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Research Article

# GROWTH PATTERN IN JUVENILE IDIOPATHIC ARTHRITIS IN RELATION TO INSULIN GROWTH FACTOR-1 AND S100A8/9 PROTEIN

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**A B S T R A C T**

**Background:** juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease which affect growth before age of 16 years. The growth hormone (GH)/insulin-like factor-1 (IGF-1) axis is a main regulator of linear growth, and the major part of circulating IGF-1 levels is liver derived. S100 calcium-binding proteins are associated with acute / chronic inflammatory disorders. The most familiar of S100 proteins is S100A8/A9 (calprotectin). The aim of our study was toevaluate the physical growth pattern in children with JIA. To measure the level of serum IGF-1 and to compare it with healthy controls subjects and also toassess serum S100 A 8/9 protein and its relation to growth pattern and IGF-1. **Methods:** The study was a case control study which included 40 patients of both sexes with (JIA), their ages will range from 6-10 years. *All patients and controls were subjected to the following:-* Growth Assessment and measure serum (IGF-1) level and S100 A8/9 protein. **Results:** There was statistically significant difference between Cases and Controls regarding height-for-age z-score (HAZ), 37.5% of cases were short stature were 10% in controls. There was statistically significant decrease in Weight and BMI among Cases versus Controls. Percentage of underweight of cases were higher among cases versus controls. There was statistically significant decrease in serum Insulin-like growth factor 1 among Cases versus Controls. There was statistically significant increase in S100A8/9 Protein among Cases than Controls**.** There were statistically significant positive correlation between IGF-1 and height**.Conclusion:** Short stature is common among JIA patients. Underweight of cases were higher among cases versus controls. Growth data were shifts. The levels of CRP were significantly higher in patients compared to controls. We reported that IGF-1 levels were significantly decreased in JIA compared to controls. Patients with JIA had significantly higher levels of S100A8/9 compared to controls. There were statistically significant positive correlation between IGF-1 and height.



## INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease with onset before 16 years of age with symptoms presenting for longer than six weeks. JIA is the most common rheumatic disease in children, with prevalence from 3.8 to 400 per 100,000 in the European population (Thierry and Fautrel, 2014). Genetic variants underlying JIA susceptibility have been reported in many studies (Prahalad, 2006; Phelan, 2006). The pathogenesis of JIA is currently unknown, but is thought to be due to a combination of environmental factors and specific immunogenic factors (Giancane *et al*., 2017).

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Growth retardation and short stature is a commonly complication in children with JIA (Wong *et al*., 2016). The etiology of growth retardation in JIA is not fully elucidated may be due to increase level of proinflammatory cytokines, delayed onset of puberty, malnutrition, and long-term glucocorticoid therapy (Al-Hemairi *et al*., 2016). The growth hormone (GH)/insulin-like factor-1 (IGF-1) axis is a main regulator of linear growth (Lundell *et al*., 2018). The myeloid-related protein (calprotectin) have recently been proposed as "alarmins", which are the endogenous molecules related to cell damage. Calprotectin and other members of S100 family are increased locally at sites of inflammation such as patients with JIA (Rusonienė *et al*., 2014). The aim of our study was to evaluate the physical growth pattern in children with JIA. To

measure the level of serum IGF-1 and to compare it with healthy controls subjects and also to assess serum S100 A 8/9 protein and its relation to growth pattern and IGF-1.

## PATIENTS AND METHODS

### *Patients*

This study was a case control study which included Forty children diagnosed with JIA, their ages ranges from 6-10 years. Forty healthy children served as a control group.

### *Selection criteria for patients*

### *Inclusion criteria*

Diagnostic Criteria for JIA according to **(Petty *et al*., 2004).**

1. Arthritis in at least one Joint.
2. Arthritis that last for at least 6 weeks.
3. Age of onset from 6-10 years before puberty.

### *Exclusion criteria*

- Cases diagnosed with JIA and associated with another chronic disease (e.g. chronic renal, cardiac, chest and endocrinal disease …etc.) that may interfere with normal growth.
- Other causes of arthritis (septic arthritis- rheumatic heart disease).
- Patients with clinical signs of acute infection or inflammation on the day of taking the blood sample.
- Genetics diseases.

### *Ethical aspects*

- Care givers of children were informed of the nature and aims of the study.
- Written informed consent was obtained from care givers of children in the study.

## METHODS

*All patients and controls were subjected to the following:-*

### *Complete history taking*

- Age and gender.
- Onset and duration of symptoms.
- Duration of morning stiffness.
- Number of affected joints.
- Number of active joint.
- Number of limited joint.
- Number of Joint with pain.
- History of medication [steroids].

### *Past history to exclude*

- Other chronic or genetic disease.
- -Other causes of arthritis and collagen.
- Endocrinal causes of growth retardation.

***Complete Clinical Examination:*** including General as well as chest, cardiac, abdominal and neurological examination, to exclude chronic or genetic disease those interfere with normal growth. Joints examination to detect sign and symptoms of disease activity.

***Growth Assessment:*** including

- Weight (using Seca scale).
- Height ((using Seca scale).
- BMI: was calculated according to formula weight/height ($m^2$)

Each of these measurements was taken as the mean of three consecutive accepted reading, following the recommendations of the international biological program using standard equipment and was interpreted with reference to Egyptian growth charts.

### *Laboratory investigations*

### *All patients and controls were subjected to measurement of*

### *Determination of serum Insulin-like growth factors 1(IGF-1)*

Insulin-like growth factors 1(IGF-1) was measured by INOVA Human IGF-1 ELISA kits**.** It is an enzyme-linked immunosorbent assay for quantitative detection of human IGF-1. BioneovanCo., Ltd, No. 18, Keyuan Road, DaXing Industry Zone, Beijing, China.

### *Determination of serum Calprotectin (CALP)*

Calprotectin (CALP) was measured by INOVA Human CALP ELISA kits**.** It is an enzyme-linked immunosorbent assay for quantitative detection of human CALP. BioneovanCo., Ltd, No. 18, Keyuan Road, DaXing Industry Zone, Beijing, China.

### *Determination of serum C-Reactive Protein (CRP)*

Measurement of human C-Reactive Protein (CRP) in serum was performed using the nephelometry. Product Code: ZK044.L.R, Minineph$^{TM}$, the Binding Site Ltd, PO Box 11712, Birmingham, B14 4ZB, U.K.

### *Statistical analysis*

The collected data were tabulated and analyzed using SPSS version 24 software (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test ($X^2$), or Fisher's exact test (FET) were used to analyze categorical variables. Quantitative data were tested for normality using KolomogrovSmirnove test assuming normality at P>0.05. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was used to analyze normally distributed variables among 2 independent groups. Spearman's correlation coefficient ( rho ) was used to assess correlation between non parametric variables.. *P value >0.05 is non significant (N-S). P<0.05 is significant (S)*

## RESULTS

Results are illustrated in table (1) to table (8).

There was positive consanguinity (11/40) 27.5% of the cases and affected family member with JIA was (8/40) 20%. Also there was no statistically significant difference between Cases and Controls regarding age (years) and Sex distribution (Table 1).

**Table 1** Demographic data of the cases and control.

| | | | Cases | Controls | test | P. value |
|---|---|---|---|---|---|---|
| Age (years) | Range | | 6.10 - 10 | 6.20 – 10.2 | t. test | .531 |
| | Mean ± SD | | 8.74 ± 1.07 | 8.1 ± 1.02 | 2.65 | |
| Consanguinity | | | (11/40) 27.5% | 0% | | |
| Sex | Female | No. | 27 | 24 | $X^2$ | .485 |
| | | % | 67.5% | 60.0% | | |
| | Male | No. | 13 | 16 | .487 | |
| | | % | 32.5% | 40.0% | | |
| Affected family member with JIA | (8/40) 20% | | | | | |

Table (2) shows the frequency of Joint pain (27 %), Morning stiffness (50 %), Siding (45 %) and Fever (77.5%) among the cases group.

**Table 2** Frequency of various Clinical manifestations among cases group.

| | | No. | % |
|---|---|---|---|
| Clinical manifestation | Joint pain | 30 | 27 |
| | Morning stiffness | 20 | 50 |
| | Siding | 18 | 45 |
| | Fever | 31 | 77.5 |

There was statistically significant difference between Cases and Controls regarding height-for-age z-score (HAZ); 37.5% of cases had height-for-age z-score (HAZ) ≤ - 2 standard deviation while only 10% among controls. (Table 3).

**Table 3** Comparison between Cases and Controls regarding height-for-age z-score (HAZ).

| | | | Cases | Controls | $X^2$ | P. value |
|---|---|---|---|---|---|---|
| height-for-age z-score (HAZ) | height-for-age z-score (HAZ) ≤ - 2 standard deviation | No. | 15 | 4 | 8.3 | .003 |
| | | % | 37.5% | 10% | | |
| | height-for-age z-score (HAZ) of more than minus two standard deviation(-2 SD) | No. | 25 | 36 | | |
| | | % | 62.5% | 90.0% | | |

There was statistically significant difference between Cases and Controls regarding weight-for-age z-score (WAZ); 85% of cases had weight t-for-age z-score (HAZ) ≤ - 2 standard deviation while only 10% among controls. (Table 4).

**Table 4** Comparison between Cases and Controls regarding weight-for-age z-score (WAZ).

| | | | Cases | Controls | $X^2$ | P. value |
|---|---|---|---|---|---|---|
| weight-for-age z-score (WAZ). | weight t-for-age z-score (HAZ)≤ - 2 standard deviation | No. | 34 | 4 | 45.1 | .000 |
| | | % | 85.0% | 10% | | |
| | weight -for-age z-score (HAZ) of more than minus two standard deviation (-2 SD) | No. | 6 | 36 | | |
| | | % | 15.0% | 90.0% | | |

There was statistically significant difference between Cases and Controls regarding BMI Z score; 85% of cases had BMI) z-score ≤ - 2 standard deviation while only 5% among controls. (Table 5).

There was statistically significant increase in hs-CRP (mg/L) and S100A8/9 Protein (ng/ml) among Cases than Controls, while There was statistically significant decrease in IGF-1 ng/ml among Cases than Controls. (Table 6).

Shows that there were statistically significant positive correlation between IGF-1 ng/ml and (Weight(kg), Height(cm), BMI, S100 A8/9 Protein. There were no statistically significant correlation between IGF-1 ng/ml and other variable. (Table 7).

Show there were statistically significant negative correlation between S100 A8/9 Protein and (Weight(kg), Height(cm), BMII), There were no statistically significant difference between S100 A8/9 Protein and other variable. (Table 8).

**Table 5** Comparison between Cases and Controls regarding BMI Z score

| | | | Cases | Controls | $X^2$ | P. value |
|---|---|---|---|---|---|---|
| BMI Z score. | (BMI) z-score ≤ - 2 standard deviation | No. | 34 | 2 | 51.873 | .000 |
| | | % | 85.0% | 5.0% | | |
| | (BMI) z-score between – 2 and 2 standard deviation | No. | 6 | 36 | | |
| | | % | 15.0% | 90.0% | | |
| | (BMI) z-score > 2 standard deviation | No. | 0 | 2 | | |
| | | % | .0% | 5.0% | | |
| | (BMI) z-score > 3 standard deviation | No. | 0 | 0 | | |
| | | % | .0% | .0% | | |

**Table 6** Comparison between Cases and Controls regarding hs-CRP, S100A8/9 Protein and IGF-1 ng/ml

| | | Cases | Controls | t. test | P. value |
|---|---|---|---|---|---|
| hs-CRP (mg/L) | Range | 3.8 - 110.0 | 3.8 - 72.0 | 4.603 | .000 |
| | Mean ± SD | 38.79 ± 31.45 | 13.35 ± 15.236 | | |
| S100A8/9 Protein (ng/ml) | Median | 315 | 277.50 | MW. test 694.50 | .031 |
| | Range | 95 - 590 | 105 - 740 | | |
| | Mean ± SD | 326.43 ± 142.90 | 305.72 ± 173.34 | | |
| IGF-1 ng/ml | Median | 57.500 | 78.000 | MW. test 598 | .02 |
| | Range | 30.0 - 330.0 | 42.0 - 492.0 | | |
| | Mean ± SD | 83.38 ± 64.45 | 107.57 ± 106.65 | | |

**Table 7** Correlation between IGF-1 ng/ml and other variable.

| Correlation | Pearson's correlation | |
|---|---|---|
| | r | p |
| age (years) * IGF-1 ng/ml | -.055- | .629 |
| Wt (Kg) * IGF-1 ng/ml | .071 | .030 |
| Ht (Cm) * IGF-1 ng/ml | .127 | .026 |
| BMII * IGF-1 ng/ml | .007 | .049 |
| Hb (g/dl) * IGF-1 ng/ml | .118 | .296 |
| TLC * IGF-1 ng/ml | -.125- | .269 |
| Plt * IGF-1 ng/ml | .061 | .593 |
| ESR (mm/hr) * IGF-1 ng/ml | -.120- | .289 |
| hs-CRP (mg/L) * IGF-1 ng/ml | -.096- | .398 |
| S100 A8/9 Protein * IGF-1 ng/ml | .225 | .045 |

**Table 8** Correlation between S100 A8/9 Protein and other variable

| Correlation | Pearson's correlation | |
|---|---|---|
| | r | p |
| age (years) * S100 A8/9 Protein | -.124- | .274 |
| Wt (Kg) * S100 A8/9 Protein | -.075- | . 04 |
| Ht (Cm) * S100 A8/9 Protein | -.054- | .033 |
| BMII * S100 A8/9 Protein | -.071- | .029 |
| Hb (g/dl) * S100 A8/9 Protein | -.065- | .569 |
| TLC * S100 A8/9 Protein | -.070- | .537 |
| Plt * S100 A8/9 Protein | -.041- | .720 |
| ESR (mm/hr) * S100 A8/9 Protein | -.004- | .975 |
| hs-CRP (mg/L) * S100 A8/9 Protein | -.044- | .699 |

## DISCUSSION

This study showed that, there was no statistically significant difference between Cases and Controls regarding age and Sex distribution. Our study showed positive consanguinity in 27.5% of the cases and 20% affected family members with JIA. Genetic variants underlying JIA and positive consanguinity with affected family members have been reported extensively (Prahalad; 2006).

This study showed that, there was statistically significant decrease in height among Cases versus Controls. There was statistically significant difference between Cases and Controls regarding height-for-age z-score (HAZ), 37.5% of cases were short stature versus 10% among controls. This is in agreement with (Aghamahdi *et al*., 2018) who found that, short stature is common among JIA patients (35%). Short stature found in

about 1/3 of our cases, more than the number in the studies done by Souza *et al*., (2006) which found only 10.4% and (Uettwiller *et al*., 2014) who revealed only 19%. Short stature associated with JIA cases in different studies ranges from 10 - 40 percent (Umlawska *et al*., 2010). Early treatment can improve the growth (Jafari-Adli *et al*., 2016).This study showed that; there was statistically significant decrease in Weight and BMI among Cases versus Controls. Percentage of underweight of cases were higher among cases versus controls.

This is in agreement with (Alsulami *et al*., 2017) who found that, 36% cases had growth curve in both height-for-age and weight-for-age percentiles below normal and 31% in weight-for-height percentiles. The most complications of JIA is growth retardation (Murakami *et al*., 2012).

In the present work, there was statistically significant increase in CRP among Cases than Controls

This is in agreement with (Rusonienė *et al*., 2014) who found that, the levels of CRP were significantly higher in JIA patients.

Our study showed that, there was statistically significant decrease in Insulin-like growth factor 1 among Cases than Controls

This is in agreement with (Bilginer *et al*., 2010; Lundell *et al*., 2018) who found significantly decreased IGF-1 levels in JIA patients.

Several studies reported interactions between IGF-1 and proinflammatory cytokines, which are commonly elevated in JIA patients (Benedetti and Martini, 2005).

This study showed that, there was statistically significant increase in S100A8/9 Protein among Cases than Controls

This is in agreement with (Aljaberi *et al*., 2020) who found that, patients with JIA had significantly higher levels of S100A8/9 compared to controls.

This finding was in accordance also with the study of (Rusonienė *et al*., 2014) who found that, the levels of S100A8/A9 were significantly higher in patients compared to the levels in healthy individuals.

This study showed that, there were statistically significant positive correlation between IGF-1 and height.

This is in agreement with Bang *et al*., (2015) who revealed that deficiency of IGF- may be associated with serious clinical impacts in children leading to growth failure and ultimately short adult height.

These results were in accordance also with (Lundell *et al*., 2018) who found that, height correlated strongly to serum IGF-1 levels.

## CONCLUSION

Short stature is common among JIA patients. Percentage of underweight cases was higher among cases versus controls. Growth data were shifts towards lower percentiles among JIA patients. The levels of CRP were significantly higher in JIA cases. IGF-1 level was significantly low in JIA cases. Patients with JIA had significantly higher levels of S100A8/9 compared to controls.

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***Competing Interest:*** All authors declare no conflict of interest.

***Data Availability Statement:***

The data which supporting our study with the corresponding author upon request.

## References

Aghamahdi F, Setoodeh A, Ziaee V, Rabbani A. Growth Failure in a Series of Iranian Patients with Juvenile Idiopathic Arthritis, Iran J Pediatr. 2018 ; 28(3):e11156.

Al-Hemairi, M. H., Albokhari, S. M., &Muzaffer, M. A. (2016). The Pattern of Juvenile Idiopathic Arthritis in a Single Tertiary Center in Saudi Arabia. International Journal of Inflammation, 2016, 1–8. doi:10.1155/2016/7802957

Aljaberi, N., Tronconi, E., Schulert, G. *et al*. The use of S100 proteins testing in juvenile idiopathic arthritis and autoinflammatory diseases in a pediatric clinical setting: a retrospective analysis. PediatrRheumatol 18, 7 (2020). https://doi.org/10.1186/s12969-020-0398-2

Alsulami, R., Alsulami, A. and Muzaffer, M. (2017): Growth Pattern in Children with Juvenile Idiopathic Arthritis: A Retrospective Study. *Open Journal of Rheumatology and Autoimmune Diseases*, 7, 80-95

Bang P., Polak M., Woelfle J., Houchard A., and on behalf of the EU IGFD Registry Study Group, "Effectiveness and safety of rhIGF-1 therapy in children: the European Increlex® growth forum database experience," *Hormone Research in Pædiatrics*, vol. 83, no. 5, pp. 345–357, 2015.

Benedetti F. de and Martini A., "Targeting the interleukin-6 receptor: a new treatment for systemic juvenile idiopathic arthritis?" *Arthritis and Rheumatism*, vol. 52, no. 3, pp. 687–693, 2005.

Bilginer Y., Topaloglu R., Alikasifoglu A. *et al*., "Low cortisol levels in active juvenile idiopathic arthritis," *Clinical Rheumatology*, vol. 29, no. 3, pp. 309–314, 2010.

Giancane G., Alongi A., and Ravelli A., "Update on the pathogenesis and treatment of juvenile idiopathic arthritis," *Current Opinion in Rheumatology*, vol. 29, no. 5, pp. 523–529, 2017. View at: |

Jafari-Adli S, Qorbani M, Heshmat R, Ranjbar SH, Taheri E, Motlagh ME, *et al*. Association of short stature with life satisfaction and self-rated health in children and adolescents: the CASPIAN-IV study. *J PediatrEndocrinolMetab*. 2016;29(11):1299-306.

Lewander P., Dahle C., Larsson B., Wetterö J., and Skogh T., "Circulating cartilage oligomeric matrix protein in juvenile idiopathic arthritis," *Scandinavian Journal of Rheumatology*, vol. 46, no. 3, pp. 194–197, 2016.

Lundell, A.-C., Erlandsson, M., Bokarewa, M., Liivamägi, H., Uibo, K., Tarraste, S., … Pullerits, R. (2018).*Low Serum IGF-1 in Boys with Recent Onset of Juvenile Idiopathic Arthritis. Journal of Immunology Research, 2018, 1–10.* doi:10.1155/2018/3856897

Mondal R, Sarkar S, Das NK *et al*. (2014) Growth of children with juvenile idiopathic arthritis. Indian Pediatr 51, 199–202.

Murakami, M., Tomiita, M. and Nishimoto, N. (2012)Tocilizumab in the Treatment of Systemic Juvenile Idiopathic Arthritis. Open Access Rheumatology Research and Reviews, 4, 71-79.

Phelan JD, Thompson SD, Glass DN: Susceptibility to JRA/JIA: complementing general autoimmune and arthritis traits.Genes Immun 2006, 7(1):1-10.

Petty RE, Southwood TR, Manners P, *et al*. (2004): International League of Associations for Rheumatology classification ofjuvenile idiopathic arthritis: second revision, Edmonton,. J Rheumatol; 31: 390-2.

Rusonienė S, Panavienė V, Eidukaitė A, Jakutovič M.Proinflammatory S100 proteins as clinical markers of juvenile idiopathic arthritis. ActamedicaLituanica 2014; 21:151-159.

Souza L, Machado SH, Bredemeier M, Brenol JC, Xavier RM. Effect of inflammatory activity and glucocorticoid [corrected] use on nutritional variables in patients with juvenile idiopathic arthritis. *J Rheumatol*. 2006;33(3):601-8.

Thierry S., Fautrel B., I.Lemelle, and F. Guillemin, "Prevalence and incidence of juvenile idiopathic arthritis: a systematic review," *Joint, Bone, Spine*, vol. 81, no. 2, pp. 112–117, 2014.

Uettwiller F, Perlbarg J, Pinto G, Bader-Meunier B, Mouy R, Compeyrot-Lacassagne S, *et al*. Effect of biologic treatments on growth in children with juvenile idiopathic arthritis. *J Rheumatol*. 2014;41(1):128-35.

Umlawska, W. and Prusek-Dudkiewicz, A. (2010) Growth Retardation and Delayed Puberty in Children and Adolescents with Juvenile Idiopathic Arthritis. Archives of Medical Science, 6, 19-23. https://doi.org/10.5114/aoms.2010.13501

Wong S. C., Dobie R., Altowati M. A., Werther G. A., Farquharson C., and Ahmed S. F., "Growth and the growth hormone-insulin like growth factor 1 axis in children with chronic inflammation: current evidence, gaps in knowledge, and future directions," *Endocrine Reviews*, vol. 37, no. 1, pp. 62–110, 2016.

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