

# Impact of Therapeutic Strategies on Growth in Pediatric Inflammatory Bowel Disease

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## Abstract

Growth retardation is a common complication of pediatric inflammatory bowel disease (IBD), which may have long term effects on final adult height and carries significant social and psychological implications. Etiology may be multifactorial including undernutrition, metabolic dysregulation, inflammatory impact on hormonal growth axis and the effect of drugs such as glucocorticoids. Control of disease activity and minimizing the need for corticosteroid therapy are necessary measures in order to facilitate normal growth. However, in many cases these strategies are not sufficient. Currently, there is inconsistent evidence regarding the efficacy of available therapeutic agents to induce long-term effect on growth. The new era of biologic therapies which carries a greater potential to achieve mucosal healing, holds promise for better growth even in children with severe growth impairment. It becomes apparent that prompt recognition of growth impairment combined with aggressive tailored therapeutic approach may offer the best chance for catch-up growth. This review will discuss the definition, prevalence and mechanism of growth retardation in children with IBD and highlight the specific benefits of current therapeutic strategies.

**Keywords:** Crohn's disease; Ulcerative colitis; Height; Height velocity

## Introduction

Approximately 25% of patients with inflammatory bowel disease (IBD) are diagnosed during childhood or adolescence. Growth impairment is commonly seen in children diagnosed with IBD, mainly those with Crohn's disease (CD).

The etiology of poor growth in children with IBD is multifactorial and not fully understood. Malnutrition, poor intake, increased nutritional needs, elevated inflammatory cytokines, genetic factors (parental height, CD susceptibility genes) and corticosteroid therapy are hallmarks of the underlying mechanism.

Growth failure may be present years before diagnosis of IBD, and it commonly persists despite disease specific treatments with implications on final adult height. Due to the above as well as significant social and psychological implications, growth failure presents a challenge for the treating physician. However, the long term benefit of current treatment strategies on linear growth is not clear, including the effects of nutrition therapy and mucosal healing.

This paper reviews the current epidemiological data, highlights the pathophysiology of poor growth and discusses therapeutic approaches in order to promote growth in children with IBD, with an emphasis on children with CD.

## Definition and prevalence

Linear growth failure in children is defined as height below the 3<sup>rd</sup> percentile or height z-score of below a standard deviation score (SDS) of -2. Another suggested definition is a decrease in height SDS since

diagnosis of  $\geq 0.75$  [1], however, the formal definitions preclude children with subnormal growth velocity who experience decline in their growth within the defined limits. Another pitfall of these definitions is that static height is primarily influenced by genetic determinants reflecting both parents' height. Linear growth can be also expressed as height velocity which represents growth status at a particular point of time and might present a more sensitive marker for the impact of disease on normal growth, particularly in peripubertal children. Severe growth impairment has been defined as height velocity SDS below -1 [2].

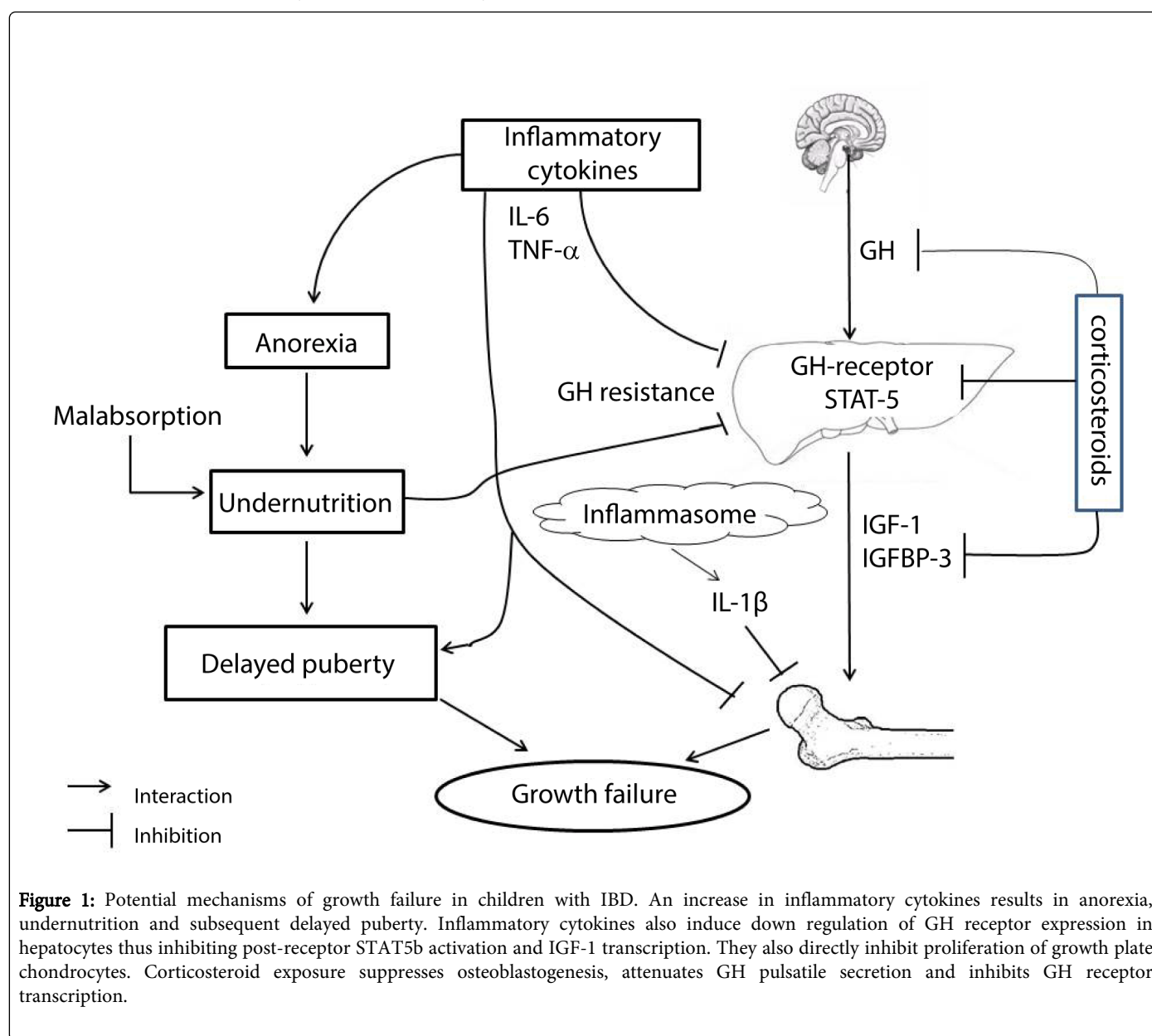
The rate of growth impairment in pediatric IBD at diagnosis varies with the type of disease (CD vs. ulcerative colitis [UC]), gender, and the time of diagnosis [3-11]. Apparently, the age and pubertal stage at diagnosis are key factors for growth potential. Malik et al. [12] have demonstrated that children with CD at pre-pubertal age did not improve their height velocity SDS during mean follow-up of 4.6 years while most children diagnosed at pubertal age did achieve normal height velocity SDS during follow-up. One of the most important risk factors for reduced height during the course of disease is the time from symptom onset to diagnosis [13]. Proximal small bowel disease location in children with CD was also implicated as a contributing factor to growth delay [14,15], possibly attributed to increased burden of systemic inflammation and malabsorption of micronutrients. Growth impairment in pediatric CD patients was also associated with positivity of ASCA antibodies [16]. Most children are diagnosed either during or just prior to the pubertal growth spurt [17,18], thus, the disease, which prevails during this short period of growth acceleration, might play a crucial role in achieving final height. Growth impairment was shown to be relatively common in both CD and UC [19,20]. Nevertheless, it is clear that CD affects growth more profoundly. Lee et al. [21] reported that 88% of pediatric CD patients suffered from growth impairment at diagnosis compared to 12% of pediatric UC

patients. Lower parental height and minimum patient height Z-score were significant predictors of lower final adult height in IBD. Kanof et al. [6] have demonstrated that 46% of children with CD will have a reduced height velocity before the appearance of suggestive symptoms and only 12% continue to follow normal growth patterns at the time of diagnosis while Malik et al. [12] reported that the percentage of children with height velocity SDS between -1 and -2 was 49% at diagnosis. Unfortunately, the natural course of CD results in decreased adult height in 11-35% of pediatric patients [8,14,21]. Furthermore, growth impairment in children with CD was found to be a predictor for more disabling disease [22]. The association between disease severity and growth impairment is mainly seen in CD, as it is found in only 3-10% of pediatric UC patients at diagnosis [7,8]. Data on final height in pediatric UC patients is limited but it is evident that it is less frequently affected [21]. The reasons for the observed difference between CD and UC are not entirely clear but are probably related to

the subtle presentation of CD which might delay diagnosis, the more commonly significant inflammatory burden and the higher prevalence of poorly controlled disease in children with CD.

### Pathogenesis

The etiology of growth impairment in children with IBD is multifactorial, yet still not clearly defined. Nevertheless, undernutrition (poor intake and malabsorption), a relative catabolic state (increased nutritional needs and losses), genetic factors (parental height, CD susceptibility genes and cytokine polymorphism), effects of inflammatory cytokines on the growth hormone (GH)/insulin like growth factor-1 (IGF-1) axis and chronic or recurrent corticosteroid therapy are major determinants. Most probably, a complex interplay exists which interrupts the normal regulation of growth (Figure 1).



**Figure 1:** Potential mechanisms of growth failure in children with IBD. An increase in inflammatory cytokines results in anorexia, undernutrition and subsequent delayed puberty. Inflammatory cytokines also induce down regulation of GH receptor expression in hepatocytes thus inhibiting post-receptor STAT5b activation and IGF-1 transcription. They also directly inhibit proliferation of growth plate chondrocytes. Corticosteroid exposure suppresses osteoblastogenesis, attenuates GH pulsatile secretion and inhibits GH receptor transcription.

## Undernutrition

Chronic undernutrition was shown to be the rule rather than the exception in children with IBD [23,24] with a greater prevalence in CD patients (60%-80%) than UC (about 35%) at diagnosis [25,26]. Indeed, correction of energy and nutrient deficits by nutritional supplementation improves linear growth in children with CD [27].

Disease related anorexia is, in part, mediated by inflammatory cytokines (Figure 1). In a colitis-induced rat model Ballinger et al. [28] demonstrated that tumor necrosis factor alpha (TNF- $\alpha$ ) suppresses feeding through interactions with hypothalamic appetite pathways. Unlike anorexia, malabsorption does not seem to be a significant contributor to growth impairment in IBD. In fact, only a very small proportion of children with profound small bowel disease or following extensive ileal resection are at risk for malabsorption [29,30].

The effect of IBD on energy needs is not clearly known. Older studies suggested that increased resting energy expenditure (REE) is associated with increased disease activity but with no change in total energy needs due to decreased physical activity [31]. In contrast, most studies did not find significant differences between measured and predicted REE [32-34]. However, newer studies suggest that REE correlates with disease activity in both CD [35] and UC [36]. Also, children with CD failed to reduce their REE in-parallel to weight loss when compared with children with anorexia-nervosa who lost similar amount of weight [37]. This relative catabolic state caused by failure to reduce energy expenditure is attributed to the effect of chronic inflammation [37]. This concept was further strengthened by Varille et al. [38] who demonstrated a significant reduction in REE, 4 weeks post-surgery, in children undergoing localized resection for stricturing disease despite maintaining preoperative nutritional and therapeutic regimens.

## Growth hormone/Insulin growth factor-1 axis

Undernutrition cannot solely explain growth impairment in children with IBD. The systemic GH/IGF-1 axis was shown to be variably affected in poorly growing children with IBD [39]. IGF-1 is produced by the liver in response to GH stimulation, subsequently stimulating the proliferation and hypertrophy of chondrocytes in the growth plate of long bones. Ballinger et al. [40], using a rat model of chemical colitis, showed that IGF-1 levels decreased dramatically in the colitic mice in comparison with healthy mice fed similar diet. More accurately, 53% of the total depression of IGF-1 was attributed to diet restriction while the remaining 47%, to inflammation. Administration of IGF-1 to the colitic mice increased linear growth. A complex cascade of cytokines is involved in the inflammatory process of IBD which includes TNF- $\alpha$ , interferon- $\gamma$  and various interleukins such as IL-6, IL-12, IL-17 and IL-23 [41]. Interestingly, children with IBD have normal GH secretion, either stimulated or spontaneous [42,43]. However, these children manifest reduced plasma concentrations of IGF-1 and IGF binding protein (IGFBP) [44] implying to "GH resistance". The reduction in IGF-1 was shown to be correlated with increase in multiple inflammatory cytokines, mainly IL-6 and TNF- $\alpha$  [44,45]. TNF- $\alpha$  has been demonstrated to induce hepatic GH resistance through downregulation of GH receptor expression in hepatocytes thus inhibiting post-receptor STAT5b activation and IGF-1 transcription [46-49] (Figure 1). IL-6, which was found in higher levels in patients with CD when compared to UC [50] inhibits IGFBP-3 production which results in reduced half-life of IGF-1 [51]. In animal models, administration of IL-6 resulted in significant

decrease in IGF-1 levels while neutralization of IL-6 in colitic rats led to increased plasma IGF-1 and improved linear growth [52,53]. Patients with genetic risk factors such as IL-6 promoter polymorphism might be in increased risk for growth impairment [54]. Eivindson et al. [55] demonstrated a direct correlation between the inflammatory burden reflected by high inflammatory markers and levels of IGF-1, IGF-2 and IGFBP-3. Chronic glucocorticoid therapy was shown to further decrease IGF-1 production hence contributing to growth impairment in children with corticosteroids dependent disease [56] (Figure 1).

## Direct effect of inflammatory cytokines

Inflammatory cytokines have also a direct effect on bone and on the growth plate [57]. Animal experiments have shown that TNF- $\alpha$  and IL-1 $\beta$  inhibit proliferation and increase apoptosis of growth plate chondrocytes [58,59] (Figure 1). Indeed, colitic rats demonstrate reduced proliferative zones in their growth plates [60]. Addition of serum from children with CD to fetal rat bone culture resulted in altered osteoblast function [58] further suggesting a direct detrimental impact of systemic inflammation on bone development.

In recent years there is an increasing interest in cytosolic multi-protein complexes named Inflammasomes which are found in cells of the innate immune system including intestinal epithelial cells [61]. The activation of the inflammasome is, largely, initiated by toll like receptor which recognizes bacterial lipopolysaccharide and in turn initiates activation of the NF- $\kappa$ B pathway. Evidence of increased caspase-1 and NLRP3 (a well characterized inflammasome) expression was identified in intestinal tissue and in macrophages from patients with both UC and CD [62-64]. Despite the lack of evidence regarding the effect of inflammasomes on growth it is evident that the end products of inflammasome formation are inflammatory caspases which are important for the cleavage of pro-IL-1 $\beta$ /IL-18 into their mature form [65]. As mentioned before, high levels of IL-1 $\beta$  which are correlated with disease activity in IBD patients [66] were shown to directly affect growth plates (Figure 1).

## Delayed puberty

Delayed puberty is prevalent in children with IBD [17,67] contributing to decreased height velocity in comparison to age-matched controls. Animal data suggests that both undernutrition and systemic inflammation are principle contributors to this phenomenon [68] (Figure 1). Inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\alpha$  were shown to suppress gonadotropin-releasing hormone (GnRH) secretion [69,70] and impair end-organ responsiveness to circulating testosterone [70] hence delaying pubertal development. Inflammation-induced anorexia was shown to reduce leptin levels which in turn, affect fat mass and subsequently results in delay of puberty [71].

## Corticosteroids effect

Repeated corticosteroids courses are not uncommon in children with severe IBD. Corticosteroid therapy carries substantial short- and long-term adverse effects, in particular growth retardation and decreased bone mineralization. The mechanisms by which corticosteroids suppress growth are complex. Corticosteroid exposure has an acute suppressive effect on osteoblastogenesis, with promotion of osteoblast apoptosis, resulting in reduced bone formation [72,73]. Animal studies demonstrated an attenuation of GH pulsatile secretion due to an increase in hypothalamic somatostatin effect [74] (Figure 1).

Corticosteroids therapy might further contribute to growth impairment via its inhibiting effect on GH receptor transcription and IGF-1 production [51] (Figure 1). Glucocorticoids also act at the growth plate level altering GH receptor expression and IGF-1 binding [75] (Figure 1). Even glucocorticoids with low systemic activity such as budesonide, used for remission induction in mild to moderate CD patients, appear to suppress linear growth [76]. Nevertheless it is impossible to isolate the effect of corticosteroids treatment on growth weighing its anti-inflammatory properties against its described impact on GH/IGF-1 axis and on the growth plates. Furthermore, as catch-up growth is expected following cessation of a short course of glucocorticoid therapy it is not clear whether limited usage of glucocorticoids for remission induction is detrimental for long-term growth.

### Genetic factors

Finally, genetic factors are also implicated in the pathogenesis of growth failure in IBD patients including the presence of stature-associated alleles, CD susceptibility alleles [77] and specific polymorphisms such as in the IL-6 promoter locus [54], further complicating the otherwise complex interplay altering growth in IBD.

### Impact of therapeutic strategies on growth

Based on the described pathophysiology of growth impairment in children with IBD it is intuitive that optimization of growth should rely on restoration of appropriate nutrition, minimizing inflammation and avoiding long-term or frequent corticosteroid therapy. The new era of biologic therapies, particularly anti TNF- $\alpha$  agents, enables greater achievement of therapeutic goals such as mucosal healing and deep remission which, theoretically, are more likely to promote normal growth. There is a clear correlation between treatment success and normalization of growth [23]. Nevertheless, it remains unclear whether more aggressive approaches which strive to achieve mucosal healing are necessary in order to optimize linear growth, and whether the nature of remission is related to improvement of growth.

The importance of sustained remission early in the course of disease is magnified by the rather narrow window for growth that exists till adult height is achieved. Hood et al. [78] have recently demonstrated that most patients with IBD attain adult height within normal timing for the population suggesting that despite more common pubertal delay, timing for linear growth cessation is not delayed accordingly.

Naturally, studying the impact of a single therapeutic approach on growth is confounded by common changes in therapy and the frequent use of combination therapy. Moreover, growth estimation cannot be made in parallel to the timing of treatment as there is an inherent interval of several months before the effect of therapy on growth can be reliably measured. However, there is sufficient evidence to draw crude conclusions regarding the efficacy of various therapeutic approaches for short and long-term growth optimization.

### Exclusive enteral nutrition (EEN)

EEN is now considered as the first line therapy for pediatric CD. It is administered exclusively for 6-8 weeks, followed by reintroduction of normal feeding over a short period of time. Polymeric formulas have shown similar efficacy in comparison to elemental formulas [79] with inherent advantages including better palatability, reduction of the need for tube feeding and improved adherence [80]. In children, EEN was demonstrated to be as effective as corticosteroids in inducing

remission [81-83] and was superior in inducing mucosal healing [84,85]. EEN downregulates pro-inflammatory cytokines including TNF- $\alpha$  and IL-6 [86,87], induces prompt reduction in inflammatory markers with a consequent increase in IGF-1 and IGFBP-3 within 14 days of treatment [85,88,89]. The combination of nutritional supplementation and anti-inflammatory effect of EEN is associated with short-term improvement in height velocity in comparison to steroid therapy [81]. The long-term effect of inducing remission with EEN on growth is limited and though recurrent corticosteroid treatment can be avoided or at least postponed [90], previous studies have described improvement in BMI but not in linear growth [90-92]. However, first Papadopoulou et al. [93] and recently, Lambert et al. [94] have shown a significant (though small) benefit in height z-score at 1 and 2 years respectively, following a single course of EEN at diagnosis in comparison with initial corticosteroid treatment. Several strategies for long-term partial enteral nutrition exist including cyclical EEN (EEN for 1 month in every 4 months) and nocturnal EEN (EEN 4-7 nights per week with unrestricted daytime diet) which showed, in a retrospective cohort, significant benefit on growth compared to no nutritional treatment [95], or other conventional therapies [96]. It may be concluded that when growth is concerned, EEN is superior to corticosteroid therapy in the short-term and that nutritional supplementation during maintenance phase may contribute to linear growth. However, the benefits of long-term enteral nutrition are not clear and are restricted by compliance difficulties.

### Immunosuppressive therapy

Azathioprine and 6-mercaptopurine (6-MP) are commonly used as first line maintenance therapy for CD and for moderate-severe UC. These drugs allow corticosteroid withdrawal and maintain clinical remission at the first 2 years of treatment in 44%-80% of pediatric patients [97-99]. The only pediatric CD randomized, placebo controlled trial reported by Markowitz et al. [97] failed to demonstrate any benefit of 6-MP on growth parameters compared to placebo after 18 months of follow-up. This study is limited by small sample size and relatively high number of withdrawals from the placebo arm. Nevertheless, it seems that the use of azathioprine/6-MP is associated with only minimal effect on growth if any [100]. Methotrexate (MTX) is a therapeutic alternative for children with CD either as first line maintenance treatment or for children unresponsive or intolerant to thiopurines. Data on the efficacy of MTX is limited but it appears that it is more or less similar to thiopurines in both adults [101,102] and children [103-105]. A retrospective study by Turner et al. [104] showed a significant effect on linear growth manifested as an improvement in mean height velocity z-score from -1.9 to -0.14 at one year. In contrast, Malik et al. [12] found that height SDS was associated negatively with the use of either azathioprine or methotrexate. Unfortunately, current data is insufficient to draw any firm conclusions.

### Biologic treatment

Approved biologic agents for the treatment of pediatric CD include infliximab (IFX) and adalimumab (ADA) while only infliximab is approved for pediatric UC. Both agents were shown to be safe and well tolerated [106,107] with established efficacy in inducing and maintaining prolonged remission in pediatric IBD patients [108-112]. Anti-TNF agents have a promising potential for improving growth as they were shown to induce prompt mucosal healing [110,111], reverse the pro-inflammatory cytokines cascade [113] and enable prolonged

corticosteroid withdrawal [108-110]. Indeed, numerous studies suggest an increase in height velocity and height z-score following prolonged anti-TNF treatment, providing treatment is undertaken early enough prior to or during puberty [4,106,111,112,114-120]. In contrast, Sinitsky et al. [121] reported a significant improvement in BMI z-score at one year of treatment with IFX in children with CD but failed to show significant changes in height velocity. Pfefferkorn et al. [4] did find an improvement in height velocity z-scores during the first two years following diagnosis of CD though no difference between therapy regimens was noted. This discrepancy could be attributed to a relatively advanced pubertal stage in the first study and to heterogeneity in therapeutic regimens in the second one. The REACH study which is the only randomized controlled trial using anti-TNF treatment performed in pediatric CD to date has demonstrated an increase in height z-score of 0.5 at 1 year of treatment [109] with a greater beneficial effect in children with at least 1-year delay in bone age and those who were on corticosteroids at enrollment. Recently, Walters et al. [122] published results from the prospective observational RISK study which highlighted the benefit of early institution of anti-TNF therapy for the resumption of growth in pediatric CD patients. In comparison to early immunomodulators or no immunomodulators introduction only the early anti-TNF treated group increased their height z-score at 12 months (a significant difference of +0.25). The ability of TNF- $\alpha$  blockade to restore liver GH signaling was shown by DiFedele in a murine colitis model [123], however, a study by Vespasiani et al. [124] failed to demonstrate normalization of IGF-1 levels during maintenance therapy with infliximab. IGF-1 levels did increase during induction though they returned to low baseline levels during maintenance. The short-term effect of anti-TNF therapy on IGF-1 was supported by Eivindson et al. [125]. DeBoer et al. [126] have shown, using a dextran sodium sulfate induced colitis model, that mice treated with anti-TNF- $\alpha$  antibodies demonstrated a partial normalization of pubertal timing coincident with decreased systemic inflammation. Bone metabolism is also positively affected by infliximab, at least in the short-term, manifested by improved bone formation markers [127,128].

## Surgery

Operative treatment for refractory UC is ultimately curative and should be considered for corticosteroid-dependent children with associated linear growth impairment before or after infliximab failure. Nicholls et al. have confirmed that colectomy restores growth as long as it is performed early enough in the course of puberty [129,130].

Surgical intervention is a valid and sometimes the optimal treatment for CD children with short segment ileal disease, localized internal penetrating or stricturing disease. Despite almost inevitable recurrence, the period of remission induced by surgery, which is affected by the anatomic distribution of inflammation [131,132] allows significant catch-up growth when it is performed prior to or at early puberty [12,132,133] and if no residual disease remains [40]. Recently, Blackburn et al. [134] failed to demonstrate an increase in linear growth in children who underwent surgical procedures, mainly for stricturing disease, however, these results might be confounded by relatively advanced age at surgery and lack of data regarding pubertal stage. Mechanistically, resection of the inflamed segment reduces the inflammatory burden of the disease thus enables reinstatement of growth. Beattie et al. did demonstrate a positive effect, though not statistically significant, of timely surgical intervention on the GH/IGF-1 axis [90].

## Hormonal therapy

As spontaneous and stimulated levels of GH in children and adolescents with IBD appear to be normal [43], the rationale of GH treatment in order to promote growth seems futile. It remains unclear whether high doses of recombinant GH (rhGH) can overcome the inhibitory effects of inflammatory cytokines and the resulting GH resistance. Few studies have tried to answer this question. A small case control study has shown short-term (up to 1 year) therapeutic efficacy of rhGH in improving linear growth in children with CD standard maintenance therapy [135]. In contrast, a small randomized controlled trial by Calenda et al. [136] failed to reveal any difference in growth parameters between children treated or untreated with rhGH. These findings are supported by Wong et al. [137] though again, this study was also underpowered. Two more recent randomized controlled trials which examined the effect of rhGH on linear growth in larger groups of children with CD have succeeded to demonstrate a significant beneficial effect at 6 and 12 month respectively [138,139] with an increase in height velocity from 4.5 to 10.8 cm/year and in height z-score from -1.1 to -0.4, respectively. Another postulated mechanism of rhGH which might affect growth is its demonstrated ability, in animal studies, to reduce intestinal permeability and to accelerate mucosal healing [140]. Larger studies are necessary in order to further clarify the effect of rhGH therapy on growth and final height of children with IBD.

Sex steroids treatment has the potential to induce puberty and promote growth in children with growth failure combined with significant delay in puberty. In the only reported trial Mason et al. described 8 males with delayed puberty who responded positively to testosterone treatment by advancing puberty and improving height velocity from 1.6 to 6.9 cm/year [141]. Larger studies are necessary in order to further clarify the role of sex steroids therapy in children with IBD whom impaired growth is predominantly driven by delayed puberty.

## Conclusions

Children with IBD who present with significant growth retardation during the course of their disease pose a particular challenge for the treating physician. Current data do suggest that a proportion of children with IBD will not achieve their expected final height. Thus, a timely and prompt recognition of growth impairment combined with an aggressive therapeutic approach offer the best chance for catch-up growth. Flares should be approached similarly with early adjustment of treatment in order to re-institute sustained remission. The use of corticosteroids should be minimized as much as possible. EEN should be considered as the first-line treatment in suitable pediatric patients with CD while patients with extensive or penetrating disease who experience significant growth retardation should be offered a "top down" approach, that is, early introduction of anti-TNF therapy for induction and maintenance. Finally, in patients with steroid dependent UC and in selected CD patients surgery is the most suitable therapeutic option, and it should not be delayed until late stages of puberty when the "interventional window of opportunity" is being closed.

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