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REVIEW ARTICLE

Endocrine Therapy for Growth Retardation in Paediatric Inflammatory Bowel Disease

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Abstract Inflammatory bowel disease, particularly Crohn's disease (CD), can potentially cause growth failure during childhood as well as a reduction in final adult height. The underlying mechanism is multifactorial and includes poor nutrition, chronic inflammation, and the prolonged use of steroids. Despite major advances in the treatment of CD, current cohorts of children continue to display a deficit in linear growth and may qualify for growth-promoting hormonal therapy. However, currently there is limited evidence to support the use of endocrine therapy directed primarily at improving growth. This review is aimed at summarising the current evidence for growth impairment in inflammatory bowel disease and discusses the rationale for using growth promoting therapy.

1 Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory condition that has two common phenotypes: Crohn's disease (CD) and ulcerative colitis (UC); around 25 % of cases are diagnosed during childhood [1]. Like many other chronic childhood conditions, impaired linear growth and pubertal delay are described in children with IBD and, particularly, CD [2]. It is likely that this growth impairment is due to a combination of factors such as poor nutrition, chronic inflammation and prolonged use of steroids exerting an adverse effect on the growth hormone–insulin-like growth factor (GH–IGF) axis at a peripheral or central level [2]. Pubertal delay is also reported to be a concern in IBD, particularly in those with CD, and this may also be multifactorial [3]. Persistence of poor growth and pubertal delay in children with CD who receive optimal management of their disease suggests that some children may also require additional growth-promoting therapy [4, 5]. Pubertal induction with sex steroid can be considered if there is delayed puberty, although it is unclear whether induction of puberty is sufficient for optimization of pubertal growth [6]. Management of such children needs to be undertaken very carefully and as a close partnership between the paediatric gastroenterologist and endocrinologist. In this paper, we have reviewed the underlying pathophysiological mechanisms that may lead to growth failure in children with IBD and then explored the possible therapeutic options that may be available to ameliorate the growth retardation.

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2 Growth Failure in Children with Inflammatory Bowel Disease (IBD)

2.1 Definition of Growth Failure

Growth failure and pubertal delay can be defined as 'height below the third percentile', 'velocity of linear growth and of weight gain below the third percentile', 'bone age delayed by 2 years' [7], 'height velocity (HV) less than third percentile for age and bone age >2 standard deviations below chronological age' [8], 'no signs of puberty' [9] or a decrease in height standard deviation score (HtSDS) since diagnosis of ≥0.75 [10]. Severe growth

impairment has been defined by some as height velocity standard deviation score (HVSDS) below −1 with HtSDS below −1 or a reduction from mid-parental HtSDS (MPHSDS) of more than 1.0 combined with a HtSDS of less than −2 and a decrease from MPHSDS of more than 1 [11]. Whilst some have suggested that HV and HVSDS adjusted for age and gender are a valid method of identifying growth failure [12], it is possible that change in HtSDS may be a more robust parameter in children with chronic disease where there is a high prevalence of children of peripubertal age. HVSDS may be especially difficult to calculate and interpret in older children and where children do not have prior data [4]. Measurement of bone age may improve the interpretation of growth data, especially when substantial pubertal delay is expected [13].

2.2 Growth Failure in Children with IBD

Growth failure is twice as common in CD compared with UC and may be the first manifestation of disease [14]. At diagnosis, growth failure may be present in up to 56 % of children with CD and 10 % of children with UC [15]. Furthermore, a quarter of affected children may continue to grow slowly and remain short as adults [16, 17]. Studies have consistently shown that proximal small bowel disease location was associated with reduced linear growth and this may be principally related to small bowel involvement which leads to malabsorption of micronutrients and disaccharide intolerance, resulting in shorter gut transit times, pain, and exacerbation of diarrhoea [5, 17, 18]. Furthermore, previous reports demonstrated that the male gender was more likely to be associated with reduced linear growth and this may be due to an effect on the pubertal growth spurt which occurs later and lasts longer in boys [5, 17]. Both adults and children with a chronic inflammatory condition such as IBD are now living longer and the adverse effects of chronic inflammation on growth and skeletal development have been ranked by the Crohn's and Colitis Foundation of America as one of the top areas that require further attention [19].

3 Normal Growth Hormone–Insulin-Like Growth Factor (GH–IGF)-1 Axis

GH–IGF-1 axis is the major regulator of linear growth from postnatal life throughout puberty. GH is secreted from the anterior pituitary gland in a pulsatile manner under control of hypothalamic growth hormone-releasing hormone (GHRH), which stimulates GH secretion. GH circulates in the body bound to GH-binding protein (GHBP), where it interacts with hepatic GH receptor to generate IGF-1, the main mediator of GH action. Hepatic-produced IGF-1 circulates bound to one of the six binding proteins, collectively called the insulin-like growth factor binding protein (IGFBP), which modulate the availability of IGF-1 at the tissue level. GH acts directly on germinal zone precursors of the growth plate to stimulate the differentiation of chondrocytes and the intensification of local IGF-1 secretion. This locally produced IGF-1 then stimulates bone growth by acting in an autocrine/paracrine fashion to stimulate chondrocyte clonal expansion and hypertrophy. It is now accepted that GH can stimulate linear bone growth via systemic and local IGF-1 production [20]. Studies in both GH receptor (GHR) and IGF-1 mutant mice demonstrated a growth reduction which was more severe in double GHR/IGF-1 mutants than either GHR or IGF-1 null mice alone and it is likely therefore that GH and IGF-1 have both independent and common functions [21]. In comparison with wild-type mice, the growth deficits of the tibia in the double GHR/IGF-1R null mice were similar to the sum of growth deficit noted in the single GHR and IGF-1R mutant tibia, suggesting that there may be a clear demarcation of effect of the two growth factors [21]. Although most of the circulating IGF-1 is produced by the liver under influence of GH, it seems that locally derived IGF-1 may be more important for postnatal growth. Knockout mice with selective hepatic mutation of IGF-1 showed that despite the 75 % decrease in serum IGF-1 level, these mice did not exhibit particularly marked reduction in growth [22]. However, conflicting data exist to challenge this hypothesis, suggesting that when hepatic IGF-1 secretion was restored in IGF-1 null mice, some of the growth was also restored [20]. The growth-promoting role of GH is well accepted, but the relative contributions to growth of the direct or indirect effects of GH remain unclear.

4 Pathophysiology of Growth Impairment in IBD

The mechanisms of growth failure are multifactorial and involve the GH–IGF axis at a peripheral and central level (Fig. 1) [2]. Although the exact mechanisms of disturbance of the GH–IGF axis in IBD children is still debatable [2, 23, 24], there is some evidence to show that some children have low levels of IGF-1 despite normal GH secretion [25, 26]. These findings point to growth hormone resistance as a possible mechanism that may explain growth failure in short children with CD. Recent data suggest that systemic GH–IGF-1 axis is affected to a variable extent in poorly growing children with IBD and the abnormalities may range from functional GH deficiency to GH resistance and low IGF-1 level [23, 24]. A retrospective review of 28 patients with IBD reported that peak GH levels following insulin-induced hypoglycaemia were variable and subnormal in some cases (peak GH < 3 mcg/l and IGF-1

SDS < 0) but IGF-1 concentrations were almost universally low [24].

The roles of specific genetic and immunological factors involved in growth variation in IBD in children continue to be an area of active research [16, 18, 27]. Evidence from an in vivo study reported polymorphisms in the dymeclin gene DYM are associated with growth failure in CD children [16]. Further evidence to the importance of specific gene polymorphisms comes from a study that investigated genetic variants associated with disease susceptibility that was also associated with growth impairment. They found that patients with a specific organic cation transporter 1/2 (OCTN1/2) haplotype had lower height at diagnosis [27]. A study of 153 children with CD at time of diagnosis reported that IL-6 174 GG genotype was correlated with lower HtSDS and higher circulating level of C-reactive protein [28]. Also, data from Levine et al. [29] showed that variations in the tumour necrosis factor-alpha (TNFα) promoter region of the TNFα gene may independently modify linear growth and disease severity in paediatric onset CD. They suggested that the presence of either TNF 238G/A or 863C/A polymorphism which is supposed to reduce the TNFα level was linked to higher mean HtSDS and thus had a protective effect on growth retardation whereas the other two polymorphisms were associated with disease severity.

The latest in vitro study shows that defects in innate immunity due to granulocyte macrophage colony stimulating factors autoantibodies (GM-CSF Ab) in a CARD15 deficient host is associated with growth impairment in CD and hepatic GH resistance in murine ileitis [18]. It is possible that these genetic polymorphisms are associated with variable immune function which modulates disease activity thus influencing growth.

4.1 Role of Nutrition

Over 80 % of children with CD are malnourished at the time of diagnosis [30] because of decreased nutrient intake, decreased gut nutrient absorption, increased loss and increased requirements [31]. An abnormal level of serum GH is often found in a state of malnutrition, being high in acute status but reduced in chronic nutritional deficit. However, in protein-restricted rats, administration of GH was not associated with normalisation of IGF-1 levels, suggesting a degree of GH resistance [32]. The nutrition disturbance that occurs in CD may contribute to GH resistance by several mechanisms: reduced lean body mass is one consequence for children with CD, similar to that seen in cystic fibrosis. Sermet-Gaudelus et al. [33] showed a strong correlation between low serum IGF-1 levels and reduced lean body mass in cystic fibrosis patients. Furthermore, both lower circulatory IGF-1 and IGFBP-3 levels were found in children and adults with restricted energy and protein intake. The reduction in both IGF-1 and IGFBP-3 was observed to be associated with high GH levels and authors suggest a degree of GH resistance at the receptor level in human subjects with energy restriction

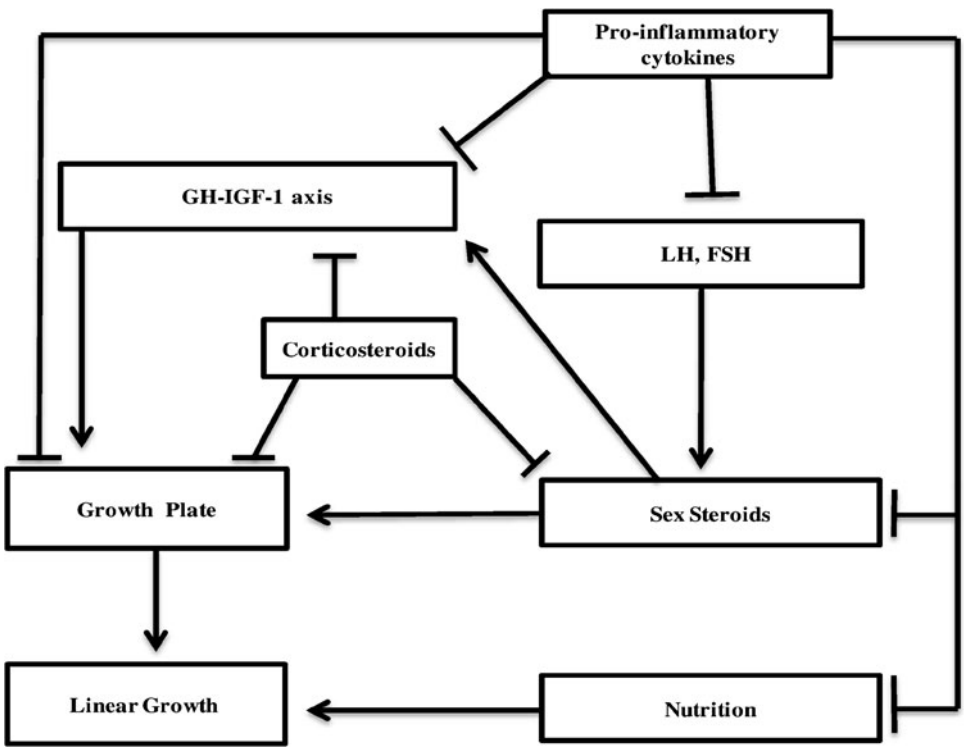

Fig. 1 Possible mechanism of growth failure in children with inflammatory bowel disease. *FSH* follicle-stimulating hormone, *GH* Growth hormone, *IGF-1* insulin-like growth factor-1, *LH* luteinizing hormone

[34]. Thus, nutritional deficit can contribute to both functional GH deficiency and resistance seen in those children. However, improving nutrition has been shown to be associated with only a partial improvement in growth in animal studies, suggesting that poor growth is not solely due to poor nutrition as over 40 % of impairment in growth was explained by inflammation [35].

4.2 Role of Inflammatory Cytokines

4.2.1 GH–IGF Axis-Dependent Pathway

Children with CD have elevated levels of circulating TNFα, interleukin (IL)-1B and IL-6 [23]. The effect of pro-inflammatory cytokines on growth has been extensively studied [36]. Negative correlation between cytokines and IGF-1 levels indicate that cytokines may impair growth through disturbance of the GH–IGF-1 axis in IBD by induction degree of GH resistance [35, 37, 38]. Drug-induced colitis in pair-fed rats is associated with impairment in growth, a normal GH level and a low IGF-1 level, suggestive of a state of GH resistance. Administration of IGF-1 to the colitis group was associated with an increase in the circulating IGF-1 level and linear growth by approximately 44–60 %, suggesting that the effect of disease on growth due to systemic GH resistance could be partially overcome by IGF-1 administration [35]. The cellular mechanisms by which inflammatory cytokines modulate the GH axis remain unclear but the possible role of suppressor of cytokines signalling (SOCS) has been suggested. SOCS proteins are a group of signalled proteins characterised by their ability to down-regulate cytokine signalling [39]. SOCS2 is uniquely identified as a primary GH receptor signalling inhibitor in vivo by its over-growth knockout phenotype in mice which are 30–40 % larger than normal littermates, and these effects appear to be mediated by increased long bone length and increased signalling through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [40]. The existing evidence showed the particular role of IL-6 in interruption of GH/IGF-1 axis is commonly seen in paediatric CD. Results from transgenic mice revealed an inverse relationship between plasma IL-6 and IGF-1 level suggesting a direct effect of cytokines on growth axis by induction degree of GH resistance in chronic inflammatory conditions [37]. It is of interest to note that administration of IL-6 antibodies to rats with colitis and growth failure was associated with a significant improvement in linear growth and IGF-1 level but administration of TNFα had no effect on circulatory IGF1 levels [28]. There is also evidence that IL-6 may decrease circulatory IGF-1 half-life by increasing the breakdown of IGFBP-3 and interfering with formation of the IGF-1/IGFBP-3/acid labile subunit (ALS) complex, and TNFα may reduce expression of GH receptors by hepatocyte and thus reduce circulatory IGF-1 [11]. An in vivo study showed that IGF-1 level and HtSDS correlated negatively with TNFα and IL-6 in paediatric CD [38]. The group proposed the possibility of immune-mediated mechanisms in growth failure. However, treatment with IGF-1 could only partially normalise the growth suppressive effects, suggesting that some of the effects may be independent of the IGF-1 system [41].

4.2.2 GH–IGF-1 Axis-Independent Pathway

In the rodent metatarsal model as well as ATDC5 murine growth plate cells, both IL-1B and TNFα inhibit growth plate chondrocyte differentiation and increase apoptosis and inhibit cartilage-specific proteoglycan synthesis [41, 42]. IL-1B and TNFα have both synergistic and additive consequences as, when combined, they more severely hinder longitudinal growth in the rodent metatarsal model [41, 42]. Additionally, data from a culture model showed that the duration of exposure to pro-inflammatory cytokines is critically vital, such that dramatic irreversible decrease in growth was associated with longer duration of exposure [42]. IL-1B may also inhibit local production of IGF-1 through the Akt-phosphatidylinositol-3-Kinase (PI3K) mechanism [43]. In addition, TNFα may suppress growth by inducing anorexia in patients with chronic inflammation by acting through the appetite regulatory centre at the hypothalamic level [44]. Removal of the source of inflammation is associated with an improvement in growth and the improvement may be more prominent than that observed with growth promoting therapy [45, 46].

4.3 Role of Glucocorticoids

4.3.1 GH–IGF Axis-Dependent Pathway

The negative effect of glucocorticoids (GCs) on growth occurs through multiple mechanisms and is an important drawback of using this medication in children with IBD [14]. Growth recovery is poorer following the use of GC as compared with enteral nutrition in the early phase of treatment of paediatric CD [47, 48]. GCs can interfere with the GH–IGF axis through attenuation of GH secretion by an increase in hypothalamic somatostatin tone and a loss of pulsatile release [49]. A steroid also causes functional IGF-1 deficiency through down regulation of liver GH receptors, thus suppressing IGF-1 production and inhibiting IGF-1 bioactivity [50].

4.3.2 GH–IGF Axis-Independent Pathway

GC may also inhibit linear growth through pathways that are independent of the systemic GH–IGF axis. They may

impair GH receptor expression at the level of growth plate thus decreasing GH action and local IGF-1 production [51]. They may also restrict chondrogenesis by reduced chondrocyte proliferation and increased apoptosis rates through down regulation of anti-apoptotic proteins [52–54] and may interfere with sex hormone secretion through direct and indirect gonadal effects [49]. In adults, GC use may be associated with both testosterone and reversible gonadotrophin deficiency [55]. Adrenal insufficiency following chronic use of GC may result in reduced androstenedione and estrogen levels. Moreover, experimental evidence suggests that circulatory levels of estrogen reduced during GC therapy impair follicle-stimulating hormone (FSH) action and consequently decrease estrogen production [49].

5 Pathogenesis of Pubertal Delay in IBD

The pubertal growth spurt accounts for around 20 % of final adult height [56]. Thus, delayed puberty is another issue in children with IBD, and especially CD, that may aggravate the growth impairment [57]. A retrospective study by Mason et al. [58] where pubertal growth was assessed by serial height measurements (peak HVSDS [PHVSDS], HtSDS at diagnosis, age at peak HV [PHV] and HtSDS at PHV) over the period of adolescence in IBD children reported that alterations in pubertal growth spurt are not uncommon, especially in boys, and may be related to both disease severity and poor nutrition. The abnormalities of the hypothalamic–pituitary–gonadal (HPG) axis include hypogonadotropic hypogonadism and abnormalities of sex steroid synthesis or action of sex steroid [59, 60]. The proposed mechanism attributed to under nutrition and inflammation is that both of these factors are postulated to induce central and peripheral hypogonadism [59, 60]. Generally, it is documented that under-nutrition is associated with decreased fat tissue with subsequent reduction in leptin level, an essential hormone for normal initiation of puberty [14]. However, investigation in rat models with colitis revealed that inflammation appears to have a detrimental effect on pubertal development and either directly inhibits puberty or potentiates the effects of under-nutrition [59]. A recent study in rats with induced colitis showed that pubertal delay in colitis cannot solely be explained by reduction in leptin level and they suggest inhibition of gonadotropin secretion by inflammatory cytokines as a conceivable explanation of pubertal delay in mice with colitis [60]. Evidence showed that proinflammatory cytokines such as TNFα and IL-1 may inhibit steroidogenesis in leydig cells, thus inducing a state of primary gonadal failure [61]. In conclusion, the negative effect of inflammation on the growth axis and puberty may provide a plausible explanation for poor growth and short adult height seen in children with IBD.

6 Therapeutic Options for Growth Failure in Children with IBD

The first step is early identification of growth impairment and close collaboration between the clinical teams overseeing the child's care. This will help in providing prompt management for children in whom growth and puberty are significant clinical issues. The management approach for growth failure should be a combination of improvement of nutritional status, controlling inflammation and hormonal therapy.

6.1 Improvement of Nutritional Status

Exclusive enteral nutrition (EEN) is increasingly considered as an effective initial method of controlling inflammation in children with active CD [14] with reported remission rates of about 80 % [62]. By controlling inflammation, enteral nutrition may avoid the use of GC and their negative impact on growth [63].

Over the last few years, improvement of nutritional status by EEN has also been associated with a short-term improvement in growth velocity and a reduction in inflammation and disease activity, suggesting that some forms of nutritional regimens may lead to growth improvement by mechanisms other than simply improving nutritional status [7, 8]. A short-term study of 12 children with active CD treated with EEN for 6 weeks showed early improvement in inflammatory markers (erythrocyte sedimentation rate (ESR), IL-6) after 3 days and in IGF-1 after 1 week of starting nutritional treatment without any significant change in nutritional status measured by weight SDS, mid upper arm circumference and triceps skin-fold thickness. The authors linked this improvement in IGF-1 to the anti-inflammatory effect of EEN rather than nutritional resuscitation [64].

A possible mechanism by which EEN may improve growth is induction of mucosal healing and reduced mucosal production of pro-inflammatory cytokines [65, 66]. Fell et al. [65] reported that 8 weeks of enteral nutrition in paediatric patients with active CD was associated with macroscopic and histological mucosal healing. In a report where mucosal biopsies were obtained from patients with CD and controls incubated with elemental diet, casein or whey showed that elemental diet may have a direct inhibitory effect on mucosal inflammation by increasing the anti-inflammatory: pro-inflammatory cytokine ratio in CD [66]. This anti-inflammatory effect may not be particularly due to amino acid composition, as diets containing casein have similar anti-inflammatory effects. However, while EEN has been shown to improve short- and medium-term nutritional status as well as short-term growth, velocity studies have not shown any long-term effect on height SDS/final adult height in isolation and there is a

need for other therapeutic strategies to maximise height potential in paediatric CD to be investigated [67].

6.2 Control of Inflammation

Introduction of steroid-sparing immunomodulators such as thiopurines and methotrexate should be considered early in children with elements of growth failure, thereby reducing the use of corticosteroids [3]. Some promising data regarding the growth-promoting effect of biologics are now available and will be discussed more thoroughly in the next section.

6.2.1 Effect of Biologic Therapy on Growth in Paediatric IBD

Currently biologics are a mainstay in children with more severe forms of IBD resistant to conventional treatment. Biologics are proteins which selectively neutralize or block the effects of cytokines, such as TNFα, and include both fusion proteins and monoclonal antibodies. One commonly used agent is infliximab, a monoclonal antibody to TNFα. The efficacy of infliximab for both induction and maintenance of moderate to severe paediatric CD is widely accredited [68, 69]. However, its effect on optimization of linear growth seems to be variable [14].

A number of studies have now reported that the use of infliximab is associated with improved growth in children with CD whose disease improves with the introduction of this drug (Table 1). The open-label, multicenter, randomised controlled trial (RCT) (REACH study) to evaluate efficacy and safety of infliximab therapy for treatment of moderate to severe paediatric CD in 103 children showed a positive impact of infliximab on HtSDS after 30 and 54 weeks of therapy [50]. In addition, it seemed that the growth favourable effect was sustained for longer, but these conclusions may be somewhat guarded given that the number of children studied was 15, 10 and 4 at 2, 3 and 4 years, respectively. Furthermore, growth outcome was not the main objective of the study, the subjects were not blinded and no pubertal data were available. An increase in HtSDS has also been observed after 6 months of therapy in treated subjects compared with untreated after 6 months [70]. The Assa et al. group [71] recently elucidated that a tendency towards enhanced growth velocity was found in responders compared with non-responders. Furthermore, they highlighted the gender predilection seeing as only male responders showed a considerable amplification in height velocity during treatment. The authors claimed the need for future study that may clarify sex-specific response of growth during infliximab treatment of IBD patients. However, growth data from this report need to be approached with caution as a large proportion of the cohort was on glucocorticoids which may have impaired growth.

Interestingly, Walters et al. [72] reported that infliximab therapy is associated with improvement of mean HVSDS and HtSDS in responder participants providing that infliximab commenced before or during early puberty. Thus, they argued that the time of starting infliximab is crucial in gaining control over the disease to the extent that height is an issue. Comparable observation was reported in a small prospective study by Cezard and colleagues [73], where HVSDS was significantly enhanced in ten children who had not finished their pubertal growth after 1 year of commenced infliximab therapy compared with 1 year before treatment.

A recent retrospective study conducted by Malik et al. [74] confirmed that median HtSDS and HVSDS of a group of 21 children responding to infliximab treatment improved significantly over period of 1 year, even in children who remain in the pre-pubertal stage for 6 months prior and after commencing infliximab compared with non-responders whose growth rate remain unchanged. They verified that the growth-promoting effect of infliximab in responders can be independent of reduction in glucocorticoid use and pubertal progress, emphasising the role played by controlling inflammation. This retrospective study also showed median HV in children who were receiving methotrexate therapy before starting infliximab was significantly increased after 6 months of commencing biologics whereas, for children who were not receiving methotrexate before starting infliximab, there was no significant change in their median HV. The authors suggest the beneficial effect of infliximab on growth may be more likely when a child is receiving a background of methotrexate, possibly due to their synergistic effect on disease activity. Crombe et al. [75], found significant improvement in mean HtSDS in a group of 41 CD children responding over a period of follow up compared with 41 CD children who failed to respond to infliximab therapy. Interestingly, preliminary data from a controlled study of adults with active IBD showed an opposite effect of treatment with infliximab on the GH resistance occurring in active IBD [76]. However, comparable data is unavailable from any paediatric study. Adalimumab has also recently been reported to be associated with an improvement in disease and growth. A retrospective review of 36 CD children who started adalimumab at a median age of 14.7 years demonstrated that clinical response to adalimumab treatment was associated with short-term improvement in linear growth in CD children and this improvement was more likely in patients who were in early puberty and on immunosuppression but was independent of steroid use [77].

Table 1 Summary of studies of growth in children with Crohn's disease receiving biologic therapy

References	Study design	Size	Duration of study (months)	Age at start of therapy (years)[a]	Tanner stage at start of therapy	Results
Assa et al. [71]	Retrospective	101	60	13.5 ± 3.9	NK	HV: only male responders showed increased HV ($p = 0.007$)
Malik et al. [77]	Retrospective	36	6	14.7 (11.3, 16.8)	I–V	ΔHtSDS: baseline: −0.2 (−0.7, 0.2); 6 months: 0.0 (−0.5, 0.8) ($p = 0.005$)
Malik et al. [74]	Retrospective	28	6	13.1 (9.9, 15.7)	I–III	HtSDS: baseline: −0.1 (0.00, −0.1); 6 months: 0.05 (0.00, 0.4) ($p = 0.001$)
						HV: baseline: 2 (0.3, 7.1); 6 months: 6.4 (2.3, 9.1) in responders ($p = 0.004$)
Crombe et al. [75]	Retrospective	82	32	18.0 (16, 21)	NK	HtSDS: only responders showed an improvement
						baseline: −0.57 ± 1.1; 32 months: −0.25 ± 0.99 ($p = 0.04$)
Hyams et al. [101]	Prospective	20	48	13.3 ± 2.5	NK	HtSDS: baseline: −1.64; 24 months: 0.82; 36 months: 1.01; 48 months: 1.56
Sinitsky et al. [79]	Retrospective	16	12	13.0 ± 4.2	NK	HtSDS: baseline: −0.5 (−2.5, −0.6); 12 months: −0.8 (−2.8, −1.4) (p = NS)
Diamanti et al. [78]	Retrospective	14	10	13.0 (11.5, 15)	NK	Ht: case baseline: 146.1 ± 0.2 cm; 10 months: 147.8 ± 0.3 cm
						Control baseline: 147.4 ± 0.2 cm; 10 months: 148.5 ± 0.1 cm (P = NS)
Thayu et al. [102]	Prospective RCT	103	12	13.3 ± 2.5	NK	HtSDS: baseline: −0.76 ± 1.24; 12 months: −0.49 ± −0.50 ($p < 0.002$)
Hyams et al. [69]	Prospective RCT	20	12	13.3 ± 2.5	NK	HtSDS: baseline: −1.5; 12 months: 0.5 (<0.001)
Walters et al. [72]	Retrospective	27	12	14.3	I–V	HVSDS (Tanner I–III): baseline: −2.8 ± 1.7; 12 months: 1.1 ± 3.6 ($p < 0.001$)
						HVSDS (Tanner IV–V): baseline: 0.46 ± 3.4; 12 months: 0.68 ± 1.1 (p = NS)
Wewer et al. [80]	Retrospective	24	36	≤17	NK	HV: baseline 0.35 cm/month; 36 months: 0.38 cm/month (p = NS)
Borrelli et al. [70]	Prospective	18	6	13.0 (6, 18)	NK	HtSDS (treated group): baseline: −0.99 ± 0.62; 6 months: −0.74 ± 0.71 ($p < 0.01$)
						HtSDS (untreated group): baseline: −0.86 ± 0.42; 6 months:−0.83 ± 0.40 (p = NS)
Cezard et al. [73]	Prospective	10	12	15.0 ± 2.0	NK	HVSDS: baseline −0.45 (−1; 1.3); 12 months: 0.5 (0; 1.3) ($p = 0.004$)

ΔHtSDS change in HtSDS, *HtSDS* number of standard deviation from the mean for height for normal children for the same age and gender, *HV* height velocity (cm/year), *HVSDS* number of standard deviation from the mean for height velocity for normal children for the same age and gender, *NK* not known, *NS* not significant, *RCT* randomised controlled trial

[a] Age is represented as mean (±SD) or median (range)

On the other hand, three retrospective studies failed to find any association between use of infliximab and improvement of linear growth in IBD children [78–80]. Nevertheless, the retrospective nature of reports, relatively small sample size and lack of cohort pubertal data make it difficult to interpret the results with any certainty. A similar unfavourable outcome on growth was reported by the Pfefferkorn et al. group [5]. The researchers prospectively investigated 176 newly diagnosed IBD children younger than 16 years and tanner score from I to III to evaluate growth outcomes with current regimens. They found that, although disease activity significantly improved in 64 IBD patient receiving infliximab, HtSDS remain impaired despite the improvement in HVSDS in many children with CD after 2 years of diagnosis [5]. Malik et al. [4] also found that slow growth and short stature remain a problem in 30 % of CD children despite advances in treatment of paediatric CD and this diverse group may benefit from specific growth-promoting treatment or novel therapeutic approaches.

In conclusion, despite the improvement on growth in some studies, there continues to be some controversy about the overall beneficial effects of biologic therapy on growth. The retrospective nature and heterogeneity in methods of some of these studies, as well as the lack of documented pubertal status in some of these data and the relatively small sample size and uncontrolled nature in others, thus renders those results questionable. Furthermore, well designed, adequately powered, prospective, controlled cohort studies on biologics and growth, puberty and final height of IBD children are needed as this will not only improve the knowledge of the effect of biologics on growth but also might direct future research for elucidating the mechanisms and exploring novel therapeutic strategies to improve growth outcomes in a sundry group of children.

6.3 Endocrine Therapy

Persistence of disorders of linear growth and puberty in a substantial cohort of children with IBD remains a problem, despite optimisation of their disease by using contemporary treatment strategies, necessitating the consideration of growth-promoting agents to address these issues [4, 5]. Endocrine treatment modalities that have been previously reported include sex steroids and recombinant human growth hormone (rhGH), and these should only be considered in poorly growing children after prior optimization of their disease management [6].

6.3.1 Effect of Sex Steroid on Growth and Puberty in Paediatric IBD

Sex steroids refer to estrogen and androgen (testosterone, dihydrotestosterone and oxandrolone). Testosterone can favourably influence growth velocity at a systemic level by an increase in GH and IGF-1 secretion principally through its aromatisation into estrogen, and at a local level by its direct action on the growth plate through androgen and estrogen receptors. However, dihydrotestosterone and oxandrolone increase height velocity through the GH/IGF-1-independent pathway, suggesting that nonaromatisable androgens have a direct stimulatory effect on the androgen receptor within the growth plate cartilage [56]. A short course of testosterone or low doses of oxandrolone have been found to be effective and safe therapy for improving growth and puberty in healthy boys with constitutional delay of growth and puberty (CDGP), with no considerable impact on final height [56].

Pubertal induction with sex steroids may be considered if there is evidence of marked delay in puberty in children with chronic inflammatory conditions [6, 59, 81]. In a prospective cohort study of five boys with cystic fibrosis and pubertal delay treated with testosterone for 3 months, mean HV increased from 2.2 cm/year at baseline to 7.2 cm/year at end of follow up. The authors suggested that a short course of testosterone was an effective and safe way of improving the rate of growth in cystic fibrosis boys with delay of puberty [81]. To date, in children with IBD there is only one small retrospective report of sex steroid use for growth and pubertal delay which involved testosterone therapy in eight boys and which was associated with adequate virilisation in seven boys and enhancement in growth velocity up to 50 % in six. In the remainder, the increase in HV was <50 % of baseline despite sexual maturation. The authors suggest the possible role of other forms of growth-promoting therapy in children who do not show growth response after pubertal induction. This study also reported significant negative association between markers of disease activity (median C-reactive protein) and HV that highlighted the importance of controlling disease before the introduction of any growth- or puberty-promoting therapy [6]. They also argue for routine monitoring of pubertal status in children with IBD, especially in those with poor growth. Moreover, the role of female sex hormones for induction of puberty in girls with IBD needs to be investigated to clarify whether it may also be a useful therapy in this patient group.

6.3.2 Effect of Recombinant Human Growth Hormone (rhGH) Therapy on Growth in Paediatric IBD

GH is a potent anabolic agent known to stimulate linear growth, osteoblast activity and protein synthesis. In the UK, rhGH is licensed in children for treatment of GH deficiency, Turner syndrome, chronic renal insufficiency, Prader Willi syndrome and in children who are born small for gestational age [82]. GH therapy for children with

impaired growth and chronic inflammatory disease such as juvenile rheumatoid arthritis and cystic fibrosis has been investigated in a number of clinical trials. Paediatric studies involving use of rhGH in children with chronic inflammatory diseases such as juvenile rheumatoid arthritis and cystic fibrosis show significant improvement of linear growth [83, 84].

Table 2 summarises studies on the effect of rhGH therapy on linear growth in children with IBD [85–90]. The first report that investigated the effect of rhGH on linear growth of IBD children was conducted in 1974 [90]. In this study, rhGH at a dosage of 9 mg/week for 6 months was used in three adolescents with poor growth and IBD and the study showed no improvement in their height velocity compared with their prior growth rate. However, two of the participants had a bone age of 16 and 18 years and would have completed most of their growth prior to therapy. In a preliminary study of 10 subjects with CD who received rhGH at a dosage of 0.05 mg/kg/day for a variable duration (seven for 1 year, three for 6 months), the group showed significant improvement in their HtSDS from -1.7 ± 0.5 at baseline to -1.2 ± 0.6 at end of study ($p = 0.03$). This study also illustrated a significant positive effect of rhGH on bone metabolism and lean body mass without any significant changes in carbohydrate metabolism or disease activity score [88].

In comparison with previous data, another RCT in seven IBD children with growth impairment, in which the participants were randomised to either rhGH (0.05 mg/kg/day) or placebo (phase I for 1 year; in phase II all children received rhGH for a further 1 year), showed no significant difference in mean HtSDS between the two groups [85].

In 2008, an open-labelled controlled trial in eight children with IBD and short stature for 1 year using a rhGH dose of 0.043 mg/kg/day showed a significant increase in the HtSDS, weight SDS and bone density in the rhGH-treated group ($p < 0.01$, $p < 0.01$ and $p = 0.03$, respectively) compared with the control group [87]. Recently, an RCT was performed in two UK tertiary paediatric hospitals [89]. In this study, 22 participants with paediatric IBD were randomly allocated to either rhGH (0.067 mg/kg/day, $n = 11$) or no rhGH ($n = 11$) for 6 months. They found that HV (from 4.5 cm/year [0.6, 8.9] at baseline to 10.8 cm/year [6.1, 15] at 6 months, $p = 0.003$) and HtSDS (from -2.8 [-4.2, -1.5] at baseline to -2.4 [-3.7, -1.2], $p = 0.003$) were significantly increased compared with baseline in the treated group, whereas no significant change was detected in HV ($p = 0.58$) and HtSDS in the untreated group when compared with baseline. This study also showed a considerable improvement in biomarkers of growth. Median IGF-1 SDS adjusted for bone age improved from -2.9 (-3.7, 2.9) at baseline to -0.1 (-2.7, 2.2) after 6 months in the rhGH group ($p = 0.04$) whilst it

Table 2 Published studies of rhGH therapy in inflammatory bowel disease

References	Study design	Group	rhGH dose (mg/kg/day)	Duration of rhGH therapy (months)	Duration of study (months)	Primary end point	Results
Wong et al. [89]	RCT	20 CD/1 UC	0.067	6	6	Linear growth	HV: baseline: 4.5 cm/year (0.6, 8.9); 6 months: 10.8 (6.1, 15) $p = 0.003$ HtSDS: baseline: -2.8 (-4.2, -1.5); 6 months: -2.4 (-3.7, -1.2) $p = 0.003$ No significant change observed in control group
Denson et al. [86]	RCT	20 CD	0.075	12	12	Disease activity	HtSDS: baseline: -1.1 (-1.6, -0.6); 12 months: -0.4 (-1, 0.2) $p = 0.004$
Heyman et al. [87]	Open-label prospective	8 CD	0.043	12	12	Linear growth	HV: baseline: 3.00 ± 1.39 cm/year; 12 months: 8.32 ± 3.20 $p = 0.003$ HtSDS increased by 0.76 ± 0.38
Calenda et al. [85]	Placebo RCT	7 CD	0.05	12	24	Linear growth	No change in growth
Mauras [88]	Open-label prospective	9 CD, 1 IC	0.05	6	6–12	Linear growth	HV: baseline: 3.5 ± 0.4 cm/year; 6 months: 7.4 ± 1.1 $p = 0.001$

CD Crohn's disease, *HtSDS* number of standard deviation from the mean for height for normal children for the same age and gender, *HV* height velocity (cm/year), *IC* indeterminate colitis, *RCT* randomised controlled trial, *rhGH* recombinant growth hormone, *UC* ulcerative colitis

remained unchanged in the control group. Similar change was found in median alkaline phosphatase (ALP) in the treated participants where it increased from 202 U/l (72, 506) to 290 U/l (113, 547) over the subsequent 6 months ($p = 0.003$) with no significant change detected in the control group (217 [70, 462] to 265 U/l [93, 518], $p = 0.66$) over the corresponding period. This study also revealed no significant change in disease activity or bone age in both groups at baseline and 6 months. This was the first study to assess insulin sensitivity as well and showed that despite scant use of glucocorticoids, children with IBD were insulin resistant at baseline and the degree of resistance increased in those on rhGH. This increase in insulin resistance was not associated with impaired glucose tolerance as none of the children who had an oral glucose tolerance test 6 months after receiving rhGH injections was found to have asymptomatic diabetes mellitus.

Similar results were reported by Denson and associates [86] who investigated whether rhGH therapy (at dose of 0.075 mg/kg/day) for 52 weeks in 20 participants aged between 7 and 18 years stimulated linear growth in CD children compared with controls. They found mean HtSDS (−1.1 [−1, −0.6] at baseline) and HVSDS (−1.3 at baseline) considerably increased to −0.4 (−1, −0.2), $p = 0.04$, and 2.4, $p = 0.000$, respectively compared with baseline in the GH group. Moreover, a rise in fasting insulin level was documented without impairment in glucose level.

Beside a growth promoting effect, GH therapy may have an effect on disease status as reported in a number of human and animal studies [86, 91, 92]. Slonim et al. [92] conducted an RCT to investigate the effect of rhGH on disease status in adult patients with CD with 37 adults with moderate to severe CD allocated to either receive rhGH loading dose, 5 mg/day subcutaneously for 1 week, followed by a maintenance dose of 1.5 mg/day ($n = 19$) or placebo ($n = 18$). They found that the Crohn's Disease Activity Index score decreased by a mean of 143 ± 144 points in the rhGH group, as compared with a decrease of 19 ± 63 points in the control group ($p = 0.004$), suggesting a beneficial effect of GH in improving disease activity. A paediatric study by Denson et al. [86] showed that that 65 % of CD children on GH therapy and corticosteroids achieved clinical remission measured by Paediatric Crohn's Disease Activity Index (PCDAI) by 12 weeks compared with only 20 % of patients in the control group ($p = 0.03$). At week 12, 40 % of participants in the rhGH and corticosteroid arm achieved asteroid-free remission compared with 20 % of subjects in the control group. There was a trend towards improvement in endoscopic disease activity in the rhGH group at week 12; however, this did not reach statistical significance. Furthermore, other markers of disease activity such as faecal calprotectin and ESR were similar in both groups. Although disease activity index improved in this study, as HtSDS/HVSDS is a component of the PCDAI, the use of PCDAI to assess disease in studies promoting growth may be flawed by a concurrent improvement in growth rate. Data from Wong et al. [89] reported no significant difference in disease status based on an abbreviated paediatric CD activity index (APCDAI), which was only based on subjective symptoms and physical examination after 6 months between the intervention and control groups. Additionally, other markers of disease activity (such as ESR, CRP, Hb, HCT, albumin and inflammatory cytokines: TNF, IL1 and IL6) were similar between the two groups.

These initial results suggest that rhGH may have a positive effect on growth over the short term and is not associated with any deterioration in the disease status. However, there is a need to be judicious in the use of this drug, especially if used for a longer period given that there are scant data for efficacy and safety over the longer term. Children with juvenile idiopathic arthritis (JIA), and especially those who receive GC, may develop a more profound impairment of glucose tolerance [93], and given that inflammation may itself alter insulin sensitivity, there is a need to perform regular assessment of insulin sensitivity and glucose tolerance in children who receive rhGH. Future studies should also aim to investigate the effect of rhGH on disease outcomes using several different assessment methods.

6.3.3 Effect of rhIGF-1 Therapy on Growth in Paediatric IBD

Considering that the abnormality may occur at multiple levels of the GH/IGF-1 axis, the possible use of other forms of growth-promoting agents such as rhIGF-1, either alone or in combination with rhGH for promoting growth, requires further investigation [3]. There are a number of reasons why combination treatment of rhGH with rhIGF-1 may be more beneficial for growth and metabolism. Human data showed that combined therapy resulted in a higher serum concentration of IGF-1 compared with IGF-1 alone, probably linked to the negative feedback effect of IGF-1 on GH secreted by the pituitary [94]. 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 [94–96].

Furthermore, administration rhIGF-1 alone results in hypoglycaemia, thus concomitant treatment with rhGH may attenuate the glucose-lowering effect of rhIGF-1. An experimental rat model of uraemia showed that concomitant treatment with rhIGF-1 and rhGH was more effective in improving growth than rhIGF-1 or rhGH therapy alone and that concomitant treatment with rhGH inhibits the

hypoglycaemia that may occur with use of rhIGF-1 alone [97]. Patients with chronic inflammation may have relative hyperinsulinaemia even before they have been exposed to rhGH [98]. Although this may be related to the use of glucocorticoids, the relationship with TNFα concentrations confirms the coexistence of the previously reported relationship between inflammation and hyperinsulinaemia [98]. Finally, 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 have a degree of insulin resistance due to their state of chronic inflammation as well as glucocorticoid excess [86]. A double-blind placebo-controlled crossover trial of seven pre-pubertal cystic fibrosis children showed that rhIGF-1 for 6 months was associated with an improvement in glucose homeostasis [99]. More recently, Rao et al. [100] reported the use of mathematical modelling to determine the dose of rhIGF-1 necessary to maintain circulating IGF-1 in the physiological range during rhIGF-1 therapy in children with IBD and growth failure. However, such pharmacokinetic studies also need to provide an estimate of bioavailable IGF-1.

7 Conclusion

We have reviewed the pathophysiology of growth impairment and pubertal delay in IBD and the therapeutic options. Growth failure and pubertal delay are some of the major issues for children with IBD and may lead to short adult height. The multifactorial nature of growth impairment necessitates a careful therapeutic approach. Biologics confer beneficial short-term effects on growth that will need to be confirmed by larger adequately powered prospective controlled cohort studies of growth, puberty and final height of IBD children. Although some preliminary evidence supports the positive effect of rhGH therapy, the long-term effect of GH therapy on final height as well as glucose status remains unknown. In affected children with growth impairment, the use of rhIGF-1, alone or in combination with rhGH, needs further investigation through carefully designed studies.

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