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Growth And The Growth Hormone-Insulin Like Growth Factor 1 Axis In Children With Chronic Inflammation: Current Evidence, Gaps In Knowledge And Future Directions

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Abstract

Growth failure is frequently encountered in children with chronic inflammatory conditions like juvenile idiopathic arthritis, inflammatory bowel disease and cystic fibrosis. Delayed puberty and attenuated pubertal growth spurt is often seen during adolescence. The underlying inflammatory state mediated by pro-inflammatory cytokines, prolonged use of glucocorticoid and suboptimal nutrition contribute to growth failure and pubertal abnormalities. These factors can impair growth by their effects on the growth hormone-insulin like growth factor axis and also directly at the level of the growth plate via alterations in chondrogenesis and local growth factor signaling. Recent studies on the impact of cytokines and glucocorticoid on the growth plate studies further advanced our understanding of growth failure in chronic disease and provided a biological rationale of growth promotion. Targeting cytokines using biologic therapy may lead to improvement of growth in some of these children but approximately one third continue to grow slowly. There is increasing evidence that the use of relatively high dose recombinant human growth hormone may lead to partial catch up growth in chronic inflammatory conditions, although long term follow-up data is currently limited. In this review, we comprehensively review the growth abnormalities in children with juvenile idiopathic arthritis, inflammatory bowel disease and cystic fibrosis, systemic abnormalities of the growth hormone-insulin like growth factor axis and growth plate perturbations. We also systematically reviewed all the current published studies of recombinant human growth hormone in these conditions and discuss the role of recombinant human insulin like growth factor-1.

1. Introduction

2. Background physiology of normal linear growth

1. Introduction

Impaired linear growth is commonly encountered in children with chronic inflammatory conditions such as juvenile idiopathic arthritis (JIA) (1) inflammatory bowel disease (IBD), especially those with Crohn's disease (CD) (2,3) and cystic fibrosis (CF) (4,5). This may be associated with delayed onset of puberty and attenuated pubertal growth spurt (6), especially

in those with IBD as these children tend to present in late childhood and adolescence [Figure 1]. Poor growth may lead to short stature and a reduction in adult height is seen in a sub set of these patients despite contemporary medical therapy (7-9) which may have an impact on their quality of life (10).

Sub-optimal nutrition, prolonged use of glucocorticoid (GC) and chronic inflammation itself contribute to the underlying pathophysiology of growth failure (11,12). This may be through effects on the systemic growth hormone (GH) axis that regulates linear growth or through direct effects at the level of the growth plate (13) [Figure 2]. Chronic inflammation may lead to a continuum of abnormalities in the systemic GH/ insulin like growth factor-1 (IGF-1) axis including relative GH insufficiency, GH/IGF-1 resistance due to impairment of IGF binding proteins, down regulation of GH/IGF receptors and / or impairment of local GH and IGF-1 signaling pathways [Figure 3].

Determining the prevalence of growth failure from current published studies in children with JIA, IBD and CF is very challenging due to the different definitions used. Studies defining growth failure based on stature are not helpful, as this may underestimate the prevalence of faltering growth, given that a child with relatively normal height may have been growing very poorly over a period of time. Stature also needs to be interpreted in the context of the child's mid-parental height.

Evaluating growth rate (height velocity) maybe a better method to determine the prevalence of growth failure but in a group of children where a degree of delayed puberty maybe relatively common, comparing height velocity (HV) purely based on age and gender may be misleading. Due to the unpredictability of the inflammatory process, HV is also likely to vary depending on the disease status rather than time course from diagnosis compared to other conditions where treatment protocols may be fixed (eg childhood cancers). HV needs to be interpreted in the context of pubertal staging or bone age as it varies according to gender and pubertal status (14). In healthy girls, peak HV is attained at the age of approximately 12 years, corresponding to early breast stage (stage 2) whereas in healthy boys this is usually at the age of 13.5 years corresponding to later stages of puberty (genital stage 4, 10-12 ml testes)

(15,16). There is no consensus regarding the most appropriate method to interpret HV in these children. In addition, normative data for HV are from small groups of children evaluated in the 70s.

Consideration must be given to bone age assessment in children with chronic disease. Interpretation of bone age may be inaccurate if performed in the hand affected by arthritis (17). The use of change in height (Ht) SDS maybe a better method of defining growth problems in longitudinal growth studies in children with chronic disease as recently suggested as a way to report response to growth promoting therapy (18) but may also need to be interpreted in the context of puberty and/or skeletal maturation for adolescents.

Targeting the inflammatory process aggressively using immunomodulators (eg azathioprine, methotrexate) and anti-cytokine therapy (eg infliximab, etanercept, adalimumab), minimizing the use of systemic GC to achieve adequate control of inflammation and optimizing nutrition may be associated with improvement in markers of the GH-IGF axis and are paramount for ensuring normal growth and pubertal development (19,20). However, almost one third of children with JIA and CD treated with contemporary regimens continue to grow slowly (18) and improvement in disease activity does not seem to normalize linear growth in these children (21,22). In adolescents with CF, faltering growth often precedes the diagnosis of CF related diabetes (23). Whilst treatment with insulin may improve lung function and body mass index (BMI) in children with CF related diabetes (24,25), the impact of insulin on improving growth and pubertal development is still unclear (23). In an individual with CF and faltering growth, assessment of glucose homeostasis should be performed to exclude CF diabetes. Optimization of metabolic control with insulin should be performed in those already with established CF related diabetes and poor growth.

Pubertal induction with sex steroid may be considered in those individuals who are growing slowly in association with delayed puberty despite optimization of disease status and nutrition, although the timing, route of administration, dose of sex steroid and duration of treatment is unclear. Abnormal bone development is also seen in these adolescents (26-28) and in these individuals with chronic disease, decisions regarding pubertal induction will also

need to include careful assessment of bone mass and the potential benefit of sex steroid on bone acquisition. It is beyond the scope of this current review to address issues of pubertal induction in chronic disease which we feel is an area of research often neglected.

The availability of recombinant human growth hormone (rhGH) in the past 30 years has led to its use in non-growth hormone deficient conditions (29) such as Turner Syndrome (30-32), small for gestational age (33,34), idiopathic short stature (35) , short stature homeobox (SHOX) deficiency (36), Prader Willi Syndrome (37) and chronic renal insufficiency (38). In younger pre-pubertal children with chronic disease and in those with pubertal delay who continue to grow slowly despite pubertal induction, rhGH may be a therapeutic option. Emerging therapeutic clinical trials of rhGH in pediatric JIA, IBD and CF suggest that short term linear growth may improve with rhGH therapy. These studies demonstrate that rhGH, especially at a higher dose, may be able to overcome the relative GH resistant state seen in chronic disease (39).

The review aims to provide the most up to date summary of growth failure, systemic abnormalities in the GH/IGF-1 axis and local growth plate disturbances observed in children with JIA, IBD and CF. In addition, we will summarize and critically evaluate the published literature on the role of rhGH and rhIGF-1 as growth promoting therapies in these children.

This review is timely given that management of chronic disease has changed significantly over the last 15 years. Modern therapies have opened up the therapeutic options of management of these childhood chronic disease but a subset are still non responders to these treatment and in some instances the occurrence of significant adverse effects preclude the use of these modern therapies. It is for these reasons that poor growth and abnormalities of pubertal development may still be encountered and the management of these children and adolescents can be particularly complex. The full PubMed database was searched with no time restriction in July 2015 using the following keywords: inflammatory bowel disease, crohn's disease, crohn disease, ulcerative colitis, cystic fibrosis, juvenile idiopathic arthritis, juvenile arthritis, juvenile rheumatoid arthritis in combination with growth hormone, insulin

like growth factor-1 and IGF-1. Non-English articles were excluded. Relevant articles were obtained and information synthesized into this literature review by the authors.

2. Background physiology of normal linear growth

In this section, we will review the normal regulation of linear growth via systemic and local factors. The reader is however referred to other recent thorough and excellent reviews on this area (40-42). It is generally accepted that the GH/IGF-1 axis is a main regulator of linear growth via its endocrine effects at a systemic level and also via local autocrine/paracrine mechanisms. Understanding of the systemic and local regulation of normal linear growth has advanced significantly over recent years. Information on how the systemic GH/IGF-1 axis interacts with local paracrine factors in the regulation of normal linear growth is still unknown. Chronic disease via chronic inflammation, glucocorticoid and poor nutrition can impact growth at multiple levels via their effects on the GH/IGF-1 axis systemically and at the level of target organ.

2.1 Systemic regulation of linear growth

The endocrine regulation of normal linear growth involves pituitary derived GH and the IGF system. It was initially thought that GH itself did not exert its effects directly on target organs but did so via IGF-1, produced in the liver. It is now known that both GH and IGF-1 exert separate and independent effects on growth. GH can act to induce the expression and action of local IGF-1 at the level of the growth plate to lead to increase bone growth (43).

Local injection of GH directly into cartilage growth plates of the hind limbs of hypophysectomised rats produced significant increase in lengths of the injected limb compared with the non injected contra lateral limb, pointing to the direct effect of GH on regulating growth (44). In addition, if all the growth promoting actions of GH are mediated by IGF-1, then the GH receptor and IGF-1 null mice should be similar to the double GH receptor and IGF-1 receptor mutant mice (45). Lupu et al showed that post natal mice with combined GH receptor gene and IGF-1 gene deletion had the smallest size, whereas mice with GH

receptor gene deletion only were larger in size than those with IGF-I gene deletion (45). Several other groups also found that body size and tibial growth rate of mice with GH gene deletion were lower than those with IGF-I gene deletion (46-48). Numerous studies have produced conflicting results and are unable to pinpoint to the precise mechanism of the action of GH and IGF-I on the epiphyseal growth plate (49,50).

The relative contribution of hepatic generated IGF-1 to epiphyseal bone growth is currently unclear (51). In the liver IGF-I deficient (LID) mice, deletion of the liver gene of IGF-I reduced circulating IGF-I to 25% of the wild type mice. Bone length and body size of the LID mice were not different from the wild type mice. IGF-I mRNA expression in a variety of tissues including heart, muscle, fat, spleen and kidney were similar between the LID mice and the wild type mice, suggesting that there is no compensation from IGF-I derived from other tissues accounting for the preservation of linear growth in the LID mice (52). A combined knock out of LID, acid labile subunit knock-out (ALSKO), IGF binding protein 3 knock-out (BP3KO) had significantly reduced systemic levels of IGF-1 but only a modest degree of growth retardation, pointing to the possibility of the importance of local factors regulating bone growth (53).

Mice with targeted deletion of IGF-I in chondrocytes had normal systemic levels of IGF-I but 40% reduction in local IGF-I. Body length was however reduced by 27% (54). On the other hand, elevated systemic levels of IGF-1 were able to rescue the growth impairment in IGF-1 null mice pointing to the role of systemic IGF-1 on autocrine/paracrine effects (55). The IGF-1 null mice also have compensatory increase in local IGF-2 locally which may explain the modest growth impairment in that model. GH promote growth plate chondrogenesis independent of local IGF-1 and IGF-2 levels (56) and addition of rhIGF-1 to rhGH treatment in healthy female mice did not lead to improvement in bone growth (57). A study in a knock in mouse model of mutated IGF-1 with markedly low total IGF-1 and formation with IGFBPs but high levels of unbound IGF-1 showed significantly increased body size pointing to the role of free bioavailable IGF-1 on regulation of growth (58)

It has been suggested that an element of redundancy may exist between local and endocrine growth factors like IGF-1, where the absence of one source (systemic vs. local) may be compensated by the other. The regulation of GH and IGF-1 systemically and at local level may differ in health and in chronic disease (41).

2.2 Growth plate

The process of bone growth relies upon chondrocytes produced at the epiphyseal growth plate, which are progressively synthesized and replaced by bone with accompanying longitudinal (endochondral) bone growth. Growth plate (epiphyseal plate) is a layer of hyaline cartilage in growing bone located in the metaphysis between the epiphysis and diaphysis. It is left over cartilage from the endochondral ossification. The epiphyseal plate consists of four zones (59)

The zone of resting cartilage is near the epiphyses and consists of a small, scattered chondrocytes. These cells do not function in bone growth therefore; these are termed as "resting". Resting zone chondrocytes replicate at a slow rate (60) and act as stem cells that replenish the pool of proliferative chondrocytes (61).

The zone of proliferating cartilage consists of slightly larger chondrocytes arranged like stack of coins. Chondrocytes divide to replace those that die at the diaphyseal surface of the epiphyseal plate. Proliferative zone chondrocytes replicate at a high rate and the cells line up along the long axis of the bone (60,62)

The zone of hypertrophic cartilage consists of even larger chondrocytes that are also arranged in columns. The lengthwise expansion of the epiphyseal plate is the result of cell division in the zone of proliferating cartilage and maturation of the cells in the zone of hypertrophic cartilage. During the hypertrophic phase, chondrocytes increase their height about 6-10 fold. Hypertrophic differentiation makes a significant contribution to longitudinal growth (63). These chondrocytes calcify the surrounding extracellular matrix and produce factors that attract the invading bone cells and blood vessels (64). Prior to blood vessels invading the chondrocytes lacuna, they undergo apoptosis (65)

2.2.1 Local growth plate regulation

GH acts locally to recruit resting chondrocytes into the proliferative state as well as stimulate local production of IGF- which in turn stimulates proliferation of proliferative chondrocytes. Infusion of IGF-1 to hypophysectomized rats stimulate chondrocytes at all the stages of differentiation, including the hypertrophic zone, clearly pointing to a role of IGF-1 at the local level (66,67).

At a local level, GH action may be regulated by suppressor of cytokine signalling 2 SOCS2) (68). The SOCS2 knockout mice exhibit an overgrowth phenotype associated with increased GH/IGF-1 signalling leading to wider proliferative and hypertrophic zones of the growth plate (69). Studies using chondrocytes and metatarsals from the SOCS2 knockout mice showed increased GH signalling locally and maybe independent of local IGF-1 (70).

The local regulation of growth also involves several other paracrine signalling like fibroblast growth factors, Indian hedgehog, parathyroid hormone-related protein, bone morphogenetic proteins and vascular endothelial growth factor (40). How these systems interact with GH/IGF-1 regulation in health and disease is currently still unknown.

3. Inflammation and growth plate abnormalities

3.1 Effects of inflammatory cytokines on the growth plate

Various cell and organ culture approaches have borne evidence demonstrating the adverse effects of proinflammatory cytokines on growth plate chondrogenesis (71) [Figure 4]. IL-1-β and TNFα decrease both the width of the proliferating zone and the rate of endochondral bone growth; a possible consequence of altered chondrocyte proliferation, differentiation and apoptosis rates (71-74). Furthermore, IL-1β and TNFα reduce chondrocyte expression of cartilage matrix proteins including aggrecan and collagen types-II and -X (71,75,76). The addition of IL-6 alone appears to have little effect on growth plate chondrocytes although it may be able to inhibit the early differentiation steps of chondrocyte precursors (71,73,77-79). It is possible that IL-6 needs to be added in combination with

soluble IL-6R to have an effect on chondrocyte proliferation, differentiation and bone growth (73,80,81). Importantly both IL-1β and TNF-α are also produced locally by growth plate chondrocytes to regulate physiological bone growth and that the inhibition of endogenous levels leads to improved longitudinal bone growth (82,83). The growth and long bone length of the IL-1 receptor type 1 knock-out mouse were however normal despite a narrower growth plates due to a smaller hypertrophic zone (84).

The direct analysis of proinflammatory cytokines on linear bone growth has been aided by the study of cultured fetal metatarsal bones. IL1-β, IL-6 and TNF-α inhibit linear growth and in combination they have an additive growth inhibitory effect (71,73,81). Furthermore, TNF-α and IL1-β also act in synergy to induce IL-6 production in fetal metatarsals (81). There is also restricted potential for recovery of growth plate chondrogenesis and longitudinal bone growth following prolonged exposure to pro-inflammatory cytokines (71) [Figure 5]. This mirrors the clinical impression of greater degree of growth impairment in those children with longer periods of symptoms prior to diagnosis (85). Addition of antibodies to TNF-α and IL1-β lead to partial rescue of bone growth in the metatarsal model (73) [Figure 6a].

In addition to analyzing the effects of recombinant cytokines on metatarsal growth, approaches using biological fluids from children with JIA have also been informative. These preliminary studies disclosed that serum from affected children disturbed chondrogenesis and linear bone growth. The results with synovial fluid were less consistent, emphasizing the interindividual variation of the observed effects (86) . As opposed to the partial rescue of bone growth in metatarsals exposed to cytokines (TNF-α and IL1-β), addition of antibodies to TNF-α, IL1-β and IL-6 failed to show any improvement in metatarsal growth when exposed to biological fluid from a child with systemic JIA where a whole range of inflammatory cytokines may be detected other than TNF-α, IL1-β and IL-6 (86) [Figure 6b].

Inflammatory cytokines may disrupt growth plate function by inhibiting IGF-1 intracellular signaling (87,88) . Evidence for this is however limited as neither TNF-α, IL-6 nor IL-1β appear to affect IGF-1 receptor expression (71,74,89-91). Alternatively,

proinflammatory cytokines may disrupt signaling downstream of the IGF-1R. TNF-α, IL-6 and IL-1β can attenuate IGF-1-induced activation of both the MAPK/ERK 1/2 and the PI-3K pathways in chondrocytes (74,92). In myoblasts, IL-1β can inhibit the ability of IGF-1 to phosphorylate tyrosine residues on both of its downstream docking proteins, IRS-1 and IRS- 2 but it is as yet unknown if this also occurs in chondrocytes (87). Proinflammatory cytokines may also disrupt chondrocyte GH signaling. IL-6 and oncostatin M can activate JAK/STAT signaling leading to down-regulation of type II collagen, aggrecan core, and link protein transcription in articular chondrocyte (80,93). Likewise, IL-1β can antagonize GH signaling through STAT5 in hepatocytes whilst activating STAT3 in mouse kidney tumor cells (94,95). Whilst the mechanisms by which JAK/STAT signaling is blunted in inflammatory conditions are unclear, there is an emerging body of evidence implicating a role for the SOCS family of proteins which can inhibit JAK2 and STAT activation in a negative feedback loop, and whose expression is stimulated pro-inflammatory cytokines (96-101).

3.2 Effects of glucocorticoid on the growth plate

The growth-suppressing effects of GC appear multifactorial with some GC actions modifying skeletal responses to the GH/IGF-I axis whereas other evidence indicates a direct effect of GH on growth plate chondrocytes. Common to both mechanisms is the interaction of GC with its cytosolic receptor (GR) which results in the modulation of gene transcription. This is accomplished via several different mechanisms. First, GCs bind to a cytosolic GC receptor attached to a heat-shock protein (HSP). The HSP dissociates, and the GR dimerizes and translocate to the nucleus and binds to promoters on the target gene known as GC response elements (GRE), resulting in the activation or repression of a specific set of transcription factors (102,103). It has also been shown that the GR is capable of binding directly to specific transcription factors such as nuclear factor-κB (NFκB) and activator protein-1 (AP-1) which are involved in the up-regulation of inflammatory genes. This

mechanism is ligand-independent and does not require receptor dimerization, therefore rendering it genetically separable from transcriptional activation (104).

GCs block the activation of the GH-receptor (GHR) and the IGF-1 receptor (IGF-IR) in chondrocytes, inhibit pulsatile GH release and reduce IGF-1R and GHR expression by chondrocytes. GCs also impair IGF-1 signaling, predominantly via the PI3K pathway at the growth plate (92,105-110). Studies of linear bone growth have shown that dexamethasone (Dex) and IGF-1 have opposite effects, with Dex decreasing and IGF-1 increasing cell proliferation. Furthermore, IGF-1 is able to ameliorate Dex-induced growth impairment suggesting that IGF-1 may protect the growth plate against the adverse effects of GC (111).

Evidence for a direct effect of GC on the growth plate comes from a study in which pharmacological levels of local Dex infusion significantly decreased tibial growth compared with the contralateral limb (112). The GR has since been localized to proliferating and hypertrophic chondrocytes in the rat (113) as well as hypertrophic chondrocytes in the human growth plate (114). GC inhibit chondrocyte proliferation and differentiation whilst stimulating chondrocyte apoptosis and autophagy (105,110,111,115-117). The inhibitory effects of GCs on chondrocyte proliferation are consistent with GCs disrupting cell cycle progression and promoting cell cycle exit (118,119). Whilst chondrocyte p21 expression is increased by Dex this increase does not contribute to GC-induced growth retardation (120,121).The role of other cyclin dependent kinase inhibitors such as p27 in mediating GC inhibition of chondrocyte proliferation has also been questioned (122).

GCs may stimulate apoptosis by altering the relative amounts of pro-apoptotic members of the Bcl-2 family such as Bax and Bid and thereby promote mitochondrial apoptosis (123,124). The Bax deficient mice display resistance to GC induced growth failure, confirming that increased apoptosis as a crucial factor in GC induced growth impairment. (123)The global effects of pharmacological GC doses on chondrocyte gene expression have been investigated using microarray technologies. Both down-regulated genes such as secreted frizzled-related protein and IGF-I, and upregulated genes including serum/GC-regulated kinase, connective-tissue growth factor and lipocalin 2 have been identified (125,126).

Novel GCs that have the anti-inflammatory properties of conventional steroids without one or more of the side-effects have been described (127,128). One of these compounds AL-438 acts through the GR and whilst retaining full anti-inflammatory efficacy it has a GC sparing effect on chondrocyte proliferation and longitudinal bone growth (115,129) . This, and similar compounds, could prove important in the search for new anti-inflammatory treatments for children. GC excess and GH deficiency impair longitudinal bone growth. After remission, growth often accelerates beyond the normal growth rate for that particular age, a phenomenon called catch-up growth (130,131). This has also been observed in many growth-retarding conditions such as Cushing's syndrome (132), hypothyroidism (133), celiac disease (134) and anorexia nervosa/malnutrition (132). However catch-up growth in children with chronic inflammation may not be complete even after discontinuation of GC treatment if the inflammatory insult is ongoing, which is often the case.

Studies in rabbits in which Dex was infused directly in the tibial growth plate resulted in slow bone growth of the treated bone but not of the contralateral vehicle-treated bone (135). After cessation of Dex infusion, tibial bone growth rate was increased compared with the contralateral leg, thereby demonstrating catch-up growth (136). Based on these findings, Gafni and Baron (137) proposed that the underlying mechanism for catch-up growth was intrinsic to the growth plate. Specifically, the decrease in chondrocyte proliferation noted during GC treatment conserves the proliferative capacity of chondrocytes and delays chondrocyte senescence. Therefore, after discontinuation of GC treatment, the growth plate chondrocytes are less senescent *i.e.* have greater proliferating potential and thereby explaining the increased growth rate. *In vitro* studies have also shown that Dex-treated cells retain the capacity to re-enter chondrogenesis following the withdrawal of GC (119). This implies that, although Dex arrests growth and differentiation of chondrocytes, the capacity for cells to undergo chondrogenesis is maintained in the presence of GC despite the fact that progenitor cells are quiescent.

3.3 Effects of malnutrition on the growth plate

There is no doubt that undernutrition impairs skeletal growth and contributes to the growth failure in children with chronic disease. In a rat model of colitis, inflammation itself, independent of poor nutrition, explains 40% of the growth impairment (138). Aggressive nutritional therapies are often considered in children with IBD and CF, including the use of supplemental feeds and gastrostomy feeding. In the last few decades, in CD, the use of exclusive enteral nutritional (EEN) during acute relapse is generally used in place of oral GC as first line, except in those with severe disease, in most countries (139).

Rat studies show that undernutrition lead to reduction in GH production (140) but also reduction in hepatic GH sensitivity due to decreased GH receptor mRNA in the liver and resultant low systemic IGF-1 (141,142). In humans, malnutrition is associated with hepatic GH resistance but associated with elevated systemic GH levels (143,144). Short periods of fasting (2-3 days) in animal studies report reduction in linear growth by 30% compared with control animals, associated with reduction in all zones of the growth plate and decrease in chondrocyte number. In addition, GH receptor and IGF-1 expression is reduced in growth plates of mice with food restriction (145).

GH resistance during fasting maybe a metabolic adaptation and fibroblast growth factor 21 (FGF21) has been identified as a key regulating factor inducing gluconeogenesis, fatty acid oxidation and ketogenesis. Short periods of fasting can lead to elevation of FGF21 (146,147). The link between FGF21 and growth is demonstrated by the fact that transgenic mice over expressing FGF21 have reduced bone growth and hepatic GH resistance (148). On the other hand, FGF21 knockout mice subjected to 4 weeks of food restriction did not exhibit reduction in linear growth and did not show GH resistance (145). Increased FGF21 during periods of undernutrition affect GH sensitivity by directly inhibiting GH binding in growth plate chondrocytes with no impact on the number of GH receptors locally. This may be an indirect effect via the effects of two transmembrane proteins, LEPROT and LEPROTL1, which are increased during fasting, leading to reduction in GH binding and action at the growth plate (149). Recently it has been shown that fasting is associated with significant

increase in microRNA-140 specifically at the level of chondrocytes, although its precise mechanism on malnutrition growth failure is still unclear (150).

4. Animal models of chronic disease and growth disorders

Animal models of arthritis and colitis confirm the direct effects of chronic inflammation on growth, the GH/IGF axis systemically and at a local level. In addition, they have also provided evidence of the direct role of inflammation on delayed puberty and poor pubertal growth.

The IL-6 transgenic mice have an adult size that is 50-70% smaller compared to non-transgenic littermates, even after controlling for food intake (151). This was associated with normal systemic GH but low IGF-1 and low IGFBP-3. ALS levels on the other hand remained normal (151,152). The low IGF-1 was seen to be due to increased renal clearance whilst the low IGFBP-3 was due to increased proteolysis (152). Blocking IL-6 reversed the growth phenotype and normalized IGF-1 levels, pointing to the role of IL-6 on growth failure in chronic inflammation (153).

In a study of rats with *Mycobacterium butyricum* induced arthritis, weight gain was three fold lower than controls. This was associated with low IGF-1 but increased IGFBP-3 due to decrease in proteolysis (154-156). Pituitary GH and liver IGF-1 gene expression were reduced (157). In a study using a mouse model of systemic arthritis, C-natriuretic peptide overexpression in chondrocytes prevented endochondral growth retardation and reduced articular cartilage damage (158). This is thought to be mediated via an increase in chondrocyte proliferation, differentiation, hypertrophy, matrix production and local resistance to the effects of pro-inflammatory cytokines (158).

Following trinitrobenzenesulphonic acid (TNBS) induced colitis, rats demonstrate growth retardation independent of under-nutrition, leading to only 30% of the growth rate of healthy rats (159,160), associated with normal systemic GH levels but low IGF-1 (159) . The IL-6 colitis rat also has 30% of the growth rate of controls, associated with low IGF1 levels (161).

Studies in TNBS colitis rats and dextran sodium sulphate (DSS) colitis demonstrated that inflammation causes delayed puberty inconsistent with changes in food intake, body weight, leptin and corticosterone levels (162-164). Plasma levels of 17β-estradiol in females and testosterone in male rats with colitis were significantly lower, although basal gonadotropin levels were similar (162). In females DSS mice with colitis, estradiol and gonadotropin levels were not lower (164). In males DSS mice with colitis, there was no difference in testosterone levels but stimulated LH, basal and stimulated FSH levels were lower in those male mice (163). In our opinion, these animal data suggest that cytokines may affect the secretion or sensitivity of gonadotropins, or act at the level of the gonadotropin releasing hormone which may differ depending on gender. Administration of inflammatory cytokines (165,166) via intracerebroventricular injection and peripheral injection of lipopolysaccharide (167) have been shown to decrease levels of LH and FSH. Although TNF-α and IL1-β can inhibit steroidogenesis in leydig cells (168), the animal models of colitis do not support an effect of cytokines on the gonads causing primary gonadal failure as the etiology of delayed puberty.

CF mice with a null mutation in the CFTR were significantly lighter and shorter compared with wild type mice associated with significantly lower systemic IGF-1 levels. Marginal reduction in GH levels were seen only in the female mice (169). CF mice have mild pancreatic pathology with little or no exocrine pancreatic dysfunction. They however exhibit growth failure suggesting that pancreatic exocrine status may not play a significant role in poor growth in this animal model (170). A study in pigs with CF demonstrated growth deficits at birth with associated lower IGF-1 levels which is due to the lack of CFTR impairing GH secretion (171).

Adjuvant induced arthritis in rats treated with rhGH showed increased body weight (156,172) associated with increase levels of systemic IGF-1 and IGFBP-3 (156,172), with reduction in IGFBP-1 and IGFBP-2 (156). Also, transgenic mice overexpressing GH with induced colitis had similar weight trajectory as controls. Compared with wild type mice with induced colitis, transgenic mice with induced colitis had higher systemic IGF-1 levels (173).

In contrast, rhGH treatment in interleukin 10-null mice with colitis improved weight gain but did not raise systemic IGF-1 levels (174). Whilst systemic IGF-1 levels were higher in rhGH treated rats with colitis, they were still lower than levels in control rats (175). In response to rhGH therapy, animal models of colitis have reduced hepatic activated tyrosine phosphorylated STAT5 (176,177). Currently, there are no studies evaluating the growth plate phenotype in animal models of chronic inflammation treated with rhGH. rhGH in rodent models may also activate the prolactin receptor. To the best of our knowledge, there are no animal studies of rhGH in chronic disease specifically targeting the GH receptor.

5. Juvenile idiopathic arthritis (JIA)

5.1 Disease and management

Juvenile idiopathic arthritis comprises a heterogeneous group of disease subtypes involving inflammatory arthritis's beginning before the age of 16 years with symptoms presenting for greater than 6 weeks (178). The pathogenesis is currently unknown although it is thought to be due to a combination of environmental triggers and specific immunogenic factors (179,180). There are currently seven subtypes of JIA according to the International League of Associations for Rheumatology (ILAR) classification (178,181,182). In currently published literature regarding growth and pubertal development, distinction is generally only made between those patients with oligoarticular, polyarticular and systemic JIA.

Management of JIA differs depending on the subtype. There is currently no cure for JIA and treatment is focused on achieving optimal function of joints, preserving or ensuring normal mobility for day to day activity, ensuring normal growth development and minimizing negative impact on the child and family (183). Pain relief is achieved with the use of non-steroidal anti-inflammatory drugs (NSAID).

In those with more severe joint involvement that do not respond to NSAID, intra-articular GC injection is used as second line treatment. Response is usually seen within days

of injection and a response rate of 60-70% is maintained for several months (184-186). Early use of intra-articular GC injections, may result in fewer local long term consequences like contractures, muscle atrophy and leg length discrepancy (187,188). Reports of children treated with intra-articular GC and development of Cushingoid features exist in the published literature (189-191). The effect of intra-articular GC injections on linear growth in JIA is unclear. One study of 21 patients showed no adverse effects on linear growth (192). In a report of 2 patients with JIA (193), leg growth of the contralateral leg was reduced using knemometry after intra-articular GC injection. This could reflect local overgrowth of the affected inflamed limb which can occur in these children (194).

For those with severe arthritis, oral GC may be needed. In some instances, intravenous GC (methylprednisolone) for a short period may also be required especially awaiting the therapeutic effects of background immunomodulator(eg methotrexate) (195). Other aspects of disease management in subtypes of JIA will be summarized in the next sub-sections.

5.1.1 Oligoarticular JIA

This is the commonest subtype of JIA accounting for almost 50% of all children with JIA (196). These children have 4 joints or less affected. The arthritis is generally asymmetrical and predominantly involves the large joints of the lower extremities excluding the hips. The most commonly affected joints in decreasing order are the knees, ankles, elbows and the wrists (196,197). A subgroup of patients with oligoarticular JIA have extension of joint involvement such that there is > 4 inflamed joints after the first six months of disease, termed extended oligoarticular JIA. Approximately 50% of those who present with ≤ 4 inflamed joints at diagnosis show subsequent extension of involved joints (198,199). It is unclear if this is a separate entity or if these patients in fact have polyarticular JIA.

5.1.2 Polyarticular JIA

This group of children with JIA have 5 or more joints inflamed. All children with polyarticular JIA generally are likely to require a disease modifying anti-rheumatic drug (DMARD) such as methotrexate, sulphasalazine or leflunomide; anti-TNF therapy eg etanercept - or both classes of drugs. It is not uncommon, especially in those with severe disease, for a short bridging course of oral GC to be used. Current data suggests that methotrexate is the DMARD of choice in polyarticular JIA with approximately 86% responders at 2 years (200). Sixty three percent of children with polyarticular JIA will respond to treatment with methotrexate (201).

In those with recalcitrant disease, anti- (tumor necrosis factor) TNF therapy offers the possibility of improving inflammation in these children. Etanercept (Enbrel) is the anti-TNF of choice in JIA. Etanercept is a soluble, dimeric fusion protein consisting of the human p75 TNF receptor fused to the Fc region of the human IgG1. Approximately 74% of children with methotrexate resistant JIA will respond to treatment with etanercept (202,203). Adalimumab (Humira), a humanized monoclonal antibody against TNF-α, has also been shown to be effective in methotrexate resistant polyarticular JIA (204). Several studies have demonstrated the efficacy of etanercept in improving linear growth in children with JIA,mostly children with polyarticular JIA (22,205,206). Improvement in growth is greatest in those with lower Ht SDS at baseline and those not treated with GC. Growth response is modest, with a recent study from a large group of 191 children demonstrating that change in Ht SDS was only 0.29 SD after two years of therapy (22).

5.1.3 Systemic JIA

The initial description of children with systemic JIA involves the observation of the classical triad of remittent fever, typical macular, salmon colored rash and arthritis. The arthritis could be oligoarticular initially but often progress to polyarthritis with resulting significant deformity leading to disability. The systemic signs of fever and rash can precede arthritis up to several months. Growth failure is frequently seen in children with systemic JIA, especially during acute flare (207). Predictors of poor prognosis in systemic JIA include age

of onset < 6 years, disease duration > 5 years or persistent systemic features at 6 months of disease including fever, need for GC and thrombocytosis (208). Whilst anti-TNF therapy is often used as first line biologic agent in systemic JIA, it is generally less effective compared to polyarticular JIA. 54% of patients with systemic JIA show poor response to etanercept (209)

Evidence suggests that systemic JIA is in fact more driven by IL1-β and IL-6 (210,211). Anakinra (Kineret) is a recombinant human (rh) IL-1 receptor antagonist shown to be effective in several preliminary open label and retrospective studies of children with GC dependent systemic JIA (211-213). Two recent randomized trials of Anakinra in children with systemic JIA have documented its efficacy in reduction of inflammation (214,215). Only about 45% of these children are IL-1 blocker responders and responders are those with lower number of active inflamed joints, higher absolute neutrophil count (212), suggesting that IL-1 may not be the only driving cytokine in some children with systemic JIA.

In systemic JIA, elevated levels of IL-6 have also been seen and appear to correlate with arthritis, fever and thrombocytosis (216). Tocilizumab (Actemra) is a humanized monoclonal antibody against the IL-6 receptor (217) and has been shown to be effective in early phase III trials of children with systemic JIA despite DMARD and anti TNF therapy (218). A recent study in a group of children with systemic JIA treated with Tocilizumab showed that growth rate improve significantly following 2 years of therapy with resultant normalization of IGF-1. These children however remained relatively short as Ht SDS only improved by +0.3 SD after 2 years. Ht SDS at baseline was approximately -2.0 SD (219).

5.2 Clinical evidence of growth failure in JIA

Localized growth impairment is not uncommon even in those with oligoarticular JIA and may result in significant leg length discrepancy as knees are commonly affected (194). The temporomandibular joint can also be affected in those with systemic and poly-articular JIA and may result in relative micrognathia, irregular growth of the jaw (220,221). Recent 3D facial asymmetry quantification confirms unilateral destruction of cartilage of the mandibular

condyle (222) in JIA. All these clinical observations point to the role of local bone growth impairment associated with chronic inflammation.

In JIA, poor growth is more common in children with poly-articular (especially those with rheumatoid factor positive) and systemic JIA (207,223,224) although approximately 12% of children with oligoarticular JIA have recently been shown to have > 1SD reduction in Ht SDS at adult height (AH) compared with Ht SDS at diagnosis (225). Evaluation of the clinically unaffected knee with MRI in a group of children with oligoarticular JIA revealed abnormalities in 40% (226). It is possible that clinical evaluation may not be sensitive enough to detect the more widespread joint involvement in some of these children classified as oligoarticular JIA (227). Children with very early onset of systemic JIA (≤ 18 months) have a more severe disease phenotype and unsurprisingly poor growth is more frequent (228).

Onset of puberty maybe delayed in JIA by about 0.4 to 2.2 years compared to healthy children (229,230). Progression through puberty can be compromised in JIA. None of the adolescents with JIA reached breast and genital stage 5 at 16 years despite the onset of puberty between 12-13 years in one study (230). A few studies have reported that onset of puberty may be earlier in children with systemic JIA in comparison with the other subtypes of JIA (229,231). These preliminary data need to be interpreted with care as the onset of puberty was defined by genitalia stage from patient self-assessment rather than clinical examination of testicular volume. Menarche in girls with JIA is delayed by one year compared to healthy girls and also to maternal age of menarche. Age of menarche was significantly later in those with systemic JIA in this study (232). Other studies found no difference for age at menarche for girls with JIA (233,234).

Pubertal growth spurt in JIA may be attenuated and is often poorest in those with systemic JIA (231). In one study, actual HVs for children with oligoarticular and polyarticular JIA were approximately 1.5 cm/ year for those children aged 12-16 years whilst HV was only approximately 0.5 cm/ year for those with systemic JIA. A substantially compromised magnitude of peak height velocity (2.8 cm/year) was reported in this study. Peak height velocity was 3.6 cm/year for oligo-articular JIA, 4.9 cm/year for polyarticular JIA and 1.7

669 cm/year for systemic JIA (231). HV for healthy children in puberty ranges from about 4-8
670 cm/year on average.

671 Current published studies report significant reduction in adult height (AH) in JIA
672 (198,207,235-239) [Table 1]. However, these studies were published over a decade ago which
673 would have included children treated in the 1980s. The use of immunomodulators and anti-
674 cytokine have only been incorporated into routine clinical practice in the last 10-15 years.
675 Current studies of AH in JIA include different numbers of the various subtypes of JIA. The
676 study by Simon et al from 2002 which reported a mean AH of -2.0 SD only included children
677 with systemic JIA who were treated for approximately 7 years with continuous oral GC, a
678 practice that is less common these days even in children with severe systemic JIA (207). AH
679 of individuals with JIA treated with contemporary immunomodulators and anti-cytokine
680 therapy is currently unknown. In addition, there is increasing use of intra-articular injection of
681 GC instead of prolonged use of oral GC which may be beneficial for controlling joint
682 inflammation but has less systemic side effects. It is possible that there may be growth
683 suppressive effects of intra-articular GC especially for those children who require multiple
684 repeated injections.

685 Growth and pubertal development in other less common inflammatory rheumatologic
686 conditions such as systemic lupus erythromatosus (SLE), dermatomyositis, and systemic
687 sclerosis are not well studied. In a 2 year follow up study of 331 children with SLE, short
688 stature was uncommon at baseline of study visit (median Ht SDS -0.4, median parent adjusted
689 Ht SDS -0.3). However, Ht SDS continued to deteriorate despite institution of therapy,
690 particularly pronounced in boys. Parents adjusted Ht SDS < -1.5 was seen in 25% and 15% of
691 males and females at end of study, respectively (240). In SLE, delayed onset of puberty was
692 seen in 15.3% of girls (breast stage 2) and 24% of boys (testes ≥ 4ml). Over twenty per cent
693 of adolescent girls with SLE had delayed menarche (>15 years) or absent menarche. Irregular
694 menses and secondary amenorrhea was seen in fewer than fifty per cent. In the group of older
695 adolescent girls, delay onset of puberty, pubertal tempo or menarche was seen in over one

696 third of girls whereas in older boys, delay onset of puberty and pubertal tempo was seen in
697 almost fifty per cent (241).

698 Some studies have reported an association between GC and growth failure in JIA
699 (236,242) whilst others have not (227,237,243). One study evaluated the relationship between
700 inflammatory cytokines and linear growth in 79 children JIA. HV Z score was associated
701 with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and IL-6. IL-6 was the
702 only significant factor (independent of other disease markers and GC dose) influencing
703 growth rate on regression analysis in this study, highlighting once again the importance of
704 disease itself on growth failure (244). Although it is often difficult to separate the impact of
705 GC and inflammation on growth impairment, judicious use of oral GC may have less impact
706 on growth than uncontrolled inflammatory status. However, undoubtedly, prolonged high
707 dose of systemic GC will have a negative effect on growth.

708 To summarize this section, significant growth impairment leading to short stature is
709 often seen in children with severe poly-articular JIA and systemic JIA. The recent report of
710 long term growth problems in children with oligo-articular JIA needs to be confirmed in
711 further studies. The extent of long term growth failure and short stature at AH in a cohort of
712 individuals with JIA managed with modern therapies is currently unknown.
713

714 **5.3 Systemic abnormalities in GH/IGF-1 axis in JIA**

715 Chronic inflammation in JIA is associated with a state of relative GH resistance. A
716 biochemical picture of GH resistance was seen in six slowly growing children with systemic
717 JIA who had normal GH secretion from overnight GH sampling, normal GH response to two
718 provocative tests (clonidine and ITT) but low IGF-1 and IGFBP-3 levels (245). Nine out of
719 ten children with JIA underwent overnight GH sampling had normal GH secretion (246).
720 Following 4 days treatment with rhGH (0.23 mg/kg/wk), IGF-1 and IGFBP-3 only increased
721 by 31% and 14% respectively in JIA, whilst IGF-1 and IGFBP-3 rose by 85% and 73% in 8
722 children with constitutional delay in puberty (247). The resistance to GH in JIA is due to a
723 reduction in GH receptor gene expression. Following a 2 year follow up period, GH receptor

mRNA in lymphocytes of JIA increased, paralleled by improvement in disease activity, reduction in IL-6 levels and increase in IGF-1 levels (248)

Impairment of GH secretion is also seen in children with JIA. Twenty three out of 63 children with JIA who had been treated with GC for a mean of approximately 4 years at mean 0.2 mg/kg/day Prednisolone at evaluation had evidence of GH deficiency by clonidine and/or arginine stimulation test (249). In a group of children with JIA not on oral GC, abnormal GH secretion was diagnosed in 50% based on results of overnight GH sampling and L-Dopa stimulation test, suggesting that inflammation itself may also impair GH secretion. The cut off for GH sufficiency was taken at the level equivalent to 10 mcg/L (250). The recommended peak GH of < 10 mcg/L has not been validated and this arbitrary cut off may need to be altered with the availability of newer monoclonal GH assays (251,252). These may vary depending on the provocative agent used. However, the clinical studies in JIA mirrors results experimental studies in animal models of chronic inflammation induced by lipopolysaccharide and endotoxin demonstrating that pituitary derived GH production can be reduced (154,253). The impact of intra-articular GC injections on GH secretion in children with JIA is unknown.

Impairment of IGF binding proteins have also been reported in children with JIA. In 26 children with systemic JIA, normal levels of ALS, low IGF-1 and markedly low IGFBP-3 due to increase proteolysis of IGFBP-3 were reported (152). In another study of 17 children with JIA (majority olio-articular JIA) and mild growth failure, normal IGF-1, marginally low IGFBP-3 but disproportionately low ALS was reported (254).

Whilst low levels of IGF-1 are generally seen in most studies of childhood arthritis, some studies suggest that poorly growing children with inflammatory rheumatic conditions may have IGF-1 in the normal ranges, which suggest that a functional state of relative IGF-1 resistance may exist (246,255,256). In 23 children with JIA, mean IGF-1 SDS adjusted for age was -0.84. Five of those individuals had relatively "high" IGF-1 SDS > +1 SD (216). It is possible GC treatment in the presence of inflammation reduces IGF-1 sensitivity. A study of 32 adults with rheumatoid arthritis (16 on Prednisolone) showed that IGF-1 was significantly

higher in the group on Prednisolone (mean 221 microgram/L vs. 122 microgram/L). Twelve weeks treatment with anti-TNF therapy (adalimumab) led to normalization of the raised IGF-1 in the group on Prednisolone such that the levels were similar in both groups. (256).

To summarize this section, studies of the systemic GH-IGF axis in children with JIA point to a state of GH resistance in the majority of the cases. Abnormalities in GH secretion may also exist in non-GC treated children, although this could be due to the impact of intra-articular GC. Abnormalities of IGF binding proteins are reported in children with JIA but comprehensive studies of the ternary complex are still currently unavailable. IGF-1 resistance especially in those treated with high dose GC may also occur. Whilst GH/IGF-1 resistance occurs in JIA, there is insufficient scientific evidence to determine the contribution of systemic hormone resistance on growth impairment in children with JIA.

5.4 Efficacy of rhGH on linear growth in JIA

Earlier non-randomized studies that included children with JIA who were relatively older reported that HV can improve by over 100% with rhGH (247,257-264) [Table 2]. Subsequent randomized controlled trials including one with a placebo arm have confirmed these findings and suggest a modest effect on short to medium term catch-up growth [Table 3] (39,250,265-268)

Two studies that compared different doses of rhGH suggested better growth response with the "higher" dose compared with the "lower dose" (0.16 mg/kg/wk vs. 0.33 mg/kg/wk and 0.15 mg/kg/wk vs. 0.30 mg/kg/wk) (247,260). A recent trial in JIA has investigated even higher doses of rhGH (0.47mg/kg/week) (268). The growth response appears to be better in this study but the subjects in this trial had shorter duration of disease and GC exposure.

The only randomized study with AH data in chronic inflammatory disease was conducted as an RCT using rhGH 0.33 mg/kg/wk for a mean duration of 8.4 years and it reported a mean difference of 14.3 cm at AH between the two groups. Treatment led to a net gain of Ht SDS of +2.3 SD as the control group lost 0.7 SD from baseline to AH. At AH, rhGH treated patients were still relatively short with mean AH of -1.6 SDS. However,

780 untreated children had a mean AH of -3.4 SDS (39) [Fig 8]. The efficacy of rhGH on AH in
781 JIA is similar to gains seen in children with chronic renal insufficiency (CRI) treated with
782 rhGH (269,270).

783 In a non-randomized study using rhGH 0.33 mg/kg/week, using data from some of
784 the children previously included in a randomized trial and patients clinically treated with
785 rhGH off label, mean total pubertal height gain was 7.3 cm better with rhGH treatment.
786 Similarly, mean AH in the rhGH group was – 1.7 SD whilst the AH of the matched controls
787 was -3.2 SD (249). Total pubertal growth with rhGH in JIA is comparable to children with
788 idiopathic GH deficiency treated with rhGH and healthy children during puberty
789 (249,271,272).

790 To evaluate the role of "early" use of rhGH before significant short stature is present,
791 Simon et al conducted an RCT using rhGH 0.47 mg/kg/wk in a group of prepubertal children
792 with JIA who were growing at less than 3cm/year and had a mean Ht SDS of about -1.0.
793 These children had a relatively short duration of disease of approximately 2 years at baseline.
794 After 3 years of rhGH, the relative Ht gain was +1.5 SD (268). These data suggest that early
795 introduction of rhGH in the course of JIA before the onset of severe growth impairment may
796 normalize growth rate. The benefit of "early" treatment with rhGH before the onset of severe
797 growth failure needs further evaluation particularly in light of newer therapeutic development
798 in JIA disease management, although we know that catch-up growth following anti-cytokine
799 therapy may only be modest (22).

800 There is now sufficient evidence to show that the use of relatively high dose rhGH
801 leads to improvement of linear growth in children with JIA. Only one study with information
802 on AH using rhGH dose similar to those used in conditions like TS and CRI report fairly
803 similar AH outcome. Larger, adequately powered trials of rhGH in JIA are now needed to
804 confirm long term AH outcome and address issues like optimal dose of rhGH and timing of
805 starting rhGH. The impact of rhGH in those with systemic JIA, often the ones most severely
806 affected, is still unclear, as current trials have included only a small number of such children.
807 Future rhGH studies will also need to stratify for JIA subtypes at inclusion.

5.5 Factors affecting the growth response to rhGH in JIA

5.5.1 Disease status and glucocorticoid

Studies of rhGH in JIA have demonstrated that the growth response to rhGH is negatively associated with inflammatory markers such as CRP (39,260) and ESR (39). Some studies also found a negative association between cumulative prednisolone dose and growth rate during rhGH therapy (255,261,265,266). The association between prednisolone dose and growth rate was not statistically significant when the analysis was performed in a regression model, suggesting that inflammation plays a greater role in modulating growth response (39). One study showed that children with polyarticular JIA grew better on rhGH than those with systemic JIA although the number of children with systemic JIA was relatively small (263)

5.5.2 Systemic IGF-1 levels

A modest positive association has been reported between growth rate with IGF-1 and IGFBP-3 in response to rhGH. AH of the rhGH and control patients in the study by Bechtold et al showed a modest association with average IGF-1 and IGFBP-3 in JIA (r= 0.61 for IGF-1 and IGFBP-3) over the treatment period (39).

5.6 Efficacy of rhGH on disease process in JIA

There are no published studies of rhGH on its effects on experimental arthritis, but there is currently no evidence to suggest any specific concerns about worsening of inflammatory arthritis.

6. Inflammatory bowel disease (IBD)

6.1 Disease and management

Inflammatory bowel disease is a group of inflammatory disorders of the gastrointestinal tract characterized by chronic inflammation. IBD has a relapsing and

remitting nature, which is often unpredictable. IBD has classically been categorized into ulcerative colitis (UC) and Crohn's disease (CD) on the basis of combinations of clinical presentation, radiological and endoscopic and histopathological features. Recent evidence suggests that the underlying etiology of IBD is due to the interaction of three factors: genetic susceptibility, environment abnormal immune host response and commensal gut microbiota (273). It is believed that the pathogenesis of IBD occurs from errors in the interpretation or regulation of immune perception and responsiveness to endogenous microbiota and thus disruption in mucosal homeostasis. This results in the initiation of immune responses in genetically predisposed individuals (274). Familial aggregation of IBD has long been recognized (275-278), but in the last twenty years detailed mapping of a region on chromosome 16 resulted in the identification of the NOD2/CARD15 gene. This gene encodes a cytoplasmic protein designated NOD2 or CARD15, which serves as a pattern recognition receptor for bacterial lipopolysaccharide and regulates activation of nuclear factor-kβ and secretion of a-defensins by ileal paneth cells (279-281). Numerous other candidate genes have subsequently been identified but only accounts for a small proportion of pediatric IBD (282-284).

Focusing specifically on growth and genetic influences in pediatric IBD, studies have shown that patients with an OCTN1/2 haplotype (285) and those with the IL6-174 GG genotype had lower height at diagnosis (161). Another study revealed that patients with TNF-α promoter polymorphism had higher Ht SDS at diagnosis (286). A much more recent study reported significant association between growth impairment in CD and a stature related polymorphism in the dymeclin gene (287). To date, it is unclear if these associations with genetic factors are independent of the severity of inflammation

6.1.1 Ulcerative colitis

UC is a condition where the inflammatory response and morphologic changes remain confined to the large intestine, with rectal involvement in about 95% of cases. In UC, inflammation is limited to the mucosa and consists of continuous involvement of variable severity, with ulceration, edema and hemorrhage along the length of the colon. Characteristic

histopathological findings are chronic mucosal inflammation with extensive polymorph nuclear leukocytes, mononuclear cells, crypt abscesses, and distortion of mucosal goblet glands and goblet cells. Induction of remission at diagnosis and subsequent acute relapse is with oral GC. Maintenance of remission in UC is with background therapies like amino salicylates (mild disease) or immunomodulators (eg azathioprine, methotrexate) and anti-cytokine disease. In UC, major surgery with total colectomy and ileal pouch anal anastomosis is curative (288). The efficacy of anti-cytokine therapy in UC is unclear and as such not used as frequently (289).

6.1.2 Crohn's disease

In contrast, CD is inflammation that can involve any part of the gastrointestinal tract from the oropharynx to the perianal area. Diseased and inflamed segments are separated by normal healthy bowel otherwise known as "skip lesions". Inflammation can be transmural, often extending to the serosa, resulting in sinus tracts or fistula formation. Typical histopathological findings include small superficial ulcerations over a Peyer's patch and focal chronic inflammation extending to the submucosa and sometimes accompanied by non caseating granuloma formation. Common sites involved are the ileocecal region, terminal ileum, small bowel and isolated colonic involvement.

In CD, induction of remission of mild to moderate disease is often with exclusive enteral nutrition (EEN) (290). This is the provision of an exclusive liquid diet for a duration of 8-12 weeks which has been shown to be just as effective as GC for reduction of inflammation and but has no adverse effects on growth and bone metabolism (291). EEN is commonly used in Europe and is gaining popularity in the United States and the rest of the world. Background maintenance therapy using amino salicylates or immunomodulators with azathioprine are often used in moderate to severe disease close to the time of diagnosis. Methotrexate can be used as a second line immunomodulatory (292).

Escalation to anti-cytokine therapy like infliximab and adalimumab will be considered in those children with severe disease who are not responsive to GC and those with

chronic low grade inflammation but who are GC dependent. In the real world setting, the use of anti-TNF therapy in paediatric CD is associated with modest response with 56% achieving remission after 12 months (293). Safety issues like significant acute reactions and long term safety concerns including lethal forms of lymphoma preclude its use over extended periods of time (294,295). There is no doubt that the use of anti-TNF therapy in CD is associated with improvement in linear growth (296-298). Similar to the experience in children with JIA, this improvement is only modest with studies reporting increased in Ht SDS of between 0.2 to 0.3 SD over 12 months of therapy (299).

6.1.3 Inflammatory bowel disease unclassified

CD involving the colon only is commoner is children than in adults which makes it challenging to distinguish CD and UC for some individuals. In these instances, the term IBD unspecified (IBDU) is used (previously known as indeterminate colitis). Observational studies suggest that children with IBDU could be considered a distinct subtype of IBD as the disease often takes an aggressive and progressive course (300)(REF).

6.2 Growth failure in children with IBD

In IBD, growth impairment appears to be more frequent and severe in children with CD than those with UC (18,301,302).(303,304) A UK IBD register that collected data for new cases presenting between 1997 and 2003, reported that, at diagnosis, mean Ht SDS was -0.3 for both boys and girls with CD whereas it was -0.1 and +0.22 for boys and girls with UC, respectively (305). Ht SDS < -2.0 is present in approximately 10% of children with CD at diagnosis (18,306,307). In another recent study, mean Ht SDS for 102 children with CD (mean age 11.9 years) was -0.2, but those with *Saccharomyces cerevisiae* antibody (ASCA) had significantly lower height that those without (308). Whilst height reduction at diagnosis as a group appears to be mild, deteriorating height velocity is known to occur before the diagnosis of CD and can occur in the absence of gastrointestinal symptoms (309). A retrospective study of 116 children with CD provided further evidence for this as these

920 children were shorter than their genetic potential at diagnosis with mean Ht SDS of -0.5
921 compared with mid-parental Ht SDS +0.2 (18).

922 Several contemporary studies show that despite modern therapies, growth failure and
923 short stature is still seen in a subset of children and adolescents with IBD (18,307,310). A
924 study in a cohort of contemporary children and adolescents with IBD showed that Ht SDS
925 showed a negative association with the body image domain of the pediatric IBD specific
926 quality of life score IMPACT III, with higher scores indicating poorer quality of life (10) [Fig
927 8]. Further research on the impact of abnormal growth and pubertal development and the
928 impact on quality of life in children with IBD and other groups of chronic disease are needed.
929 This is a challenging area to acquire meaningful information as there needs to be distinction
930 between the impact of poor growth and the impact of the disease itself on quality of life.

931 Delayed onset of puberty has been previously reported to be common in CD (6,311-
932 313), although careful evaluation of pubertal status by clinician examination is currently
933 limited (10,311). Other current published studies have used age of menarche, bone age delay
934 and age at initiation of growth spurt as assessment of pubertal delay (6,312-314). A report
935 from the mid-90s showed that onset of breast development was delayed by 1.5 years in
936 children with CD and UC. Boys in that study had 0.8 years delay in onset of testicular
937 enlargement consistent with early puberty. This report is from a time when
938 immunomodulators and certainly biologic therapy would not been used in clinical practice
939 with heavy reliance on long term oral GC therapy.

940 Although the treatment of children with IBD has changed considerably, a study from
941 a contemporary cohort of children who analyzed retrospective pubertal growth data reported
942 persisting evidence of delayed puberty as judged by the age at peak height velocity in those
943 with CD. This delay was more likely in those with a higher ESR or lower BMI. Peak HV SDS
944 adjusted for pubertal age was also reduced, suggesting that the pubertal growth spurt may be
945 attenuated. This study however, excluded children who were treated clinically with growth
946 promoting therapy like sex steroid and / or rhGH, who by default are likely to be those with
947 significant short stature or severe growth retardation (6). Therefore it is possible that there is

948 greater impact on puberty and pubertal growth spurt despite modern therapy. A recent
949 prospective study of a cohort of children and adolescents with IBD suggests that pubertal
950 delay was uncommon with only 0.3 years of bone age delay. Adolescent boys had attenuated
951 growth rate during puberty whereas marginally delayed onset of puberty was seen in
952 adolescent girls with IBD in this contemporary cohort (10).

953 Two studies demonstrated bone age delay of approximately one year in children with
954 CD (312,313,315), which is within acceptable limits, including one study from patients
955 managed between 2007-2009 with 60% of patients on immunomodulators and 20% on
956 infliximab (315) In girls, age at menarche occurred after 16 years in 73% with CD in a cohort
957 managed between 1968 and 1983 (314). In a cohort managed between 2007-2009, girls with
958 CD reached menarche at median age of 13.9 years (313)compared with healthy controls of 12
959 years.

960 Several contemporary studies of growth in children with IBD show lack of adequate
961 catch up growth despite advances in primary disease therapy. In a study of 176 children with
962 CD, Ht SDS at diagnosis, 1 and 2 years remain unchanged at approximately -0.5 SD. The
963 percentage of children with Ht SDS < -2.0 however was slightly less frequent by 2 years: 10%
964 at diagnosis, 8% 1 year, 6.5% 2 year. This cohort was largely managed with oral GC
965 (Prednisolone) for induction of remission as only 4% had primary enteral nutrition therapy
966 within 3 months of diagnosis. (306). Another study of 116 children with CD where enteral
967 nutrition was more commonly used for induction of remission (63% of cases from diagnosis),
968 Ht SDS (approximately -0.5 SD) remained the same from diagnosis to a mean final follow-up
969 of 4.6 years after diagnosis (18).

970 In contrast to JIA, only a modest reduction in AH has been reported by most studies
971 in adults with childhood-onset IBD (3,8,9,303,314,316-319) [Table 4]. AH is significantly
972 lower in childhood onset CD with onset before puberty, although definition of puberty in this
973 study was unclear (320). In a relatively contemporary cohort of 123 patients with CD, AH
974 was only 2.4 cm lower than target height. However almost twenty per cent achieved a AH that
975 was more than 8cm below their mid-parental height suggesting that a small sub-group of

adults with childhood onset CD may have significant long term growth impairment leading to short stature. Longer duration of symptoms prior to diagnosis and jejunal disease were related to AH in that study but these factors require further study (9). Conventional assessments with endoscopy and barium studies often do not identify jejunal disease adequately, questioning the relationship with AH in that study. Parents' heights were also obtained from patient estimation. In another study of AH in IBD where 108 patients had AH and parental height measurements performed by researchers, 28 out of 108 (26%) who had more than one Ht SDS < -1.6 during growth (defined as growth impaired group) had AH of 0.9 SD lower than mid-parental Ht SDS. In those with no evidence of growth impairment, defined as those who did not have Ht SDS < -1.6 more than once during growth, AH was only 0.1 SD lower than mid-parental Ht SDS. (319).

Published evidence suggests that short term linear growth may be better in those children managed with enteral nutrition during acute relapse compared with oral GC (321,322), although the effects of EEN practice on long term growth outcome is less convincing. AH in CD (-0.4 SD) did not differ between an American study (319) and a United Kingdom study (-0.3 SD) (9) where the agent of induction of remission differed: oral GC in the American study and EEN in the United Kingdom study. Similarly, in a group of children with CD managed with EEN at initial diagnosis and who were encouraged to continue to take supplemental enteral nutrition, weight and BMI SDS increased up to 2 years follow-up, whereas Ht SDS remained unchanged (323).

Numerous studies of anti-cytokine therapy using infliximab and adalimumab in CD show significant improvement in growth rate (296-298), although some did not demonstrate any improvement in linear growth (324,325). The improvement in growth in these children may be independent of progression in puberty, reduction in GC, and maybe better in those who are concurrently treated with methotrexate. However approximately 30% of these children may still have poor growth following biologic therapy (296).

Clinical studies in children with IBD have largely shown no relationship between GC and linear growth (304,326). Saha et al, reported no difference in Ht and HV SDS in

prepubertal children with CD and UC treated with GC versus those who did not receive GC. (243). A more recent study of a cohort of 102 children with CD treated with long term low dose oral GC in the form of Prednisolone (mean dose of 0.2 mg/kg/day for mean 14.4 months) showed that almost twenty per cent of the cohort showed growth failure, although HV was not adjusted for delayed puberty. Of those with growth failure, only one third showed catch up growth after discontinuation of GC (327).

Several studies have evaluated the association between cytokines with linear growth and markers of the GH-IGF axis in children with IBD. In 37 children with IBD (17 CD), IGF-1 levels were lower whilst IGFBP-2 was higher compared with controls during relapse. IL1-β levels were related to negatively with IGF-1 and positively with IGFBP-2 (328). Levels of lipopolysaccharide was significantly higher in children with CD lower height at diagnosis and follow-up (329).Several studies of genetic polymorphism in genes regulating cytokine production have shown a relationship with growth impairment in pediatric IBD. Children with CD with the -174 GG promoter polymorphism which affects IL-6 transcription had significantly lower Ht SDS at diagnosis (161). The presence of 238G/A and 863C/A polymorphism on the TNF-α promoter gene has been shown to be associated with better height and linear growth in children with CD and appears to be independent of disease activity (286).

Current studies suggest that a sub-group of children with IBD especially those with CD have significant growth failure leading to short stature at AH. Despite the introduction of modern GC sparing therapies including anti-cytokine therapies, poor growth is still encountered, although significantly delay in onset of puberty is perhaps less common. The authors believe that the persistence of poor growth in a small group of these children reflect the fact that some children with CD still do not achieve disease remission with current therapies or adverse effects preclude the use of aggressive modern therapies. Given the short window for growth in CD, as the age of presentation is often in the adolescent years, adjuvant growth promoting therapies may still need to be explored in this small subset. Finally, the

growth outcome of children with IBDU who may have a more severe disease course is still currently unclear.

6.3 Systemic abnormalities in the GH/IGF-1 axis in children with IBD

Similar to children with JIA, growth failure in IBD is associated with a state of GH resistance. Early evaluation of the GH axis in 10 children with IBD showed excessive rather than impaired response, using overnight GH profile, propranolol-glucagon and ITT, supporting the notion that these children may be GH resistant (330). IGF-1 levels have been shown to be low in these children, although again delayed maturation may contribute to these result (331). Similarly, in 14 children with CD and growth failure who were not on oral GC, normal GH response to ITT was seen in most of the children. Four out of 14 (29%) of these children had peak GH levels < 6 mcg/L suggesting abnormalities in GH secretion (332). In a study of 5 children with CD with poor growth and delayed puberty (median age 15 years, median bone age 11 years and all except one patient was in Tanner I and II), three out of the 5 had inadequate five hour mean GH levels and peak GH during sleep-further evidence that subtle abnormalities in GH secretion may exist. However, only one child had low GH peak to ITT and none of these 5 children were on oral GC (333).

Abnormalities in the GH axis may be present at diagnosis of children with IBD (330). In addition, abnormalities in the GH-IGF axis in children with chronic inflammation are not permanent as they have been shown to be responsive to primary disease therapeutic intervention using Prednisolone (334), enteral nutrition (335,336), infliximab (337) and surgical resection (336).

It is now recognized that a range of abnormalities in GH and IGF-1 secretion and sensitivity exists in children with IBD and growth failure (338) [Fig 9]. In 28 children with IBD (25 CD) evaluated with an ITT, 11 (39%) had peak GH > 6 mcg/L and IGF-1 SDS < 0 (biochemical functional GH resistance). Biochemical functional GH deficiency defined as peak GH < 3 mcg/L and IGF-1 SDS < 0 was seen in 4 (14%). Biochemical functional GH insufficiency defined as peak GH < 6 mcg/L but ≥ 3 mcg/L and IGF-1 SDS < 0 was seen in

11 (39%). Two children had normal GH levels and IGF-1 SDS ≥ 0 suggestive of biochemical functional IGF-1 resistance.

Comprehensive studies of the IGF binding protein and ternary complex in children with IBD are currently not available. In a contemporary group of children and adolescents with IBD, pubertal onset was not delayed but abnormal pubertal growth was observed. This was associated with reduction in IGF-1 levels but marginally elevated IGFBP-3, which was postulated to lead to reduction in bioavailability of free IGF-1 (10). A recent study reported gender differences in IGF-1 and IGFBP-3 levels in children with CD such that boys had significantly lower levels even after adjusting for bone age delay, although Ht SDS was similar in both groups (315). A previous study suggested that females with CD had a more severe disease course, although males were more likely to exhibit growth failure (339). One study previously reported that IGFBP-2 is significantly higher in children with CD at relapse and that this was associated with IL-6 (328). The role of IGFBP-2 and regulation of linear growth is unclear but it is thought that it may lead to reduction of the formation of ternary complex and may have a direct inhibitory role at the level of the growth plate (340,341).

In summary, growth failure in children with IBD is associated with a range in defects in secretion and sensitivity of the GH-IGF1 axis. The relative contribution of inflammation, use of GC and nutrition on these systemic abnormalities is difficult to tease out from current studies. Indeed, the contribution of these systemic abnormalities on the growth phenotype of these children is unclear. Studies with comprehensive evaluation of IGF binding proteins are limited in children with IBD. IGFBP-2 may be a marker of disease in children with IBD but whether IGFBP-2 plays an inhibitory role on linear growth in childhood IBD is still unknown.

6.4 Efficacy of rhGH on linear growth in IBD

Compared to studies in JIA, there is a paucity of data of rhGH in children with IBD [Table 5 (342-348) and Table 6 (349-351)]. A non-randomized study of rhGH (0.35 mg/kg/wk) in 10 children (Mean age 11.9 yrs, Ht SDS of -1.8) reported an 85% increase in HV at 6 months rising from 4.0 cm/yr. to 7.4 cm/yr. This improvement was maintained in a

subgroup of seven children who continued treatment for a further 6 months (344). The only RCT of rhGH at 0.45 mg/kg/wk, for improving linear growth in children with IBD, conducted by Wong et al reported that HV increased by a median of 140% in the rhGH group compared with an 8% reduction in the control group at six months [Fig 10]. Therapy over the six months period was associated with a median difference of 3.3 cm of height gain between the rhGH and control group; equivalent to a median relative gain in height SDS of +0.4SD (351). rhGH therapy in this trial was associated with significantly higher levels of total IGF1, but no significant changes in IGFBP-3, ALS, free IGF-1 and IGFBP-2 (352).Another RCT of rhGH (0.53 mg/kg/wk) in children with CD designed to evaluate the role of rhGH in improving disease process, showed that HV improved by 60% in the rhGH group at 12 weeks. Eighteen of the 20 children who showed disease clinical remission at 12 weeks continued rhGH for a total of 52 weeks. Ht SDS of this group improved from -1.1 to -0.4 (350).

Given the results of the preliminary studies of rhGH in children with IBD, there now needs to be larger definitive trials of rhGH in slowly growing children. Challenges include interpretation of growth rate during puberty and evaluation of disease activity. It is possible that the growth response to rhGH may be more favorable in those with shorter duration of disease and where nutrition is optimized. In that regard, future clinical trials of rhGH in IBD should target those with shorter duration of disease since diagnosis and explore the benefit of concurrent supplemental feeding.

6.5 Factors affecting the growth response to rhGH in IBD

6.5.1 Disease and glucocorticoid

In IBD, HV was inversely related to pediatric crohn's disease activity index (PCDAI) and ESR. However, in individuals on rhGH but not the control group, HV showed a positive association with hemoglobin, negative associations with ESR and PCDAI. Cumulative prednisolone dose was not associated with growth response but the dose of prednisolone used in that cohort was negligible (351).

6.5.2 Systemic IGF-1

In children with IBD treated with rhGH, IGF-1 showed a modest but weak statistically significant association with growth rate during the period of treatment (351).

6.6 Efficacy of rhGH in on disease process in IBD

Several animal models of colitis suggest a direct effect of rhGH on chronic inflammation via a reduction of both mucosal apoptosis and IL-6 dependent signal transducer and activator of transcription3 (STAT3) activation (173,174,353). rhGH can also directly alter systemic markers of inflammation. rhGH in children with growth hormone deficiency (GHD) may lead to reduction in systemic pro-inflammatory cytokines although the data of rhGH in children with non-GHD states are conflicting (354-358). In a study by Slonim et al with the primary aim of assessing the effects of rhGH treatment on reduction of inflammation, 32 adults with CD were randomized to rhGH (17 rhGH) or placebo injections for four months. rhGH treatment was administered at 5mg daily for one week followed by 1.5 mg daily thereafter. Reduction in Crohn's disease activity index (CDAI) was significantly greater at 4 months with rhGH: -143 points in the rhGH group and -19 in the placebo group. There was however no significant change in Hb, hematocrit (HCT), ESR, prealbumin, ferritin or iron levels after 4 months (347).

To explore the role of rhGH on disease activity in pediatric CD, Denson et al conducted an RCT in 20 children (19 rhGH) with CD (10 rhGH-0.53 mg/kg/wk). The authors' concluded that rhGH may be an adjunct for treatment of inflammatory disease based on improvement in PCDAI (350). In the rhGH group, PCDAI was 32 and 8 points at baseline and 12 weeks. In the control group, PCDAI was 33 and 22 at baseline and 12 weeks. The percentage of GC usage in the rhGH group was lower at 12 weeks, although the dose of prednisolone was similar in both groups. Other markers of disease activity including endoscopic severity, fecal calprotectin and ESR were also similar.

Whilst generally accepted and validated as a disease index, there is a potential pitfall in the use of PCDAI (359) in rhGH studies. PCDAI is made up of three domains:

(1) Subjective patient recall of symptoms

(2) Laboratory parameters and clinical examination

(3) Auxology: weight and HV SDS. HV SDS accounts for 10 points if HV SDS < -2.0 SD, 5 points if < -1.0 SD but > -2.0 SD and 0 points if HV SDS > -1.0.

In the study by Denson et al, HV SDS was -1.0 and -1.8 at baseline in the rhGH and control group. At 12 weeks, HV SDS was +2.0 and -2.1 in the rhGH and control group (350). We believe that the lower PCDAI in the rhGH group in that study merely reflects improvement in linear growth independent of reduction of inflammation. The possibility that rhGH may improve inflammation directly in pediatric CD remains an open question but need to be explored in future studies using other disease end points other than the PCDAI.

In the study by Wong et al. PCDAI was lower after 6 months therapy with rhGH which could be interpreted as improvement in disease activity. However, when data was analyzed using the abbreviated PCDAI which omits the laboratory, physical examination and auxology domains, there was no difference in disease activity over the 6 months in both groups. ESR, CRP, Hb, HCT, albumin, TNF, IL-1 and IL-6 were similar in both groups and after the 6 months period (351). Extensive evaluation of 28 cytokines, chemokines and inflammatory growth factor using the Multiplex assay in that clinical trial showed no differences over the six months period in rhGH or control group and they also did not differ between the two groups (352). Careful disease evaluation including the use of fecal calprotectin, endoscopy or new imaging techniques like MRI should be considered in future rhGH trials in IBD.

7. Cystic fibrosis (CF)

7.1 Summary of disease and management

Cystic fibrosis (CF) is an autosomal recessive genetic condition, primarily affecting the lungs but also the pancreas, liver, intestine and other organs. The defect is on the CF transmembrane conductance regulator (CFTR) gene (7q31.2) on the long arm of chromosome 7 which leads to absence of normal CFTR protein which is a c-AMP activated ion channel.

As a result of this, decreased chloride secretion and increased sodium absorption across epithelial surface is seen. In the airways, this causes depletion of the airway surface liquid and impaired mucociliary clearance which leads to pulmonary infection and inflammation of the airways. This starts early in life and progresses to chronic infection and pulmonary inflammation. Proteases, inflammatory cells and cytokines like IL-8, IL-6, TNF-α in CF(360,361)may lead to ongoing airway wall inflammation, remodeling and eventually bronchiectasis. Inflammatory mediators like neutrophil elastase and bacterial lipopolysaccharide in turn mediate the inflammatory effects by activating the transcription factor nuclear factor-κβ which regulates pathways that induce production of cytokines. Pathogens such as Pseudomonas aeruginosa, Burkolderia cepacia, Staphylococcus aureus and Haemophilus influenza eventually colonize the airway secretions of CF individuals.

Recent studies show that TNF gene polymorphism is associated with disease progression and severity of pulmonary function (362,363), whilst another study found an association with gene polymorphism in IL1-β, IL-8 and IL-10 to be associated with more severe lung disease in CF (364). Cytokines in CF may also impact on the GH-IGF axis as demonstrated in studies relating inflammatory cytokines to systemic markers of the GH axis. In a group of young adults with CF, IL-6 was positively associated with IGFBP-2 (365). Similarly, in a group of prepubertal children with CF, change in IL-6 was positively associated with change in IGFBP-2 (366).

In CF, gastrointestinal symptoms and signs including failure to pass meconium in a new born infant is seen. In severe instances this could be associated with meconium ileus in a small proportion of infants. Exocrine pancreatic insufficiency occurs in the majority of individuals and requires pancreatic enzyme supplementation. In CF with pancreatic insufficiency, mucosal inflammation is often seen with raised fecal calprotectin. Fecal calprotectin in CF is also associated with height SDS (367). Endocrine defects involving damage to islet cells of the pancreas may lead to CF related diabetes. CF related diabetes with features of both type 1 and type 2 diabetes mellitus is increasingly recognized especially in

late adolescents. This is often parallels deterioration in lung function, growth and abnormal bone development.

Current management of CF requires early treatment and prevention of pulmonary infections with antibiotics, physiotherapy and nutritional support. Allergic bronchopulmonary aspergillosis is an exaggerated immune response to Aspergillus fumagitus which is seen in about 4-11% of individuals with CF, which will lead to worsening of lung function(368,369). Oral GC is often used for prolonged periods as inhaled GC is not effective in this condition(370).

Structured CF multidisciplinary services and easy access to health carers cognizant to the issues in CF have improved clinical outcome in CF over the last few decades (371). With increasing survival of people with CF, issues relating to growth and pubertal development have become a greater concern.

7.2 Growth failure in children with CF

Growth failure and short stature in CF may not have been given as much attention but with the increasing age of survivial of these individuals, they may become more important issues to consider. Severe short stature in CF may not be a common occurrence. In a recent study of 169 children with CF in the Netherlands, prevalence of short stature was 8%. However, when target height was taken into account, this was only 5%. When both delayed maturation and target height were taken into account (height for bone age adjusted for target height), this was only 1% (372). Similar to children with JIA and IBD, severe short stature in contemporary groups of children with CF is uncommon although poor growth is still seen (372).

Improved clinical care through multidisciplinary teams and the introduction of neonatal screening for CF has been shown to be associated with improvement in growth. Studies have shown that ongoing clinical care in specialist centers all throughout the life cycle leads to improvement in growth parameters, although it is unclear which aspects of clinical care is associated with improvement in growth. Interestingly, improvement in growth in those

managed in specialist centers was not associated with in improvement in pulmonary function (373,374). Most current published studies report some association between height and pulmonary/pancreatic function (375-377) although other studies show no association of growth with colonization with Pseudomonas aeruginosa (378) and respiratory function as assessed by FEV1 (379), highlighting the multifactorial nature of poor growth in CF.

Addressing nutrition in CF is paramount and may improve linear growth in CF but this needs to be assessed on an individual basis. Long term supplemental enteral feeding in children with CF using gastrostomy feeding show improvement in height although height often improves at least after 18 months of gastrostomy feeding (380-383). In a contemporary group of children with CF, the prevalence of malnutrition was only 7%, whereas 15% were overweight and 8% were obese (384) and therefore overzealous nutritional management should be avoided

Evidence suggest that children with CF identified from screening exhibit better linear growth compared with those diagnosed due to clinical symptoms (385). In a study of 89 CF children identified from neonatal screening, one third of that cohort had height below the 3rd centile and half of that cohort had height below the 10th centile (386) whereas in an older study of children diagnosed from clinical symptoms, 40% had height below the 5th centile at diagnosis (387).

With the introduction of neonatal screening, it is now recognized that infants with CF are lighter, shorter and have smaller head circumference at birth (388-391), associated with reduction in systemic IGF-1 levels from analysis of blood spot screening (171). CF genotype itself may have an impact on growth and this is still poorly documented in current growth studies in children and adolescents with CD. Children homozygous for ΔF508 mutation had Ht SDS approximately 1 SD below the mean from infancy to early adolescence (392). Thus, the condition itself via mechanism still unknown can predispose to growth failure and this deserves further research.

Poor growth often precede the onset of CF related diabetes (23), and can impact on pubertal growth and adult height (393). Poor growth associated with CF related diabetes may

not be normalized with insulin treatment even when started early (393), although currently studies of insulin treatment in CF diabetes with linear growth outcomes are limited. CF diabetes is often diagnosed in mid to late adolescents, although with increased awareness and screening, diagnosis in childhood is not uncommon.

Short stature in CF may have an impact on disease severity as short stature in CF is an independent predictor of mortality, which may reflect a sub- group with poorer nutrition or low grade chronic inflammation and ongoing pulmonary exacerbations (394). A poorly growing child with CF and short stature may also have lower lung reserve. The possible benefit of rhGH therapy on pulmonary function in CF will be discussed in a later section.

Similar to children with IBD and JIA, pubertal abnormalities are also seen in children with CF. Delay in skeletal maturation, onset of puberty, attenuated pubertal growth spurt has been reported in adolescents with CF. Bone age was reported to be delayed by more than 24 months in 25% of adolescents and compared to healthy children, age of peak height velocity as a marker of onset of puberty was delayed by 9-10 months in boys and 10-14 months in girls. Girls with CF reach menarche 2 years later than their healthy peers (395). Older studies show that delayed puberty is present especially in girls with CF despite good clinical status, with an association of delayed pubertal onset especially in those with the ΔF508 mutation (396). However, a recent retrospective study including 729 contemporary children with CF, showed that delayed onset of puberty was not a common occurrence (379)

Adolescents with CF may have lower peak HV compared with healthy adolescents with constitutional delay in growth and puberty (397). Those individuals with CF with delayed puberty appear to also have poorer HV during pubertal progression (4,379). One study reporting body proportions in a group of younger adolescents with CF showed that their legs were shorter than trunks, although pubertal assessment was not reported (5). Delayed puberty and short stature in CF correlated with less participation in social activities, which may be related to the degree of pulmonary function and disease state. Delayed puberty in CF was associated with poorer degree of ideal formation and less positive body attitude (398).

Table 7 summarizes studies with information on AH in CF (4,379,388,399-403). Interpretation of AH prognosis in CF from published studies is difficult given the fact that it is possible that mortality in some of the more severely affected individuals in adolescence may lead to more favorable AH of those studies with measurements conducted in adulthood. On the other hand, survival and treatment have also improved over the last few decades.

The existing literature of growth in CF suggests that nutritional issues and pulmonary exacerbations are not sufficient to explain the growth abnormalities in these children. There is now sufficient evidence to suggest that poor growth in CF is already seen in the neonatal period and that CF genotype (ΔF508) plays a contributing role. Whether this is due to underlying chronic inflammation or other unknown factors is yet to be determined. In adolescence, further worsening of growth and pubertal disorders may herald the onset of CF related diabetes and this requires early diagnosis and treatment, even though growth may not fully normalize with insulin therapy. The complex interplay between CF genotype, inflammation, nutritional and endocrine perturbations on growth requires further investigation. The impact of CF neonatal screening on improvement in long term growth outcome needs clarification.

7.3 Systemic abnormalities in GH/IGF-1 axis in children with CF

In CF, it is generally accepted that GH resistance also exists although studies of GH secretion is limited. Using arginine and clonidine as pharmacological stimulant of the GH axis in a small group of adolescents with CF, approximately 50% had peak GH levels < 6 mcg/|L and IGF-1 SDS -0.5, suggesting that relative GH resistance and GH insufficiency can occur. It was unclear if sex steroid priming was used in this group of children with delayed puberty as bone age was delayed at least by 2.5 years (404).

Low IGF-1 and IGFBP-3 have been previously reported in studies in children with CF and show associations with pulmonary outcomes. In a study of a group of prepubertal and pubertal children, IGF-1 SDS was -1.2 SD and IGFBP-3 SD was -0.7 during acute pulmonary exacerbation, although another study reported low IGF-1 with normal IGFBP-3 (365). IGF-1

correlated with forced expiratory volume 1 (FEV1) and forced vital capacity (FVC); whereas IGFBP-3 correlated with FVC. (405). In a group of prepubertal children with CF, systemic IGF-1 and bioavailability of IGF-1 correlated with serum TNF-α, providing further evidence to the role of inflammation on the GH-IGF axis in these children. Systemic IGF-1 showed an association with height in children with CF although the relationship is modest at best (366,406-408). In addition, systemic IGF-1 in CF may also be associated with weight, protein catabolism (408), lean body mass (409) and pulmonary function (405,410).

Other studies report abnormalities in IGF binding proteins with normal systemic IGF-1 in CF in particular significantly lower IGFBP-3 and higher IGFBP-1 (406). Reduction in bioavailability of IGF-1 due to abnormalities in IGF binding proteins could account for the growth failure in CF (366,411) or alternatively "normal" IGF-1 in the face of growth failure in CF could also point to IGF-1 resistance. The direct role of IGFP-1 on growth is unclear, although it shows an association with insulin secretion in CF, suggesting that IGFBP-1 may have a role in growth impairment via its effects on glucose homeostasis in CF (237). Changes in IGF-1 and bioavailability of IGF-1 also correlated with progressive insulin deficiency (412,413). Finally, IGFBP-2 has also been reported to be higher in CF compared to healthy controls. Change in IGFBP-2 was associated with changes in IL-6 over a 12 months period (366).

In summary, systemic evaluation of the GH-IGF axis in CF have produced mixed results. Low IGF-1 may be present in infants with CF within the first few weeks of life. The interlink of IGFBP-1 with insulin secretion and IGFBP-2 with inflammation may provide further insight into growth failure in CF, but comprehensive studies of the IGF axis and the contribution to linear growth are needed.

7.4 Efficacy of rhGH in CF

Clinical trials of the use of rhGH in CF have recently been evaluated in two systematic reviews including meta-analysis of published studies (414,415). Both reviews have included studies where height or growth rate were not reported as some of the published

studies have been powered to assess the effects of rhGH on metabolic consequences, body composition and disease parameters.

For this review, we have focused on studies of rhGH in CF with growth outcomes: Table 8 (416-421) and Table 9 (422-427). To date, there are 6 RCT of rhGH therapy on linear growth in children with CF. The longest duration of rhGH clinical trials in CF currently in the literature is 12 months. Change in Ht SDS with rhGH treatment over 12 months in CF range from +0.2 to +0.6. The majority of published trials in CF have used rhGH at a dose of 0.3 mg/kg/wk. One RCT consisted of two treatment groups; a lower dose rhGH at 0.273mg/kg/wk and a higher dose rhGH at 0.49 mg/kg/wk in comparison to a untreated group of controls (425). Both doses of rhGH in that study led to significantly better growth rate over a short term period of 6 months but there appears to be a dose dependency of rhGH dose on linear growth. It is worth noting that current clinical studies have excluded individuals with CF who have abnormalities of glucose homeostasis/ CF related diabetes and those who are colonized with Burkholderia cepacia. These reflect a sub-group of individuals who may be more severely affected who may be more likely to present with growth failure in the clinical practice to pediatric endocrinologists. It is therefore possible that rhGH may be less effective in these individuals and care must be taken in extrapolating results of current clinical trials of rhGH in CF when faced with clinical decisions of the role of rhGH in such individuals.

The three largest RCT of rhGH in CF all show that HV is approximately 150% higher in the rhGH treated group compared with control/placebo (422,424,425). In the study by Schnabel et al including two doses of rhGH, the “lower” dose of rhGH was comparable to the dose used by Hardin et al (424) and Stavley et al (422). In that study, height velocity in the group treated with the “higher” dose of rhGH of 0.49 mg/kg/week was approximately 180% higher than the control group; whereas height velocity in the group treated with the “lower” dose of 0.273 mg/kg/wk was approximately 150% higher than the control group (425)

The individuals included in the RCT by Schnabel et al (425) were in mid adolescents as the inclusion criteria was bone age of 8-18 years, whereas the studies by Hardin et al (424) and Stalvey et al (422) were younger, pre pubertal at baseline. Pubertal progression was

reported by Stalvey et al (422) and did not differ between the rhGH and control group. Hardin et al (424) and Schnabel et al (425) reported no progression in bone age over the treatment period. No individual trial has reported response to rhGH depending on pubertal staging. In the meta-analysis of pooled data by Phung OJ et al (414), prepubertal children appeared to have greater increase in HV compared to pubertal children, whereas pubertal children appear to have better weight gain than prepubertal children with CF treated with rhGH. In the trial by Hardin et al a sub-analysis of change in Ht SDS was similar in those with Ht SDS < -2.2 and those with Ht SDS > -1.2 (424).

Short term studies of up to 12 months in children and adolescents with CF, show improvement in Ht SDS of +0.2 to +0.6 SD. However, none of the clinical trials have included older adolescents with CF related diabetes and therefore the efficacy of rhGH in these adolescents is unknown. Given the information that suggests that children with CF are already shorter at birth and in infancy with low IGF-1 levels, there is a case to consider future clinical trials of rhGH in younger children. Children with the ΔF508 genotype should also be targeted for future rhGH studies given the strong link with growth failure in those with the genotype. Compared with JIA and IBD, published trials of rhGH in CF have included relatively large number of subjects but duration of follow-up is only 6-12 months. Conducting clinical trials in these individuals can be challenging given the rest of the burden of clinical care of CF and quality of life measures should be evaluated in future studies.

7.5 Factors affecting growth response to rhGH in CF

7.5.1 Disease and glucocorticoid

Clinical studies of rhGH in CF have not related clinical outcome, pulmonary function or GC use with responsiveness to rhGH therapy.

7.5.2 Systemic IGF-1

In CF, pooled data from subjects previously enrolled in clinical trials of rhGH revealed that IGF-1 was significantly correlated with height and growth rate (408).

7.6 Efficacy of rhGH on disease process in CF

A role of rhGH in improvement of pulmonary disease in CF has been postulated to be due to increase in absolute lung volume as a result of increased growth. Another mechanism could be due to improvement in lean body mass via the potential anabolic effect of rhGH. In individuals with CF, the ability of alveolar macrophages to kill Pseudomonas aueroginosa was reduced compared with healthy controls and this was associated with reduction in lower IGF-1 levels from broncho-alveolar lavage. Exposure of the macrophages to IGF-1 enhanced their ability to kill Pseudomonas suggesting that the GH-IGF axis may have a role in regulation of the immune system in CF (428). Preliminary evidence also suggest that IGF-1 may increase cystic fibrosis transmembrane conductance regulator which is defective in individuals with CF, leading to altered airway composition and therefore pulmonary infections (429).

In CF, several rhGH studies have shown a reduction in number of days of hospitalization and the use of intravenous antibiotics (424,427). These are from studies which did not include a placebo group. Current rhGH studies in CF have shown differing results on objective measures of pulmonary function. One study noted significant improvement in exercise tolerance measured by peak power output and VO2 max on cycle ergometer in the rhGH treated children (426). Another rhGH study in a group of children and young adults with CF (10-23 years) showed that maximal work load and VO2 max increased significantly with rhGH therapy over 12 months (430). In randomized studies in CF, FVC and percentage predicted FVC increased significantly in the rhGH group. FEV1 on the other hand increased significantly in rhGH treated children but not percentage predicted FEV1.

It is generally accepted that pulmonary function should be reported as percentage predicted (normalized to height). It is possible that improvement in pulmonary function may not parallel improvement in height in the short term and that objective improvement in lung function may happen later. In addition, a very short child with poor lung function may have a relatively “normal” percentage predicted values as his/her lung function has been matched to a younger shorter child, making interpretation of changes in pulmonary status in growth

promoting studies difficult. Future studies should include newer methods of assessing pulmonary disease in CF which are more sensitive to short term changes in respiratory status and may not be related to body size.

8. Side effects of rhGH therapy in chronic disease

8.1 Glucose tolerance and insulin sensitivity

rhGH treatment has been reported to be associated with a decrease in insulin sensitivity in some of the studies in children Turner syndrome (431,432), Prader Willi Syndrome (433,434), small for gestational age (435) and idiopathic short stature (436). It may also be associated with an increased risk of type 2 diabetes mellitus in children with risk factors such as Turner Syndrome, Prader Willi Syndrome (437). Some of these conditions themselves have an increased risk of reduction insulin sensitivity.

Children with inflammatory conditions may also be at risk of developing insulin resistance as a result of the inflammatory process (438) as well as the use of concurrent GC therapy (439). Approximately 50% of children with chronic rheumatic conditions on GC had impaired glucose tolerance on oral glucose tolerance test (OGTT) (255) In JIA, rhGH is associated with reduction in insulin sensitivity, reflected by increased fasting and stimulated insulin levels (261,263,268). In 43 children with JIA who had previously been treated with rhGH, impaired glucose tolerance was observed in 37% and transient diabetes mellitus in 5%. There was a higher incidence of impaired glucose tolerance in those who were treated late possibly reflecting a longer duration of disease and greater exposure to exogenous glucocorticoid. The two cases that developed frank diabetes were also overweight (440) .

In children with IBD, therapy with rhGH over a six months period led to increase in fasting insulin with no abnormalities of glucose homeostasis. This cohort consisted of the majority of individuals who have not been previously treated with GC. Despite the fact that fasting insulin levels increased following rhGH therapy in IBD, the clinical significance of this is still unclear. The highest level of fasting insulin was 16 mU/L in a group of individuals in mid and late adolescence (351). A recent consensus suggests that the threshold of fasting

insulin for diagnosis of insulin resistance should be a level of ≥ 30 mU/L for those in tanner stage 3 and 4; and ≥ 20 mU/L for those individuals in tanner stage 5 (441).

As mentioned previously, current clinical trials in CF have included individuals with no abnormalities in glucose homeostasis and/or CF related diabetes. The impact of rhGH treatment on glucose homeostasis in a child with CF and established diabetes is unknown. In current clinical trials in CF, rhGH increases fasting glucose but there were no changes in post prandial or peak glucose with OGTT. Increased fasting glucose was not seen in shorter term rhGH studies (6 months). OGTT results were only available from short term 6 months studies. HbA1C also did not change with rhGH therapy (414). However, given the glucose variability in CF related diabetes, future studies should evaluate glucose homeostasis using continuous glucose monitoring, which is increasingly recommended for diagnosis of CF related diabetes (25,442).

To summarize this section, studies of the use of rhGH in children with chronic disease treated with GC (JIA studies) show that its use may lead to impaired glucose tolerance and type 2 diabetes in approximately 50% and 5% of treated individuals, respectively. In published rhGH trials in IBD and CF, where use of GC is low, reduction in insulin sensitivity is seen but no diabetes mellitus have been reported, although duration of rhGH treatment in those studies are relatively short. The clinical significance of raised insulin especially in the prepubertal child during rhGH treatment on long term metabolic outcome in these children is unclear. The extent by which rhGH therapy can affect glucose homeostasis in individuals with CF and established diabetes needs further exploration.

8.2 Skeletal complications

Skeletal complications such as scoliosis (443), Legg-Calve-Perthes disease (444,445), slipped capital femoral epiphysis (446,447) and osteochondirtis (448) have been described in children following commencement of rhGH therapy but systematic surveillance of the spine especially in rhGH trials in children with chronic inflammatory disease has not taken place. In one study, lumbar lordosis and scoliosis developed in similar numbers of rhGH and control

subjects (5 in each group) with JIA (39). Only one patient with JIA treated with rhGH developed hip osteochondritis (263); whereas there are no reports of Legg-Calve-Perthes disease in JIA or IBD. Slipped upper femoral epiphyses have never been reported in this group of patients.

There is a concern that the use of higher doses of rhGH may advance bone age and accelerate pubertal progression but this has not been observed in children with JIA and IBD (39,351). Age of onset of puberty in children with JIA with follow-up data at final adult height did not differ between the rhGH and control group (39)

8.3 Disease complications

The current published trials in children with chronic disease do not raise concerns about rhGH worsening disease process. Previous studies in GHD and non GHD children following rhGH injections suggest that the immune system may be activated although it is unclear if the net effect is an up regulation or down regulation of inflammatory cytokines (354-358). Six months therapy with rhGH was not associated with any significant changes in a range of pro- and anti-inflammatory cytokines in children with IBD (Ref).

Intestinal fibrosis leading to strictures is a complication of CD, due to an excessive, irreversible healing response to chronic inflammation. This is associated with overgrowth of the muscularis mucosa, muscularis propria, excessive collagen deposition (449) and mesenchymal cell hyperplasia (450). In a rat model of colitis, rhGH was reported to stimulate collagen accumulation in intestinal myofibroblasts (451) but rhGH has also been reported to reduce the severity of fibrosis via the induction of suppressor of cytokine signaling proteins (452). There is a need to study this further especially when rhGH is administered in IBD.

8.4 IGF-1 levels and cancer

The use of replacement rhGH therapy for GH deficiency in children previously treated for childhood cancer has not been shown to be associated with tumor recurrence or development of new tumors. The Childhood Cancer Survival Study (CCSS) identified an

increased risk of meningioma in children treated with rhGH (453,454), although most of those children had also received radiation to the brain which by itself could be associated with the development of meningioma (453,454). In addition, the CCSS did not match rhGH treated patients with rhGH naive patients matched for potential confounders for development of second tumors. A recent study that matched for age, site of primary diagnosis, date of radiotherapy, radiation dose and fractionation found no increased risk of tumor recurrence or development of second tumors in rhGH treated patients (455).

An association between increased risks of malignancies has been reported in children with JIA (456-458) and IBD (459,460) which may seem to be unrelated to treatment with immunomodulators and biologic therapy. Currently there are no reported associations between cancer in children with JIA and IBD treated with rhGH. Patients with acromegaly with excessively high GH and IGF-1 levels have an increased risk for thyroid, breast and colorectal carcinoma (461-463) . Preliminary evidence also suggests that patients with IGF-1 deficiency due to genetic mutations in the GH receptor with very low/undetectable IGF-1 levels appear to be protected from cancer development (464).

In JIA and IBD, rhGH leads to an increase in IGF-1 and IGFBP-3 levels. Bechtold et al's RCT of rhGH (0.33 mg/kg/wk) in JIA showed, reassuringly, that IGF-1 and IGFBP-3 remained within the normal reference ranges. Average IGF-1 SDS and average IGFBP-3 SDS during rhGH were -0.93 and -0.24, respectively (39). Following rhGH (0.53 mg/kg/wk) for active CD, IGF-1 SDS increased from -0.4 at baseline to +1.8 SD at 12 weeks and + 3.3 SD at 24 weeks. IGF-1 SDS was as high as +5SD at 24 weeks which is an issue to be of concern (350) .

Even if systemic IGF-1 levels may not be excessively raised with relatively "high" dose rhGH in children with chronic disease, there is the concern that systemic IGF-1 levels may not reflect local expression of IGF-1 (465) . Animal models of colitis treated with rhGH do not show increased expression of local IGF-1 (173,175). Suppressor of cytokine signaling 2 (SOCS2) which may be altered in chronic inflammation and which negatively regulates GH action, has been reported to limit intestinal GH action (466,467) . It is possible that this may

be a protective mechanism against high systemic IGF-1 (68,468). However, in the mouse model, the protective effect of SOCS2 on the intestines was only seen in older animals. Clearly, long term surveillance of rhGH treated patients with JIA, IBD and CF is crucial.

9. IGF-1 and combined GH / IGF-1 in chronic inflammatory disease

As discussed, GH mediates its effects on target tissues via direct and indirect effects (41). The direct effects of GH are those mediated via the GH receptor; indirect effects are mediated largely via GH related peptides like IGF-1 but also IGF binding proteins. Whilst systemic factors (GH and IGF-1) have independent effects on target organs like the growth plate, local IGF-1 levels may play a more important role in regulation of longitudinal growth.

Given the possibility of a state of functional GH resistance with resultant secondary IGF-1 insufficiency in chronic inflammation, rhIGF-1 maybe a therapeutic option for these children (469). The use of rhIGF1 in children with primary IGF-1 deficiency due to mutations in the GH receptor is effective in improving linear growth. As opposed to complete catch up growth that is seen in children with GH deficiency treated with rhGH, children with primary IGF-1 deficiency due to mutations in the GH receptor treated with long term rhIGF-1 still remain significantly short (470,471).

Whilst there are currently no studies of rhIGF-1 in children with JIA or IBD, one small randomized trial of rhIGF-1 (80 mcg/kg twice daily) compared with placebo, in 7 children with CF failed to show an effect on linear growth despite normalization of serum IGF-1. The study showed a reduction in insulin sensitivity with rhIGF-1 treatment. The dose of rhIGF-1 used in the study is within the recommended starting dose for children with primary IGF-1 deficiency. Doses up to 120 mcg/kg twice daily, can be used in those children (472). The lack of improvement of linear growth with conventional dose of rhIGF-1 in the study with CF may point to a degree of functional IGF-1 resistance. Therefore, higher doses of rhIGF-1 may be needed to be evaluated in future studies. The potential adverse effect of hypoglycemia, may preclude the use of higher dose of rhIGF-1.

Interestingly, systemic IGFBP-3 did not increase with rhIGF-1 in the study of children with CF. On the other hand, some but not all studies of rhGH in chronic inflammatory conditions have shown that IGFBP-3 can increase with rhGH treatment. rhIGF-1 may in fact reduce the level of IGFBP-3 and IGF-2 in children with idiopathic short stature (473). IGFBP-2 did increase with rhIGF-1 treatment in those children. There is also the theoretical possibility that rhIGF-1 administration may suppress endogenous GH secretion. In TNBS rats with colitis treated with rhIGF-1, there was a rise in IGF1 levels and improved linear growth linear growth, although growth rate was only 50% of those of control rats (138).

A trial of rhIGF1 in children with idiopathic short stature and "low" IGF1 who were approximately 7 years at baseline, also raised the concern that rhIGF-1 may accelerate skeletal maturation, which would be disadvantageous for adult height prognosis. Twelve children (14.1%) in the two rhIGF-1 arms (80 mcg/kg and 120 mcg/kg twice daily) as opposed to one (4.4%) in the control arm entered into puberty during the one year (473). This is in contrast to the use of higher dose of rhGH in idiopathic short stature which does not lead to increase in skeletal maturation and advancement of pubertal progression (474).

A pilot pharmacokinetic study of rh-IGF-1 at 120 mcg/kg/day in eight children with severe CD lead to significant increase in systemic IGF-1 with almost half the cohort reaching IGF-1 SDS > +2.0 (475). The authors developed a mathematical model that allows prediction of a dose of rhIGF1 that could be used to maintain systemic IGF-1 below +2.5 SD of the mean accounting for age, weight and PCDAI. Whether this mathematical model is valid over a longer period of time where changes like growth and puberty may play a greater role is unclear. In addition, given the fluctuating nature of CD, it is unclear how well the PCDAI may reflect disease activity in this model. A randomized trial of dose titration of rhGH based on systemic IGF-1 in children born small for gestational age show less favorable growth response, although IGF-1 levels remained in the physiological ranges in the dose titrated group (476) .

Given the importance of GH and IGF-1 in longitudinal growth, combined treatment with rhGH and rhIGF-1 may be more physiological and beneficial for growth. Reports of

combined use in humans show a higher serum concentration of IGF-1 in those who had combined therapy versus those who had IGF-1 alone, possibly related to the negative feedback effect of IGF-1 on pituitary GH secretion. A recent study in female rats, however showed that combined rhGH and rhIGF1 therapy did not lead to further improvement in linear growth despite an improvement in cortical bone mass (57). On the other hand, in an experimental rat model of uremia, combination therapy appears to be more effective than rhIGF-1 or rhGH alone as growth promoting therapy (477). The addition of rhGH to rhIGF-1 may reverse the insulin suppressive effects of the latter and may have anti-catabolic effects on protein synthesis and muscle mass in seven calorie restricted adults (478). Given the uncertainties of the efficacy of high dose rhGH in improving muscle mass in children with chronic inflammation thus far, combination therapy may confer advantages in that respect. Combining rhGH with rhIGF-1 may prevent the glucose lowering effect of IGF-1 (478). Up to 20% of children with idiopathic short stature treated with rhIGF1 120 mc/kg twice daily were hypoglycemic (478). The use of IGF-1 may itself counter the insulin- resistant state that may be induced by the use of high dose rhGH therapy in a group of children who may be insulin resistant due to their state of chronic inflammation as well as the use of GC.

Given the evidence of relative GH resistance in children with chronic inflammation, there is good biological rationale to explore the use of rhIGF1 on its own or in combination with rhGH in future well designed collaborative RCTs.

10. Summary and perspective

10.1 Clinical studies of growth and pubertal disorders

It is clear that clinical outome studies on growth, pubertal development and AH in JIA, IBD and CF treated with contemporary treatment regimens are needed. Height, especially AH, needs to be interpreted in the context of the child's midparental height. As degrees of delayed puberty can occur in these children, interpreting HV needs to be in the context of bone age or pubertal staging. The use of change in Ht SDS may be a better method of defining poor growth given the paucity of normative longitudinal data for HV. Ideally,

newer studies should consider reporting growth problems in these children by describing Ht SDS and change in Ht SDS or HV adjusted for bone age/puberty (372). Undoubtedly, studies of AH are needed from contemporary groups of children with chronic disease, due to the constantly changing landscape of therapies of chronic disease. Published data on AH may never be reflective of current cohort of individuals managed in the clinic, given the time it takes to acquire information on long term growth outcome and the possibility of new therapies.

Outstanding questions in the clinical aspect of growth and pubertal disorders include:

(1) What are the clinical predictors of persistent growth failure in children with chronic disease? Are there informative biomarkers eg disease parameters, inflammatory cytokines, genetic factors or novel biomarkers early on in the course of the disease?

(2) What are early predictors for catch-up growth following anti-cytokine therapy in JIA and IBD? What is the utility of systemic vs local markers of inflammation for prediction of growth response? Can composite assessment of systemic inflammation and systemic markers of the GH/IGF axis increase the prediction?

(3) How much does poor growth and pubertal disorders contribute to abnormal bone accrual and muscle development in children with chronic disease?

(4) What is the impact of poor growth, short stature and delayed puberty on the quality of life of adolescents with chronic disease and do they differ from children with no underlying chronic condition? Are adolescents with chronic disease more bothered about short stature/poor growth than delayed puberty?

10.2 Systemic abnormalities of GH/IGF-1 in chronic disease

This review identified a number of heterogenous studies of the GH/IGF-1 axis suggesting multiple defect in the secretion and sensitivity of the GH/IGF-1 axis. Studies have evaluated IGF-1 and IGFBP-3, although ALS have not been extensively studied in these conditions.

Important questions to be answered in this area include:

(1) How does inflammation impact on formation of the ternary complex and how does this change following therapy of chronic disease especially anti-cytokine?

(2) What is the link between inflammation and comprehensive studies of the ternary complex?

(3) The direct role of IGF binding proteins on long bone growth in chronic disease is unclear. We have touched on the possible role of IGFBP-1 and -2 which requires further clarification. A consideration of the differential effects of all the binding proteins in chronic disease is needed. For instance, is there compensatory changes in IGF binding proteins with chronic inflammation and what is the impact on regulation of growth in chronic disease?

(4) What is the IGF-1 response to rhGH injections as part of the IGF- generation test and how does this GH sensitivity change with disease factors?

10.3 Growth plate regulation in chronic disease

Recent growth plate studies have demonstrated that pro-inflammatory cytokines have a direct effect at the level of the growth plate. GC treatment and malnutrition can lead to impairment at the level of the growth plate.

Critical research questions to be answered in this area which may impact on clinical management and research include:

(1) How does cytokine, GC and malnutrition impact on local GH and IGF-1 signalling?

(2) How do intrinsic growth plate factors interact with extrinsic systemic factors in the regulation of growth in chronic disease?

(3) What is the role of IGF binding proteins at the local level in chronic disease?

(4) What is the interaction between FGF21 and cytokines and how may that impact on local bone growth/local growth factor signalling?

10.4 Endocrine growth promoting therapies in chronic disease

There is a need to perform larger, more conclusive studies of rhGH therapy which explore the issues raised in this review. Close collaboration with pediatric rheumatologists, gastroenterologists and respiratory clinicians would ensure that appropriate assessment of disease status is performed. Given the complexity of the management of children with chronic disease and ongoing burden of the disease, the opinion of the young person and their families should be sought in the design of future therapeutic trials of growth promoting therapies.

Disease activity should be assessed using a range of methods. For CD, caution is needed if the PCDAI is used. Data should be presented for the different domains of the PCDAI, if that is to be used as a disease marker. In CF, more objective assessment of disease should be evaluated in future studies other than hospitalizations. Evaluation of inflammatory state using inflammatory cytokines should include assessment of more than 1 cytokine and in addition measurements of cytokines at local organs (eg gastrointestinal tract, synovial fluid) may be more accurate but more challenging to obtain in research studies.

Research agenda to be considered include:

(1) A definitive trial of rhGH on improving growth in children with chronic disease especially in children with IBD is needed. This would require collaboration at a national level at the least.

(2) It is clear that a degree of functional GH insensitivity exists in chronic disease and a higher dose of rhGH may be needed. A study on dose comparison addressing longer term growth outcome and potential adverse events (abnormalities in glucose homeostasis) in these groups of children are needed. Preliminary evidence from the dose comparison trial of rhGH in CF suggest that the percentage increase in growth rate with the “higher” dose of rhGH leads to marginal improvement in growth velocity (425) .

(3) It is unclear whether the dose of rhGH should be titrated by systemic IGF-1 or growth response and this requires further research.

(4) It is possible that in most children a short course of therapy for 12 months or during periods of poor growth may be sufficient for improving growth and

prolonged therapy may not be necessary. Intermittent therapy with rhGH during periods of relatively poor growth may also be more cost effective. This method of using rhGH as opposed to continued use until final height needs further exploration.

(5) Future rhGH studies should also examine the effect of therapy on disease, bone health, body composition, cardiovascular health and quality of life in these children with chronic disease. It is also unclear if long term outcome of addition of rhGH to sex steroid confers better height prognosis in those groups of children who are growing slowly with delayed puberty.

(6) Given that some children with chronic disease continue to grow slowly with anti-cytokine therapy (18) and that improvement in height with anti-cytokine maybe marginal (21,219), the role of rhGH in addition to anti-cytokine therapy should also be explored in future studies

(7) The impact of pubertal induction on growth in chronic disease deserves higher research priority. There are numerous unanswered questions on the dose, duration, route of administration and timing of introduction of sex steroid in chronic disease.

(8) Given the relative GH resistant state in chronic inflammation, the role of combination therapy of rhIGF-1 with rhGH or rhIGF-1 on its own may need to be explored in future well designed trials.

(9) Given the range in deficits in systemic levels of GH/IGF-1 in chronic disease, can these be used to determine choice of growth promoting therapies ie rhGH, rhIGF-1 or combination therapies and therefore growth response?

11. Recommendations for clinical practise

In the absence of extensive data, the off label use of rhGH in chronic disease in countries where rhGH may be available needs to be considered very carefully and discussed thoroughly with the young person and the family. rhGH therapy should only be considered

after the primary disease has been treated as aggressively as possible, GC use has been minimized and the nutritional status has been optimized. In patients with delayed puberty, this should be addressed before the consideration of rhGH, although data on pubertal induction in these children is limited (479,480). If rhGH is used, the definition of response in children with chronic disease is unclear but may be better defined as change in Ht SDS (> +0.5 SD over twelve months).

It is our opinion that fasting glucose and HbA1C should be considered in all children with chronic disease prior to commencement of rhGH therapy. Ideally, an OGTT should be performed at baseline as well. Given the challenges in interpretation of insulin levels in groups of children who are in puberty, there is a case to omit its measurement in the clinical monitoring of children with chronic disease treated with rhGH therapy. It is our opinion that results from an OGTT may be more useful for clinical decision making and should therefore be perfomed at annual intervals following rhGH therapy as fasting glucose and HbA1C are poor predictors of abnormal glucose homeostasis in children with chronic disease treated with rhGH (Simon 2010). In CF, there may be a role of continuous glucose monitoring for monitoring of glucose homeostasis. In children with evidence of diabetes (eg CF diabetes) or impaired glucose tolerance at baseline, there needs to be careful discussion with the family regarding the risk and benefit of rhGH therapy. In our opinion, the detection of impaired glucose tolerance requires reconsideration of therapy. If oral GC dose can be reduced, we recommend close monitoring with earlier re-evaluation with OGTT. If this is not possible, or type 2 diabetes mellitus is diagnosed on OGTT, reduction of dose of rhGH is recommended, provided that grwth response is favourable.

Annual assessment of IGF-1 level should be undertaken but interpretation of IGF-1 levels needs to take into account of delayed puberty in these children. Regular assessment of puberty and annual bone age is also important. Care must be taken in the interpretation of bone age in children with inflammatory arthritis. Ideally, this should be performed in the hand not affected by arthritis.

12. Conclusion

The pathophysiology of growth failure in children with chronic inflammation is multi-factorial although the precise mechanism of the effects of cytokine, glucocorticoid and malnutrition on systemic and local growth factors is still unclear. The relative contribution of those factors on growth failure and the GH/IGF axis is unclear. Clinical studies in children with JIA, IBD and CF point to multiple levels of defect of the GH/IGF-1 axis although comprehensive evaluation of systemic growth factors in these children especially in relation to modern therapy is still limited. The interaction of the endocrine effects of the GH/IGF-1 axis with local growth plate regulating factors and the impact on linear growth in chronic disease is unclear and needs to be studied.

Although there is some preliminary evidence of the effects of rhGH on short term linear growth in children with chronic disease, catch-up growth maybe incomplete. Longer term treatment studies and its effects on adult height in these children should be performed. The impact of improvement in linear growth on quality of life in these children is unknown. The cost effectiveness and implication of treatment (burden of injections) needs careful consideration. Most children with chronic inflammatory disease will achieve their genetic potential with aggressive disease control and nutritional support. A small subgroup may have persistent growth failure leading to significant short stature and these children may benefit from adjuvant growth promoting therapy. Collaborative clinical trials and translational studies are needed and to be encouraged.

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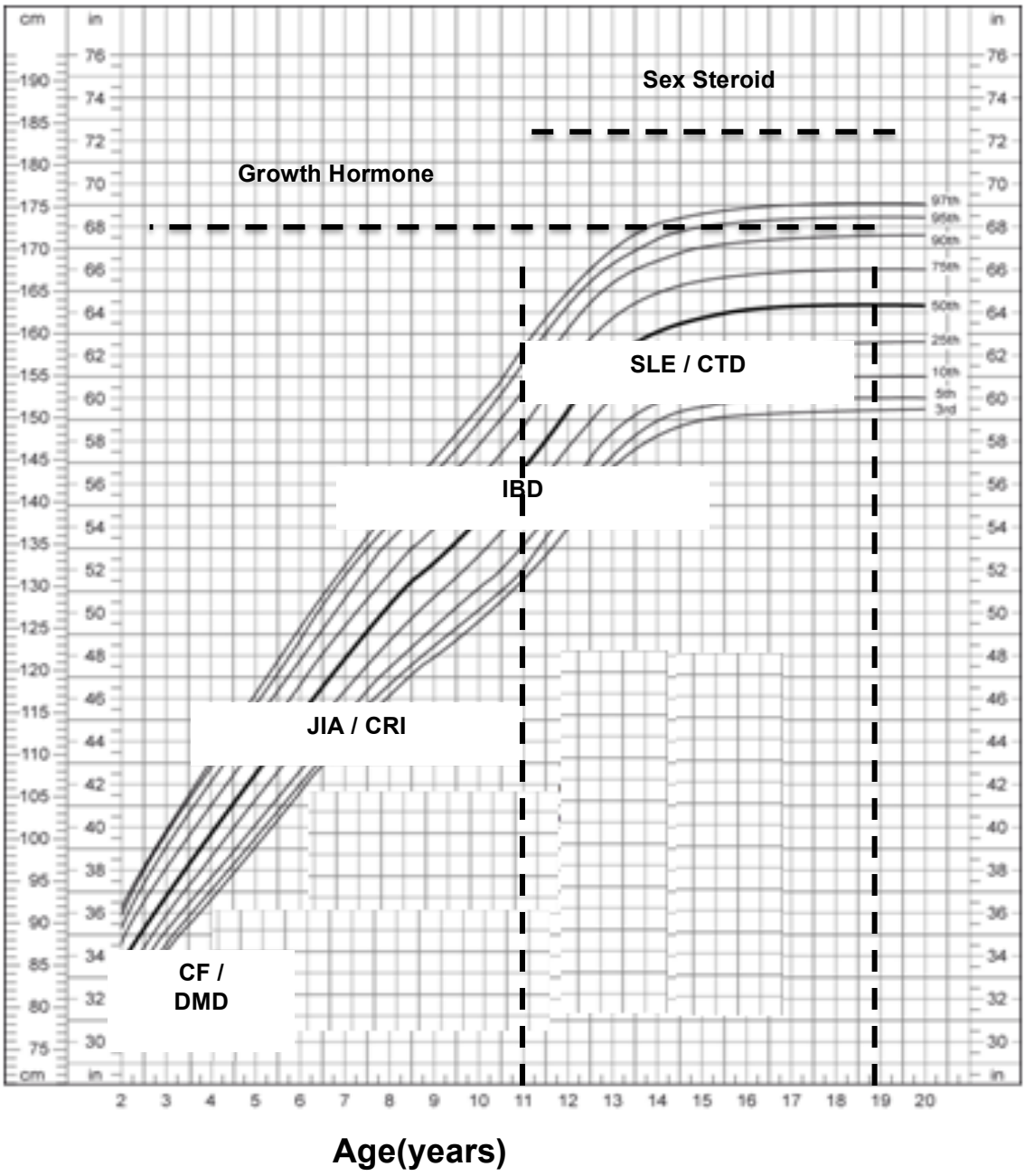
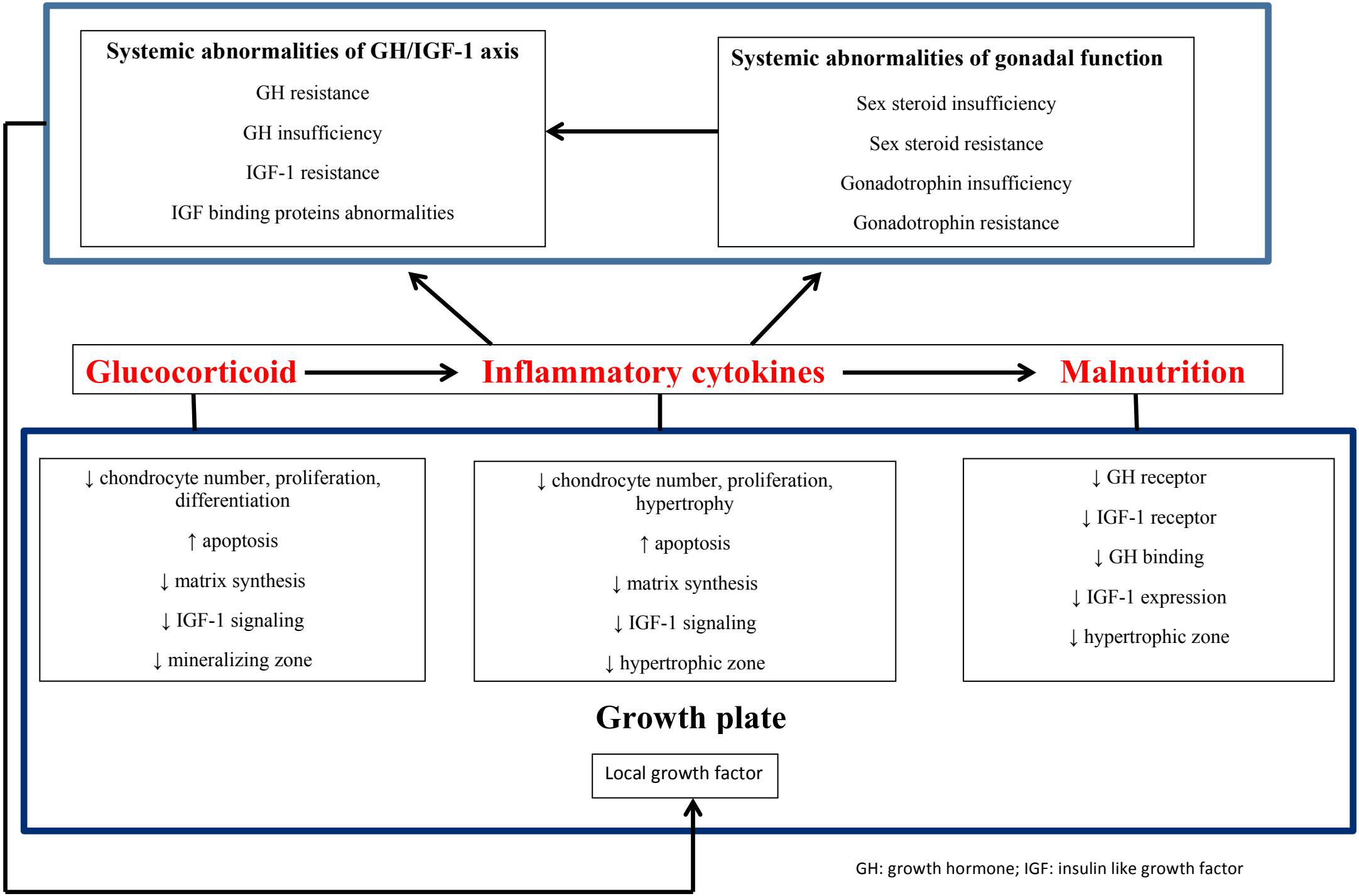


Figure 1: Age Of Presentation Of Chronic Disease In Childhood

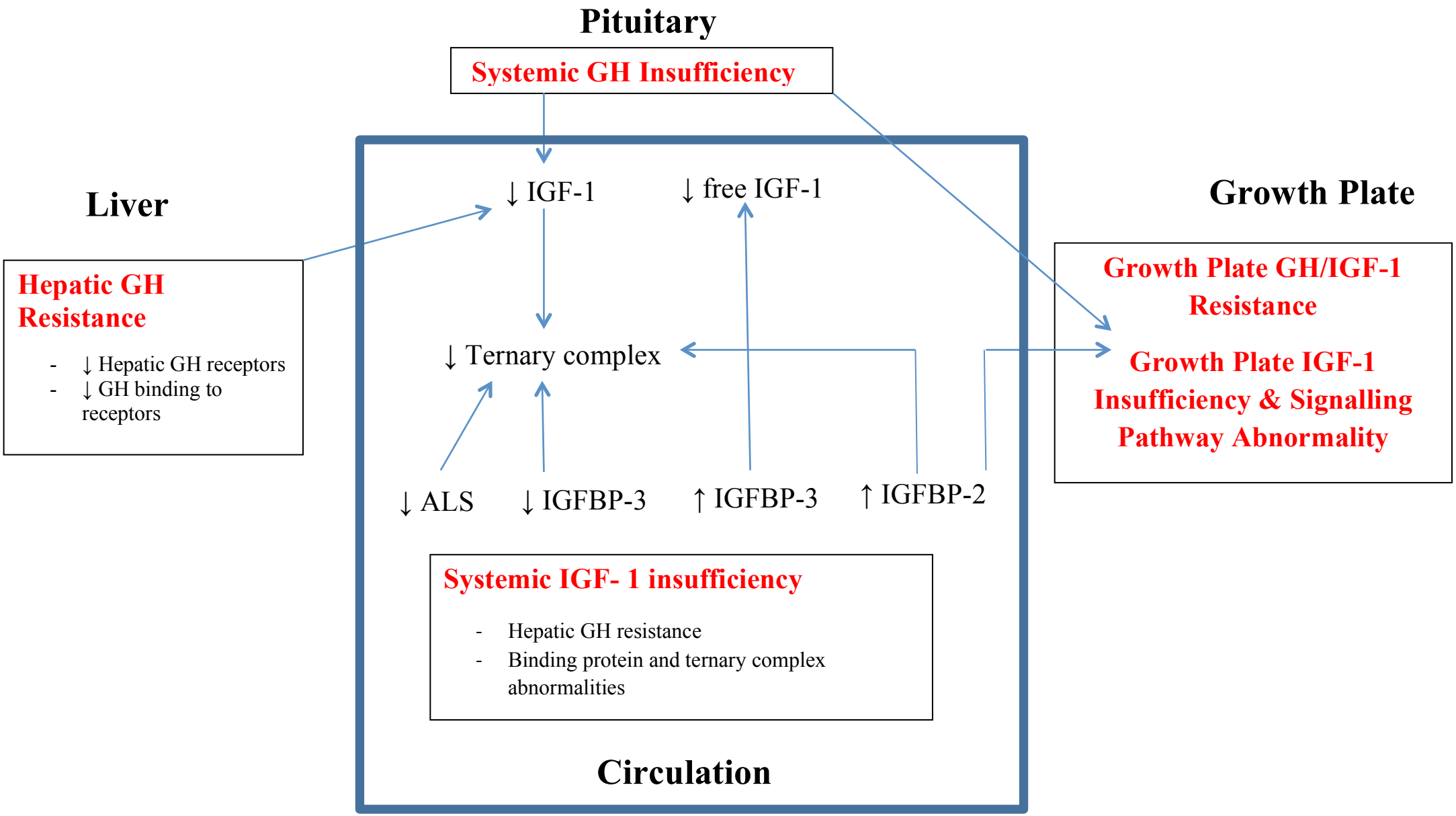
CF: cystic fibrosis, DMD: duchenne muscular dystrophy; JIA: juvenile idiopathic arthritis; CRI: chronic renal insufficiency; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; CTD: connective tissue diseases

Figure 2: Mechanism Of Growth Failure In Chronic Inflammatory Disease



GH: growth hormone; IGF: insulin like growth factor

Fig 3: Multiple Level Of Defect Of the GH/IGF-1 Axis In Children With Chronic Disease



GH: growth hormone; IGF-1: insulin like growth factor-1; IGFBP: insulin growth factor binding protein

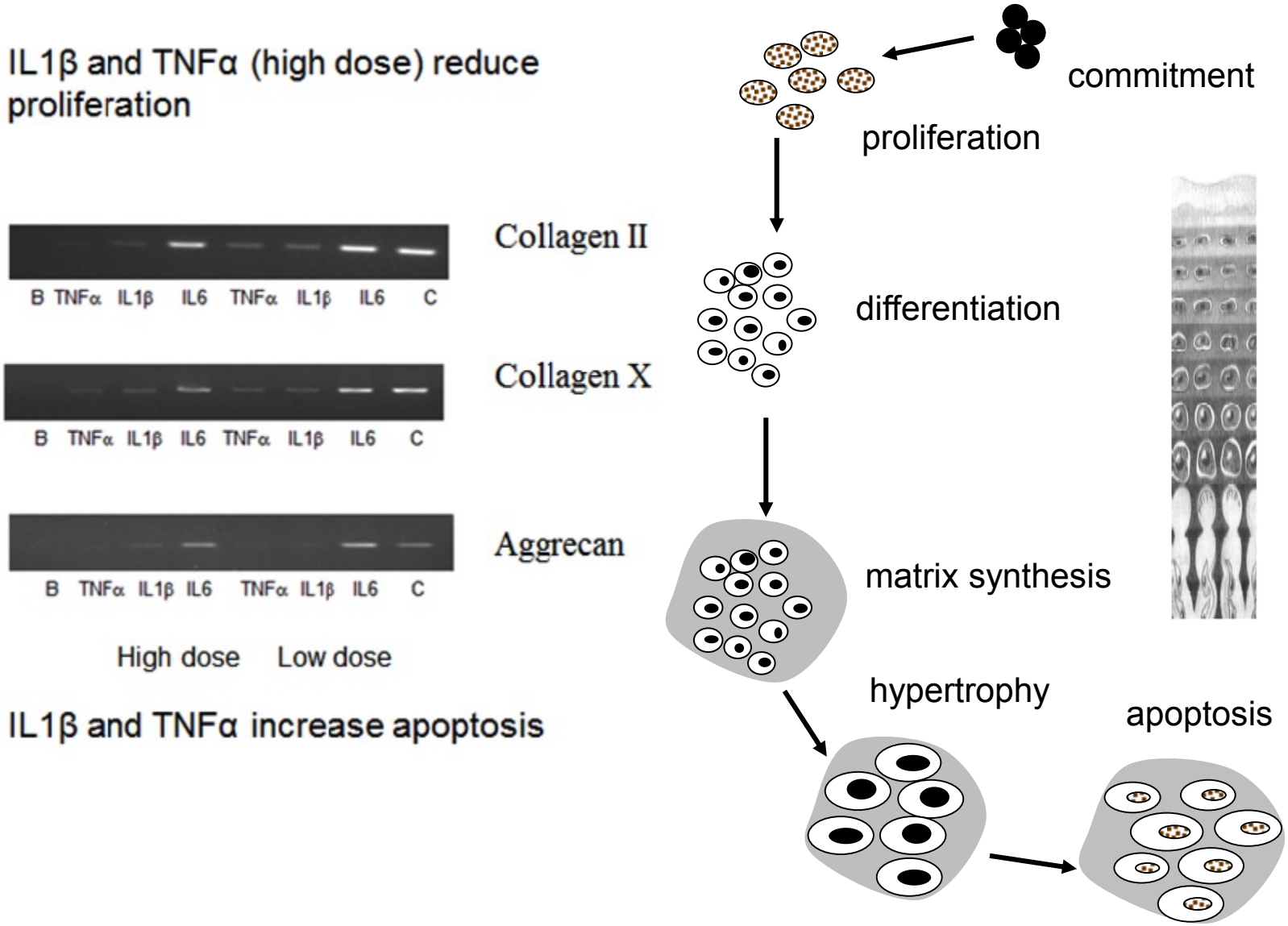
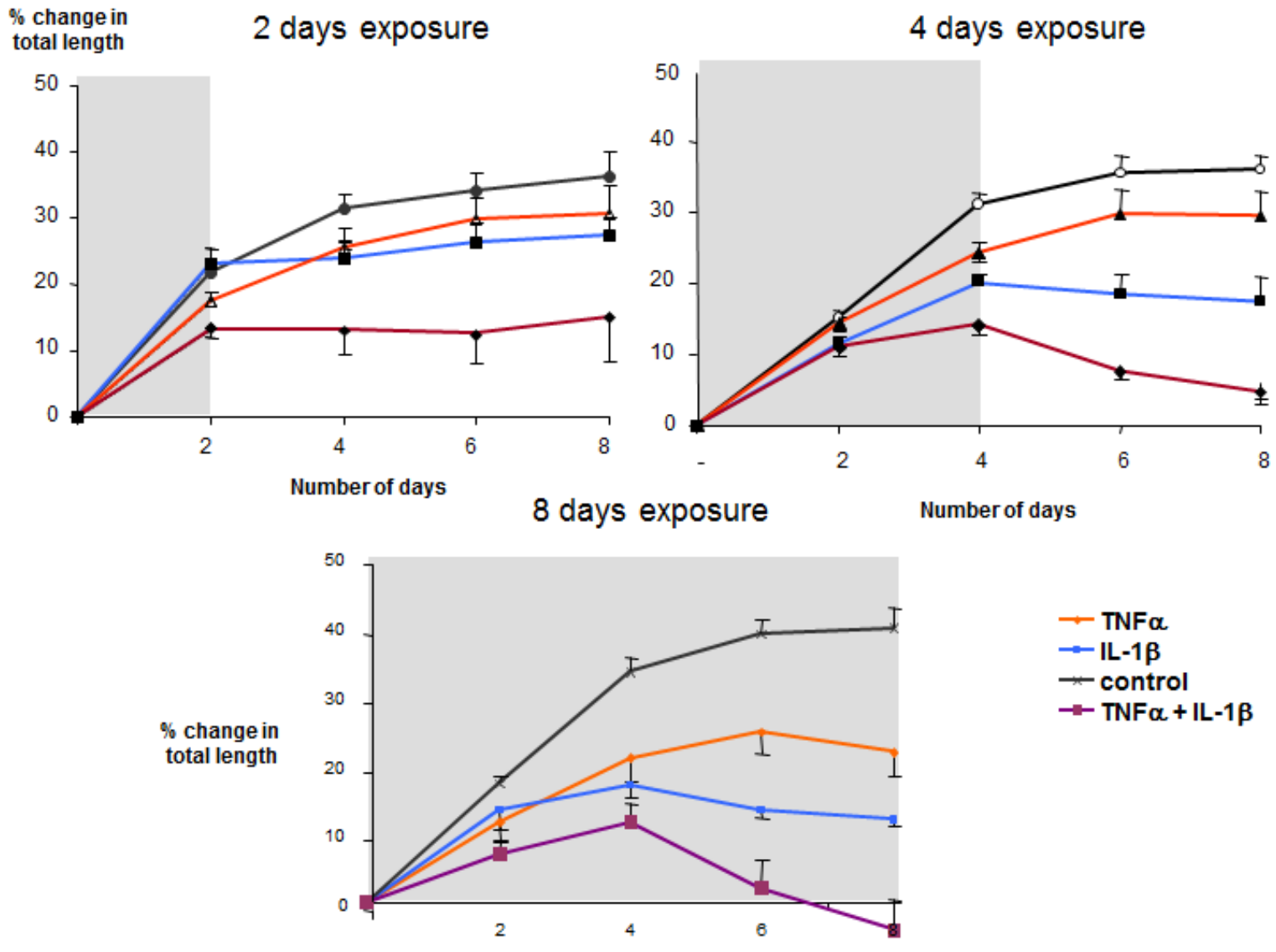


Figure 4: Effects Of TNFα And IL1β On ATDC5 Cell Line Chondrogenesis

MacRae VE et al J Endocrinol 2006; 189: 319-28 [71]



MacRae Ve et al J Endocrinol 2006; 189: 319-28 [71]

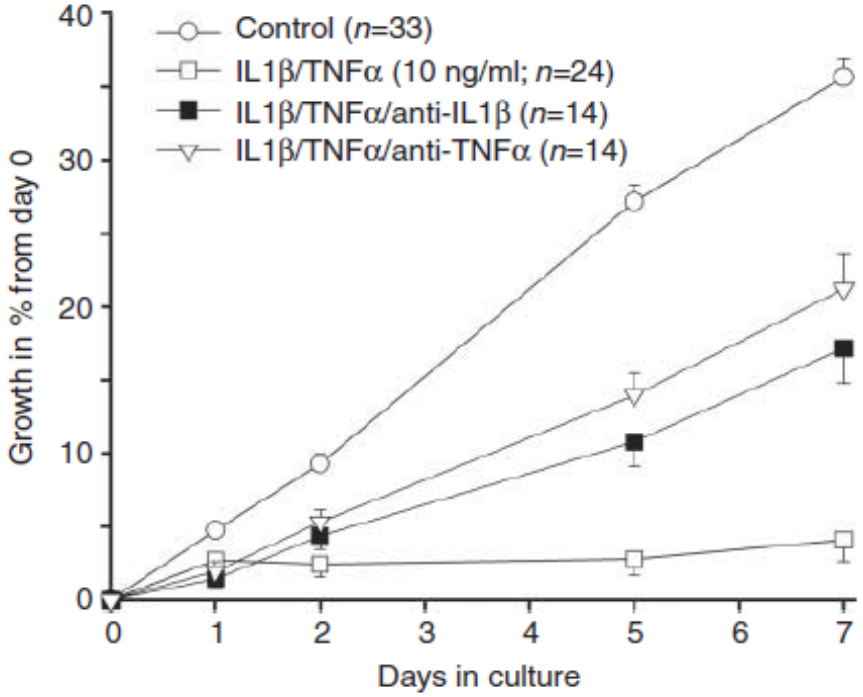


Figure 6a: Effects of addition of antibodies to metatarsals exposed to TNFα and IL1β

Martensson K et al J Bone MinerRes 2004; 19:1805-12 [73]

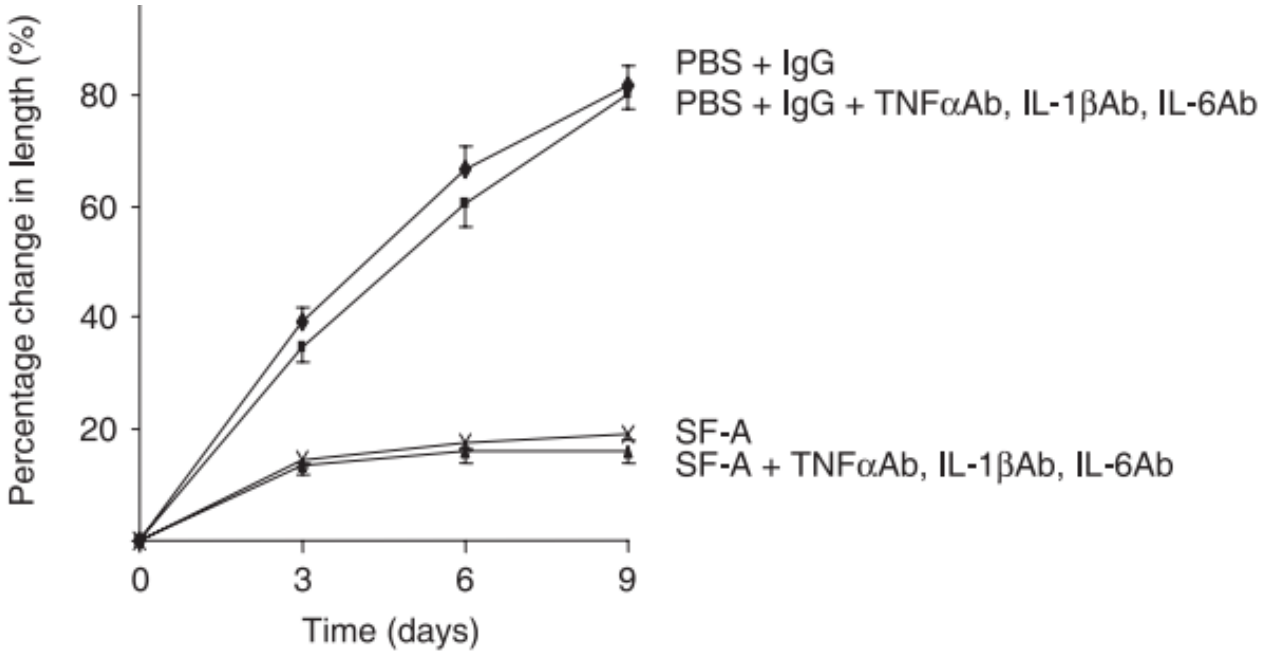


Figure 6b: Effects of addition of antibodies to metatarsals exposed to synovial fluid of a child with systemic JIA during acute relapse

MacRae VE et al Clin Endocrinol 2007; 67:442-8 [86]

PBS: phosphate buffered solution; SF-A: synovial fluid from child A; Ab: antibody

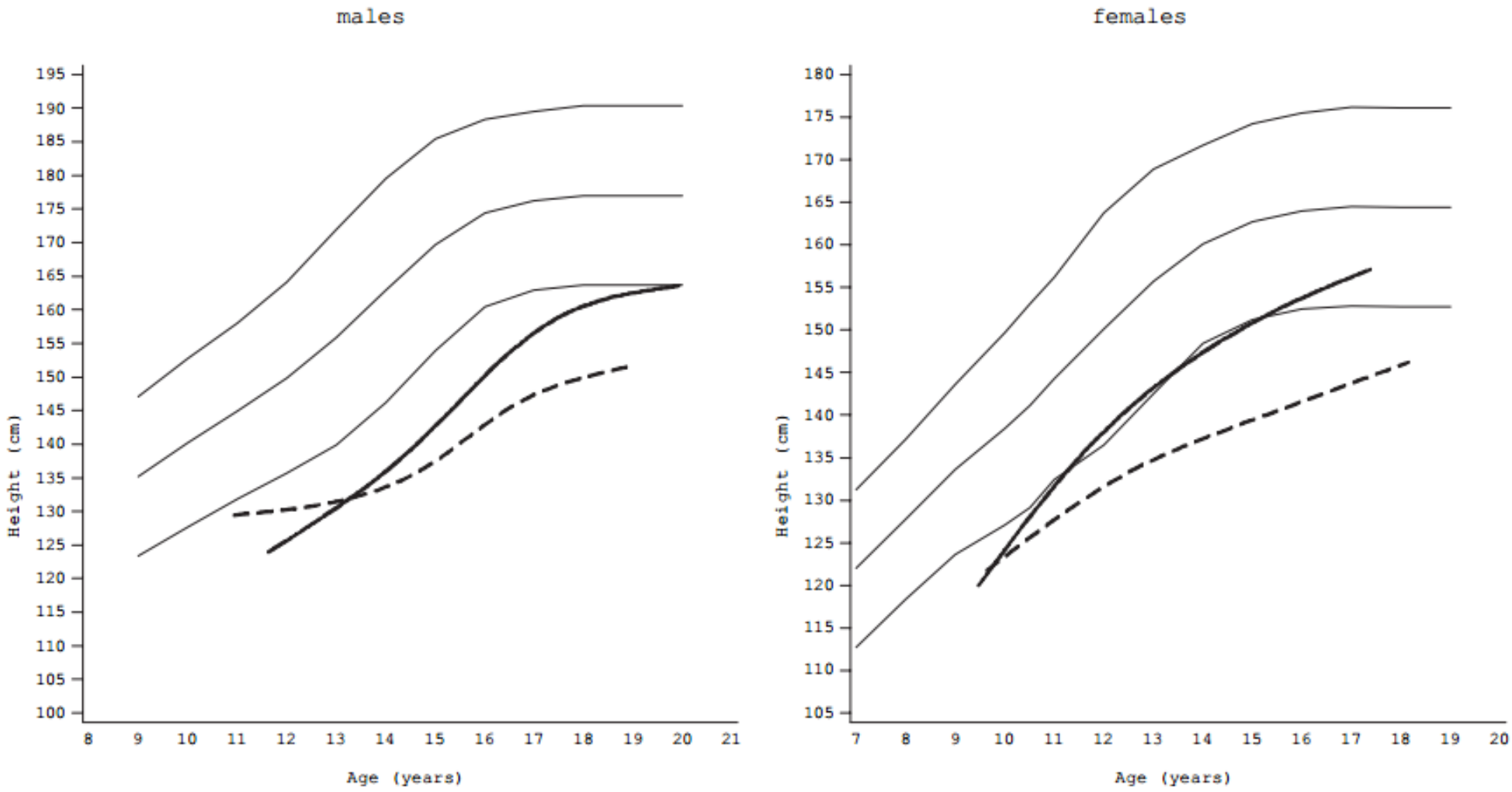


Figure 7: Synchronized mean growth curves from baseline to adult height in 13 children with JIA treated with rhGH (solid lines) in comparison with 18 controls (dashed lines)

Bechtold S et al J Clin Endocrinol Metab 2007; 92: 3013-8 [39]

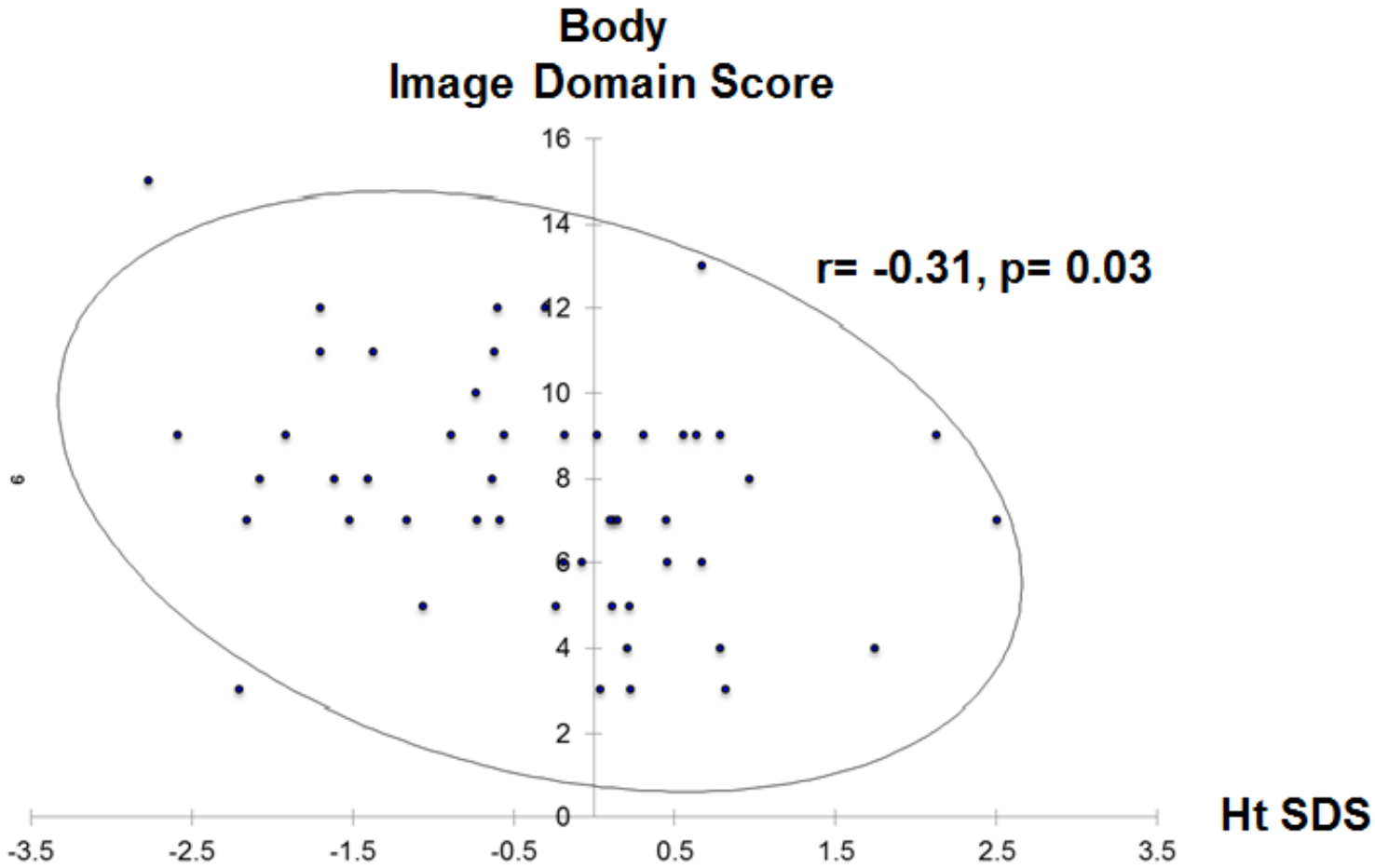


Figure 8: Height SDS In Children And Adolescent With IBD And Body Image Domain Score On IMPACT III Questionnaire

(Mason A et al Horm Res Pediatr 2014; 83:45-54)

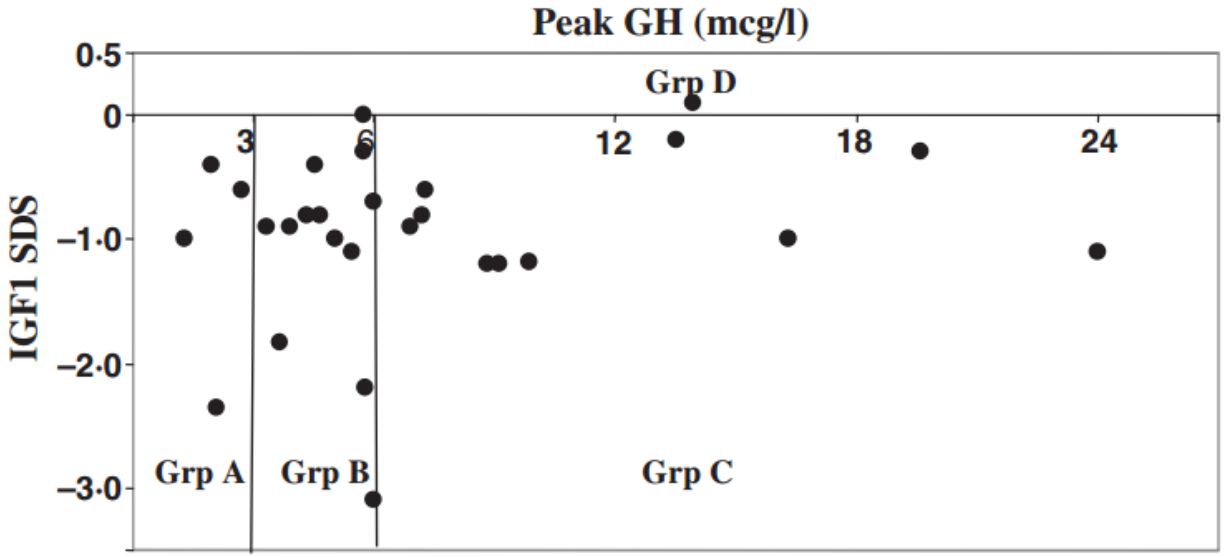


Figure 9: Peak Growth Hormone (GH) and Insulin-Like Growth Factor 1 (IGF1) To Insulin Tolerance Test (ITT) In Children With Inflammatory Bowel Disease (IBD).

IGF1: insulin-like growth factor 1, GH: growth hormone, SDS: standard deviation score.

Grp A: Peak GH < 3 mcg/l, IGF1 SDS < 0 (Functional GH deficiency).

Grp B: Peak GH < 6 mcg/l but ≥3 mcg/l, IGF1 SDS < 0 (Functional GH insufficiency).

Grp C: Peak GH ≥ 6 mcg/l, IGF1 SDS < 0 (Functional GH resistance).

Grp D: IGF1 SDS ≥ 0 (Functional GH-IGF1 resistance).

Wong SC et al Clin Endocrinol 2011; 74: 599-607 [338]

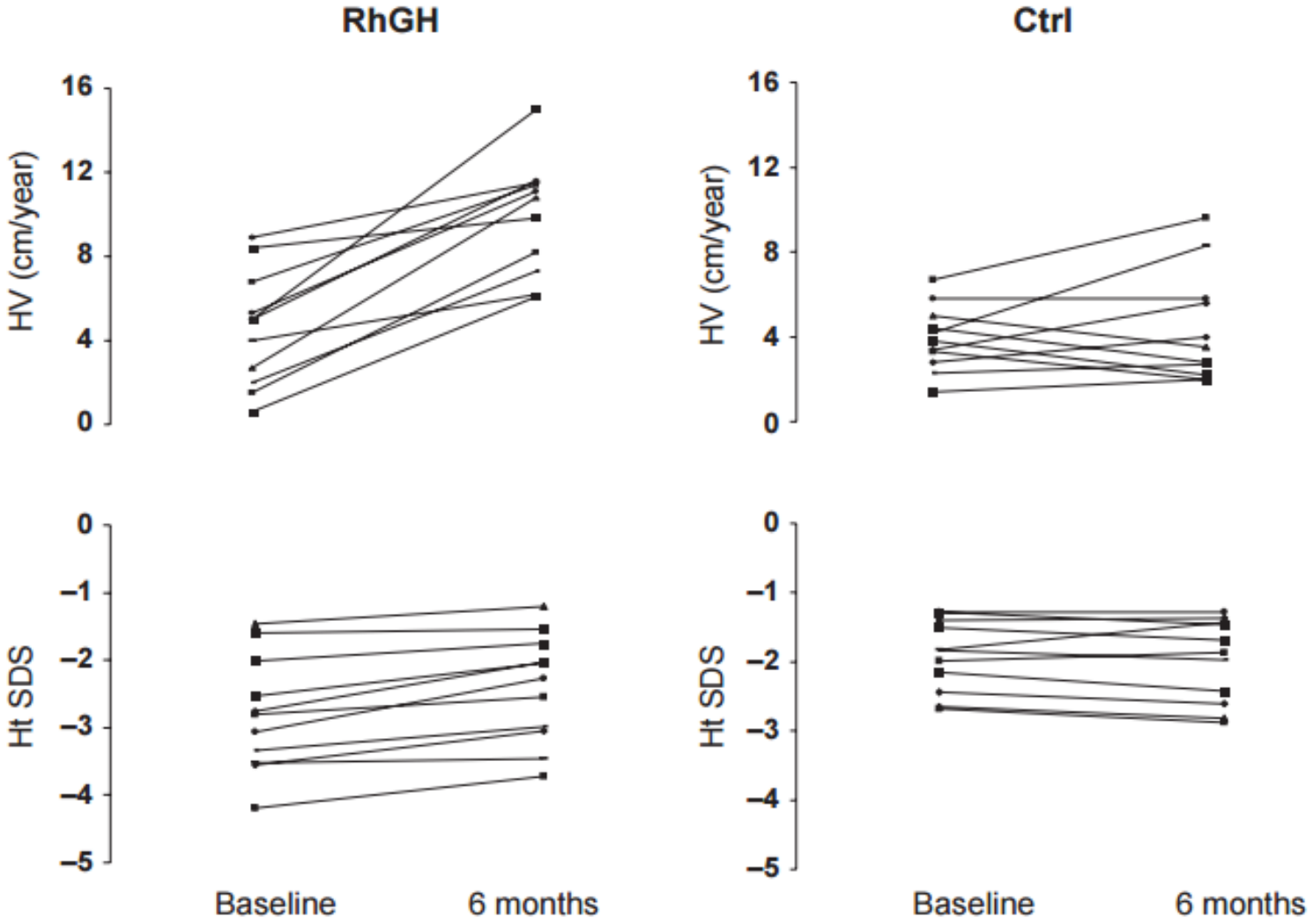


Figure 10: Height velocity (HV) and height SDS before and after 6 months of therapy with recombinant human growth hormone (rhGH) or no therapy (Ctrl) in inflammatory bowel disease.

HV: $P = 0{\cdot}003$ (rhGH – baseline *vs*6 months), $P = 0{\cdot}58$ (Ctrl – baseline *vs* 6 months) Ht SDS: $P = 0{\cdot}003$ (rhGH – baseline *vs* 6 months),$P = 0{\cdot}14$ (Ctrl – baseline *vs* 6 months).

Wong SC et al Clin Endocrinol 2011; 74:599-607 [351]

	No patients	Age at assessment	Adult height result	Deviation from mid-parental height
Gare et al (1995) [232]	124 (33 oligo, 58 poly, 2 systemic, 30 others)	18 yrs	Females 165.9 cm, males 176.9 cm	ND
Zak et al (1999) [233]	65 (21 oligo, 39 poly, 5 systemic)	26 yr	Ht SDS -0.3 (11% Ht SDS < -2.0)	ND
Minden et al (2002) [195]	215 (85 oligo, 30 poly, 30 systemic, 30 others)	23 yrs	Females 166 cm, males 179 cm	ND
Packham et al (2002) [236]	259 (70 oligo, 78 poly, 52 systemic, 61 others)	28 yrs	Ht SDS females -1.1 Ht SDS males -0.7	ND
Wang et al (2002) [234]	33 (7 oligo, 18 poly, 8 systemic)	20 yrs	Infrequent GC 165.6 cm Intermittent GC 165.8 cm Prolonged GC 147.6 cm	Infrequent GC +3.0 cm above MPH Intermittent GC +1.0 cm above MPH Prolonged GC -12.0 cm from MPH
Simon D et al (2002) [204]	24 systemic	25 yrs	Ht SDS -2.0 41% Ht SDS < -2.0	-1.7 SD below MPH SDS (87% below MPH SDS)
Minden et al (2009) [235]	141 JIA	18 ys	Females 165 cm, males 176 cm Female poly Ht SDS -0.5 Males poly Ht SDS -0.6 Females systemic Ht SDS -0.5 Males systemic Ht SDS -2.1	ND

Table 1: Published Studies Of Adult Height In Childhood Onset Juvenile Idiopathic Arthritis

JIA: juvenile idiopathic arthritis; Ht: height; cm: centimeter; SDS: standard deviation score; ND: no details; GC: glucocorticoid; MPH: mid-parental height

	Study design	No patients	Duration (yrs)	rhGH dose (mg/kg/wk)	Age baseline (yrs)	HV baseline (cm/yr)	HV follow-up (cm/yr)	% change HV	Ht SDS baseline	Ht SDS follow-up	Change Ht SDS
Butenandt et al (1979) [256]	Retrospective	20	Variable	0.18	13.0	2.7	6.2 (1st yr)	130%	-	-	-
Svantesson et al (1991) [259]	Retrospective	6	Variable	0.16-0.46	13.7	2.8	6.7 (1st yr)	139%	-3.4	-	-
Davies et al (1994) [257] (1997) [244]	Prospective	10 low dose 10 high dose	1.0	0.15 0.30	9.2 10.6	2.4 2.0	4.5 6.1	88% 205%	-3.0 -3.4	-	-
Touati et al (1998) [260]	Prospective	14	1.0	0.46	10.8	1.9	5.4	184%	-4.3	-4.3	0
Al-Mutair et al (2000) [254]	Retrospective	10	Variable	0.16-0.30	11.9	2.5	4.8 (1st yr) 5.4 (2nd yr)	92% 116%	-	-	-
Simon et al (2003) [258]	Prospective	14	3.0	0.46	12.5	2.0	6.0 (1st yr) 5.0 (2nd yr) 4.1 (3rd yr	200% 150% 105%	-4.6	-4.5 (1st yr) -4.3 (2nd yr) -4.3 (3r yr)	+0.1 +0.3 +0.3
Bechtold et al (2004) [255]	Prospective	11	4.0	0.25-0.33	10.3	-	-	-	-3.9	-2.1	+1.8

Table 2: Published Non Randomized Studies Of Recombinant Human Growth Hormone On Linear Growth In Children With Juvenile Idiopathic Arthritis

yrs; years; rhGH: recombinant hman growth hormone; mg: milligram; kg: kilogram; wk: week; cm; centimetre; HV: height velocity; Ht: height; SDS: standard deviation score

	Study design	No patients	Duration (yrs)	rhGH dose (mg/kg/wk)	Age baseline (yrs)	HV baseline	HV follow-up	% change HV	Ht SDS baseline	Ht SDS follow-up	Change Ht SDS
Bechtold et al (2001) [266]	RCT	14 rhGH 5 rhGH (GHD) 16 Ctrl	2.0	0.33 0.16	9.7 10.5 7.8	-2.9 SD -3.1 SD -3.2 D	+0.3 SD -0.5 SD -1.2 SD	-	-3.7 -2.6 -2.9	-2.9 -2.4 -3.2	+0.8 +0.2 -0.3
Bechtold et al (2003) [265]	RCT	18 rhGH (9GHD)	4.0	0.33 (0.20 for GHD)	10.5	2.4 cm/yr	4.7 cm/yr	96%	-3.3	-2.3	+1.0
		20 Ctrl			9.6	2.3 cm/yr	3.4 cm/yr	48%	-2.3	-3.0	-0.7
Saha et al (2004) [250]	RCT (Cross-over trial rhGH vs placebo)	24	0.5	0.23	9.0	-	+2.0 SD (rhGH) -0.1 SD (placebo)	-	-2.1 -2.2	-1.9 -2.0	+0.2 +0.2
Grote et al (2006) [267]	RCT	10 rhGH 7 Ctrl	2.0	0.32	8.0 8.1	-	-	-	-1.4 -1.9	-1.0 -2.1	+0.4 -0.2
Simon et al (2007) [268]	RCT	15 rhGH 15 Ctrl	3.0	0.47	5.6 5.7	2.7 cm/yr 2.6 cm/yr	6.5 cm/yr 5.0 cm/yr	141% 85%	-1.1 -1.0	-0.4 -1.8	+0.7 -0.8
Bechtold et al (2007) [39]	RCT	13 rhGH 18 Ctrl	13.7 14.4	0.33	4.8 4.0	-2.2 SD -2.6 SD	-	-	-2.7 -3.5	-1.6 -3.4	+1.1 +0.1

Table 3: Published Randomized Trials Of Recombinant Human Growth Hormone On Linear Growth In Children With Juvenile Idiopathic Arthritis

RCT: randomized controlled trials; yrs; years; rhGH: recombinant hman growth hormone; mg: milligram; kg: kilogram; wk: week; cm; centimetre; HV: height velocity; Ht: height; SDS: standard deviation score

	No patients	Age at assessment	Adult height result	Deviation from mid-parental height
Castile et al (1980) [316]	177 CD	23 yrs	Medically managed Ht SDS -0.6 Surgically managed Ht SDS -0.3	ND
Griffiths et al (1993) [3]	67 CD	17 yrs and HV < 1 cm/yr	Females Ht SDS -0.5 Males Ht SDS -1.0	ND
Markowitz et al (1993) [317]	48 IBD (38 CD, 10 UC)	21 yrs	CD: 56% < 25th centile UC: 25% < 5th centile	ND
Hildebrand et al (1994) [303]	124 IBD (46 CD, 60 UC18 IBDU)	>16 yrs or HV < 0.5 cm/yr	CD Ht SDS +0.4 UC Ht SDS +0.2 IBDU Ht SDS -0.1	ND
Ferguson et al (1994) [314]	70 IBD (50 CD, 20 UC)	ND	CD males 175 cm, CD females 157 cm UC males 175 cm, UC females 159 cm	ND
Alemazedeh et al (2002) [318]	135 CD	≥ 18 yrs	Prepubertal onset Ht SDS -1.0 Pubertal onset -0.1 Adult onset +0.1	Prepubertal onset 2.1 cm below MPH Pubertal onset 0.6 cm above MPH Adult onset 0.9 cm above MPH
Sawczenko et al (2003) [8]	43 CD	> 16 yrs	Ht SDS -0.7	5.9 cm below MPH
Sawczenko et al (2006) [9]	123 CD	HV < 1 cm/yr	Ht SDS -0.3	3 cm below MPH but 20% were ≥ 8 cm below MPH
Lee et al (2010) [319]	141 IBD	≥ 18 yrs	"Growth impaired" Ht SDS -1.3 "Not growth impaired" Ht SDS -0.1	"Growth impaired" -0.7 SD lower than MPH SDS "Not growth impaired" -0.1 SD lower than MPH SDS

Table 4: Published Studies Of Adult Height In Childhood Onset Inflammatory Bowel Disease

IBD: inflammatory bowel disease; CD: crohn's disease; UC: ulcerative colitis; IBDU: inflammatory bowel disease unclassified; Ht: height; cm: centimeter; SDS: standard deviation score; ND: no details; MPH: mid-parental height

	Study design	No patients	Duration (yrs)	rhGH dose (mg/kg/wk)	Age baseline (yrs)	HV baseline	HV follow-up	% change HV	Ht SDS baseline	Ht SDS follow-up	Change Ht SDS
McCaffery et al (1974) [342]	Retrospective	2	0.5	10 mg for 5 days then 3 mg three times per week	-	6.5 cm/yr	9.2 cm/yr	42%	-	-	-
Henker et al (1996) [343]	Retrospective	3	2.0	0.9-1.0 mg daily	16.2	5.0 cm/yr	10.4 cm/yr	108%	-3.4	-1.6	+1.8
Mauras et al (2002) [344]	Prospective	10	0.5-1.0	0.35	11.9	4.0 cm/yr	7.4 cm/yr (1^{st} yr)	85%	-	-	-
Wong et al (2007) [345]	Retrospective	7	Variable	0.15-0.31	15.9	2.5 cm/yr	3.7 cm/yr (0.5 yrs)	48%	-2.2	-1.9	+0.3
Heyman et al (2008) [346]	Prospective	8 rhGH 24 historical Ctrl	1.0	0.30	12.6 12.5	3.0 cm/yr 4.0 cm/yr	8.3 cm/yr 4.9 cm/yr	177% 23%	-2.0 -1.8	-1.2 -1.6	+0.8 +0.2
Slonim et al (2009) [348]	Retrospective	4	4.5-7.5	0.18-0.20	13.8	-	-	-	-3.5	-1.9	+1.6

Table 5: Published Non-Randomized Studies Of Recombinant Human Growth Hormone On Linear Growth In Children With Inflammatory Bowel Disease

yrs; years; rhGH: recombinant human growth hormone;Ctrl: control; mg: milligram; kg: kilogram; wk: week; cm; centimetre; HV: height velocity; Ht: height; SDS: standard deviation score

	Study design	No patients	Duration (yrs)	rhGH dose (mg/kg/wk)	Age baseline (yrs)	HV baseline	HV follow-up	% change HV	Ht SDS baseline	Ht SDS follow-up	Change Ht SDS
Calenda et al (2005) [349]	RCT (Placebo cross-over)	3 rhGH 4 Ctrl (placebo)	1.0	0.35	11.0	-	-	-	-	-	+0.1 SD +0.2 SD
Denson et al (2010) [350]	RCT	10 rhGH 10 Ctrl	0.25	0.53	12.0 13.0	-	+2.0 SD -2.1 SD	-	-	-	-
Wong et al (2011) [351]	RCT	11 rhGH 11 Ctrl	0.5	0.45	14.7 13.7	4.5 cm/yr 3.8 cm/yr	10.8 cm/yr 3.5 cm/yr	140% -7.9%	-2.8 -1.8	-2.5 -1.9	+0.3 -0.1

Table 6: Published Randomized Trials Of Recombinant Human Growth Hormone On Linear Growth In Children With Inflammatory Bowel Disease

RCT: randomized controlled trial; yrs; years; rhGH: recombinant human growth hormone;Ctrl: control; mg: milligram; kg: kilogram; wk: week; cm; centimetre; HV: height velocity; Ht: height; SDS: standard deviation score; SD: standard deviation

	No patients	Age at assessment	Adult height result	Deviation from mid-parental height
Hauesler et al (1994) [388]	139	19 yrs	Males 173 cm (25th centile) Females 161.5 cm (25th centile)	ND
Morrison et al (1997) [403]	1604 males 1452 females	20 yrs	Males Ht SDS -0.7 Females Ht SDS -0.9	ND
Lai et al (1999) [399]	30	Males 19 yrs Females 17 yrs	Males Ht SDS -1.2 Females Ht SDS -0.1	48% below MPH
Aswani et al (2003) [400]	US: 27349 males, 23797 females Canada: 4315 males, 3816 females	≥ 25 yrs	25th centile	ND
Assael et al (2009) [401]	112 “mild disease” 112 “ severe disease”	> 20 ys	“Mild disease “ males 172.4 cm “Mild disease” female 161.3 cm “Severe disease” males 171.1 cm “Severe disease” females 160.1 cm	ND
Boumez et al (2012) [379]	398 males 331 females	19 yrs	Males Ht SDS -0.7 Females Ht SDS -0.5	ND
Djik et al (2011) [402]	38 clinical diagnosis 41 neonatal screening	18 yrs	Clinical diagnosis -1.2 Neonatal screening -0.2	ND
Zhang et al (2013) [4]	1862 (269 with parental height)	21 yrs	160 cm (28th centile)	MPH 53d centile

Table 7: Published Studies Of Adult Height In Childhood Onset Cystic Fibrosis

CF: cystic fibrosis; Ht: height; cm: centimeter; SDS: standard deviation score; ND: no details; MPH: mid-parental height

	Study design	No patients	Duration (yrs)	rhGH dose (mg/kg/wk)	Age baseline (yrs)	HV baseline	HV follow-up	% change HV	Ht SDS baseline	Ht SDS follow-up	Change Ht SDS
Huseman et al (1996) [420]	Prospective	9	1.0	0.30	7.0	5.7 cm/yr	7.8cm/yr	37%	-1.3	-0.8	+0.5
Hardin et al (1997) [417]	Retrospective	24	1.0-2.0	0.29	10.3	3.7 cm/yr	7.8 cm/yr (1st yr) 6.5 cm/yr (2nd yr)	111% 76%	-3.2	-	-
Alemzadeh et al (1998) [419]	Prospective	15	2.0	0.35	3.2	-	-	-	-2.8	-0.9	+1.9
Hardin et al (1998) [419]	Prospective	9	1.0	0.35	5.4-12.2	5.6 cm/yr	8.0 cm/yr	43%	-1.9	-1.3	+0.6
Sackey et al (1998) [421]	Prospective	7	1.0	0.16	7.9	0.3 cm/yr	4.1 cm/yr (0.5 yrs)	1141%	-	-	-
Hardin et al (2005) [416]	Retrospective	13 rhGH 12 historical Ctrl	1.0	0.30	13.8 14.3	5.1 cm/yr 5.0 cm/yr	8.0 cm/yr 5.0 cm/yr	57% 0%	-1.9 -1.9	-	-

Table 8: Published Non-Randomized Studies Of Recombinant Human Growth Hormone On Linear Growth In Children With Cystic Fibrosis

yrs; years; rhGH: recombinant human growth hormone;Ctrl: control; mg: milligram; kg: kilogram; wk: week; cm; centimetre; HV: height velocity; Ht: height; SDS: standard deviation score

	Study design	No patients	Duration (yrs)	rhGH dose (mg/kg/wk)	Age baseline (yrs)	HV baseline	HV follow-up	% change HV	Ht SDS baseline	Ht SDS follow-up	Change Ht SDS
Hardin D et al (2001) [423]	RCT	10 rhGH 9 Ctrl	1.0	0.30	10.2 11.4	3.9 cm/yr 4.0 cm/yr	8.0 cm/yr 4.0cm/yr	105% 0%	-0.5 -0.6	-0.3 -0.9	+0.2 -0.3
Hutler et al (2002) [426]	RCT	6 rhGH 4 Ctrl	0.5	0.27-0.35	12.1	-	9. cm/yr 5.4 cm/yr	-	139 cm 139cm	141.1 cm 143.3 cm	-
Hardin et al (2005) [427]	RCT	9 rhGH 9 Ctrl	1.0	0.30	11.6 11.1	-	8.0 cm/yr 3.8 cm/yr	-	-1.7 -1.7	-1.1 -1.7	+0.6 0.0
Hardin et al (2006) [424]	RCT	32 rhGH 29 Ctrl	1.0	0.30	10.3 9.7	-	8.0 cm/yr 5.0 cm/yr	-	-1.8 -1.9	-	-
Schnabel et al (2007) [425]	RCT	20 high dose 22 low dose 21 Ctrl (placebo)	0.5	0.49 0.27	14.3 13.8 14.6	-	6.8 cm/yr 5.6 cm/yr 3.8 cm/yr	-	-2.1 -1.8 -2.5	-	-
Stalvey et al (2012) [422]	RCT	36 rhGH 32 Ctrl	1.0	0.30	9.4 9.4	-	8.2 cm/yr 5.3 cm/yr	-	-1.8 -1.9	-1.4 -1.9	+0.4 0.0

Table 9: Published Randomized Trials Of Recombinant Human Growth Hormone On Linear Growth In Children With Cystic Fibrosis

yrs; years; rhGH: recombinant human growth hormone;Ctrl: control; mg: milligram; kg: kilogram; wk: week; cm; centimetre; HV: height velocity; Ht: height; SDS: standard deviation score