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Growth Pattern in Children with Juvenile Idiopathic Arthritis: A Retrospective Study

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Abstract

Aim of this study is to assess growth pattern in children with juvenile idiopathic arthritis (JIA) and factors associated with growth retardation. **Methods:** A retrospective chart review of all cases of JIA following up at Pediatric Department of King Abdulaziz University Hospital, between July 2000 to July 2016. Demographic, clinical and biological data were collected and analyzed as risk factor for growth retardation. These included age, gender, age at diagnosis, disease duration, type of JIA, the presence of uveitis, rheumatoid factor (RF) positivity, antinuclear antibody (ANA) titer and treatment. Growth pattern was assessed as the percentile for height-for-age, weight-for-age and weight-for-height in reference to the Growth Chart for Saudi Children and Adolescents. Change in percentile rank was divided into 3 categories: regression (a drop of ≥1 percentile); stable (uphold of the same percentile); and progression (change for a superior percentile). **Results:** A total 78 children were eligible, 52.6% females, mean ± SD age = 9.94 ± 4.92 years, and age at diagnosis = 7.44 ± 4.52 years, mean ± SD [range] disease duration = 2.93 ± 2.70 [6 months; 15 years]. The most frequent types of JIA were systemic (33.3%), oligoarticular (30.8%) and polyarticular negative RF (26.9%). Other parameters included positive ANA in 41.0%, positive RF in 7.7% and uveitis in 9.0%. The most frequent treatment was methotrexate (59.0%), followed by biological therapy (47.4%), non-steroid anti-inflammatory drugs (43.6%) and prednisolone (33.3%). Growth data were available for 67 (85.9%) children, and assessments showed 36% cases of break of the growth curve in both height-for-age and weight-for-age percentiles and 31% in weight-for-height percentiles. In all three parameters, there were shifts towards lower percentiles from time of diagnosis to last follow-up, in both males and females. Correlation and regression analysis showed low age at diagnosis and disease duration to be significant predictors for growth retardation severity. **Conclusion:** One in three children with JIA has growth retardation, the severity of which is predicted by low age at disease onset and long disease duration.

Keywords

Juvenile Idiopathic Arthritis, Growth Pattern

1. Introduction

Juvenile idiopathic arthritis is a heterogeneous group of inflammatory diseases characterized by chronic arthritis with various clinical presentations [1]. Although genetic and environmental factors have been identified, the origin and pathophysiology of the disease are not well elucidated [1]. It is considered to be one of the most frequent chronic diseases in pediatric patients; its prevalence ranges from 3.8 to 400 per 100,000 with frequently reported female predominance [2] [3] [4]. In the United States, it is estimated that 250,000 children are affected with juvenile idiopathic arthritis [5].

The International League of Associations for Rheumatology (ILAR) classified JIA into 7 sub-types according to the degree and extent of arthritis and biological markers [6]. Besides having different clinical features, each sub-type has a particular prognosis profile and response to the different therapies [7]. In Saudi Arabia, the most common sub-types of JIA are systemic onset and oligoarticular forms [8].

The disease course is characterized by successive flare-ups with more or less disease activity and generally short-remissions [9]. There are various therapeutic approaches in JIA, aiming generally to reduce the number of flare-ups and inflammatory activity, relieve pain and limit the progression of the disease [10]. Steroids and non-steroid anti-inflammatory drugs (NSAIDs) have been for many years the main pharmacological resource; and methotrexate and anti-tumor necrosis factor (anti-TNF-α) such as etanercept and infliximab have been introduced later, all having a limited efficacy and considerable adverse effects. More recently, anti-interleukin 6 (anti-IL-6) therapies such as tocilizumab and anti-IL-1 therapies have demonstrated better results, especially in systemic-onset JIA [11]. It is crucial to diagnose and treat JIA early to prevent irreversible joint damage and soft-tissue deformities; which are more frequent and sever in polyvarticular form with positive rheumatoid arthritis [12] [13]. Number of other complications are reported with uveitis being the most frequent extra-articular characterized with severs outcomes, such as glaucoma, cataract and irreversible vision loss [7] [14] [15].

Growth impairment is a frequent complication of JIA found in 35% to 40% of the afflicted children [16] [17]. It can have generalized form causing short body stature [18], or may interest the affected limb exclusively [9]. Growth disorders are associated with long-term disability, which impacts the patient's and family quality of life and represents substantial economic burden [19]. Like other JIA complications, growth disorder are function of disease duration and activity, with more severe cases observed in patients with high, long-term inflammatory profiles, such as systemic and polyarticular JIA sub-types [7] [20]. Other associated risk factors

such as low age of onset and long-term use of corticoids may significantly contribute in severity of growth retardation [17] [21]. Therefore, assessing growth pattern in children and adolescents with JIA is a crucial indicator of disease activity and therapeutic success. It should be systematically used as a complement for treatment efficacy assessment. Furthermore, there is lack of data in the Middle-Eastern region regarding growth patterns and growth impairment among JIA children. We conducted this study to explore growth pattern among children afflicted with JIA in Saudi Arabia; and to assess prevalence and risk factors of growth retardation.

2. Methods

A retrospective chart review was carried out on all children (aged < 20 years) following up for JIA at the Pediatric Department of King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between July 2000 to July 2016.

All cases were diagnosed according to the International League of Associations for Rheumatology (ILAR) criteria for JIA based on onset age < 16 years, 6-week or more disease duration, and with exclusion of other conditions [6] [22]. Type of JIA (systemic, oligoarticular, extended oligoarticular, polyarticular with negative rheumatoid factor (RF), polyarticular with positive RF, psoriatic, enthesitis-related arthritis and undifferentiated arthritis) was determined according to ILAR classification for JIA [6] [22] [23].

Classification of weight and height was done using the Growth Charts for Saudi Children and Adolescents (endorsed by The Health Services Council of Saudi Arabia No.29, 24/6/2007) [24]. Growth pattern was assessed as the change in percentile rank for height-for-age, weight-for-age and weight-for-height, from time of diagnosis (T0) to last follow-up (T1). Change in percentile rank was divided into 3 categories: regression (a drop of ≥1 percentile); stable (uphold of the same percentile); and progression (change for a superior percentile).

Demographic, clinical and biological data were collected and analyzed as risk factor for growth retardation. These included age, gender, age at diagnosis, disease duration, type of JIA (systemic, polyarticular RF−, polyarticular RF+, oligoarticular and extended oligoarticular), presence of uveitis, rheumatoid factor (RF) positivity, antinuclear antibody (ANA) titer and treatments used (NSAIDs, methotrexate, prednisolone, and biological treatments).

Statistical Methods

Statistical analysis was performed with the Statistical Package for Social Sciences Version 21.0.0.0 for Windows (SPSS Inc., Chicago, IL, USA, 2012). Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean ± standard deviation (SD). Growth pattern was classified as regression, stable or progression according to loss, maintain or win in percentile rank from diagnosis time to last follow-up, respectively. Analysis of growth impairment-associated risk factors was done using two categories: regression/no regression. Correlations of growth patterns and growth impairment with demo-

graphic and clinical factors were analyzed using chi-square test in categorical variables, and independent t-test or One-Way Analysis of Variance (ANOVA) in continuous variables, as appropriate. Analysis of the severity of growth impairment indicated by the number of percentile ranks lost from diagnosis time to last follow-up was carried out using univariate and multivariate ordinal regression models; results were presented in scatter plots and fit curve, with calculation of odds-ratios and 95%CI. A p value of <0.05 was considered to reject the null hypothesis.

3. Results

3.1. Patients' Characteristics

A total 78 children with JIA were eligible for the study, 52.6% females, mean ± SD age = 9.94 ± 4.92 years, and age at diagnosis = 7.44 ± 4.52 years. They were followed up for a mean ± SD [range] disease duration = 2.93 ± 2.70 [6 months; 15 years]. The most frequent types of JIA were systemic (33.3%), oligoarticular (30.8%) and polyarticular negative RF (26.9%). Other parameters included positive ANA in 41.0%, positive RF in 7.7% and uveitis in 9.0%. The most frequent treatment was methotrexate (64.1%), followed by biological therapy (47.4%) (Table 1).

Table 1. Demographic and clinical characteristics of children with juvenile idiopathic arthritis.

Parameter	Value	Frequency/mean	Percentage/SD
Age	Range = 9 months; 20.00 years	9.94	4.92
Gender	Male	37	47.4
	Female	41	52.6
Age at diagnosis	Range = 6 months; 16.00 years	7.44	4.52
Weight at diagnosis	Range = 6.60; 63.00 Kg	28.85	16.44
Height at diagnosis	Range = 63; 167 cm	119.76	27.23
Disease duration	Range = 2 months; 15.00 years	2.93	2.70
Diagnosis	Systemic	26	33.3
	Polyarticular RF+	5	6.4
	Polyarticular RF–	21	26.9
	Oligoarticular	24	30.8
	Extended Oligoarticular	2	2.6
Treatment	NSAIDs	34	43.6
	Methotrexate	50	64.1
	Prednisolone	26	33.3
	Biological	37	47.4
ANA	Negative (<1:40)	46	59.0
	Mild positive (1:40 - 1:160)	22	28.2
	Moderately positive (1:320 - 1:640)	6	7.7
	Strongly positive (>1:640)	4	5.1
Rheumatoid Factor	Negative	72	92.3
	Positive	6	7.7
Uveitis		7	9.0

SD: Standard deviation; RF+: positive rheumatoid factor; RF–: negative rheumatoid factor; NSAIDs: non-steroid anti-inflammatory drugs; ANA: antinuclear antibody.

3.2. Growth Parameters

Growth data were available for 67 (85.9%) children only. Analysis of weight, height and weight-for-height percentiles showed 46.2%, 46.2% and 39.7% breaks of the respective growth curves between time of diagnosis and last follow-up (Table 2). In all three growth parameters there were shifts towards lower percentiles from time of diagnosis to last follow-up, which was observed in both genders (Figures 1-3).

Table 2. Growth parameters of children with juvenile idiopathic arthritis.

Parameter	Value	Frequency/Mean	Percentage/SD
Weight			
At diagnosis	Mean, SD (Kg)	28.85	16.44
At last follow-up	Mean, SD (Kg)	37.14	23.81
	Regression	36	46.2
Growth pattern[1]	Stable	20	25.6
	Progression	11	14.1
Height			
At diagnosis	Mean, SD (cm)	119.76	27.23
At last follow-up	Mean, SD (cm)	166.50	129.27
	Regression	36	46.2
Growth pattern[1]	Stable	16	20.5
	Progression	15	19.2
Weight-for-height			
	Regression	31	39.7
Growth pattern[1]	Stable	21	26.9
	Progression	16	20.5

[1]Growth pattern was assessed according to the change in percentile rank from time of diagnosis to last follow-up, which was classified into 3 categories: regression = drop to a lower percentile; stable = maintaining the same percentile; progression = change to a superior percentile.

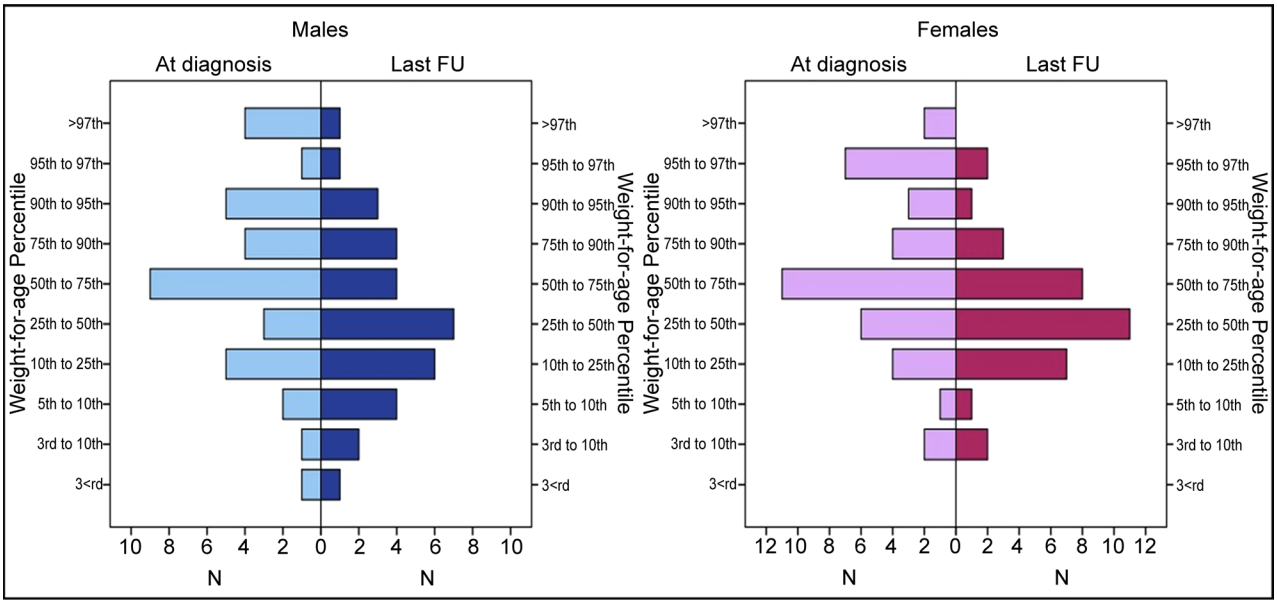

Figure 1. Weight-for-age percentiles in male and female children with juvenile idiopathic arthritis, at diagnosis and at last follow-up visit (median [range] follow-up duration = 2.00 [0.20 - 13.00] years in males and 3.00 [0.50 - 12.00] years in females; p = 0.086 Mann-Whitney U test).

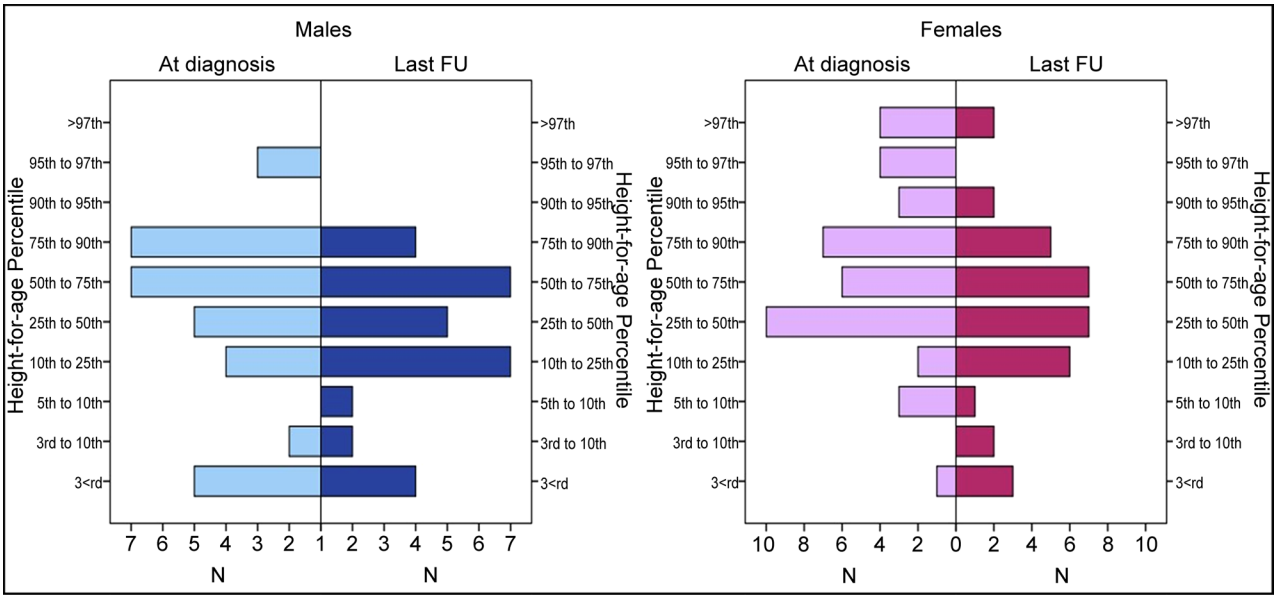

Figure 2. Height-for-age percentiles in male and female children with juvenile idiopathic arthritis, at diagnosis and at last follow-up visit (median [range] follow-up duration = 2.00 [0.20 - 13.00] years in males and 3.00 [0.50 - 12.00] years in females; p = 0.086 Mann-Whitney U test).

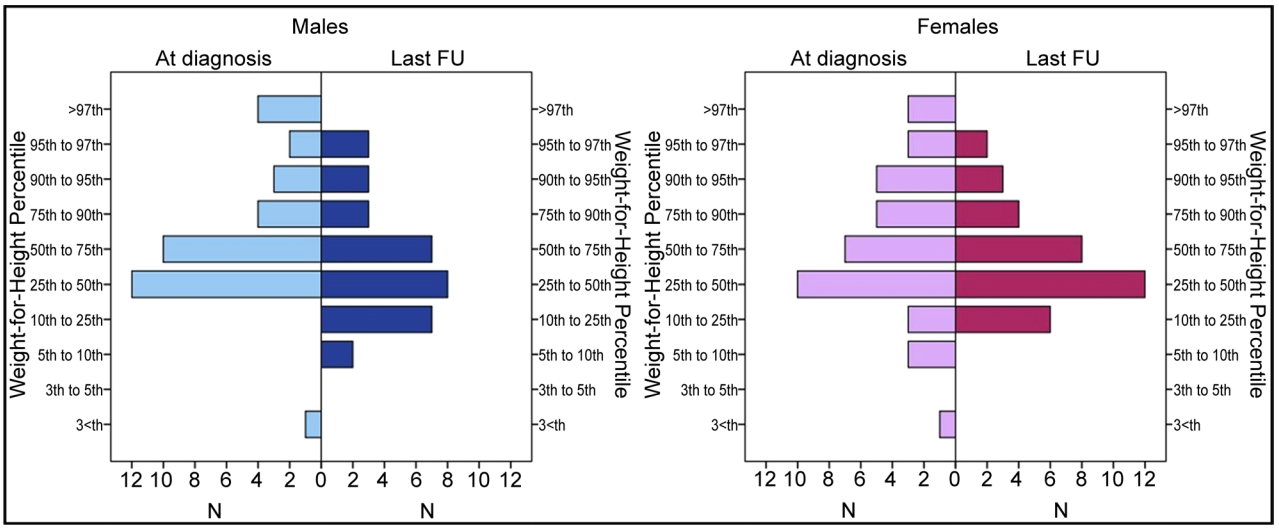

Figure 3. Weight-for-height percentiles in male and female children with juvenile idiopathic arthritis, at diagnosis and at last follow-up visit (median [range] follow-up duration = 2.00 [0.20 - 13.00] years in males and 3.00 [0.50 - 12.00] years in females; p = 0.086 Mann-Whitney U test).

3.3. Demographic and Clinical Factors Correlated with Growth Impairment

Correlation of height-for-age growth curve with demographic and clinical factors showed that children who regressed in the percentile rank from T0 to T1 had lower age at diagnosis than those who did not regress (mean ± SD age = 6.69 ± 4.02 versus 8.54 ± 4.88 years, respectively; p = 0.093) and longer disease duration (3.31 ± 2.21 versus 1.97 ± 1.28 years; p = 0.004, respectively). Analysis of the other factors, such as gender, JIA sub-type, treatment or biological data showed no significant difference between the two groups.

Regarding weight-for-age, children who regressed had longer disease duration than those who did not regress (3.20 ± 2.10 versus 2.10 ± 1.57 years; p = 0.020, respectively). No difference was observed in other factors; except a higher proportion of prednisolone use among children who had growth retardation versus who had normal growth (68.0% versus 32.0%), however, this result was not statistically significant (p = 0.071) (Table 3).

Table 3. Demographic and clinical factors correlated with break of the growth curve (regression) among children with JIA.

Parameter/Value	Height-for-age					Weight-for-age				
	Regression		No regression		p-value	Regression		No regression		p-value
	Freq.	%	Freq.	%		Freq.	%	Freq.	%	
Gender										
Male	16	50.0	16	50.0	0.558	19	59.4	13	40.6	0.376
Female	20	57.1	15	42.9		17	48.6	18	51.4	
Age at diagnosis (mean, SD; years)	6.69	4.02	8.54	4.88	0.093*	7.01	4.15	8.17	4.88	0.298
Disease duration (mean, SD; years)	3.31	2.21	1.97	1.28	0.004*	3.20	2.10	2.10	1.57	0.020*
Diagnosis										
Systemic	13	52.0	12	48.0		12	48.0	13	52.0	
Polyarticular RF+	1	20.0	4	80.0		1	20.0	4	80.0	
Polyarticular RF–	11	64.7	6	35.3	0.529	12	70.6	5	29.4	0.331
Oligoarticular	10	55.6	8	44.4		10	55.6	8	44.4	
Exd. oligoarticular	1	50.0	1	50.0		1	50.0	1	50.0	
NSAIDs										
No	19	48.7	20	51.3	0.331	21	53.8	18	46.2	0.982
Yes	17	60.7	11	39.3		15	53.6	13	46.4	
Methotrexate										
No	13	56.5	10	43.5	0.740	12	52.2	11	47.8	0.853
Yes	23	52.3	21	47.7		24	54.5	20	45.5	
Prednisolone										
No	21	50.0	21	50.0	0.427	19	45.2	23	54.8	0.071
Yes	15	60.0	10	40.0		17	68.0	8	32.0	
Biological treatments										
No	19	57.6	14	42.4	0.534	19	57.6	14	42.4	0.534
Yes	17	50.0	17	50.0		17	50.0	17	50.0	
ANA titer										
Negative	22	62.9	13	37.1		17	48.6	18	51.4	
Mild positive	11	50.0	11	50.0	0.305	13	59.1	9	40.9	0.788
Moderate positive	2	33.3	4	66.7		4	66.7	2	33.3	
Strong positive	1	25.0	3	75.0		2	50.0	2	50.0	
Rheumatoid factor										
Negative	35	56.5	27	43.5	0.174§	35	56.5	27	43.5	0.174§
Positive	1	20.0	4	80.0		1	20.0	4	80.0	
Uveitis										
No	34	56.7	26	43.3	0.236§	33	55.0	27	45.0	0.696§
Yes	2	28.6	5	71.4		3	42.9	4	57.1	

Freq.: frequency, *: statistically significant result (p < 0.005); RF+: positive rheumatoid factor; RF–: negative rheumatoid factor; Exd. Oligarticular: extended olilgarticular; §: significance calculated using Fisher's exact test.

3.4. Predictors for Growth Retardation Severity

Age at diagnosis and disease duration were analyzed as predictors for growth retardation severity in children with JIA, which was indicated by the number of percentile ranks lost from diagnosis to last follow-up. Regarding height-for-age, severity of growth retardation was predicted by low age at diagnosis and long disease duration in both univariate and multivariate models (**Table 4**), showing significant correlations with the number of percentile ranks lost from diagnosis to last follow-up (**Figure 4(a)**, **Figure 5(a)**). Regarding weight-for-age, severity of growth retardation was only predicted by disease duration (**Table 4**; **Figure 4(b)** and **Figure 5(b)**).

4. Discussion

4.1. Epidemiology of Growth Retardation in JIA

Growth retardation and developmental abnormalities are common complications of JIA and are associated with significant impact on patient's physical and psychological health and overall quality of life [25] [26] [27]. This retrospective study showed high incidence of growth retardation among the local patients. Almost 1 child in 2 had breaks in growth curve, in at least one of the three growth parameters including weight-for-age, height-for-age and weight-for-height. In other studies, pattern of growth varies according to the study population and methodology and to other associated risk factors. Some authors report 10% to 20% of growth retardation in children with severe forms of JIA [28], while others reported up to 40% in all sub-types [21]. A prospective case-control study from India found no significant difference between JIA children and healthy controls. Authors compared weight, height, body mass index and growth velocity over 6 months of children with JIA versus healthy children [29]. This shows relatively high proportion of growth impairment among our study population, which points towards the existence of other probable risk factors.

4.2. Pathophysiology of Growth Retardation in JIA

Pathophysiology of growth retardation in children and adolescents with JIA is

Table 4. Predictors for break of the growth curve among children with JIA (ordinal regression).

Dependent variable/predictor	Univariate model				Multivariate model			
	OR	95% CI		p-value	OR	95% CI		p-value
Height								
Age at diagnosis (years)	1.11	1.01	1.22	0.034*	1.15	1.04	1.28	0.005*
Disease duration (years)	0.70	0.55	0.88	0.002*	0.62	0.48	0.80	0.000*
Weight								
Age at diagnosis (years)	1.05	0.95	1.15	0.335	-	-	-	-
Disease duration (years)	0.77	0.61	0.96	0.022*	-	-	-	-

*Statistically significant result ($p < 0.05$); OR: odds-ratio; 95% CI: 95% confidence interval for OR.

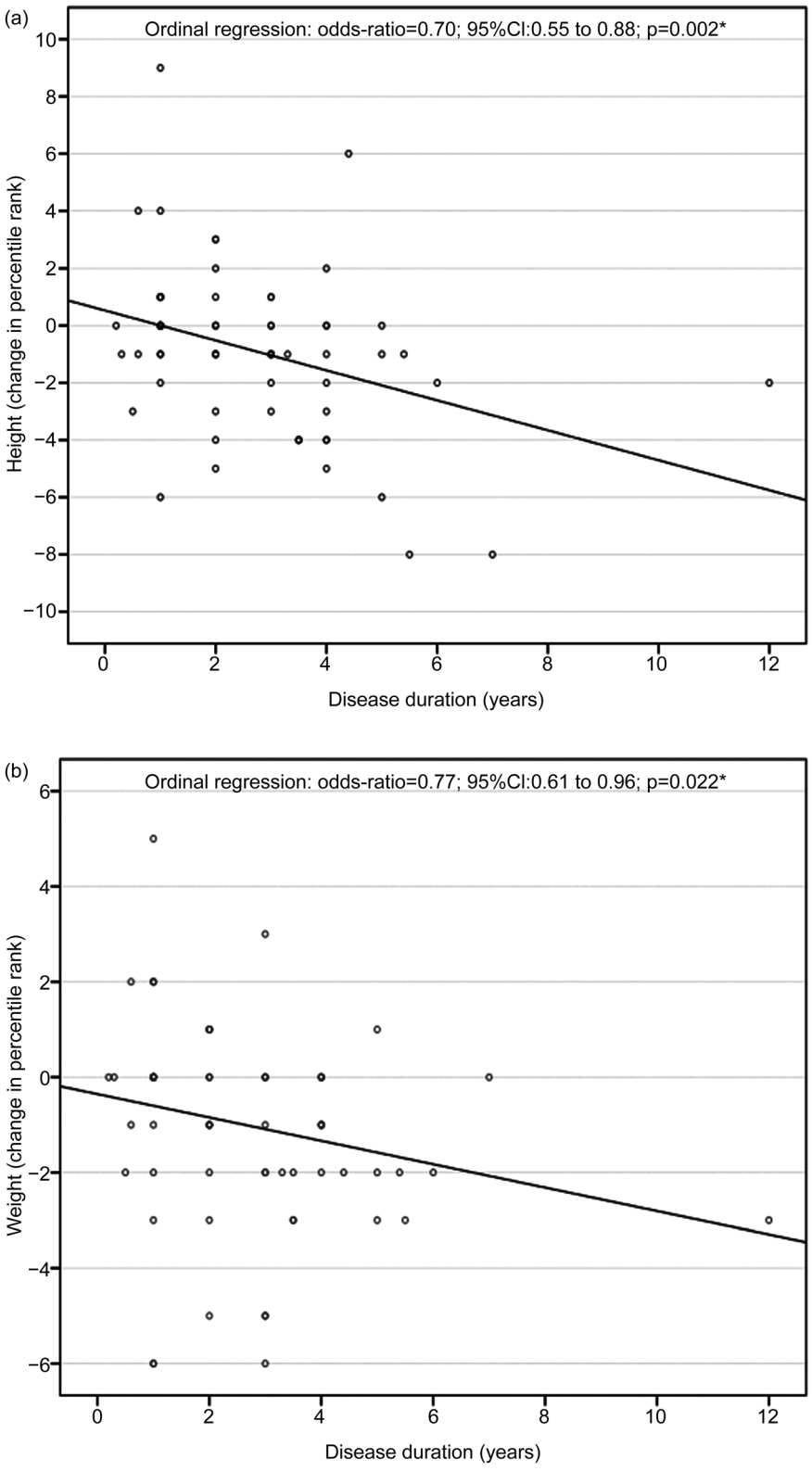

Figure 4. Correlation between disease duration and change in percentile rank for height (a) and weight (b) in children with JIA. Ordinal regression showed that disease duration is a significant risk factor for growth impairment considering both height for age (OR = 0.70; 95% CI: 0.55 to 0.88; p = 0.002*; **Figure 4(a)**) and weight for age (OR = 0.77; 95% CI: 0.61 to 0.96; p = 0.022*; **Figure 4(b)**).

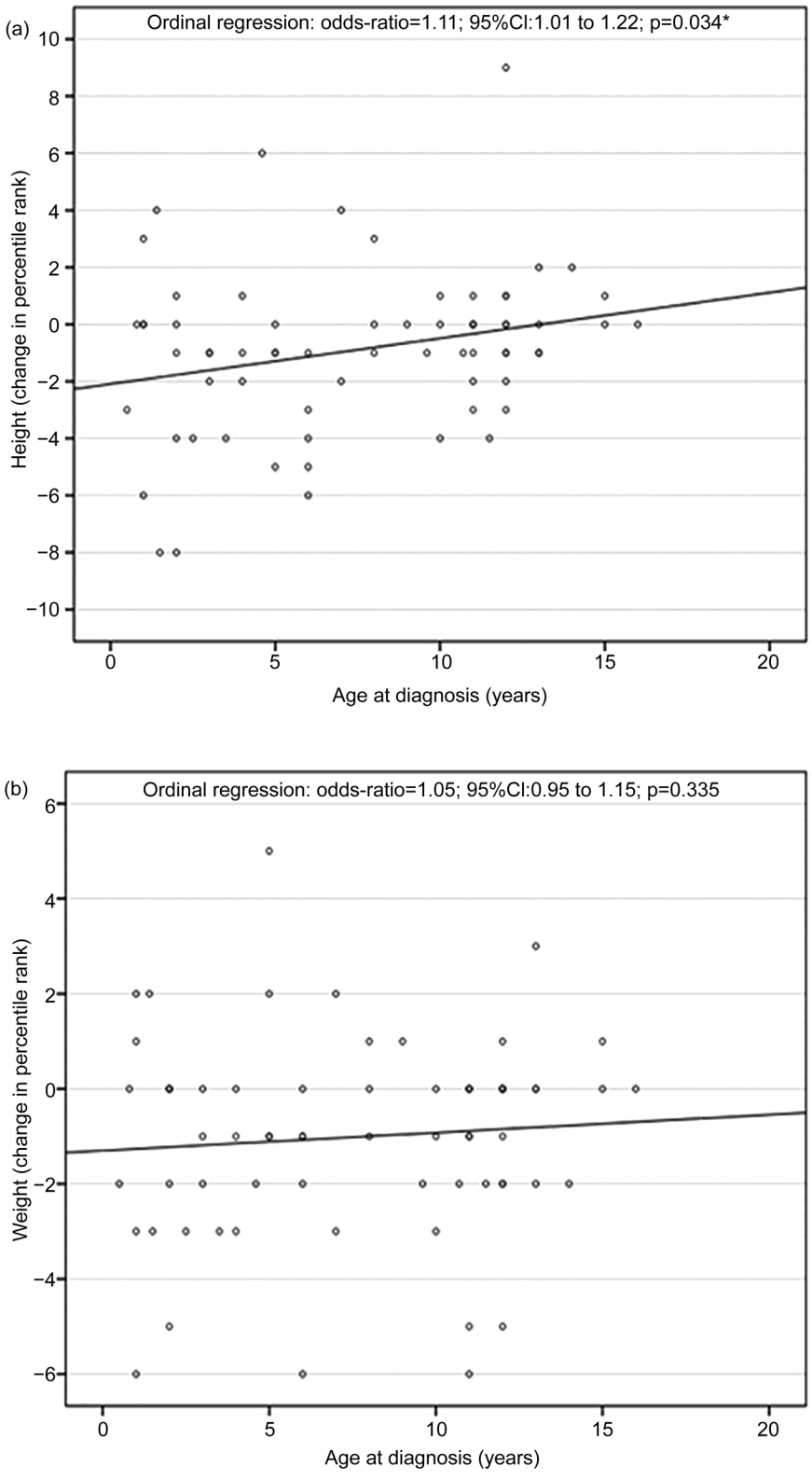

Figure 5. Correlation between age at diagnosis and change in percentile rank for height (a) and weight (b) in children with JIA. Ordinal regression showed that age at diagnosis is a significant predictor for growth impairment, considering height for age (OR = 1.11; 95% CI: 1.01 to 1.22; p = 0.0034*; **Figure 5(a)**) but not weight for age (OR = 1.05; 95% CI: 0.95 to 1.15; p = 0.335; **Figure 5(b)**).

mainly related to excessive cytokine levels and their pro-inflammatory action; distinctive of severe forms of JIA [30] [31]. There is strong evidence indicating the existence of systemic and local modulating effect of cytokines (especially IL-6) on growth plate of long bones [30] [32] [33]. In addition, cytokines have indirect action involving insulin-like growth factor-I, which was observed to be reduced in serum of patients with systemic JIA and correlated to excessive production of IL-6 [27]. Number of other hormonal and metabolic factors such as parathyroid dysfunction, sex steroids and vitamin D metabolites contribute in growth retardation by modulating growth hormone/insulin-like growth factor-I axis, resulting in impaired bone growth [8]. Growth retardation may also be induced by prolonged use of corticosteroids, especially when initiated in the young age [8] [27]. Other pathophysiological mechanisms include other cytokine-induced epigenetic changes [34] and malnutrition [35].

4.3. Effect of Age at Diagnosis

Age at diagnosis and disease duration was the only significant factors correlated with growth retardation. Average age at diagnosis of the population was 7.44 ± 4.52 years, which was in line with other studies [29] [36] Both the occurrence and severity of height retardation were predicted by the low age at diagnosis of the patient; while the no effect was observed on weight growth. This is generally supported by literature; and may be explained by the level of growth hormone secretion in the childhood, which is physiologically lower than in adolescent, resulting in greater impact of the disease activity (cytokines) on insulin-like growth factors-I secretion in the young; and consequently a delayed long bone growth [8] [37].

4.4. Effect of Disease Duration

We demonstrated that disease duration was a significant predictor for the occurrence of growth retardation in both height and weight. In addition, severity of growth retardation, as indicated by the number of percentile ranks lost, was linearly correlated with the number of years of disease duration. In other words, children with long disease duration represent the most frequent and most severe cases of growth retardation among children with JIA. These observations are concordant with data from literature showing greater growth delay in children with long disease duration; which is a common point between all children chronic inflammatory diseases [8] [31] [38].

4.5. JIA Sub-Types and Growth

No difference was found between different JIA sub-types in any of the analyzed growth parameters; whereas Mondal *et al.* reported greater impact on growth velocity in children with polyarticular RF+ form, while children with systemic JIA had the greatest impact on height and weight by comparison to those with other sub-types [29]. Similarly, Okumus *et al.* reported significantly smaller height in systemic JIA [39]. Severe cases of growth retardation are generally reported in

polyarticluar forms with multiple joint involvement or systemic forms with extensive damage [21].

4.6. Effect of Treatments on Growth

This study demonstrated no significant effect of treatments on growth, be it positive of negative. This may be explained by a relatively short disease duration (2.93 ± 2.70 years), which may be insufficient to observe an effect of treatments. The use of corticosteroids has been demonstrated to induce or exacerbate growth retardation, in a duration- and dose-dependent manner [21]. Furthermore, children treated by corticosteroids in a young age are highly exposed to delayed puberty than those on other treatment regimen [40]. On the other hand, biological therapy, such as anti-TNF-α and anti-IL-6 have been shown to restore growth, both by reducing disease activity and limiting the use of corticosteroids [41]. Another study demonstrated a strong growth-restoring effect of anti-TNF-α in children with polyarticluar JIA, which was correlated to the decrease in disease activity, independently from corticosteroids effect [42]. However, in systemic JIA, growth restoring effect of biologic treatments seems to be less remarkable [43]. Analysis of these observations, among other therapeutic outcomes, justified the current trend of early initiation of aggressive treatment, using several combination of different agents to improve allover disease outcomes including growth [44]. On the other hand, the use of growth hormone has shown good results in restoring growth of JIA patients and should be considered in the management of these patients [45].

None of the other disease-related parameters including ANA, RF and uveitis were significantly associated with growth retardation.

The major limitation of this study was a small sample size, which limited the power of sub-groups analysis; in addition to growth data being missing in number of files, which further reduced the sample size. One other notable limitation was the short follow-up duration of the patients, which prevented from observing significant effects of treatments and other factors on growth. In addition, other growth parameters, such as sexual maturation and bone density were not assessed in this study, both showing to be impaired in JIA in other studies [40] [46].

Despite these limitations, this study provided a sound epidemiological picture of growth retardation among children with JIA and highlighted the importance of systemic and careful assessment of growth parameters in these children.

Future prospective, multicenter studies are warranted to provide a more accurate picture of the growth pattern among JIA children in Saudi Arabia; and investigate further population-specific risk factors associated with this high prevalence. Such study should also assess other parameters including sexual maturation, bone density and local growth abnormalities.

Preventing growth impairment and restoring growth velocity should be among priorities of therapeutic goals. It is achieved through effective decrease of time and severity of disease flare-ups and enhancement of remissions. This requires

appropriate use of pharmacological treatments along with systemic, close monitoring of physical development and interdisciplinary management involving pediatricians, rheumatologists and clinical anthropologists [21].

5. Conclusions

Juvenile idiopathic arthritis is associated with up to 46.1% cases of growth retardation in Saudi Arabia, which is high by comparison to other studies. Children with young age at diagnosis and long disease duration are at greater risk and represent the most severe cases of growth retardation. The impact of other clinical factors such as JIA sub-types, uveitis and treatments could not be observed; because of the relatively short follow-up and small sample size. Further risk factors for growth retardation in JIA patients should be investigated in this specific population.

Growth is an important, multifactorial complication of JIA that should be detected earlier via systemic and careful assessment, with timely management of further preventable or reversible associated risk factors.

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