.0. The chi-square test, the unpaired student t-test, and the ANOVA test had been applied to evaluate the association between the variables when indicated. A p-value < 0.05 was considered as significant at a 95% confidence interval (95% CI) for the correlation.

RESULTS

Table-1: Age and gender Distribution of Study Subjects between Cases and Controls (n=75+25)

Variable	Category	Group A (n=75) No. (%)	Group B (n=25) No. (%)
Age group (years)	4–8	24 (32.0%)	1 (4.0%)
	9–13	39 (52.0%)	14 (56.0%)
	14–18	12 (16.0%)	10 (40.0%)
	Total	75 (100.0%)	25 (100.0%)
Sex	Male	43 (57.3%)	16 (64.0%)
	Female	32 (42.7%)	9 (36.0%)
	Total	75 (100.0%)	25 (100.0%)

Table-1 shows 75 were cases and 25 children were in control group. Most of cases and controls were in the age group 9-13 years (52 % and 56 % respectively) with the predominance of male.

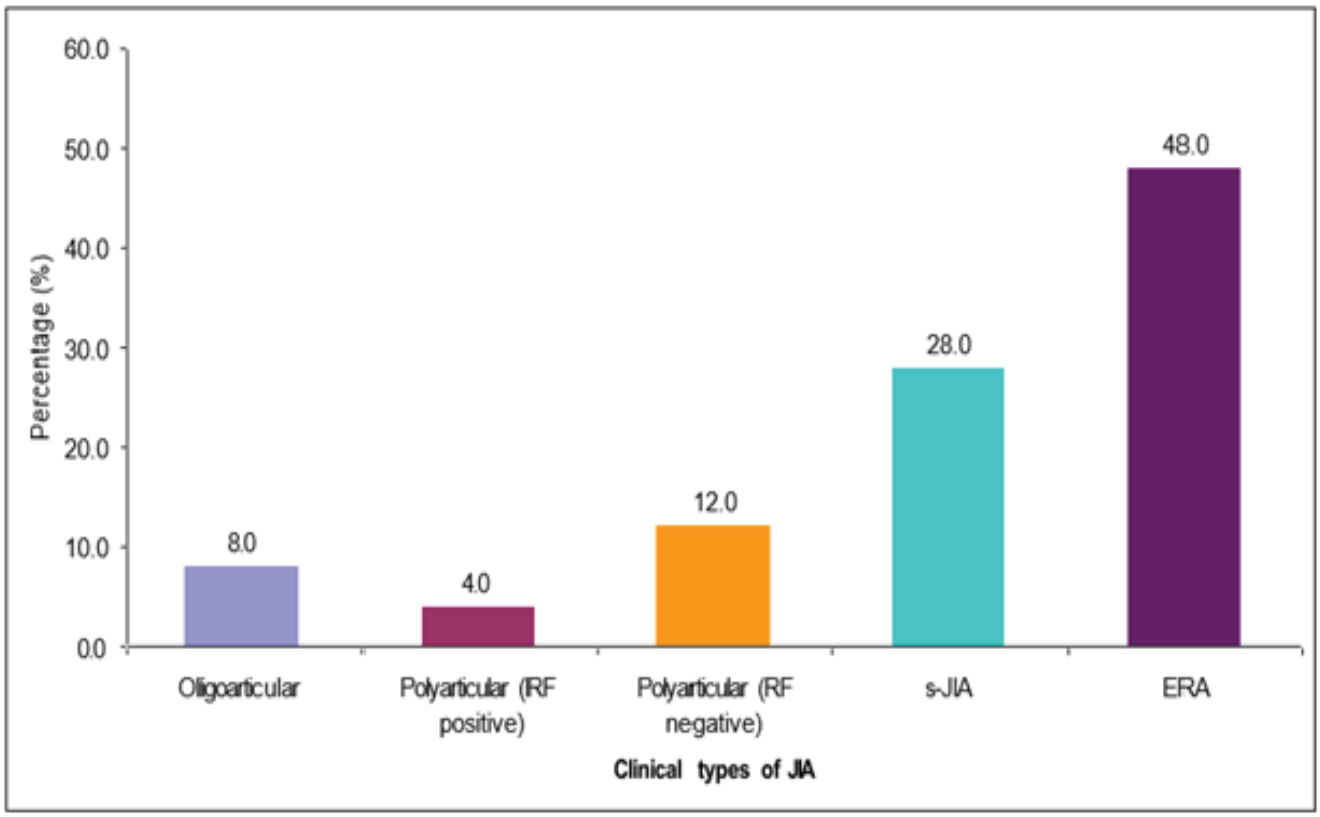

Figure-1: Different Type of JIA Cases (n=75)

Figure-1 shows distribution of cases in five subtypes of JIA. Enthesitis-related arthritis (ERA) was the most common (48%), followed by systemic JIA (28%) and polyarticular RF-negative (12%).

Table-2: Comparison of 25(OH) D Level between Cases and Controls (n=100)

25(OH) D level	Group A (n=75) No. (%)	Group B (n=25) No. (%)	p-value
Deficiency (<20 ng/ml)	52 (69.3%)	17 (68.0%)	
Insufficiency (20–32 ng/ml)	16 (21.3%)	4 (16.0%)	
Sufficiency (32–100 ng/ml)	7 (9.3%)	4 (16.0%)	
Total	75 (100.0%)	25 (100.0%)	
Mean 25(OH)D level (mean±SD)	18.66±10.22	21.3±4.07	0.303

Data expressed as frequency, percentage and mean±SD. Unpaired student t-test was performed to compare between two groups.

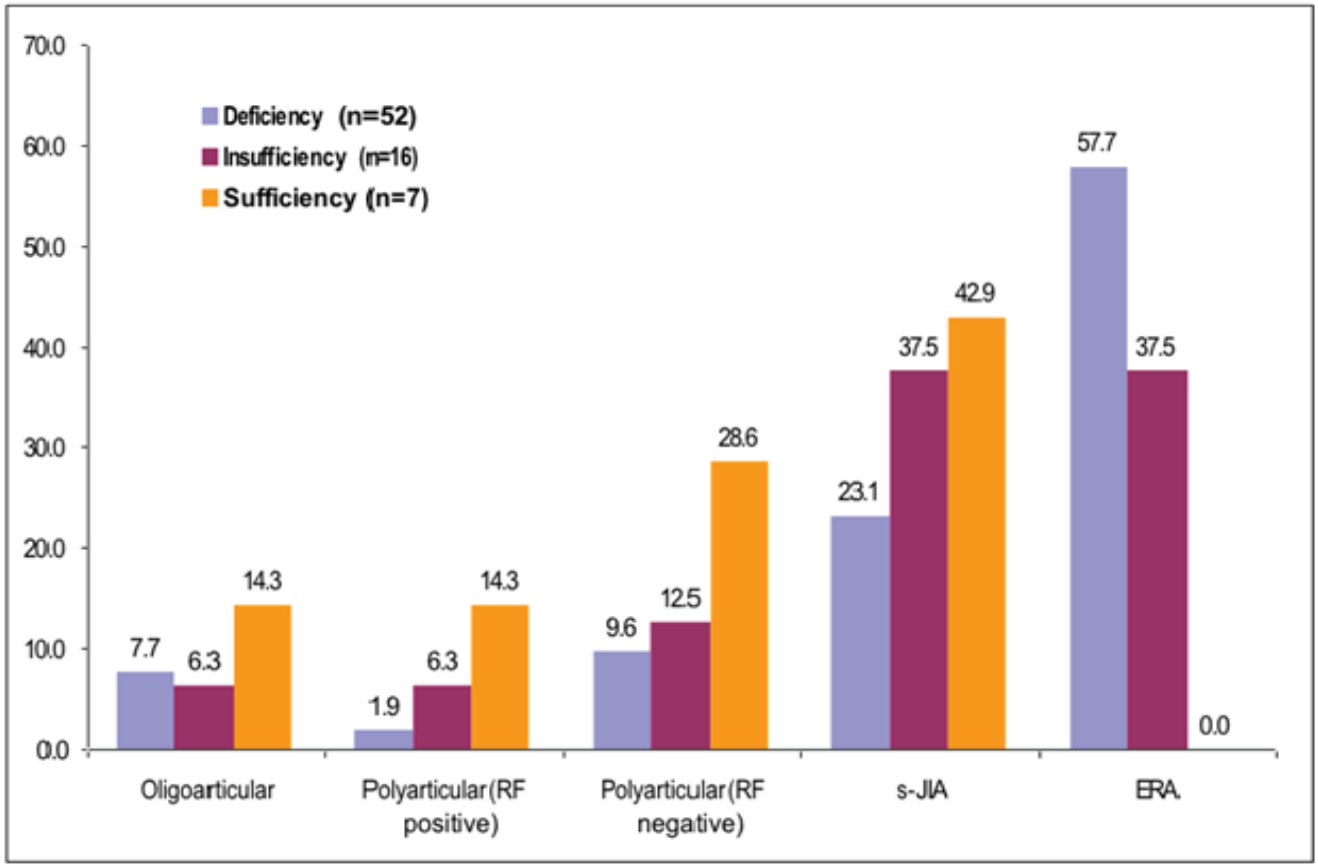

Figure-2: Bar Diagram Showing the Extent of 25 (OH) D in Different Type of JIA cases.

Table-3: Duration of Illness at Diagnosis and Relation with Vitamin D Levels (n=75)

Duration of Illness	Frequency	Percentage (%)	25(OH)D Level (ng/ml)		
			Deficiency (n=52) No. (%)	Insufficiency (n=16) No. (%)	Sufficiency (n=7) No. (%)
<6 months	33	44.0	23 (44.2%)	6 (37.5%)	4 (57.1%)
6 months – 1 yr	17	22.7	13 (25.0%)	3 (18.8%)	1 (14.3%)
>1 yr	25	33.3	16 (30.8%)	7 (43.8%)	2 (28.6%)
Total	75	100.0	52 (100.0%)	16 (100.0%)	7 (100.0%)
		p-value		0.818	

Chi-squared Test (x^2) was done to analyze the data.

Figure 2 shows 25(OH)D status in different subtypes. 25(OH)D deficient were 52 cases (69.4%), insufficient were 16 cases (21.3%), and sufficient were 7 cases (9.3%). There was no significant difference between duration of illness and 25 (OH) D status (Table 3).

Table-4: Serum Concentrations of Calcium in Different Subtypes of JIA (n=75)

Subtypes of JIA	n	Mean±SD (mg/dl)	p-value
Oligoarticular	6	9.51±0.27	0.798
Polyarticular (RF positive)	3	9.26±0.41	
Polyarticular (RF negative)	9	9.34±0.73	
S-JIA	21	9.44±0.55	
ERA	36	9.51±0.35	
Total	75	9.46±0.46	

Data were expressed as mean±SD

ANOVA test was performed to compare among groups

Table-5: Comparison of Serum Calcium with Vitamin D Levels in JIA patients (n=75)

25(OH) D level	n	Calcium level (mg/dl) Mean±SD	p-value
Deficiency (<20 ng/ml)	52	9.49±0.42	0.785
Insufficiency (20-32 ng/ml)	16	9.41±0.62	
Sufficiency (32-100 ng/ml)	7	9.38±0.33	
Total	75	9.46±0.46	

Data were expressed as mean±SD

ANOVA test was performed to compare among groups

The mean calcium level was 9.46 ± 0.46. There was no statistically significant difference in serum calcium level with different types of JIA (Table-4). Table 5 shows no statistically significant correlation of serum 25(OH)D level with serum calcium level.

Table-6: BMD Z-score of Study Cases and Controls at Lumbar Region, Right Femur Neck, and Left Femur Neck (n=75+25)

BMD Z-score	Lumbar Region		Right Femur Neck		Left Femur Neck	
	Group A (n=75) No. (%)	Group B (n=25) No. (%)	Group A (n=75) No. (%)	Group B (n=25) No. (%)	Group A (n=75) No. (%)	Group B (n=25) No. (%)
Normal (> −2)	2 (2.7%)	10 (40.0%)	23 (30.7%)	14 (56.0%)	22 (29.3%)	14 (56.0%)
Low bone mass (≤−2)	73 (97.3%)	15 (60.0%)	52 (69.3%)	11 (44.0%)	53 (70.7%)	11 (44.0%)
Total	75 (100.0%)	25 (100.0%)	75 (100.0%)	25 (100.0%)	75 (100.0%)	25 (100.0%)
p-value	<0.001		0.023		0.016	

Figures in parentheses indicate corresponding percentage; Chi-squared Test (x^2) was done to analyze the data.

About 97.3% of JIA cases had low bone mass in the lumbar region (Table-6). A significant difference was found between cases and controls (P=<0.001). Table 6 also shows that at the neck of both femurs, low bone mass was present compared to the control group (69.3% of cases had low bone mass in the right femur and 70.7% of cases had low bone mass in the left femur), and the result is statistically significant (P = 0.023 (right) and P = 0.016 (for left).

Table-7: Clinical Types of JIA and BMD Z-score at Lumbar Vertebra, Right Femur Neck, and Left Femur Neck (n=75)

Type of JIA	n	Lumbar Vertebra		Right Femur Neck		Left Femur Neck		p-value
		Normal (>−2) No. (%)	Low bone mass (≤−2) No. (%)	Normal (>−2) No. (%)	Low bone mass (≤−2) No. (%)	Normal (>−2) No. (%)	Low bone mass (≤−2) No. (%)	
Oligoarticular	6	0 (0.0%)	6 (100%)	1 (16.7%)	5 (83.3%)	2 (33.3%)	4 (66.7%)	Lumbar: NS R.Femur: 0.007 L.Femur: 0.035
Polyarticular (RF positive)	3	0 (0.0%)	3 (100%)	2 (66.7%)	1 (33.3%)	1 (33.3%)	2 (66.7%)	
Polyarticular (RF negative)	9	1 (11.1%)	8 (88.9%)	2 (22.2%)	7 (77.8%)	2 (22.2%)	7 (77.8%)	
S-JIA	21	0 (0.0%)	21 (100%)	1 (4.8%)	20 (95.2%)	1 (4.8%)	20 (95.2%)	
ERA	36	1 (2.8%)	35 (97.2%)	17 (47.2%)	19 (52.8%)	16 (44.4%)	20 (55.6%)	
Total	75	2 (2.7%)	73 (97.3%)	23 (30.7%)	52 (69.3%)	22 (29.3%)	53 (70.7%)	

Figures in parentheses indicate corresponding percentage; NS = Not Significant.

All subtypes of JIA had low bone mass at lumbar vertebrae and both femurs (Table 7), except polyarticular RF-positive at the right femur neck. The Z score of BMD at both femur necks was significant in different types of JIA (P=0.007 for the right and P=0.035 for the left femur neck). There was no significant relation between BMD at 3 sites and duration of illness (Table 8).

Table-8: Relationship of BMD Z-score with Duration of Illness (N=75)

Duration of illness	BMD Z-score at lumbar spine		BMD Z-score at Right femur neck		BMD Z-score at Left femur neck	
	> -2 No. (%)	≤ -2 No. (%)	> -2 No. (%)	≤ -2 No. (%)	> -2 No. (%)	≤ -2 No. (%)
<6 months (n=33)	1 (3.0)	32 (97.0)	12(36.4)	21 (63.6)	12(36.4)	21 (63.6)
6 months-1yr (n=17)	0 (0.0)	17 (100)	3 (17.6)	14 (82.4)	3(17.6)	14 (82.4)
> 1 yr (n=25)	1 (3.0)	24 (96.0)	8 (32.0)	17 (68.0)	17(72.0)	18 (72.0)
p-value	0.721		0.391		0.381	

DISCUSSION

This cross-sectional case-control study showed majority of both the JIA patients and control group were in between 9-13 years of age. This was very similar result observed in a study done previously in Bangladesh (14). There were more males than females. Perhaps male predominance could be due to the reasons reflecting majority of the patients were of Enthesitis related arthritis variety; which is more common in males. Moreover, in a report from India, similar results were found (15). While classifying subtypes of JIA, the most common type was enthesitis-related arthritis (48%), followed by systemic JIA (28%). Probably children of Asian origin are more susceptible to enthesitis-related arthritis (5). The duration of the disease at presentation was less than six months in 44%. The duration of the presentation to us was earlier than the previous study, in which the majority was more than one year (14). This may be due to awareness of

clinicians about JIA and early referral to the pediatric rheumatology clinic.

In this study 90.6% of patients had hypovitaminosis D (both deficiency and insufficiency), as shown in Table 4. This result is similar to the study on Moroccan JIA children, in which 75% had hypovitaminosis D (deficiency and insufficiency) (16,17). Research carried out with polyarticular JIA in Brazil found 25% (OH)D deficiency and insufficiency in 27% and 47%, respectively (18). Another study conducted on adults with rheumatoid arthritis showed that 90% of patients had hypovitaminosis D (19).

Mean 25 (OH) D levels in cases and healthy controls were also low in this study, 18.66±10.22 and 21.3±4.07, respectively (Table 2). These findings perhaps indicate that vitamin D deficiency may persist in the general population in Bangladesh, our country. Zaman et al. found 93.58% of healthy children of the 6-11-year group of Bangladesh had hypovitaminosis (20). Another group of researchers did not find any difference in 25(OH)D level between JIA patients and controls (21). For the high frequency of deficiency or insufficiency in both control and JIA groups, a potential explanation could be skin pigmentation, traditional clothing, air pollution, and limited outdoor activity (20). Among JIA cases, vitamin D levels were further low, maybe due to poor intake, disease activity, and decreased physical activity. The relation of vitamin D level with duration of illness was not significant (p=0.818, Table 3), similar to another research study in 2013, which also found no association between them (18).

Serum level of calcium was normal in 93.3% and low in 6.7% of JIA patients. This result is similar to the studies showing levels of serum calcium normal in all patients (16, 17). It is expected that serum calcium levels would be normalized in JIA patients as a part of a bodily compensatory mechanism by secreting increased serum parathormone. There was no significant correlation between the extent of 25(OH) D level and serum calcium level.

Low bone mass of the cases was found in the lumbar, neck of the right femur, and neck of the left femur: 97.3%, 69.3%, and 70.7%, respectively. In the control group, these were 60%, 44%, and 44%, respectively. BMD at all the sites was significantly lower among JIA cases than controls (p=<0.001, 0.023, 0.016). A similar result (low BMD in 50% of JIA patients) was found in another research study (17). Low bone mass was found in 40-52% of adult patients with JIA by another group of researchers (22). No patient or control had a history of fracture in our study. Hilman et al. in their study found reduced bone mineralization, bone mineral content and bone turnover (23).

In 2007 ISCD redefined the concept of osteoporosis in children (24). This definition was used as a working definition in our study. But most of the available literature regarding the prevalence of osteoporosis and low BMD was published prior to this definition. This could be a reason for the higher prevalence of low bone mass in this study. All types of JIA had low bone mass at lumbar vertebrae. We found significant differences in right femur neck and left femur neck (P = 0.007 and 0.035, respectively) in different JIA subtypes. In this study, it was found that systemic JIA followed by polyarticular JIA had a much higher frequency of low bone mass (Table-7). Whereas no significant differences were observed in BMD between different JIA subtypes in another study (25). No association was found between duration of disease and Z-score of BMD in any site. Similar results were found in a study conducted in Spain and in India (25, 26).

Study limitations include a small sample size from a specific area and the absence of analyses on factors like nutritional status, sunlight exposure, and physical activity related to the disease process.

CONCLUSION

This study found that most patients with Juvenile Idiopathic Arthritis (JIA) and healthy controls had low vitamin D levels. Bone Mineral Density (BMD) was significantly lower in JIA patients compared to controls, with systemic JIA showing the highest incidence of low bone mass, followed by polyarticular rheumatoid factor negative type. No significant link was found between the duration of illness and vitamin D levels or BMD. JIA patients may experience decreased bone mass and a heightened risk of fragility fractures during childhood and adolescence.

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