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Original Article

Vitamin D Level and Disease Activity in Children with Juvenile Idiopathic Arthritis

Emad E. Ghobrial[1]*, Huda Marzouk[1], Mervat Khorshied[2], Eman Gado[3]

[1] Pediatrics Department, Faculty of Medicine, Cairo University, Egypt; nourelhudaahmedyousef@yahoo.com
[2] Clinical Pathology Department, Faculty of Medicine, Cairo University, Egypt; mervatkhorshied@hotmail.com
[3] Ministry of Health and Population, Cairo, Egypt; eman_gado85@yahoo.com
* Correspondence: dr.ememil@yahoo.com
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Abstract:
Background: Vitamin D deficiency is thought to aggravate juvenile idiopathic arthritis (JIA) activity.
Aim of the work: To assess serum 25-hydroxy vitamin D [25(OH) D] level in Egyptian children with JIA and correlate its level with subtypes of JIA and disease activity scoring.
Methods: This was a cross-sectional study that included 70 children with JIA of one year or less disease duration and 40 apparently healthy control children. Disease activity was measured using Disease Activity Score in 28 joints (DAS28) for polyarticular and oligoarticular JIA. Serum 25-hydroxyvitamin D [25(OH) D] was measured using Enzyme Linked Immuno- Sorbent Assay technique.
Results: Serum 25 (OH) D was significantly lower in JIA patients (mean ±SD= 17.32± 9.7 ng/mL) than in the control group (mean ± SD= 27.9± 7.4 ng/mL) (p-value =0.001). Serum 25(OH) D levels correlated inversely with the number of affected joints (r= - 0.122, p =0.316). Another inverse correlation with severity score was noted (r= - 0.2, p=0.098) but it was not statistically significant. It did not correlate with age at onset of disease (r=-0.2, p=0.096) or gender (r=-0.105, p=0.387) or duration of disease (r=-0.038, p=0.754).
Conclusion: Serum levels of 25(OH) D were lower in patients with JIA disease. Serum vitamin D levels inversely correlated with number of affected joints, but not severity of JIA. Larger studies are needed to confirm the relation between vitamin D and JIA disease activity.

Level of Evidence of Study: IIB (1).
Keywords: Disease activity; Egyptian children; juvenile idiopathic arthritis; Vitamin D; [25 (OH) D].
Abbreviations: 25(OH) D: 25-hydroxyvitamin D; JIA: juvenile idiopathic arthritis; HbA1c: glycated hemoglobin; NPH: Neutral Protamine Hagedorn; NSAIDs: non-steroidal anti-inflammatory drugs; SBGM: self-blood glucose monitoring; SDS: standard deviation scores; T1D: Type 1 diabetes.

Introduction

Juvenile idiopathic arthritis (JIA) comprises a group of heterogeneous disorders of chronic arthritis in childhood with no apparent etiology. It is the most common pediatric rheumatic disease and is associated with significant long-term morbidity (*2*). JIA is defined as arthritis (swelling or limitation of motion of the joint accompanied by heat, pain or tenderness) of unknown etiology beginning before the 16th birthday and persisting for at least six weeks where other known conditions are excluded (*3*). It can be a serious and disabling condition complicated by joint destruction, impaired joint function, limitation of growth and osteoporosis. It can also have significant effects on the emotional and social wellbeing of a child or young person (*4*).

In addition to its important metabolic activities, vitamin D also contributes to the regulation of the immune system. It is estimated that as many as one billion people worldwide suffer from vitamin D deficiency or insufficiency, and this was shown to be prevalent across all

age groups, genders and geographic regions (*5*). Experimental use of vitamin D has revealed a novel role in the immunopathogenesis of autoimmune diseases. Also, low vitamin D status was reported in JIA (*6*) and in many inflammatory rheumatic diseases and has been inversely correlated with disease activity (*7*). Vitamin D deficiency may increase the risk for the development of rheumatoid arthritis (RA) (*8*). Recently, the role of vitamin D deficiency in the pathogenesis of RA, as well as the relationship between vitamin D deficiency and the activity of RA was increasingly discussed (*9*). However, others reported no relationship between 25(OH) D and disease activity (*10*). The aim of this study was to assess serum 25-hydroxy vitamin D [25(OH) D] level in Egyptian children with JIA and correlate its level with subtypes of JIA and disease activity scoring.

Subjects and Methods

This was a cross-sectional that included 70 children with confirmed JIA following up at Pediatric Rheumatology Clinic, Children's Hospital, Cairo University and 40 apparently healthy age- and sex-matched controls recruited from the general outpatient clinic at Pediatric Hospital of Cairo University between January 2015 and August 2015. The study was approved by Higher Studies Research Committee of Faculty of Medicine, Cairo University, in compliance with Helsinki declaration guidelines (*11*).

Participants

Children with JIA between the ages of 2 and 16 years, of either sex were included in the study. Patients were diagnosed according to the classification criteria of the International League of Associations for Rheumatology (ILAR) (*12*).

Patients who had an additional chronic disease, hepatic or renal affection, any other collagen vascular disease as systemic lupus erythematosus (SLE) or familial Mediterranean fever (FMF) and those on vitamin D supplementation or anticonvulsant drugs prior to the study, were excluded from the study. Patients' were compared to 40 apparently healthy children, recruited from the out-patient general pediatric clinic and not suffering from any rheumatologic or chronic disease that may affect level of vitamin D.

Methods

Detailed history taking, careful clinical examination and scoring: were performed for all enrolled children with an emphasis on full examination of involved joints and screening of all other joints in the body. Disease activity was measured using the Disease Activity Score in 28 joints (DAS28) (DAS28 combines information on the number of painful and swollen joints, with 28 joints being selected as well as erythrocyte sedimentation rate (ESR) and patient's global assessment measured on a visual analog scale (VAS) from zero to 10 cm. DAS28 score is calculated using a mathematical formula, and the activity of arthritis can be interpreted in categorical scale). High activity of the disease was defined as a DAS28 > 5.1, moderate activity of disease as a 3.2 < DAS28 ≤ 5.1, and low activity of disease as a DAS28 ≤3.2 (11).

Laboratory investigations: in the form of complete blood count (CBC) with differential count (using hematology counter (Cell Dyne 3700), ESR by Westergen method and serum calcium, phosphorus and alkaline phosphatase using synchron CX5 autoanalyser using kit supplied by Beckman were done for the patients at the time of study.

Serum levels of 25-hydroxyvitamin D3 [25 (OH) D] were measured using Enzyme Linked Immune Sorbent Assay (ELISA) technique for patients and controls using the commercially available kits, that are based on the principle of competitive binding.

Statistical Analysis

The SPSS software (Statistical Package for the Social Sciences, version 19.0, Inc, Chicago, Ill, USA) and Microsoft Excel software program were used to tabulate the results and represent them graphically. Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as count and percentage. The one-way analysis of variance was used to test the differences between groups. The Duncan multiple comparison test was used to test the significant differences between each pair of groups. The chi-square test was used to compare the distributions between groups. The Pearson correlation coefficient test was used to

test the significant correlations between the quantitative parameters within each group. A P value less than 0.05 is considered significant.

Results

The age and gender of all participants (cases and controls) are shown in Table 1. There was no statistically significant difference between the two studied groups as regards gender and age. Out of 70 patients, 67 (95.7%) had no family history of JIA. Mean disease duration of studied cohort was 5.4 +/- 3.58 years. Mean age ±SD at enrollment in the study was 10.2±4.09 years. The mean ±SD of severity score was 2.72±1.01. The number of affected joints ranged between 1-2 joints. Table (2) shows the state of activity and vitamin D levels in JIA patients. The mean serum 25 (OH) D was 17.33±9.86 ng/dl (range: 3- 50.5ng/dL) in patients which was significantly lower than in controls (mean +/- SD: 27.91±7.56 ng/dL, range: 15-44 ng/dL) (p-value= 0.001), as shown in Figure (1).

Table 1: Demographic characteristics of studied groups.

		JIA (n=70)	Controls (n=40)	P-value
Gender	**Males (48)**	32 (45.7%)	16 (40.0%)	0.561
	Females (62)	38 (54.3%)	24 (60.0%)	
Age (year)	**Mean ± SD**	10.21±4.13	8.38±3.21	0.071
	Range	2.25-16	1.7-14	

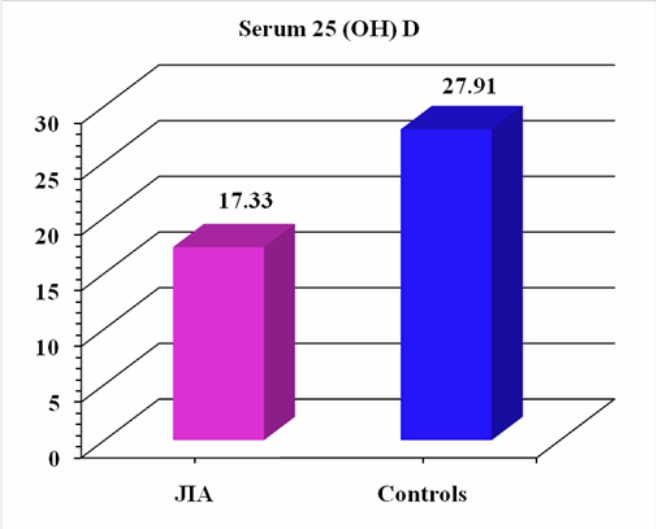

Figure 1: Comparison of vitamin D levels between JIA patients and controls.

The symptoms and signs of the enrolled patients and subtypes of JIA are shown in Table (2). The most common subtype was polyarticular, present in 31 (44.3%) patients, followed by oligoarticular type in 29 (41.4%), and systemic-onset JIA subtype in 10 (14.3%) patients. Medications used in JIA cases are presented in Table (2). The serum 25(OH) D levels were 17.4±9.81ng/dl, 17.16±10.3ng/dl and 17.65±9.61ng/dl in oligoarthritis, polyarthritis and systemic subtypes respectively with no significant difference between the 3 subtypes of JIA as regard levels of vitamin D (p = 0.990) (Table 2). The serum 25(OH) D levels inversely correlated with number of affected joints (p=0.316, r= - 0.122) and with the severity score (r= - 0.2, p=0.098) but with no statistically significant difference.

Serum 25(OH) D levels showed a significant positive correlation with calcium in the patients' group (Table 3 and Figure 3). Also, the serum 25(OH) D levels positively correlated with phosphorus, neutrophil, hemoglobin and TLC but with no statistical significance. In addition,

the serum 25(OH) D levels were inversely correlated with ESR, alkaline phosphatase, lymphocytes and platelets levels with no statistically significant value (Table 3).

Table 2: Symptoms and signs of JIA patients and medications used.

		Number	%	Mean Vitamin D Level	P value
Symptoms					
Pain	yes	58	82.9	15.25	0.21
	no	12	17.1	17.76	
Morning stiffness	yes	15	21.4	17.41	0.35
	no	55	87.6	18.12	
Signs					
Joint swelling	yes	27	38.6	16.46	0.28
	no	43	61.4	17.87	
Joint tenderness	yes	10	14.3	17.5	0.47
	no	60	85.7	17.3	
Subtype					
Oligo-arthritis	yes	29	41.4	17.40	0.363
	no	41	58.6	17.28	
Polyarthritis	yes	31	44.3	17.16	0.45
	no	39	55.7	17.65	
Systemic-onset	yes	11	14.3	17.65	0.45
	no	59	85.7	17.27	
Subtype differences					0.990
Activity Score					
Active	yes	37	52.9	15.9	0.101
Remission	yes	33	47.1	18.92	
Drugs					
Corticosteroids	yes	23	32.9	17.3	0.499
	no	47	67.1	17.32	
NSAIDs	yes	45	64.3	16.8	0.314
	no	25	35.7	18	
Methotrexate	yes	54	77.1	16.73	0.177
	no	16	22.9	19.3	
Sulfasalazine	yes	1	1.4	11	N/A
	no	69	98.6	17.4	
Biological drugs	yes	3	4.3	21.33	0.238
	no	67	95.7	17.15	

NSAIDs: non-steroidal anti-inflammatory drugs.

Table (3): Correlations between Serum 25 (OH) D and clinical and laboratory characteristics:

	Serum 25 (OH) D	
	r-	P value
Number of affected joints	-0.122	0.316
Severity score	- 0.2	0.098
ESR	-0.19	0.116
Calcium (mg/dL)	0.360*	0.002
Phosphorus (mg/dL)	0.033	0.786
ALP (IU/L)	-0.161	0.182
Neutrophils (%)	0.024	0.845
Lymphocyte (%)	-0.037	0.759
Hb (g/dl)	0.135	0.264
TLC (×10³/ml)	0.015	0.903
Platelets (×10³/ml)	-0.109	0.368

ALP: Alkaline phosphatase; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; TLC: Total leucocytic count; *: statistically significant.

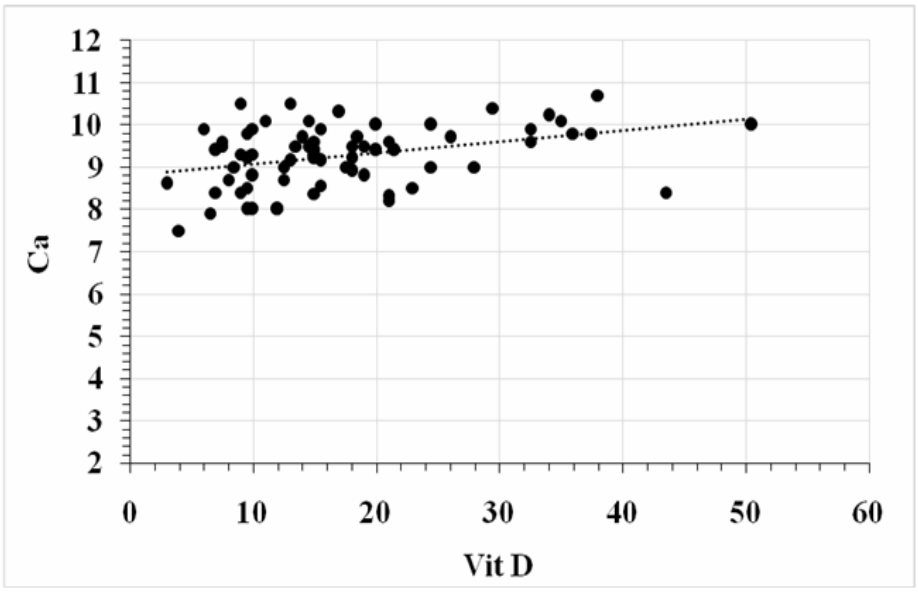

Figure 2: Correlation between Serum 25 (OH) D and calcium (Ca) in patients' group (p=0.002).

Discussion

Compromised bone mineralization health is a consequence of JIA that should be monitored irrespective of activity or received medications (*13*). The mean levels of 25 (OH) vitamin D were significantly reduced among our studied cohort with JIA compared to the control group. Bone densitometry by dual energy Xray absorptiometry, might be a valuable tool to define the extent of osteoporosis among the children with JIA with reduced vitamin D (*14*). It is not clear why the vitamin D levels were reduced among the children with JIA. The limited physical activity and subsequent limited sun exposure (*15*), or over consumption by the erosive nature of JIA (*16*) might be the causative factors. It is important to note that the decrement in vitamin D3 was not unanimous among those with JIA. It is important to note that the half-life of 25 (OH) D is about 15 days (*17*), hence the blood level reflects the past two weeks or more.

There was no correlation among our studied cohort activity, type of medications, severity of disease or its duration to level of 25 (OH) D. The lack of correlation might be because of the long half-life of 25 (OH) D, or the differential tissue uptake (*18*), rate of bone turnover and bone metabolism (*19*), hence; the serum level may not reflect true tissue levels and drug induced decrement of vitamin D (*20*). It seems plausible that the increased osteoclasts activity and bone turnover in JIA is part of the immune involvement given that the osteoclasts are the macrophage lineage (*21*). This explanation might be why in the current study, the serum 25(OH) D levels significantly negatively correlated with the number of affected joints. Also, the serum 25(OH) D levels correlated significantly with calcium level which is expected.

This could be explained also by limited physical activity, accompanying pain complaints and insufficient exposure to sunlight. An Egyptian study failed to confirm that concealing clothes is the cause of vitamin D insufficiency. Thus despite having sufficient solar source of vitamin D, other factors do play a role in these low levels (*22*).

While remission allows more activity and possible sun exposure, again there was no significant correlation with levels of 25 (OH) D among our studied cohort. Again, disease modifying antirheumatic drugs as methotrexate are known to be associated with drop of vitamin D (*20*). The bone loss associated with corticosteroid use is aggravated by suboptimal vitamin D levels, yet the levels of vitamin D were not different among users of corticosteroids and the control group (*23*) and not with the disease activity that was approximately in our study (48% patients had a high disease activity of (DAS28) 4.84 ± 1.27). ***Bouaddi et al., (2014)*** also reported drop of vitamin D levels that correlated negatively with number of affected joints among their studied cohort of Moroccan children with JIA who had higher activity score and higher population size, as well as longer duration of disease than our study cohort. This consistence suggests that overconsumption of vitamin D might be an association of JIA (*24*).

The relation of vitamin D levels to disease activity remains controversial. We did not reproduce the results of others who reported an inverse correlation between serum 25-OH vitamin D levels and disease activity (*25*, *26*). We report that we could not detect any correlation.

Vitamin D effects are not limited to bone mineralization. They extend also to immune competence (*27*, *28*). The contribution of low 25 (OH) D to clinical picture, progression of disease or its duration is not clear.

Our study did not asses the level of 1, 25 (OH)2 D in cases and controls, is a limitation of our study. Our study is also limited by the small number of the studied cohort, the cross-sectional design, lack of assessment of bone densitometry and response to vitamin D, as they were not within the scope of the study.

Conclusion

Serum levels of 25(OH) D were lower in patients with JIA disease. Serum vitamin D levels inversely correlated with number of affected joints, but not severity of JIA. Larger studies are needed to confirm the relation between vitamin D and JIA disease activity and to address the role of vitamin D replacement in optimizing outcomes in JIA. Again the need remains to address role of standardization of vitamin D supplementation in the pediatric population and particularly those with JIA.

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Author Contributions:

All authors shared in conceptualization, supervising, data curation, data analysis, writing original draft, data interpretation, writing original draft, supervising and revising. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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