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Growth assessment and vitamin D level in Egyptian Juvenile Idiopathic Arthritis Patients

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Abstract

Background

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in childhood and is frequently associated with growth retardation. Vitamin D is critical to bone mineral metabolism and to the growth and development of the skeleton. We aimed to evaluate growth pattern and Vitamin D level in patients with JIA and its different subtypes.

Materials and Methods

80 JIA patients and 80 healthy controls were included. For all patients and controls we assessed body weight, standing height, body mass index (BMI), Serum 25(OH) D3. Thyroid function tests were assessed to exclude patients with hypothyroidism or autoimmune thyroiditis, liver and renal function tests, calcium, phosphorus, alkaline phosphatase, fasting blood sugar were done to evaluate other causes of short stature.

Results

JIA patients' mean height, weight, and BMI were significantly lower compared to controls (135.4±22.1 vs. 145.7±21.8, p=0.042 for height), (34.6±13.6 vs. 39.8±11.4, p=0.039 for weight) and (18.52±3.96 vs. 21.73±5.43, p= 0.041 for BMI). Mean serum 25(OH) D3 level was significantly lower in JIA patients than controls (15.69±6.6 ng/ml vs. 31.62±4.9 ng/ml, p<0.0001), patients with systemic onset and seropositive polyarthritis (RF positive) have the lowest 25(OH) D3 level compared with other JIA subtypes. There was significant negative correlation between steroid dose, duration and JIA patients' height (r= -0.456, p=0.017 and r=-0.776, p=0.001 respectively). Serum 25 (OH) D3 level was significantly correlated with patients' height and BMI (r=0.33, p=0.029 and r=0.32, p=0.043).

Conclusion

The nutritional status of JIA patients is multi-factorial. Onset subtype and low level of vitamin D were found to have an effect on growth parameters as height and body mass index in patients with juvenile idiopathic arthritis.

Key Words: Egypt, Juvenile idiopathic arthritis, Growth, Vitamin D.

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1- INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic disease that can lead to joint pain, destruction, loss of function, and poor quality of life, and is considered to be a major pediatric rheumatic disease (1). Epidemiological studies of JIA vary widely as regards study methodology, classification criteria, and populations (2). Comparison of epidemiological studies of JIA revealed that the annual incidence is 2.6 to 23 cases per 100,000 children per year and the estimated prevalence was 15.7–140 cases per 100,000 children (2).

Most studies in Egypt are about the characteristics of JIA in Egyptian children in different areas (3). It is characterized by periods of activity and remission and is frequently associated with growth retardation (4-5), varying from generalized growth impairment to local deceleration of growth of affected limb or spinal column (5-7). Growth retardation might be due to chronic inflammation mediated by several pro-inflammatory cytokines. Other factors that might negatively contribute include the degree, extent, and duration of disease activity, age at onset, suboptimal nutrition, reduced physical activity, hormonal influence, stress related to the long term illness, and corticosteroid (4-7).

Vitamin D is considered as an immune and inflammatory mediator which is implicated in the pathogenesis of autoimmune diseases as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, Crohn's disease, and chronic childhood arthritis (8, 9). Vitamin D tends to suppress the immune response (9). Consequently, low vitamin D concentrations are associated with an increased pro-inflammatory mediator and more active disease (6, 10). The objective of the study was to evaluate the growth pattern and Vitamin D levels in patients with JIA and its different subtypes.

2- MATERIALS AND METHODS

2-1. Study design

This cross-sectional study was carried out at Rheumatology and Rehabilitation outpatient clinic, Pediatric Rheumatology clinic, Minia University Hospital, Egypt. Eighty patients diagnosed as JIA according to the International League of Associations for Rheumatology (ILAR) criteria (11), and 80 healthy controls matched for age and sex, with no musculoskeletal complaints from relatives of patients who attended the clinic or volunteered were included. The categorization and the subtyping of JIA patients were also done as per ILAR guidelines, and steroid dose and duration of treatment were calculated. Patients with JIA were assessed for body weight and standing height using the same equipment and the same observer. The weight was measured by a digital weighing machine, with minimum clothing, to the nearest 0.1 kg. Height was measured by a length board and approximated to the nearest 0.1 cm. Percentile curves for weight and length/stature by age for boys and girls from birth to 20 years (the chart from birth to 20 year) were used.

By definition, the 50th percentile is the median (the value above and below) which 50% of the observed values lie. Thyroid function tests were assessed to exclude patients with hypothyroidism or autoimmune thyroiditis, liver and renal function tests, calcium, phosphorus, alkaline phosphatase, fasting blood sugar were done to evaluate other causes of short stature. Children with chronic comorbid endocrinal, renal, hematological or other diseases which cause growth retardation were excluded from the study. The body mass index was calculated as weight in kilogram/height in meters squared (Kg/m2). All patients and controls underwent laboratory tests of Plasma 25-hydroxyvitamin D3.

2-2. 25-hydroxyvitamin D measurement

25(OH)D levels were measured in serum by enzyme-linked immunosorbent assay (ELISA) technique (from MDSS GmbH, Hanover, Germany). The assay performance was characterized by a lower detection limit of 5.6 nmol/L, and the mean of precision (intra assay of variation was 4.5-10.7%); with convert factor of 1 nmol/L=0.4ng/ml. Interpretation of resulted 25(OH)D levels was according to the Endocrine Society's Clinical Guideline: "Evaluation, treatment, and prevention, of Vitamin D deficiency" (12). Vitamin D deficiency was defined as a 25-hydroxy serum level less than 15 ng/ml, vitamin D insufficiency as 25-hydroxy serum level of 15-20 ng/ml, and severe vitamin D deficiency as 25-hydroxy serum level of less than 5 ng/ml. Vitamin D levels greater than 20 ng/ml were considered sufficient(13).

2-3. Statistical analysis

Data were analyzed by the statistical package for the social sciences (SPSS Inc., Chicago, IL, USA) version 16.0. Categorical and quantitative variables were respectively described as numbers/percentage (%), and mean ± standard deviation (SD). Variables were compared by Mann-Whitney tests for numerical variables between two groups. Analysis of Variance test (ANOVA or F-test) was used for comparison of more than 2 means. Spearman's rho correlation coefficient test was used for correlation analysis. P-value less than 0.05 was considered statistically significant at the 95% confidence level (CI).

3- RESULTS

The Baseline characteristics and onset subtypes of patients are presented in **Table.1**; there were 18 males and 62 females, their mean age was 13.1±4.8 years and their mean disease duration was 4.4±3.9 years. **Table.2** presents the clinical features and the growth characters of the patient, the mean height of the patients was (135.4±22.1 cm); 42.5% (n=34) of JIA patients were below the 5th percentile, 25% (n=20) were at the 5th percentile, 27.5% (n=22) were between the 5th and 50th percentiles. Forty-two (52.2%) patients received steroid medication, the mean dose of steroid was (10.4±5.1) mg/day, and the mean duration of steroid intake was (7.2±5.8) years. There was a significant difference between JIA patients and control group regarding mean height (135.4±22.1 vs. 145.7±21.8 cm, p=0.042), mean weight (34.6±13.6 vs. 39.8±11.4 cm, p=0.039), and BMI (18.52±3.96 vs. 21.73±5.4, p= 0.041).

Table-1: Baseline characteristics of JIA patients (n=80).

Baseline characteristics		Range	Mean ± Standard deviation
Age (years)		2-18	13.1±4.8
Disease Duration (years)		0.17-14.8	4.4±3.9
Age at onset (years)		1-15	8.9±4.1
Serum 25(OH) D (ng/ml)		31.3±6.7	15.69±6.6
		Number	%
Gender	Male	18	22.5
	Female	62	77.5
Onset subtype	Systemic onset	14	17.5
	Pauciarticular onset	18	22.5
	Polyarticular RF –ve	28	35
	Polyarticular RF +ve	14	17.5
	Enthesitis related arthritis	6	7.5

RF: rheumatoid factor; RF – ve: Rheumatoid factor negative; RF +ve: Rheumatoid factor positive.

Table-2: Clinical and growth characters of JIA patients (n=80).

Clinical data	Range	Mean ± SD
Morning stiffness (min)	0-240	54.1±38.6
Height (cm)	80-162	135.4±22.1
Weight (kg)	9-65	34.6±13.6
BMI ($Kg/m^{2)}$	13.01-31.93	18.52±3.96
Steroid dose (mg/day)	5-25	10.4±5.1
Steroid duration (years)	0-13	7.2±5.8
	Number	%
Steroid intake	42	52.2%
Growth Charts	Number	%
Below 5^{th} percentile	34	42.5
At the 5^{th} percentile	20	25
Between 5^{th} and 50^{th}percentiles	22	27.5
At the 50^{th} percentile	2	2.5
Between the 50^{th}& 95^{th} percentiles	2	2.5

SD: Standard deviation.

There was a significant difference in the patients' height when comparing patients according to the onset of subtype (p=0.037) (**Table.3, Figure.1**). Patients with systemic onset subtype had a significantly lower height than patients with oligoarticular onset (p=0.024), patients with polyarticular RF negative onset (p=0.046), and patients with polyarticular RF positive onset (p=0.020). There was a significant negative correlation between steroid dose and duration and the height (r= -0.456, p=0.017 and r=-0.776, p=0.001), respectively. The mean serum 25(OH) D3 levels was statistically significantly lower in JIA patients in comparison to controls (15.69±6.6 ng/ml vs. 31.62±4.9 ng/ml) (p<0.0001). Patients with systemic onset and seropositive polyarthritis (RF positive) have lowered 25(OH) D3 levels than patients with pauciarticular and enthesitis - related arthritis. In JIA patients 52 patients (65%) had deficient 25(OH)D3 (12.45±4.9 ng/ml), 22 patients (27.5%) had insufficient 25(OH)D3 (21.41±4.4 ng/ml) and 6 patients (7.5%) had normal 25(OH)D3 level (22.3±6.9 ng/ml) (p=0.049); while in controls 56 patients (70%) had normal 25(OH)D3 (34.14±3.1 ng/ml) and 24 patients (30%) had insufficient 25(OH)D3 level (25.73±2.7 ng/ml) (p=0.032). Serum 25 (OH) D3 level was significantly correlated with patients' height and BMI (**Figure.2**) (r=0.33, p=0.029 and r=0.32, p=0.043), respectively.

Table-3: Comparison between different JIA subtypes.

Variables	Systemic onset	Pauciarticular onset	Polyarticular RF -ve	Polyarticular RF +ve	Enthesitis related arthritis	P- value
Weight,(kg)	23.3±12.3	33.3±10.1	37.4±14.9	41±12.9	36.7±12.6	0.125
Height, (cm)	112.6±29.4	139.9±12.4	137.3±22.6	144.4±10.8	144.7±17.5	0.037
BMI (kg/m2)	16.8±4.3	17.2±2.9	19.4±5.1	19.3±4	18.6±1.7	0.569
Serum 25(OH) D3	11.97±0.87	21.17±7.51	13.76±5.81	12.59±4.65	16.7±6.8	0.49

RF – ve: Rheumatoid factor negative; RF+ve: Rheumatoid factor positive; BMI: Body mass index.

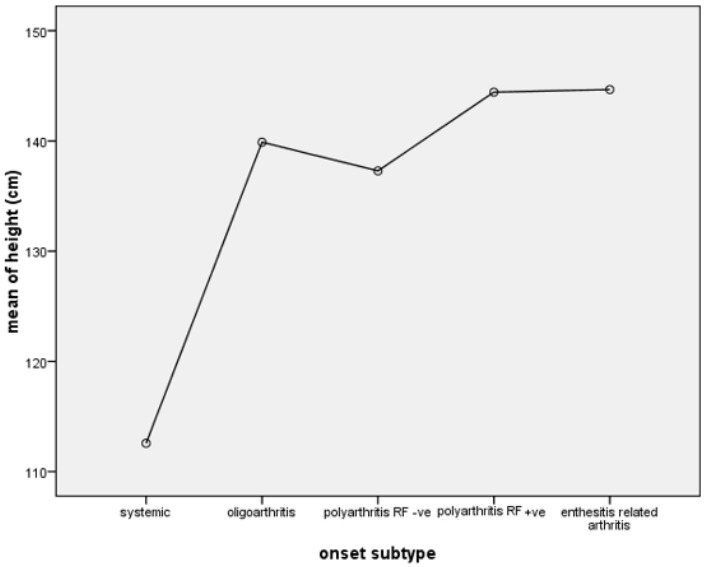

Fig.1: Mean height of the different JIA onset subtypes patients.

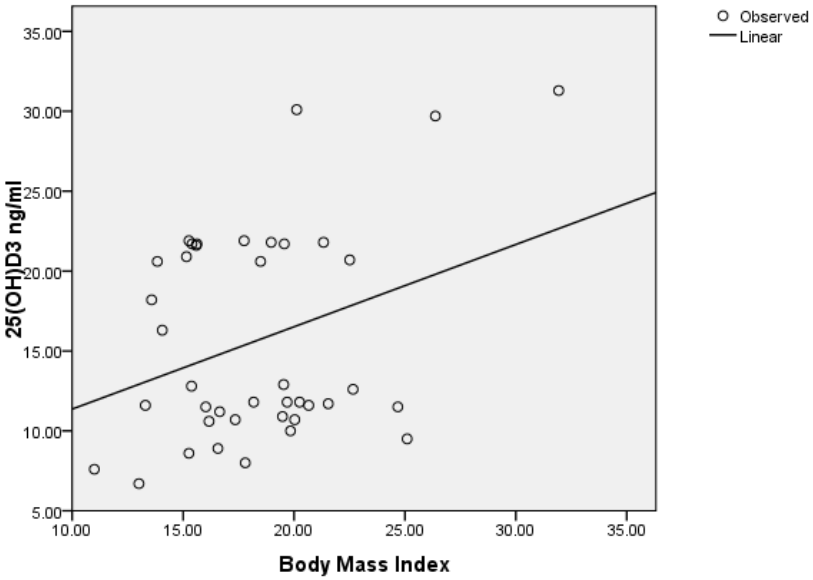

Fig.2: Correlation between body mass index and levels of 5-hydroxyvitamin D.

4- DISCUSSION

In the present study we aimed to evaluate the growth pattern and Vitamin D level in patients with juvenile idiopathic arthritis (JIA) and its different subtypes. Growth impairment is one of the complications, especially in polyarticular and systemic JIA (14, 15). Body mass index provides a valid measure of fatness in healthy children and is used as a marker of nutritional status in other pediatric diseases (16), an objective assessment of protein-energy depletion, or excess, and is a practical tool for routine anthropometric measures in clinics (17). The involvement of nutritional status has often been reported in JIA patients, but there are some

discordant reports about the nutritional status and disease subtypes (17, 18). The role of vitamin D in skeletal growth and development is well established although its biological actions are mediated primarily through its steroid hormone metabolite 1, 25-dihydroxyvitamin D, (19, 20). In the last few years, based on the results and observations of clinical and laboratory studies the possible role of vitamin D in the pathogenesis, activity, and treatment of JIA has been suggested (21). However, there were conflicting results as to whether serum 25(OH)D levels were associated with growth retardation. Some authors have found a relationship between 25(OH)D and disease activity in early inflammatory polyarthritis and RA (22, 23); while others have found no association (24, 25). In the present study, there was a significant difference in growth parameters including patients' height, weight, and BMI than those of the age-matched healthy controls.

Also, we found 42.5% of our patients below the 5th percentile, 25% at the 5th percentile and only 2.5% at 50th percentile. Patients with systemic onset subtype had the most significantly lower height, weight, and BMI than other subtypes of JIA patients. The proportion of children with JIA that are abnormally short ranges from 10 to 40% (26, 27). Growth retardation is significantly more severe in children with the systemic subtype of the disease and in children in whom many joints are affected (26, 27).In the present study, patients with systemic onset subtype had a significantly lower height than patients with oligoarticular onset, patients with polyarticular RF negative onset, and patients with polyarticular RF positive onset. The effect of corticosteroids on growth has been confirmed in short-term and longitudinal studies. In studies carried out using knemometry, the rate of growth in the lower extremities was reduced in children treated with corticosteroids, as was metabolic turnover in the bone tissue (27). In one study on children with JIA, long-term treatment with corticosteroids irreversibly reduced terminal body height, whereas treatment lasting for less than one year had no effect (28). On the other hand, in a longitudinal study on pre-pubertal children with JIA who were treated with corticosteroids, the growth rate was significantly reduced only during the first year of treatment, after which it increased. This was attributed to an improvement in the course of the disease (29). Our results were consistent with most studies as we found a significant negative correlation between steroid dose and duration and the mean height of our JIA patients.

The suppressive effects of corticosteroid therapy on growth can be a factor contributing to growth retardation in JIA (27). However, growth delay in JIA, unrelated to steroid treatment, does occur as in the study done by Liem et al. (30) who reported that no significant differences in growth were demonstrable between steroid-treated and steroid-untreated populations. Based on the Institute of Medicine's recommended classification of Vitamin D status, the presence of hypovitaminosis D is common beyond infancy (31-34), the risk of deficiency increased significantly during childhood for both sexes (34). In the present study, 30% of our control children have insufficient vitamin D level and 70% were normal, the mean serum 25(OH) D3 level was statistically significantly lower in JIA patients in comparison to controls. Patients with Systemic onset and RF positive polyarthritis have lower 25(OH)D levels than patients with pauciarticular and enthesitis-related arthritis. In a review that summarizes and evaluates evidence relating to 25-hydroxyvitamin D and chronic childhood arthritis (35), 38 studies reporting 25(OH)D3 concentrations in childhood chronic arthritis were analyzed; 32 (84.2%) reported that a significant

number of children had suboptimal (<75 nmol/L) status and it is known that there is a role for vitamin D in the inflammatory pathways, a high prevalence of 25(OH)D3 insufficiency among children with JIA, and an established link of vitamin D with other autoimmune diseases. It is not known, however, whether the optimal vitamin D status for children with JIA reduced due to the disease itself or increased utilization (36). There is no dispute over the importance of vitamin D in skeletal development and mineral metabolism. The lack of statistical relationship between plasma 25(OH)D concentrations with stature or bone mineral content does not negate the critical role of vitamin D for growth and development of the skeleton in addition to the many other potential roles to maintain health (36). From our search, we could not find any papers that study the effect of the deficient level of vitamin D in JIA patients on their linear growth or body mass index.

According to our results, serum 25 (OH) D level was significantly correlated with patients' height and BMI (r=0.33, p=0.029, and r=0.32, p=0.043), respectively. The poor nutritional status may be the result of decreased food intake because of chronic inflammatory disease, or a side effect of drugs; or increased production of tumor necrosis factor-alpha and interleukin-1 (37, 38), or reduced physical activity (39). Poor nutritional status may affect the general well-being of the patient child, and contribute to growth disturbance (40).

5- CONCLUSION

The nutritional status of JIA patients is multifactoral. Onset subtype and low vitamin D level were found to have an effect on growth parameters as height and body mass index in patients with juvenile idiopathic arthritis. So, continuous evaluation of growth parameters and Vitamin D level can improve growth outcome in JIA patients.

6- CONFLICT OF INTEREST: None.

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