CONTROVERSIES IN MANAGEMENT OF GROWTH DISORDERS IN JUVENILE IDIOPATHIC ARTHRITIS

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood and is responsible for many growth disorders. Abnormalities of growth and development in JIA can be attributed to a combination of factors, as disease process (with enhanced pro-inflammatory cytokines production), perturbation of the growth hormone (GH) - insulin-like growth factor (IGF-1) axis, and glucocorticoid treatment. The aim of study was to assess the IGF-1 level in JIA patients and to evaluate correlation between IGF-1 levels and parameters of disease activity. IGF-1 serum concentration was measured using chemiluminescent immunoassay method. We found lower IGF-1 serum levels in polyarthritis and systemic JIA comparative with control group, but with normal mean IGF-1 values in oligoarticular and enthesitis-related arthritis, respectively. Weak to moderate negative correlations were found between IGF-1 levels and disease activity parameters. These results arise a few controversial questions: should we treat certain JIA types with GH to maintain normal growth, to prevent potential growth deterioration or to catch up growth delay? Or, perhaps a good control of disease activity in juvenile arthritis would be enough to avoid or to correct abnormalities of growth and development?

Key-words: insulin-like growth factor, juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis is a heterogeneous group of diseases with chronic joint inflammation as common characteristic. Abnormalities of growth and development are frequent complications of chronic arthritis or its treatment. Growth disorders due to chronic inflammatory diseases can be attributed to a combination of systemic factors that includes disease process, poor nutrition, enhanced catabolic activity, excess of glucocorticoids, and defect in growth hormone (GH) secretion or action (1,2). In JIA patients abnormalities of growth vary from general growth retardation to local acceleration of growth in the affected limb.

In juvenile arthritis, growth disorders are correlated to an increased production of pro-inflammatory cytokines, such as interleukin (IL) -1, IL-6, and tumor necrosis factor alpha (TNF-α). Pro-inflammatory cytokines may act individually or in combination to impair child growth through systemic mechanisms and/or a local action (3). Thus, cytokines may affect growth through systemic mechanisms that alter the GH-insulin-like growth factor I (IGF-1) axis by playing a paracrine/autocrine role in GH regulation in the pituitary independently from the intracellular pathways of the GH secretagogues (4). Whereas IL-6 affects growth mainly via systemic mechanisms altering growth hormone secretion, IL-1 and TNF-α can directly affect growth plate chondrocyte dynamics as well as longitudinal bone growth (5). Growth-inhibitory effects of TNF and IL-1 are due to a combination of effects on matrix synthesis, chondrocyte proliferation and a reduction in the hypertrophic zone, with hypertrophic chondrocytes which are the principal determinant of longitudinal bone growth (6).

Two of the most important and studied regulators of postnatal bone growth are GH and IGF1. The dual effector theory of GH/IGF-1 action on the growth plate proposes that GH acts directly on germinal zone precursors of the growth plate to stimulate the differentiation of chondrocytes and then increases local IGF-1 synthesis, which will induce in turn the clonal expansion of chondrocyte columns in an autocrine/paracrine manner (7). Although liver-derived IGF-1 is the main determinant of serum IGF-1 levels, it is less important for postnatal growth than locally derived IGF-1 (8).

Material and method

Study cohort consisted of 39 patients with JIA, admitted and assessed in First Pediatric Clinic, Timisoara, Romania. Diagnosis and classification were concordant to International League Against Rheumatism (ILAR) criteria. A control group (n=13), matched for age and sex, with no musculoskeletal complaints, was evaluated as well. Assessment of study cohort included: 1) clinical examination with a 27 joint count for tender or swollen joint; 2) acute phase reactants determination (erythrocyte sedimentation rate= ESR, C-reactive protein= CRP); 3) patient assessment of well-being, measured on visual analogue scale (VAS), where 0= very well and 10= very poor; and 4) measurement of IGF-1 levels in serum.

Children's height from both groups (JIA patients and control group) was plotted on the growth references from World Health Organization (WHO) 2007, and expressed as height percentiles. Children with height situated below 3thd percentile were noted as on percentile 3.

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Composite disease activity score (JADAS) was calculated as the linear sum of the scores of its components: 1) physician global assessment (VAS), 2) parent or patient global assessment (VAS), 3) active joint count (swollen joint count and tender joint count), 4) normalized ESR (range 0 to 10).

IGF-1 levels were measured in serum by using a chemiluminescent immunoassay (CMIA) method. Detection limit of the method was 20 pg/mL3 and referential values were according to age.

Statistical analysis was performed using statistical package SPSS 17. We expressed the data as frequencies or means ± standard deviations, as appropriate. Student's t-test was used to compare the JIA patients with the control group. Regression analysis was performed to evaluate relationship between IGF-1 serum levels and other clinical features and biomarkers.

The study was approved by the ethics committees of the institution. Informed consent was obtained from parents or guardians of all participating children.

Results

Descriptive characteristics of the JIA cohort are presented in table 1. IGF-1 mean level in JIA group was 281ng/ml ±102.56 (mean ±standard deviation) and was not found significantly differences between genders (p=.032). Mean IGF-1 level in female patients was 297.68 ng/ml ±116.779 and in male children 264 ng/ml ±83.85. Median IGF-1 level in control group was 242.92 ng/ml ±84.42 and we found no significant differences (p=.861) in comparison with study group.

Comparison of IGF-1 levels between subtypes of JIA group revealed statistical significance (p=.011). Multivariate analysis showed a statistical significant (p=.045) difference in IGF-1 levels between children with oligoarthritis and patients with systemic JIA (mean difference=171ng/ml), in favour of oligoarticular type. Difference in IGF-1 serum levels in patients with polyarthritis in comparison with oligoarthritis was close to statistical significance (p=.06) with a mean difference of 114.6ng/ml favourable to polyarthritis.

Multiple comparison of mean IGF-1 levels in JIA subtypes, and control group respectively was performed using statistic ANOVA test (Boferroni option). IGF-1 serum levels in both polyarthritis (mean difference=168.5ng/ml) and systemic arthritis (mean difference=225.5ng/ml) were found significantly lower in comparison with control group (p=.001, and p=.007 respectively) (table 2 and figure 1).

Correlations between IGF-1 levels and clinical parameters

Evaluating association of IGF-1 levels with height percentiles, we found in both arthritic and control group a positive moderate correlation (rho=.556, p=.005) (figure 2).

Positive moderate correlation (rho=.583) with statistical significance (p= .01) was found between IGF-1 level and the age of disease onset (years) in children with juvenile arthritis (figure 3). We found no correlation between IGF-1 levels and duration of chronic arthritis (rho=-.122, p=.569) illustrated in figure 4.

Type of JIA (number)	Median ESR (mm/1h)	Median CRP (mg/dl)	ANA+ (no cases)	Anti-CCP+ (no cases)	Median JADAS
Systemic (3)	49.8±12.7	12.2±5.7	0	0	19.8±3.5
Oligo (15)	25.5±11.2	7.49±3.2	2	0	5.9±2.4
RF+ Poly (4)	47.1±18.6	14.2±2.9	0	2	17.5±4
RF- Poly (9)	30.8±11.6	12.6±2.8	2	2	12.9±2.6
ERA (8)	16.1±7.4	4.8±2.1	0	1	10.7±4

Table 1. Descriptive characteristics of JIA cohort

(A) Control group	(B) Type of arthritis	Mean difference (A-B)	Standard error	Significance
Control group	Oligoarthritis	53.900	41.702	1.000
	Polyarthritis	168.500	37.260	0.001
	Systemic	225.000	59.837	0.007
	ERA	89.900	33.545	0.117

Table 2. Multiple comparasion between mean IGF-1 levels of JIA subtypes and control group

Correlations between IGF-1 and disease activity

Spearman's test was used to evaluate correlations between IGF-1 levels and other parameters which characterized the group of children with chronic arthritis. We found no association between IGF-1 levels and children's VAS score of pain (rho=-.146, p=.496).

IGF-1 levels were inversely correlated (rho=-.436, p=.033) with the number of active joints (swelling or/ and tenderness) (figure 5). Similar association (rho=.456, p=.025) was found between IGF-1 levels and the number of joints with radiological evident lesions (joint space narrowing or/and erosions) (figure 6).

Analyzing the correlations between IGF-1 serum levels and inflammatory biomarkers in patients with chronic arthritis, we found a negative association (rho=-.426) with statistical significance (p=.038) between ESR values and IGF-1 levels (figure 7). Similarly, negative weak correlation (rho=-.356), but with no statistical significance (p=.088) was found between IGF-1 levels and CRP values (figure 8).

Evaluating the relationsheep between IGF-1 levels and the composite disease activity score (JADAS), there had been found a weak negative correlation (rho=-.341), but with no statistical significancy (p=.103) (figure 9).

Discussion

In our study we found no difference between mean IGF-1 levels in JIA patients and control group, but there were found significantly lower levels of IGF-1 in two subtypes of JIA: polyarthritis and systemic onset arthritis. Decreased IGF-1 levels in these two forms reflect reduced pituitary function with GH deficiency or insensitivity to GH due to chronic inflammation. In rheumatoid arthritis as well has been found a decrease in IGF-1 serum level in comparison with healthy subjects (9).

Even if it was not statistically significant in every case, our study showed a negative correlation of IGF-1 levels with the main parameters of disease activity: active joint number, ESR, CRP, JADAS score and number of joints with radiological evident lesions. Main limit of the study is the low number of cases, which could be responsible of the lack of significance. These results are in contradiction with the findings of some clinical studies performed in rheumatoid arthritis, which found no correlation between IGF-1 and CRP (10). Conversely, others studies showed that factors, which might contribute to growth suppression associated with childhood arthritis, include the degree, extent, and duration of disease activity (3).

IGF-1 is responsible for stimulating cartilage and bone extracellular matrix protein synthesis, thus decreased levels in juvenile arthritis could explain the growth disorders appeared in evolution of the disease (11). IGF-1 promotes muscle growth as well by stimulating muscle satellite cells and their differentiation. Conversely, when the levels of IGF-1 are insufficient or catabolic signals (e.g. glucocorticoids, cytokines) are increased, muscle wasting ensues (12).

In case of proved disturbance of GH-IGF-1 axis in polyarticular and systemic onset juvenile arthritis, the main controversial issue is the correct management of these JIA forms. Question is: is it enough to reduce disease activity, waiting the consequent correction of IGF-1 levels or should we intervene actively in IGF-1 produced bone and muscular growth disturbance by GH treatment? Two other questions arise further: is it efficient and is it safe to treat children with juvenile arthritis with growth hormone?

Growth hormone (GH) therapy proved to have many benefic effects in JIA: it has shown efficacy in controlling disease, positively influence body composition (increases bone mineral density and bone mass and changes bone geometry), accelerates growth velocity, increases height and promotes muscle mass recuperation (13). Despite benefic effects of GH therapy, there are, however, factors that may limit the statural gains achieved with GH, including severe inflammation, severe statural deficiency at GH therapy initiation, long disease duration and delayed puberty (13). In a four years long controlled study, Bechtold and co. showed that the mean improvement in height in the GH treated group was 1 SD, whereas the JIA patients of the control group lost 0.7 SD. Disease activity markers correlated significantly with the mean growth velocity standard deviation score. They concluded that children with mild or moderate disease and lower comedication grew and responded better to growth hormone therapy than those with active disease (14).

An earlier study of Davies and co. showed a significant increase in height velocity in almost all children during GH treatment. Children with mild to moderate disease activity grew at a better rate than those with very active disease, and children with polyarticular disease responded better than those with systemic JIA (15).

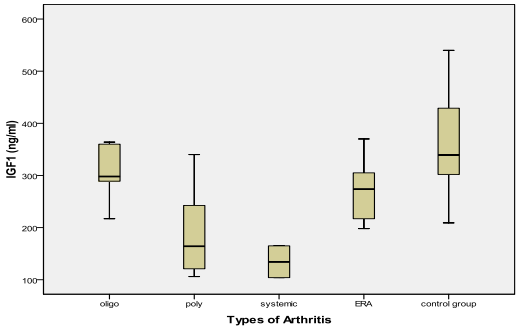

Figure 1. Comparison between IGF-1 levels in JIA subtypes and control group

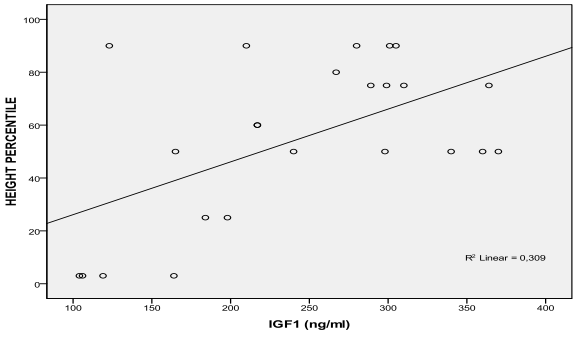

Figure 2. Correlation between IGF-1 levels and height percentiles

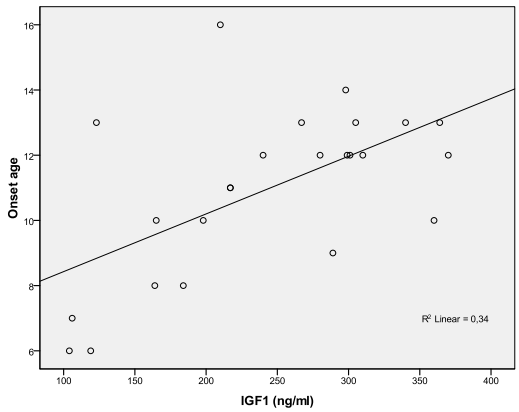

Figure 3. Correlation between IGF-1 levels and age of disease onset (years)

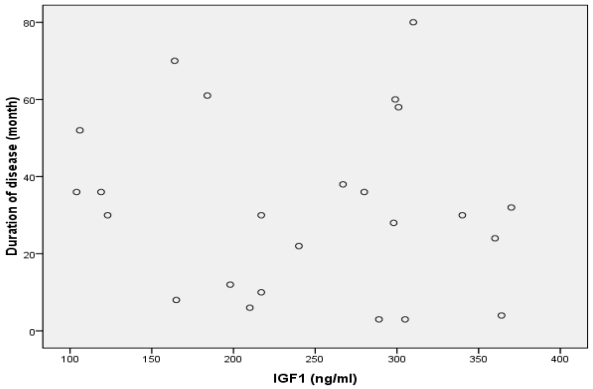

Figure 4. Correlation between IGF-1 and duration of disease (months)

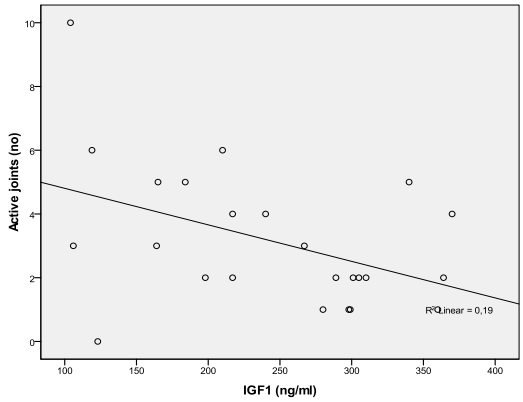

Figure 5. Correlation between IGF-1 level and active joint number

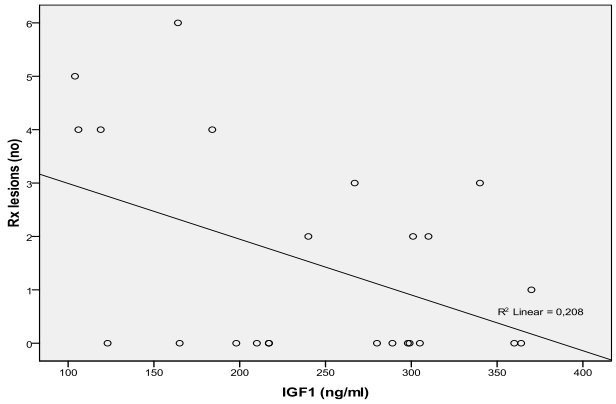

Figure 6. Correlation between IGF-1 level and Rx lesions

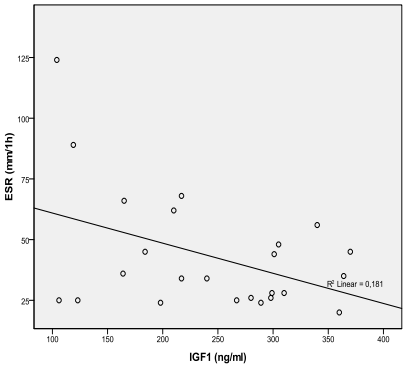

Figure 7. Correlation between IGF-1 levels and ESR

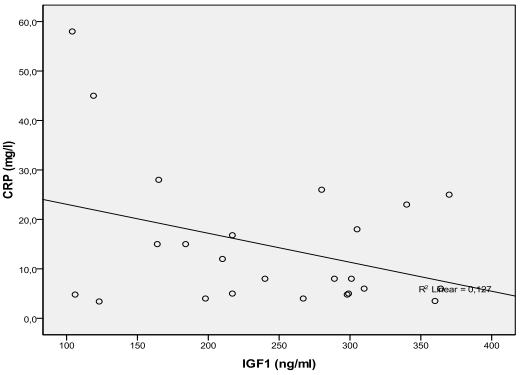

Figure 8. Correlation between IGF-1 levels and CRP values

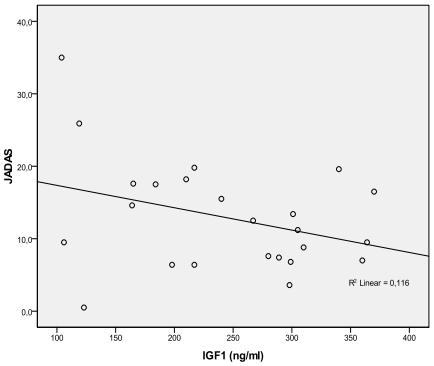

Figure 9. Correlation between IGF-1 levels and JADAS score

Davies highlighted that children receiving high dose GH grew significantly more than those on the low dose regimen. Saha and co. found a significant response to GH treatment, compared with placebo in most children (16). They treated 25 prepubertal children with severe growth retardation due to JIA with GH (6 months) and placebo (6 months afterwards).The median height velocity standard deviation score was +2.09 during the 6 month period of GH therapy and -1.11 during placebo treatment ($p = 0.0002$). The median height standard deviation score increased from -2.08 to -1.79 during GH treatment and from -2.18 to -2.02 during placebo ($p = 0.0268$). Saha and co. concluded that GH may be of benefit in the treatment of severe growth retardation in children with JIA, the response was seen after only 6 months and was independent of initial growth hormone status of the child (16).

GH treatment in children with chronic arthritis was proposed especially in cases treated with glucocorticoids. Simon and co. showed that GH treatment markedly increased growth velocity in JIA patients receiving steroid therapy, but had a minor effect on SDS height suggesting that these children will remain short at adult age (17). The study concluded that using GH earlier in these patients during the course of their disease may prevent growth deterioration and metabolic complications induced by chronic inflammation and long-term steroid therapy. Results of other studies suggested that GH may partially counteract the adverse effects of glucocorticoids on growth and metabolism in patients with chronic inflammatory disease (18). Mauras study showed that both GH and IGF-I may decrease the catabolic effects of chronic steroid use in humans, particularly by enhancing lean body mass accrual and, in children, by increasing linear growth (19). Ahmed and co. highlighted that both glucocorticoids and pro-inflammatory cytokines can adversely affect a number of components of growth plate chondrogenesis, and these effects can be ameliorated by raising local IGF-I exposure (1). However, this intervention does not lead to complete normalization of the growth plate. In children with chronic inflammation, the cornerstone of improving growth remains the judicious use of glucocorticoids while ensuring effective control of the disease process (1).Studies proved that GH treatment can normalize growth velocity and prevent the severe loss of height, however, catch-up growth markedly varies with the severity of the disease activity and the steroid doses used during GH treatment. Recently, early institution of GH treatment has been shown to maintain normal growth in children with JIA and has been proved its utility in preservation of long-term growth during disease progression (20).

Safety of GH treatment

Most of the studies proved no side effects due to GH therapy in JIA (14,16). However, GH treatment in JIA children can decrease insulin sensitivity but had only modest effects on glucose tolerance. Close monitoring by oral glucose tolerance testing is crucial before and during GH treatment, particularly during puberty and relapses (21). Available data on growth hormone therapy in glucocorticoid-treated children with JIA suggest a satisfactory safety profile. There have been few reports of adverse effects on the course of the joint disease (e.g., inflammatory flare-ups or osteoarticular complications). Despite strong concern that combined glucocorticoid and GH therapy might impair glucose tolerance, this has been uncommon in clinical trials (13). Davies and co. found that bone maturation did not exceed chronological age in GH treated JIA chidren (15).

The major objective in juvenile arthritis management is optimal disease control while maintaining normal growth. ACR recommendations are helpful guidelines in JIA treatment (22). Savendahl sustains that specific immunomodulatory therapy that targets the actions of TNFα is at least partially effective at rescuing linear growth in many children with JIA (23). Patients who do not respond to anti-TNF treatment may be candidates for therapeutic agents that target other pro-inflammatory cytokines and for GH intervention. Most of the physicians recommend close monitoring of growth velocity and bone mass accrual, and in some patients indicate additional medications such as growth hormone (24).

Timing of GH therapy initiation is also important because the extent of recovery following cytokine exposure of growth plates depends on the duration of exposure, and may be incomplete following longer periods of exposure (6). Early recognition of patients who develop prolonged growth disturbances and altered body composition is important as these abnormalities contribute to long-term morbidity and need to be addressed both diagnostically and therapeutically when treating children with JIA (25).

Although JIA is not an approved pediatric indication for GH treatment, it represents a promising area of investigation (26).

Conclusions

GH-IGF-1 axis is disturbed in polyarthritis and systemic JIA. In juvenile arthritis, IGF-1 serum levels appears to be inversely correlated to disease activity.

Careful monitoring of growth in children with JIA, especially in systemic and polyarticular forms, is mandatory. The main objective in juvenile arthritis therapy is represented by disease control through an efficient reduction of inflammatory process. However, GH therapy before onset of severe growth delay could be useful in maintaining normal growth and in preventing potential growth deterioration. Furthermore, in JIA children with growth disturbances, GH therapy could be a useful tool in the growth catch-up process.

References:

97. Ahmed SF, Sävendahl L. Promoting growth in chronic inflammatory disease: lessons from studies of the growth plate. Horm. Res. 2009 Nov;72 Suppl 1:42–7.
98. MacRae VE, Wong SC, Farquharson C, Ahmed SF. Cytokine actions in growth disorders associated with pediatric chronic inflammatory diseases (review). Int. J. Mol. Med. 2006 Dec;18(6):1011–8.

99. Gaspari S, Marcovecchio ML, Breda L, Chiarelli F. Growth in juvenile idiopathic arthritis: the role of inflammation. Clin. Exp. Rheumatol. 2011 Feb;29(1):104–10.
100. Mainardi GL, Saleri R, Tamanini C, Baratta M. Effects of interleukin-1-beta, interleukin-6 and tumor necrosis factor-alpha, alone or in association with hexarelin or galanin, on growth hormone gene expression and growth hormone release from pig pituitary cells. Horm. Res. 2002;58(4):180–6.
101. Mårtensson K, Chrysis D, Sävendahl L. Interleukin-1beta and TNF-alpha act in synergy to inhibit longitudinal growth in fetal rat metatarsal bones. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 2004 Nov;19(11):1805–12.
102. MacRae VE, Farquharson C, Ahmed SF. The restricted potential for recovery of growth plate chondrogenesis and longitudinal bone growth following exposure to pro-inflammatory cytokines. J. Endocrinol. 2006 May 1;189(2):319–28.
103. MacRae VE, Farquharson C, Ahmed SF. The pathophysiology of the growth plate in juvenile idiopathic arthritis. Rheumatol. Oxf. Engl. 2006 Jan;45(1):11–9.
104. Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu J-L, et al. Circulating levels of IGF-1 directly regulate bone growth and density. J. Clin. Invest. 2002 Sep;110(6):771–81.
105. Neidel J. Changes in systemic levels of insulin-like growth factors and their binding proteins in patients with rheumatoid arthritis. Clin. Exp. Rheumatol. 2001 Feb;19(1):81–4.
106. Lemmey A, Maddison P, Breslin A, Cassar P, Hasso N, McCann R, et al. Association between insulin-like growth factor status and physical activity levels in rheumatoid arthritis. J. Rheumatol. 2001 Jan;28(1):29–34.
107. Malemud CJ. Growth hormone, VEGF and FGF: involvement in rheumatoid arthritis. Clin. Chim. Acta Int. J. Clin. Chem. 2007 Jan;375(1-2):10–9.
108. Heszele MFC, Price SR. Insulin-Like Growth Factor I: The Yin and Yang of Muscle Atrophy. Endocrinology. 2004 Nov 1;145(11):4803–5.
109. 1Bechtold S, Dalla Pozza R, Schwarz HP, Simon D. Effects of Growth Hormone Treatment in Juvenile Idiopathic Arthritis: Bone and Body Composition. Horm. Res. 2009;72(1):60–4.
110. 14. Bechtold S, Ripperger P, Häfner R, Said E, Schwarz HP. Growth hormone improves height in patients with juvenile idiopathic arthritis: 4-year data of a controlled study. J. Pediatr. 2003 Oct;143(4):512–9.
111. Davies UM, Rooney M, Preece MA, Ansell BM, Woo P. Treatment of growth retardation in juvenile chronic arthritis with recombinant human growth hormone. J. Rheumatol. 1994 Jan;21(1):153–8.
112. Saha M-T, Haapasaari J, Hannula S, Sarna S, Lenko HL. Growth hormone is effective in the treatment of severe growth retardation in children with juvenile chronic arthritis. Double blind placebo-controlled followup study. J. Rheumatol. 2004 Jul;31(7):1413–7.
113. Simon D, Lucidarme N, Prieur A-M, Ruiz J-C, Czernichow P. Treatment of growth failure in juvenile chronic arthritis. Horm. Res. 2002;58 Suppl 1:28–32.
114. Touati G, Prieur AM, Ruiz JC, Noel M, Czernichow P. Beneficial effects of one-year growth hormone administration to children with juvenile chronic arthritis on chronic steroid therapy. I. Effects on growth velocity and body composition. J. Clin. Endocrinol. Metab. 1998 Feb;83(2):403–9.
115. Mauras N. Can growth hormone counteract the catabolic effects of steroids? Horm. Res. 2009 Nov;72 Suppl 1:48–54.
116. Simon D. Management of growth retardation in juvenile idiopathic arthritis. Horm. Res. 2007;68 Suppl 5:122–5.
117. Bismuth E, Chevenne D, Czernichow P, Simon D. Moderate Deterioration in Glucose Tolerance during High-Dose Growth Hormone Therapy in Glucocorticoid-Treated Patients with Juvenile Idiopathic Arthritis. Horm. Res. Paediatr. 2010;73(6):465–72.
118. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011 Apr;63(4):465–82.
119. Sävendahl L. The effect of acute and chronic stress on growth. Sci. Signal. 2012 Oct 23;5(247):pt9.
120. Quartier P. Current treatments for juvenile idiopathic arthritis. Jt. Bone Spine Rev. Rhum. 2010 Dec;77(6):511–6.
121. Bechtold S, Roth J. Natural History of Growth and Body Composition in Juvenile Idiopathic Arthritis. Horm. Res. 2009;72(1):13–9.
122. Denson LA. Growth hormone therapy in children and adolescents: pharmacokinetic/ pharmacodynamic considerations and emerging indications. Expert Opin. Drug Metab. Toxicol. 2008 Dec;4(12):1569–80.

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