Review

Growth in juvenile idiopathic arthritis: the role of inflammation

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ABSTRACT

Growth disorders are common among patients with juvenile idiopathic arthritis (JIA). These disorders range from general growth retardation to local acceleration of growth in the affected limb, and are associated with an increased production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Pro-inflammatory cytokines may act individually or in combination to impair child growth through systemic mechanisms and/or a local action. Whereas IL-6 affects growth mainly via systemic mechanisms altering growth hormone secretion, IL-1β and TNF-α can directly affect growth plate chondrocyte dynamics as well as longitudinal bone growth. There are emerging data suggesting that interleukin-15 and interleukin-5 may be new cytokines implicated in inflammatory diseases, but further well-designed longitudinal studies in larger groups of children are required to establish a causal relationship. Other factors, which might contribute to growth suppression associated with childhood arthritis, include the degree, extent, and duration of disease activity, age at onset, immobility, sub-optimal nutrition and corticosteroid therapy.

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease affecting the joints and represents the most common chronic rheumatic disease during childhood (1). Between 5 and 18 per 100,000 children develop JIA each year, and the overall prevalence is approximately 30–150 per 100,000 (2).

Growth is often impaired in children with chronic inflammatory diseases such as juvenile idiopathic arthritis (JIA) (3). These disorders are characterised by growth alterations ranging from general growth retardation to local acceleration of growth in the affected limb (4). The degree of growth failure is variable and includes mild decreases in growth velocity as well as severe forms of short stature (4). Several factors can impair growth, such as chronic inflammation, corticosteroid treatment, undernutrition, and reduced physical activity (5). These factors can act on the growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis, altering its function at one or more levels, centrally or peripherally (4). Delays in pubertal onset and/or a slow pubertal progression are often associated with growth impairment in young patients with chronic diseases (5).

In this review we report the current knowledge on growth disorders in children with JIA, with particular reference to the role of inflammatory cytokines as potential mediators of growth impairment.

Growth in juvenile idiopathic arthritis

Human growth is a complex phenomenon depending on the interaction of several players, including genes and environmental factors, such as nutrition, as well as hormones and growth factors. GH is the main mediator of somatic growth during postnatal life, mainly through its peripheral mediator, IGF-1 (6).

Several studies have assessed growth patterns in children and adolescents with JIA as well as in animal models of JIA and tried to understand the underlining mechanisms (3, 7).

In JIA the prevalence of short stature ranges from 10.4% in children with the polyarticular form to 41.0% in patients with the systemic form (8, 9).

To define patterns of growth in JIA, Liem *et al*. examined 67 children with different forms of JIA followed for a period ranging from 5 to 18 years (10). The group with the pauciarticular form of JIA showed relatively stable height velocity throughout the follow-up period. In contrast, the group with the systemic form manifested a progressive

decline in height velocity over time. The group with the polyarticular form had a modest decline in height velocity during the first 5 years of follow-up, followed by a tendency towards normalisation (10). Overall these results indicate that heights-for-age values in the polyarticular group tend to be lower than those in the pauciarticular group although not as low as in the systemic population (10). These data support the observations of Zak *et al*. (11), who assessed final height in 65 adults with chronic childhood arthritis. Patients with a height less than 2 standard deviations below the mean (10.8%) tended to have polyarticular or systemic onset subtypes, exposure to systemic steroid therapy, and more functional disability.

Factors which might contribute to growth suppression associated with childhood arthritis include the degree, extent and duration of disease activity, age at onset, immobility, sub-optimal nutrition, defects in GH secretion and action, corticosteroid therapy and the effect of pro-inflammatory cytokines (10).

With regards to therapy, significant deviations of adult height from mid-parental height have been reported only in children treated with systemic steroids for longer than 12 months (12). In a retrospective study of 24 children with systemic JIA (9), 87% of them had a final height less than their target height. Furthermore, no catch-up growth was observed in 30% of children following disease remission and termination of glucocorticoid therapy.

Previously, among 119 children with JIA, Ansell and colleagues (13) observed that growth retardation was associated with a long duration of active disease, but that disease remission was associated with improvement in growth velocity, leading to achievement of a normal height after 2 to 3 years, unless epiphyseal growth nuclei had already fused prematurely (13). Similarly, in a population of 64 prepubertal children with chronic juvenile arthritis, Saha *et al*. found an initial decrease in height during the first year post-diagnosis followed by an increase, suggesting that growth can normalise to pre-disease values with a good control of the disease activity (14).

In children with JIA, maintenance of growth is also influenced by a number of systemic and local autocrine/paracrine factors, including vitamin D metabolites, sex steroids, parathyroid hormone-related peptide, fibroblast growth factor, bone morphogenic proteins together with other members of the transforming growth factor superfamily (15).

Role of cytokines in growth impairment in JIA

There is growing evidence suggesting that cytokines can contribute to abnormal growth patterns in children with JIA. Cytokines, which have been reported to play a major role in JIA, include interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Table I) (16). TNF-α and IL-1β have the potential to directly affect growth plate chondrocyte dynamics, whereas IL-6 may influence growth by reducing also the systemic effects of IGF-1 (17, 18). The action of these cytokines is exerted via specific cell surface receptors resulting in changes in gene expression of target cells. Receptors of different cytokines share common signal transduction pathways allowing cross-over effects. Pro-inflammatory cytokines may act individually or in combination to affect child growth through systemic mechanisms and/or a local action at the level of the growth plate of long bones (4).

Interleukin-6

IL-6 is a pleiotropic cytokine that regulates immune response, haematopoiesis, acute-phase response and inflammation (19). In animal models of chronic inflammatory disease, such as IL-6 transgenic murine lines, IL-6 appears to be the main pro-inflammatory cytokine involved in growth retardation (20).

Circulating and synovial fluid levels of IL-6 are markedly elevated in patients with systemic JIA, and they are associated with laboratory and clinical variables of disease activity (21). An association has also been observed between inflammatory clinical activity and growth retardation (8, 10). Souza and colleagues (3) showed an inverse association between growth velocity and serum IL-6 levels as well as disease activity in 79 patients with JIA followed for 1 year. In particular, they found that the prevalence of reduced growth velocity was 25.3%. Twelve (60%) of these 20 patients presented levels of IL-6 >1pg/ml, whereas out of the 58 patients with normal growth velocity, only 16 (27.6%) showed levels of IL-6 >1pg/ml (3).

Given that the polyarticular and systemic forms are usually associated with a higher inflammatory activity, and taking into account that elevated IL-6 levels were associated with lower growth velocity Z-scores, Souza *et al*. suggested that IL-6 could be an essential link between inflammation and stunted growth (3).

Studies performed in transgenic murine models have examined the potential mechanisms by which IL-6 induces systemic effects on growth retardation. De Benedetti *et al*. (22) found that NSE/hIL-6 transgenic mouse lines expressing high levels of circulating IL-6 since soon after birth presented a reduced growth rate that led to a mice size reduction of 50–70% when compared to nontransgenic littermates. Administration of a monoclonal antibody against the murine IL-6 receptor partially reverted the growth defect. In NSE/hIL-6 transgenic mice, circulating IGF-1 levels were lower than those of nontransgenic littermates; whereas, the distribution of GH pituitary cells, as well as circulating GH levels, were normal (Fig. 1) (22).

NSE/hIL-6 mice and wild-type mice treated with IL-6 showed decreased levels of IGF-binding protein-3 (IGFBP-3) (7), the main IGF-1 binding protein, which together with the acid-labile subunit (ALS) and IGF-1, forms the ternary complex, which increases the half-life of circulating IGF-1 (23).

Patients with systemic JIA, condition characterised by a high IL-6 production, also show markedly reduced levels of IGFBP-3. The mechanism by which IL-6 induces decreased IGFBP-3 levels remains to be clarified. Whereas IGF-1 and ALS are produced by hepatocytes and their production is not affected by IL-6, IGFBP-3 is produced by Kupffer

cells (24). As Kupffer cells constitutively express IL-6 receptor, it can be hypothesised that IL-6 directly affects IGFBP-3 production. On the other hand, De Benedetti *et al*. (7) showed that both NSE/hIL-6 transgenic mice and patients with systemic JIA have increased proteolysis of serum IGFBP-3, suggesting that IL-6-induced decrease in intact IGFBP-3 levels is, at least partly, due to IGFBP-3 proteolysis. This could be related to the know ability of IL-6 to stimulate the production of several proteases including catepsin B and L (25) and, more interestingly, of metalloproteinases (MMP) from a variety of cell types (26).

Low levels of IGFBP-3 are associated with a marked decrease in IGF-1 half-life and accelerated clearance leading to low IGF-1 levels even in the presence of normal liver IGF-1 production (27). IGFBP-3 levels were directly correlated with IGF-1 levels both in NSE/hIL-6 mice and in patients with systemic JIA (7).

Generally, IL-6 has not been considered to have any direct effect on growth plate chondrocyte dynamics but to affect growth only through systemic mechanisms that alter GH/IGF-1 axis (7, 28). However, a recent study demonstrates that IL-6 directly inhibits early differentiation of growth plate chondrocytes, and that growth impairment in systemic JIA may be in part due to a direct inhibitory effect of IL-6 on committed stem cells in the growth plate (29). Nakajima *et al*. (29) evaluated the effects of IL-6 on chondrogenesis in ATDC5 cells, a clonal murine chondrogenic cell line that provides an excellent model for studying endochondral ossification at growth plate. At the epiphyseal end of the growth plate, the germinal or stem cell zone contains the resting chondrocytes (30). Owing to some unknown triggers, the stem cells enter the proliferating zone, and local and systemic factors regulate longitudinal bone growth, which involves the differentiation of committed stem cells into proliferating chondrocytes (early chondrogenesis); after a certain number of cell divisions, these cells finally differentiate into the hypertrophic phenotype that deposits a matrix that is mineralised and eventually replaced by bone (31). In the assessed murine chondrogenic cell line (ATDC5), IL-6 inhibited cartilaginous nodule formation, an important prerequisites for initiation of chondrogenesis in mesenchymal cell cultures, (29) as well as markedly reduced the expression of type II collagen, aggrecan and type X collagen (Fig. 2) (29). These data support a negative role of IL-6 in the early differentiation of chondrocytes, although these findings are limited to a specific murine cell lines.

De Benedetti *et al*. (32) evaluated the effects of chronic IL-6 over-expression *in vivo*, using the skeletons of growing prepubertal mice exposed to high circulating IL-6 levels since birth. Their study showed that during prepubertal development, IL-6 over-expression caused osteopenia, with accelerated bone reabsorption, reduced bone formation, and defective ossification, pointing to IL-6 as a pivotal mediator of the damage induced by chronic inflammation in postnatal bone development (32, 33). Enhanced bone resabsorption was due to increased osteoclastogenesis, and reduced osteoblast activity was induced by a mechanism affecting precursor proliferation and osteoblast function (32). Osteoblast differentiation appeared to be unaffected, as shown by unaltered Runx2 and alkaline phosphatase mRNA expression. The discrepancy between unchanged Runx2 expression and low expression of its downstream gene osteocalcin may be explained by possible modulation of Runx2-specific coactivators/repressors by IL-6 (34). The activation of osteoclasts in IL-6-transgenic mice, instead, was not mediated by an increased production of these cytokine by the osteogenic cells or by increased circulating levels that were not found to be changed *in vivo* (32, 35).

Nakajima *et al*. (36) assessed skeletal abnormalities in 201 healthy children with JIA aged 0-16 years, by measuring serum cartilage oligomeric matrix protein (COMP) concentrations, a protein produced mainly by chondrocytes and synovial cells. In children, serum COMP concentrations apparently reflect chondrocytes turnover in the growth plate. Their study revealed that serum COMP levels in patients with systemic JIA were decreased during active disease phase whereas its levels significantly increased after treatment with the anti-IL-6 tocilizumab (36). In the same study, serum MMP-3 concentration, which is a useful marker for predicting joint destruction and for disease activity in rheumatoid arthritis (37), and serum bone alkaline phosphatase (BAP) concentration, which is one of the bone formation markers for osteoblastic activity (38), were also assessed. MMP-3 concentrations were high during the active disease phase, whereas decreased after starting treatment with tocili-

Table I. Effects of cytokines on growth in children with JIA.

Inflammation and stunted growth in JIA
↑ IL-6
- Causes a decrease in IGF-1 levels without affecting GH production
- Induces production of several proteases including cathepsin B and L and metalloproteinases
- Causes a decrease in IGFBP-3
- Inhibits early differentiation of murine chondrogenic cell lines
- Inhibits cartilaginous nodule formation
- Reduces the expression of type II collagen, aggrecan and type X collagen
- Decreases trabecular and cortical bone
- Increases osteoclastogenesis
- Reduces osteoblast activity
- Decreases mineral apposition rate→ ossification defect
↑ IL-1 β and TNF-α
• Decrease liver IGF-1 production
• Decrease growth hormone receptor and binding proteins mRNA levels
• Reduce chondrocyte proliferation
• Reduce proteoglycan synthesis by chondrocytes
• Reduce aggrecan, collagen II and collagen X gene expression
• Increase chondrocyte apoptosis

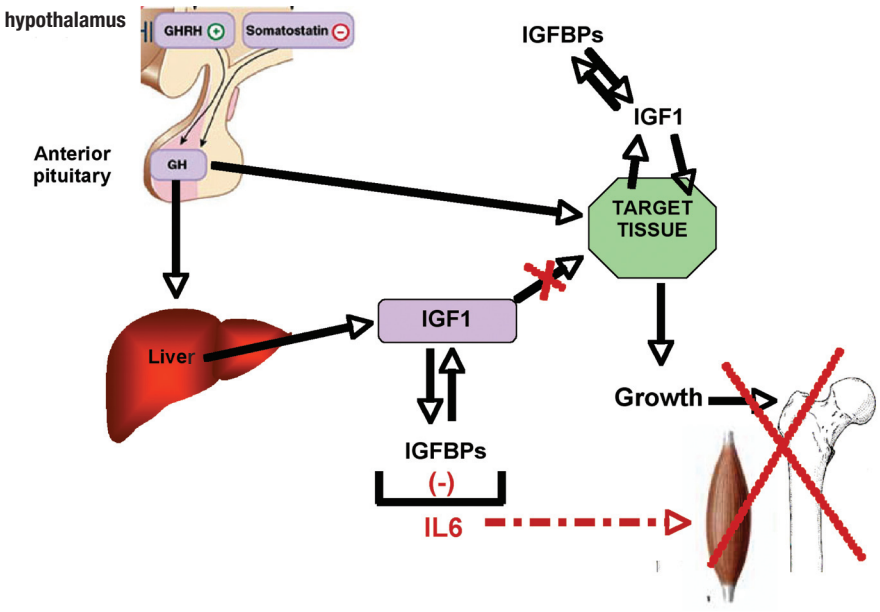

Fig. 1. Systemic effect of IL-6.

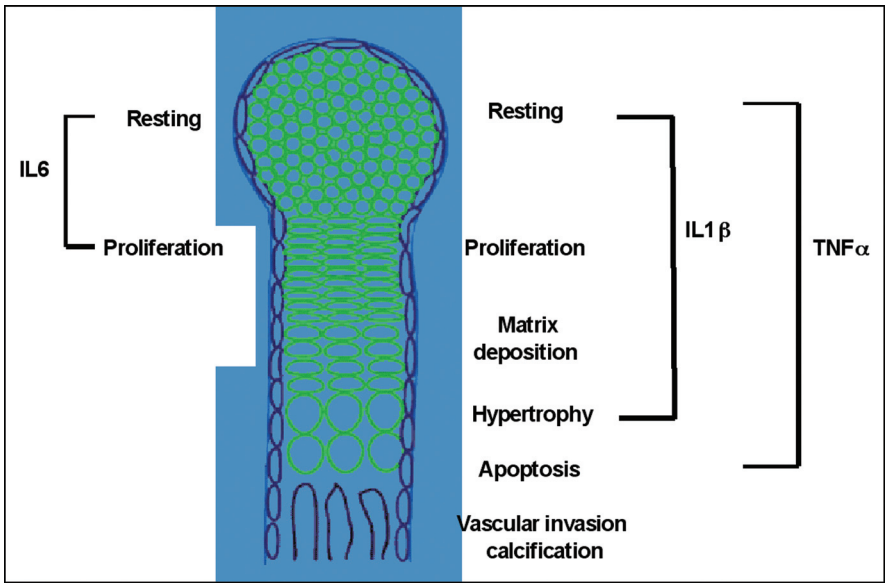

Fig. 2. Actions of proinflammatory cytokines (TNF-α, IL1β and IL6) on the chondrocyte maturational phases.

zumab (36). In contrast, serum BAP concentrations were low during active disease and then significantly increased during the remission phase, similarly to COMP, suggesting that growth cartilage and bone turnover may be improved as a result of the successful inhibition of inflammation under treatment with anti-IL-6 (36).

Tumour necrosis factor-α and interleukin 1-β

In contrast to IL-6, which affects growth mainly via systemic mechanisms that alter GH secretion, IL-1β and TNF-α can directly affect growth plate chondrocyte dynamics as well as longitudinal bone growth (18).

These cytokines inhibit the expression of a number of genes encoding chondrocyte-specific matrix molecules, including aggrecan, collagen types IX and XI (39, 15). Murine ATDC5 chondrogenic cells and postnatal metatarsals, exposed to interleukin IL-1β and TNF-α showed reduced chondrocyte proliferation and expression of aggrecan and collagen types II and X (17). Cytokine exposure particularly inhibited proteoglycan synthesis. Proteoglycans and, in particular, aggrecan together with collagen type II, provide a scaffold and stimuli for chondrocyte attachment, migration and differentiation and, thereby, maintain the structural organisation of the growth plate (Fig. 2) (40).

In a study by MacRae (17), IL-1β and TNF-α led to a 71% and 45% reduction, respectively, in metatarsal growth after 8 days of exposure. An additive effect of IL-1β and TNF-α was observed (110% decrease). Their combination led to growth being 59% lower compared with control metatarsals at the end of the recovery period. Exposure to the combination for 4 days followed by a 4-day recovery period resulted in 87% decrement compared with controls (17).

Similar data were previously reported by Mårtensson and coworkers (18) who studied the effects of cytokines on longitudinal bone growth in fetal rat metatarsal bones kept in culture. After a 7-day culture, bones were sectioned and chondrocyte proliferation was assessed. When added separately, IL-1β and TNF-α impaired longitudinal bone growth only at a high concentration (100ng/ml each). In contrast, when added in combination, IL-1β and TNF-α potently inhibited growth at lower concentrations (from 3ng/ml each). These effective concentrations of IL-1β and TNF-α are supraphysiological compared with the serum levels reported in normal children but not far from those reported in children with JIA (41). A possible explanation for the additive effect of these cytokines could be that these cytokines share some mitogen-activated protein kinase (MAPK)-signalling pathways and that both cytokines are needed to evoke effects (42). In addition, in many inflammatory diseases associated with growth retardation, more than one cytokine is upregulated, suggesting that growth retardation could be a result of the synergistic effect of two or more cytokines (16).

IL-1β and TNF-α also decreased chondrocyte proliferation and increased apoptosis (Fig. 2) (16). Apoptotic cells were almost exclusively proliferative chondrocytes with almost none of the hypertrophic cells affected.

These cytokines induced loss of early chondrocytes and depleted the growth plate of cells that are programmed to give longitudinal growth (16).

The results of these studies concur with and extend previous reports highlighting the effects of inflammatory cytokines on growth plate chondrocytes. In cultures of rabbit growth plate chondrocytes, IL-1β decreased alkaline phosphatase activity during the hypertrophic stage and suppressed an increase in cell size and type X collagen expression, suggesting an inhibition of chondrocyte terminal differentiation and hypertrophy (43). TNF-α induced apoptosis in chick growth plate chondrocyte cultures (44) and suppressed cartilaginous nodule formation and the accumulation of cartilage specific proteoglycan reduction in the ATDC5 cell line (45). Interestingly, Horiguchi *et al*. (45) noted that TNF-α (10ng/ml) increased (3H)thymidine uptake in the ATDC5 cell line which is in contrast to the data of MacRae *et al*. (17). The reason for this discrepancy is unclear; however, the reduction in chondrocyte proliferation noted in the ATDC5 cell line was confirmed in the metatarsal model. TNF-α has also been shown to synergise with IL-17 to reduce proteoglycan synthesis in fetal mouse metatarsals (46).

Several studies have suggested that longitudinal growth and especially chondrocyte hypertrophy in the metatarsal model of growth is highly dependent on IGF-1 action (47, 48).

Proinflammatory cytokines may modulate the IGF-1 signalling pathway in growth plate chondrocytes at several levels (15). It is unlikely that IL-1β and TNF-α down-regulate IGF-1 receptor expression (15, 49), affect IGF-1 receptor affinity (50) in articular cartilage or inhibit the intrinsic tyrosine kinase activity of the IGR-1 receptor (IGF-1R) (51, 52). It has been shown that TNF-α and IL-1β induce IGF-1 resistance by inhibiting insulin receptor substrate-1 (IRS-1) phosphorylation in both myoblasts (53) and breast cancer epithelial cells (51). Proinflammatory cytokines may therefore also induce IGF-1 resistance by inhibiting IRS-1 phosphorylation in growth plate chondrocytes (15).

However, proinflammatory cytokines may also act directly on the Phosphoinositide 3-kinase (PI-3K) and/or MAPK signalling pathways of growth plate chondrocytes (54). At this regard, MacRae *et al*. (55) studied the relationship between IL-1β and IGF-1, by adding the inhibitors of the PI3K (LY294002) and Erk 1/2 (PD98059) to ATDC5 chondrocyte cell line and murine fetal metatarsal cultures. IGF-1 stimulated ATDC5 chondrocyte proliferation. Addition of PD98059 or LY294002 individually to IGF-1 supplemented ATDC5 cultures partially reduced proliferation by 32%, and 66%, respectively. Total inhibition of IGF-1 stimulated ATDC5 proliferation was only observed in the presence of both inhibitors (55).

Finally, TNF-α and IL-1β may also directly interfere with GH receptor signalling. The effects of GH are generally manifested through its interaction with a specific cell surface receptor, the GH receptor (GHR) (56). GH binding to the GHR promotes the activation of the intracellular tyrosine kinase JAK2 (57). GH also stimulates tyrosyl phosphorylation of the GHR and several cellular proteins, including MAPK, extracellular signal-regulated kinase 1 and 2, and the signal transducers and activators of transcription (Stat) 1, 3 and 5, probably through pathways involving JAK kinases (58). Phosphorylated Stat proteins form multimeric complexes that bind specific DNA elements and directly regulate transcription of responsive genes (59). The peripheral mediator of GH, IGF-1, acts through a tyrosine kinase receptor (IGF-1R). Binding of IGF-1 to its receptor activates intracellular substrates, mainly IRSs, and a series of autophosphorylation events (60).

There is evidence that TNF-α and IL-1β can increase suppressor of cytokine signalling proteins (SOCS)-3 expression, and this directly inhibits IRS-1 phosphorylation by IRS-1 protein degradation (61). SOCS are cellular signalling proteins that down-regulate cytokine signalling and alter GH signalling (62). SOCS-2 knock-out mice show gigantism accompanied by deregulated GH signalling (63).

New cytokines:
Interleukin-15 and Interleukin-5

IL-15 is a pleiotropic pro-inflammatory cytokine expressed in several inflammatory disorders, including rheumatoid arthritis, psoriasis and pulmonary inflammatory diseases (64). IL-15 promotes activation of T cells, neutrophils and macrophages, and is critical for dendritic cell function in several model systems (64).

IL-5, a haematopoetic growth factor produced by T cells, and IL-15 have been shown to be elevated in serum of children with JIA (65, 66). There is emerging data to suggest that IL-15 may be a new cytokine target in inflammatory diseases (67).

Wong and colleagues were the first to examine the possible association between these cytokines and growth retardation in JIA (68). In this study, seventeen children with a median age of 6.5 years suffering from oligoarticular JIA (n=8), polyarticular JIA (n=6), extended oligoarticular JIA (n=2) or systemic JIA (n=1) were recruited at therapeutic arthrocentesis. The results demonstrated that children with a range of subtypes of JIA showed relatively normal IGF-1 and IGFBP-3 but low ALS levels in the presence of milder degrees of growth retardation. However, children with a more severe form of JIA may have normal ALS, low IGF-1 and markedly low IGFBP-3 (7). No single marker of inflammation showed significantly correlation with systemic markers of GH secretion, despite abnormalities in the ternary complex (68). However, their data emphasise that inflammatory cytokines like TNF-α, IL-1β and IL-6 may act in combination with other inflammatory mediators to exert their negative effects on growth (68, 69). In the current study, TNF-α and IL-1-β did not show any association with physical growth. However, IL-5 and IL-15 were independent factors associated with parent adjusted height of the children (68). However, given the cross-sectional design of their study it is not possible to define a causal relationship between increased IL-5 and IL-15 levels and growth retardation. Longitudinal studies will help to answer this question. In addition, further studies are required to clarify

the potential mechanisms behind the reported associations.

Conclusions

Growth retardation is often a major problem in patients with JIA and can result in a short final stature of variable degree, especially when the disease is severe. There is evidence that pro-inflammatory cytokines contribute to abnormal growth patterns in children with JIA through systemic and local effects on the GH/IGF-1 axis. The studies commented in this review highlight the concept that new therapeutic strategies in children and adolescents with JIA might consist in the development and application of cytokine inhibitors, such as anti-TNF monoclonal antibodies or humanised anti-IL-6 receptor monoclonal antibody, not only to contrast the disease but also to improve the growth disturbances often associated.

References

1. CASSIDY JT, PETTY RE: Juvenile rheumatoid arthritis. *In:* CASSIDY JT, PETTY RE (Eds): *Textbook of Pediatric Rheumatology*, 4th ed. Philadelphia, USA: WB Saunders, 2001, p. 218-21.
2. GÄRE BA: Juvenile arthritis: who gets it, where and when? A review of current data on incidence and prevalence. *Clin Exp Rheumatol* 1999; 17: 367-74.
3. SOUZA LS, MACHADO SH, BRENOL CV, BRENOL JC, XAVIER RM: Growth velocity and Interleukin 6 Concentrations in Juvenile Idiopathic Arthritis. *J Rheumatol* 2008; 35: 2265-71.
4. MACRAE VE, WONG SC, FARQUHARSON C, AHMED SF: Cytokine actions in growth disorders associated with paediatric chronic inflammatory diseases. *Int J Mol Med* 2006; 18: 1011-8.
5. SIMON D: Puberty in chronically diseased patients. *Horm Res* 2002; 57 (Suppl. 2): 53-56.
6. REINECKE M, SCHMID AC, HEYBERGER-MEYER B, HUNZIKER EB, ZAPF J: Effect of Growth Hormone and Insulin-Like Growth Factor I (IGF-I) on the Expression of IGF-I Messenger Ribonucleic Acid and Peptide in Rat Tibial Growth Plate and Articular Chondrocytes *in Vivo*. *Endocrinology* 2000; 141: 2847-53.
7. DE BENEDETTI F, MEAZZA C, OLIVERI M *et al*.: Effect of IL-6 on IGF binding protein-3: a study in IL-6 transgenic mice and in patients with systemic juvenile idiopathic arthritis. *Endocrinology* 2001; 142: 4818-26.
8. SIMON D, FERNANDO C, CZERNICHOW P, PRIEUR AM: Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. *J Rheumatol* 2002; 29: 1296-300.
9. SIMON D, LUCIDARME N, PRIEUR A-M, RUIZ J-C, CZERNICHOW P: Treatment of growth failure in juvenile chronic arthritis. *Horm Res* 2002; 58: 28-32.
10. LIEM JJ, ROSEMBERG AM: Growth patterns in juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 2003; 21: 663-8.
11. ZAK M, MULLER J, PEDERSEN FK: Final height, armspan, subischial leg length and body proportions in juvenile chronic arthritis: a long-term follow-up study. *Horm Res* 1999; 26: 99-103.
12. WANG SJ, YANG YH, LIN YT *et al*.: Attained adult height in juvenile rheumatoid arthritis with or without corticosteroid treatment. *Clin Rheumatol* 2002; 21: 363-8.
13. ANSELL BM, BYWATERS E: Growth in Still's disease. *Ann Rheum Dis* 1956; 15: 295-319.
14. SAHA MT, VERRONEN P, LAIPPALA P, LENKO HL: Growth of prepubertal children with juvenile chronic arthritis. *Acta Pediatr* 1999; 88: 724-8.
15. MACRAE VE, AHMED SF, FARQUHARSON C: The pathophysiology of the growth plate in juvenile idiopathic arthritis. *Rheumatology* (Oxford) 2006; 45: 11-9.
16. KUTUKCULER N, CAGLAYAN S, AYDOGDU F: Study of proinflammatory (TNF-alpha, IL-1 alpha, IL-6) and T-cell-derived (IL-2, IL-4) cytokines in plasma and synovial fluid of patients with juvenile chronic arthritis: Correlations with clinical and laboratory parameters. *Clin Rheumatol* 1998; 17: 288-92.
17. 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; 189: 319-28.
18. MARTENSSON K, CHRYSIS D, SAVENDAHL L: Interleukin-1 beta and TNF-alpha act in synergy to inhibit longitudinal growth in fetal rat metatarsal bones. *J Bone Miner Res* 2004; 19: 1805-12.
19. YOKOTA S: Interleukin 6 as a therapeutic target in systemic-onset juvenile idiopathic arthritis. *Curr Opin Rheumatol* 2003; 15: 581-6.
20. DE BENEDETTI F, MEAZZA C, MARTINI A: Role of interleukin-6 in growth failure: an animal model. *Horm Res* 2002; 58 (Suppl. 1): 24-7.
21. OU LS, SEE LC, WU CJ, KAO CC, LIN YL, HUANG JL: Association between serum inflammatory cytokines and disease activity in juvenile idiopathic arthritis. *Clin Rheumatol* 2002; 21: 52-6.
22. DE BENEDETTI F, ALONZI T, MORETTA A *et al*.: Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. *J Clin Invest* 1997; 99: 643-50.
23. DE BENEDETTI F, MEAZZA C, OLIVERI M *et al*.: Effect of IL-6 on IGF binding protein-3: a study in IL-6 transgenic mice and in patients with systemic juvenile idiopathic arthritis. *Endocrinology* 2001; 142: 4818-26.
24. ARANY E, AFFORD S, STRAIN AJ, WINWOOD PJ, ARTHUR MJ, HILL DJ: Differential cellular synthesis of insulin-like growth factor binding protein-1 (IGFBP-1) and IGFBP-3 within human liver. *J Clin Endocrinol Metab* 1994; 79: 1871-6.
25. GERBER A, WILLE A, WELTE T, ANSORGE S, BUHLING F: Interleukin-6 and transforming growth factor-beta 1 control expression of cathepsins B and L in human lung epithelial cells. *J Interferon Cytokine Res* 2001; 21: 11-9.
26. BARILLE S, COLLETTE M, THABARD W, BLEUNVEN C, BATAILLE R, AMIOT M: Soluble IL-6Rα upregulated IL-6, MMP-1 and MMP-2 secretion in bone marrow stromal cells. *Cytokine* 2000; 12: 1426-9.
27. 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; 21: 153-8.
28. LIESKOVSKA J, GUO D, DERMAN E: IL-6-overexpression brings about growth impairment potentially through a GH receptor defect. *Growth Horm IGF Res* 2002; 12: 388-98.
29. NAKAJIMA S, NARUTO T, MIYAMAE T *et al*.: Interleukin-6 inhibits early differentiation of ATDC5 chondrogenic progenitor cells. *Cytokine* 2009; 47: 91-7.
30. VAN DER EERDEN BC, KARPERIEN M, WIT JM: Systemic and local regulation of the growth plate. *Endocr Rev* 2003; 24: 782-801.
31. GREEN H, MORIKAWA M, NIXON T: A dual effector theory of growth-hormone action. *Differentiation* 1985; 29: 195-8.
32. DE BENEDETTI F, RUCCI N, DEL FATTORE A: Impaired skeletal development in interleukin-6-transgenic mice: a model for the impact of chronic inflammation on the growing skeletal system. *Arthritis Rheum* 2006; 54: 3551-63.
33. DE BENEDETTI F: The impact of chronic inflammation on the growing skeleton: lessons from interleukin-6 transgenic mice. *Horm Res* 2009; 72 (Suppl. 1): 26-9.
34. LIAN JB, STEIN JL, STEIN GS *et al*.: Runx2/Cbfa1 functions: diverse regulation of gene transcription by chromatin remodeling and co-regulatory protein interactions. *Connect Tissue Res* 2003; 44 (Suppl. 1): 141-8.
35. KUDO O, SABOKBAR A, POCOCK A, ITONAGA I, FUJIKAWA Y, ATHANSOU NA: Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. *Bone* 2003; 32: 1-7.
36. NAKAJIMA S, NARUTO T, MIYAMAE T: Improvement of reduced serum cartilage oligomeric matrix protein levels in systemic juvenile idiopathic arthritis patients treated with the anti-interleukin-6 receptor monoclonal antibody tocilizumab. *Mod Rheumatol* 2009; 19:42-6.
37. SUGIYAMA E: Role of matrix metalloproteinase-3 in joint destruction in rheumatoid arthritis. *Clin Calcium* 2007; 17: 528-34.
38. CAMOZZI V, TOSSI A, SIMONI E, PAGANI F, FRANCUCCI CM, MORO L: Role of biochemical markers of bone remodeling in clinical practice. *J Endocrinol Invest* 2007; 30: 13-7.
39. GOLDRING MB, BIRKHEAD J, SANDELL LJ, KIMURA T, KRANE SM: Interleukin-1 suppresses expression of cartilage-specific type-II and type-IX collagens and increases type-I

and type-III collagens in human chondrocytes. *J Clin Invest* 1988; 82: 2026-37.
40. BATEMAN JF, LAMANDÉ SR, RAMSHAW JAM: Collagen superfamily. *In* WD COMPER (Ed.): *Extracellular Matrix*, vol. 2,. Amsterdam, The Netherlands: Harvood Academic Publishers 1996, pp 22-67.
41. MANGGE H, KENZIAN H, GALLISTL S: Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. *Arthritis Rheum* 1995; 38: 211-20.
42. ANDERSEN NA, LARSEN CM, MANDRUP-POULSEN T: TNF-alpha and IFN-gamma potentiate IL-1beta induced mitogen activated protein kinase activity in rat pancreatic islets of Langerhans. *Diabetologia* 2000; 43: 1389-96.
43. KATO Y, NAKASHIMA K, IWAMOTO M *et al*.: Effects of interleukin-1 on syntheses of alkaline-phosphatase, type-x collagen, and 1,25-dihydroxyvitamin-d(3) receptor, and matrix calcification in rabbit chondrocyte cultures. *J Clin Invest* 1993; 92: 2323-30.
44. AIZAWA T, KON T, EINHORN TA, GERSTENFELD LC: Induction of apoptosis in chondrocytes by tumor necrosis factor-alpha. *J Orthop Res* 2001*;* 19: 785-96.
45. HORIGUCHI M, AKIYAMA H, ITO H, SHIGENO C, NAKAMURA T: Tumour necrosis factor-alpha up-regulates the expression of BMP-4 mRNA but inhibits chondrogenesis in mouse clonal chondrogenic EC cells, ATDC5. *Cytokine* 2000; 12: 526-30.
46. VAN BEZOOIJEN RL, VAN DER WEE-PALS L, PAPAPOULOS SE, LOWIK CWGM: Interleukin 17 synergises with tumour necrosis factor alpha to induce cartilage destruction *in vitro*. *Ann Rheum Dis* 2002; 61: 870-6.
47. CHRYSIS D, ZAMAN F, CHAGIN AS, TAKIGAWA M, SAVENDAHL L: Dexamethasone induces apoptosis in proliferative chondrocytes through activation of caspases and suppression of the Akt-phosphatidylinositol 3'-kinase signaling pathway. *Endocrinology* 2005; 146: 1391-7.
48. MUSHTAQ T, BIJMAN P, AHMED SF, FARQUHARSON C: Insulin-like growth factor-I augments chondrocyte hypertrophy and reverses glucocorticoid-mediated growth retardation in fetal mice metatarsal cultures. *Endocrinology* 2004; 145: 2478-86.
49. BLOUNT S, CRAWFORD A: Regulation of igf-1 receptors on rabbit articular chondrocytes by inflammatory mediators. *Agents Actions* 1994; 41: C177-9.
50. MATSUMOTO T, TSUKAZAKI T, ENOMOTO H, IWASAKI I, YAMASHITA S: Effects of interleukin-1-beta on insulin-like growth factor-I autocrine/paracrine axis in cultured rat articular chondrocytes. *Ann Rheum Dis* 1994; 53: 128-33.
51. SHEN WH, ZHOU JH, BROUSSARD SR, FREUND GG, DANTZER R, KELLEY KW: Proinflammatory cytokines block growth of breast cancer cells by impairing signals from a growth factor receptor. *Cancer Res* 2002; 62: 4746-56.
52. STRLE K, BROUSSARD SR, MCCUSKER RH *et al*.: Proinflammatory cytokine impairment of insulin-like growth factor I-induced protein synthesis in skeletal muscle myoblasts requires ceramide. *Endocrinology* 2004; 145: 4592-602.
53. BROUSSARD SR, MCCUSKER RH, NOVAKOFSKI JE *et al*.: IL-1 beta impairs insulin-like growth factor I induced differentiation and downstream activation signals of the insulin-like growth factor I receptor in myoblasts. *J Immunol* 2004; 172: 7713-20.
54. KOIKE M, YAMANAKA Y, INOUE M, TANAKA H, NISHIMURA R, SEINO Y: Insulin-like growth factor-1 rescues the mutated FGF receptor 3 (G380R) expressing ATDC5 cells from apoptosis through phosphatidylinositol 3-kinase and MAPK, *J Bone Miner Res* 2003; 18: 2043-51.
55. MACRAE VE, AHMED SF, MUSHTAQ T, FARQUHARSON C: IGF-I signalling in bone growth: inhibitory actions of dexamethasone and IL-1β. *Growth Horm IGF Res* 2007; 17: 435-9.
56. MALEMUD CJ: Growth hormone, VEGF and FGF: involvement in rheumatoid arthritis. *Clin Chim Acta* 2007; 375: 10-9.
57. WOJCIK J, POSTEL-VINAY MC: Signal transduction of the growth hormone (GH) receptor, and GH-binding protein. *Growth Horm IGF Res* 1999; 9: 51-5.
58. YOSHIZATO H, TANAKA M, NAKAI N, NAKAO N, NAKASHIMA K: Growth hormone (GH)-stimulated insulin-like growth factor I gene expression is tyrosine phosphorylation pathway depending on C-terminal region of human GH human GH receptor-expressing Ba/F3 cells. *Endocrinology* 2004; 145: 214-20.
59. LICHANSKA AM, WATERS MJ: New insights into growth hormone receptor function and clinical implications. *Horm Res* 2008; 69: 138-45.
60. DAVEY HW, XIE T, MCLACHLAN MJ, WILKINS RJ, WAXMAN DJ, GRATTAN DR: STAT5b is required for GH-induced liver igf-I gene expression. *Endocrinology* 2001; 142: 3836-41.
61. SHI H, TZAMELI I, BJORBAEK C, FLIER JS: Suppressor of cytokine signaling 3 is a physiological regulator of adipocyte insulin signalling. *J Biol Chem* 2004; 279: 34733-40.
62. KREBS DL, HILTON DJ: SOCS proteins: Negative regulators of cytokine signalling. *Stem Cells* 2001; 19: 378-87.
63. HORVAT S, MEDRANO JF: Lack of Socs2 expression causes the high-growth phenotype in mice. *Genomics* 2001; 72: 209-12.
64. MCINNES IB, GRACIE JA: Interleukin-15: a new cytokine target for the treatment of inflammatory diseases. *Curr Opin Pharmacol* 2004; 4: 392-7.
65. SMOLEWSKA E, BROZIK H, SMOLEWSKI P, BIERNACKA-ZIELINSKA M, DARZYNKIEWICZ Z, STANCZY J: Apoptosis of peripheral blood lymphocytes in patients with juvenile idiopathic arthritis. *Ann Rheum Dis* 2003; 62: 761-3.
66. BIERBAUM S, SENGLER C, GERHOLD K, BERNER R, HEINZMANN A: Polymorphism within interleukin 15 are associated with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2006; 24: 219.
67. BASLUND B, TVEDE N, DANNESKIOLD-SAMSOE B *et al*.: Targeting interleukin-15 in patients with rheumatoid arthritis: a proof of concept study. *Arthritis Rheum* 2005; 59: 2686-92.
68. WONG SC, MACRAE VE, GRACIE JA: Inflammatory cytokines in juvenile idiopathic arthritis: Effects on physical growth and the insulin-like-growth factor axis. *Growth Horm IGF Res* 2008; 18: 369-78.
69. GOUWY M, STRUYF S, PROOST P, VAN DAMME J: Synergy in cytokine and chemokine networks amplifies the inflammatory response. *Cytokine Growth Factor Rev* 2005; 16: 561-80.