Review Article   **Open Access**

Impact of Therapeutic Strategies on Growth in Pediatric Inflammatory Bowel Disease

Amit Assa[1]* and Raanan Shamir[1,2]

[1]*Institute of Gastroenterology, Nutrition and Liver Disease, Schneider Children's Medical Center, Petach-Tikva, Israel*

[2]*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

***Corresponding author:** Amit Assa, MD, MHA, Institute of Gastroenterology, Nutrition and Liver Disease, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel- Aviv University, 14 Kaplan St. Petach-Tikva, 49202, Israel, Tel: 972-3-9253672; Fax: 972-3-9253104; E-mail: dr.amit.assa@gmail.com

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 3rd 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 ≥ 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).
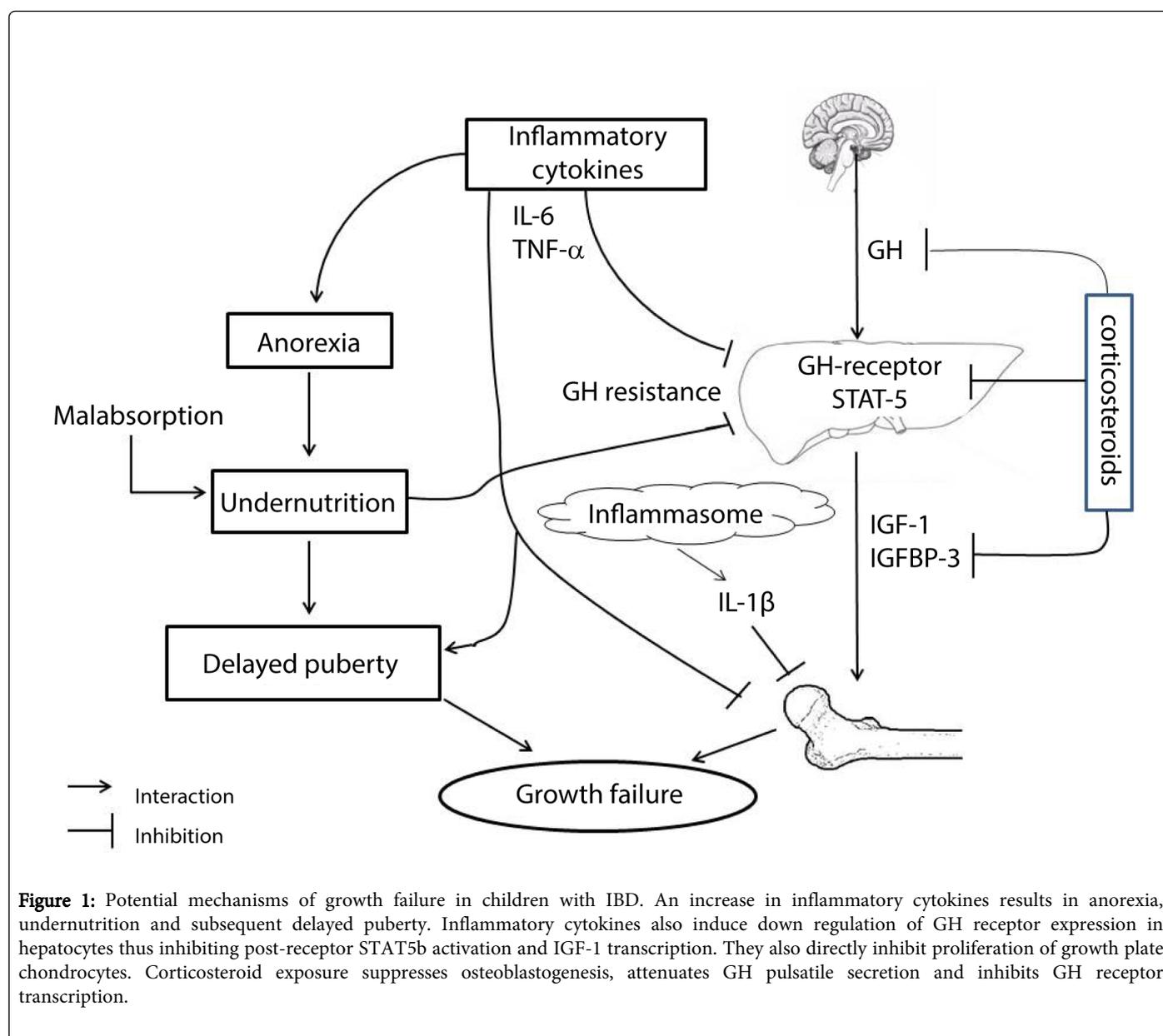

Figure 1: Potential mechanisms of growth failure in children with IBD. An increase in inflammatory cytokines results in anorexia, undernutrition and subsequent delayed puberty. Inflammatory cytokines also induce down regulation of GH receptor expression in hepatocytes thus inhibiting post-receptor STAT5b 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-α) 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-α, interferon-γ 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-α [44,45]. TNF-α 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-α and IL-1β 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-κB 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-1β/IL-18 into their mature form [65]. As mentioned before, high levels of IL-1β 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-α and IL-1α 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-α 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-α 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 reemission 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-α 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-α 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 reinstitution 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.

References

1. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, et al. (2011) Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 17: 1314-1321.

2. Wong SC, Macrae VE, McGrogan P, Ahmed SF (2006) The role of pro-inflammatory cytokines in inflammatory bowel disease growth retardation. J Pediatr Gastroenterol Nutr 43: 144-155.

3. Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM (1993) Growth and clinical course of children with Crohn's disease. Gut 34: 939-943.

4. Pfefferkorn M, Burke G, Griffiths A, Markowitz J, Rosh J, et al. (2009) Growth abnormalities persist in newly diagnosed children with crohn disease despite current treatment paradigms. J Pediatr Gastroenterol Nutr 48: 168-174.

5. Kirschner BS (1990) Growth and development in chronic inflammatory bowel disease. Acta Paediatr Scand Suppl 366: 98-104.

6. Kanof ME, Lake AM, Bayless TM (1988) Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology 95: 1523-1527.

7. Hildebrand H, Karlberg J, Kristiansson B (1994) Longitudinal growth in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 18: 165-173.

8. Markowitz J, Grancher K, Rosa J, Aiges H, Daum F (1993) Growth failure in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 16: 373-380.

9. Sawczenko A, Sandhu BK (2003) Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child 88: 995-1000.

10. Wine E, Reif SS, Leshinsky-Silver E, Weiss B, Shaoul RR, et al. (2004) Pediatric Crohn's disease and growth retardation: the role of genotype, phenotype, and disease severity. Pediatrics 114: 1281-1286.

11. Gupta N, Lustig RH, Kohn MA, McCracken M, Vittinghoff E (2011) Sex differences in statural growth impairment in Crohn's disease: role of IGF-1. Inflamm Bowel Dis 17: 2318-2325.

12. Malik S, Mason A, Bakhshi A, Young D, Bishop J, et al. (2012) Growth in children receiving contemporary disease specific therapy for Crohn's disease. Arch Dis Child 97: 698-703.

13. Timmer A, Behrens R, Buderus S, Findeisen A, Hauer A et al. (2011) Childhood onset inflammatory bowel disease: predictors of delayed diagnosis from the CEDATA German-language pediatric inflammatory bowel disease registry. J Pediatr 158: 467-473.

14. Sawczenko A, Ballinger AB, Savage MO, Sanderson IR (2006) Clinical features affecting final adult height in patients with pediatric-onset Crohn's disease. Pediatrics 118: 124-129.

15. D'Mello S, Trauernicht A, Ryan A, Bonkowski E, Willson T, et al. (2012) Innate dysfunction promotes linear growth failure in pediatric Crohn's disease and growth hormone resistance in murine ileitis. Inflamm Bowel Dis 18: 236-245.

16. Trauernicht AK, Steiner SJ (2012) Serum antibodies and anthropometric data at diagnosis in pediatric Crohn's disease. Dig Dis Sci 57: 1020-1025.

17. Mason A, Malik S, Russell RK, Bishop J, McGrogan P, et al. (2011) Impact of inflammatory bowel disease on pubertal growth. Horm Res Paediatr 76: 293-299.

18. De Greef E, Mahachie John JM, Hoffman I, Smets F, Van Biervliet S et al. (2013) Profile of pediatric Crohn's disease in Belgium. J Crohns Colitis 7:e588-598.

19. Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, et al. (2008) Guidelines for the management of growth failure in childhood inflammatory bowel disease. Inflamm Bowel Dis 14: 839-849.

20. Shamir R, Phillip M, Levine A (2007) Growth retardation in pediatric Crohn's disease: pathogenesis and interventions. Inflamm Bowel Dis 13: 620-628.

21. Lee JJ, Escher JC, Shuman MJ, Forbes PW, Delemarre LC, et al. (2010) Final adult height of children with inflammatory bowel disease is predicted by parental height and patient minimum height Z-score. Inflamm Bowel Dis 16: 1669-1677.

22. Savoye G, Salleron J, Gower-Rousseau C, Dupas JL, Vernier-Massouille G, et al. (2012) Clinical predictors at diagnosis of disabling pediatric Crohn's disease. Inflamm Bowel Dis 18: 2072-2078.

23. Kirschner BS, Klich JR, Kalman SS, deFavaro MV, Rosenberg IH (1981) Reversal of growth retardation in Crohn's disease with therapy emphasizing oral nutritional restitution. Gastroenterology 80: 10-15.

24. Thomas AG, Taylor F, Miller V (1993) Dietary intake and nutritional treatment in childhood Crohn's disease. J Pediatr Gastroenterol Nutr 17: 75-81.

25. Shamir R (2013) Nutrition and growth in inflammatory bowel disease. World Rev Nutr Diet 106: 156-161.

26. Weinstein TA, Levine M, Pettei MJ, Gold DM, Kessler BH, et al. (2003) Age and family history at presentation of pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr 37: 609-613.

27. Aiges H, Markowitz J, Rosa J, Daum F (1989) Home nocturnal supplemental nasogastric feedings in growth-retarded adolescents with Crohn's disease. Gastroenterology 97: 905-910.

28. Ballinger A, El-Haj T, Perrett D, Turvill J, Obeid O, et al. (2000) The role of medial hypothalamic serotonin in the suppression of feeding in a rat model of colitis. Gastroenterology 118: 544-553.

29. Gerasimidis K, McGrogan P, Edwards CA (2011) The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. J Hum Nutr Diet 24: 313-326.

30. Papazian A, Minaire Y, Descos L, Andre C, Melange M, et al. (1981) Relationships between the extent of ileal lesion of resection and vitamin B12, bile salt and fat absorption. Hepatogastroenterology 28: 106-109.

31. Stokes MA, Hill GL (1993) Total energy expenditure in patients with Crohn's disease: measurement by the combined body scan technique. JPEN J Parenter Enteral Nutr 17: 3-7.

32. Cormier K, Mager D, Bannister L, Fortin M, Richards H, et al. (2005) Resting energy expenditure in the parenterally fed pediatric population with Crohn's disease. JPEN J Parenter Enteral Nutr 29: 102-107.

33. Wiskin AE, Wootton SA, Culliford DJ, Afzal NA, Jackson AA, et al. (2009) Impact of disease activity on resting energy expenditure in children with inflammatory bowel disease. Clin Nutr 28: 652-656.

34. Schneeweiss B, Lochs H, Zauner C, Fischer M, Wyatt J, et al. (1999) Energy and substrate metabolism in patients with active Crohn's disease. J Nutr 129: 844-848.

35. Gong J, Zuo L, Guo Z, Zhang L, Li Y, et al. (2014) Impact of Disease Activity on Resting Energy Expenditure and Body Composition in Adult Crohn's Disease: A Prospective Longitudinal Assessment. JPEN J Parenter Enteral Nutr .

36. Sasaki M, Johtatsu T, Kurihara M, Iwakawa H, Tanaka T, et al. (2010) Energy expenditure in Japanese patients with severe or moderate ulcerative colitis. J Clin Biochem Nutr 47: 32-36.

37. Azcue M, Rashid M, Griffiths A, Pencharz PB (1997) Energy expenditure and body composition in children with Crohn's disease: effect of enteral nutrition and treatment with prednisolone. Gut 41: 203-208.

38. Varille V, Cézard JP, de Lagausie P, Bellaiche M, Tounian P, et al. (1996) Resting energy expenditure before and after surgical resection of gut lesions in pediatric Crohn's disease. J Pediatr Gastroenterol Nutr 23: 13-19.

39. Wong SC, Smyth A, McNeill E, Galloway PJ, Hassan K, et al. (2010) The growth hormone insulin-like growth factor 1 axis in children and adolescents with inflammatory bowel disease and growth retardation. Clin Endocrinol (Oxf) 73: 220-228.

40. Ballinger AB, Azooz O, El-Haj T, Poole S, Farthing MJ (2000) Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of undernutrition in a rat model of colitis. Gut 46: 694-700.

41. Roberts-Thomson IC, Fon J, Uylaki W, Cummins AG, Barry S (2011) Cells, cytokines and inflammatory bowel disease: a clinical perspective. Expert Rev Gastroenterol Hepatol 5: 703-716.

42. Tenore A, Berman WF, Parks JS, Bongiovanni AM (1977) Basal and stimulated serum growth hormone concentrations in inflammatory bowel disease. J Clin Endocrinol Metab 44: 622-628.

43. Kirschner BS, Sutton MM (1986) Somatomedin-C levels in growth-impaired children and adolescents with chronic inflammatory bowel disease. Gastroenterology 91: 830-836.

44. Thayu M, Denson LA, Shults J, Zemel BS, Burnham JM, et al. (2010) Determinants of changes in linear growth and body composition in incident pediatric Crohn's disease. Gastroenterology 139: 430-438.

45. Braegger CP, Torresani T, Murch SH, Savage MO, Walker-Smith JA, et al. (1993) Urinary growth hormone in growth-impaired children with chronic inflammatory bowel disease. J Pediatr Gastroenterol Nutr 16: 49-52.

46. Buzzelli MD, Nagarajan M, Radtka JF, Shumate ML, Navaratnarajah M, et al. (2008) Nuclear factor-kappaB mediates the inhibitory effects of tumor necrosis factor-alpha on growth hormone-inducible gene expression in liver. Endocrinology 149: 6378-6388.

47. Ram PA, Waxman DJ (2000) Role of the cytokine-inducible SH2 protein CIS in desensitization of STAT5b signaling by continuous growth hormone. J Biol Chem 275: 39487-39496.

48. Han X, Benight N, Osuntokun B, Loesch K, Frank SJ, et al. (2007) Tumour necrosis factor alpha blockade induces an anti-inflammatory growth hormone signalling pathway in experimental colitis. Gut 56: 73-81.

49. Denson LA, Menon RK, Shaufl A, Bajwa HS, Williams CR, et al. (2001) TNF-alpha downregulates murine hepatic growth hormone receptor expression by inhibiting Sp1 and Sp3 binding. J Clin Invest 107: 1451-1458.

50. Bross DA, Leichtner AM, Zurakowski D, Law T, Bousvaros A (1996) Elevation of serum interleukin-6 but not serum-soluble interleukin-2 receptor in children with Crohn's disease. J Pediatr Gastroenterol Nutr 23: 164-171.

51. De Benedetti F, Meazza C, Oliveri M, Pignatti P, Vivarelli M, et al. (2001) Effect of IL-6 on IGF binding protein-3: a study in IL-6 transgenic mice and in patients with systemic juvenile idiopathic arthritis. Endocrinology 142: 4818-4826.

52. De Benedetti F, Alonzi T, Moretta A, Lazzaro D, Costa P, et al. (1997) Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. J Clin Invest 99: 643-650.

53. Ballinger A (2002) Fundamental mechanisms of growth failure in inflammatory bowel disease. Horm Res 58 Suppl 1: 7-10.

54. Sawczenko A, Azooz O, Paraszczuk J, Idestrom M, Croft NM, et al. (2005) Intestinal inflammation-induced growth retardation acts through IL-6 in rats and depends on the -174 IL-6 G/C polymorphism in children. Proc Natl Acad Sci U S A 102: 13260-13265.

55. Eivindson M, Nielsen JN, Grønbaek H, Flyvbjerg A, Hey H (2005) The insulin-like growth factor system and markers of inflammation in adult patients with inflammatory bowel disease. Horm Res 64: 9-15.

56. Kritsch KR, Murali S, Adamo ML, Ney DM (2002) Dexamethasone decreases serum and liver IGF-I and maintains liver IGF-I mRNA in parenterally fed rats. Am J Physiol Regul Integr Comp Physiol 282: R528-536.

57. Sederquist B, Fernandez-Vojvodich P, Zaman F, Savendahl L (2014) Impact of inflammatory cytokines on longitudinal bone growth. J Mol Endocrinol .

58. Mårtensson K, Chrysis D, Sävendahl L (2004) Interleukin-1beta and TNF-alpha act in synergy to inhibit longitudinal growth in fetal rat metatarsal bones. J Bone Miner Res 19: 1805-1812.

59. Ahmed SF, Sävendahl L (2009) Promoting growth in chronic inflammatory disease: lessons from studies of the growth plate. Horm Res 72 Suppl 1: 42-47.

60. Koniaris SG, Fisher SE, Rubin CT, Chawla A (1997) Experimental colitis impairs linear bone growth independent of nutritional factors. J Pediatr Gastroenterol Nutr 25: 137-141.

61. Aguilera M, Darby T2, Melgar S3 (2014) The complex role of inflammasomes in the pathogenesis of Inflammatory Bowel Diseases - Lessons learned from experimental models. Cytokine Growth Factor Rev .

62. McAlindon ME, Hawkey CJ, Mahida YR (1998) Expression of interleukin 1 beta and interleukin 1 beta converting enzyme by intestinal macrophages in health and inflammatory bowel disease. Gut 42: 214-219.

63. Monteleone G, Trapasso F, Parrello T, Biancone L, Stella A, et al. (1999) Bioactive IL-18 expression is up-regulated in Crohn's disease. J Immunol 163: 143-147.

64. Villani AC, Lemire M, Fortin G, Louis E, Silverberg MS, et al. (2009) Common variants in the NLRP3 region contribute to Crohn's disease susceptibility. Nat Genet 41: 71-76.

65. Martinon F, Burns K, Tschopp J (2002) The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 10: 417-426.

66. Ludwiczek O, Vannier E, Borggraefe I, Kaser A, Siegmund B, et al. (2004) Imbalance between interleukin-1 agonists and antagonists: relationship to severity of inflammatory bowel disease. Clin Exp Immunol 138: 323-329.

67. Ballinger AB, Savage MO, Sanderson IR (2003) Delayed puberty associated with inflammatory bowel disease. Pediatr Res 53: 205-210.

68. Azooz OG, Farthing MJ, Savage MO, Ballinger AB (2001) Delayed puberty and response to testosterone in a rat model of colitis. Am J Physiol Regul Integr Comp Physiol 281: R1483-1491.

69. Hong CY, Park JH, Ahn RS, Im SY, Choi HS, et al. (2004) Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha. Mol Cell Biol 24: 2593-2604.

70. Rettori V, Belova N, Kamat A, Lyson K, Gimeno M, et al. (1994) Blockade by interleukin-1-alpha of nitricoxidergic control of luteinizing hormone-releasing hormone release in vivo and in vitro. Neuroimmunomodulation 1: 86-91.

71. Mantzoros CS, Flier JS, Rogol AD (1997) A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J Clin Endocrinol Metab 82: 1066-1070.

72. Vihinen MK, Kolho KL, Ashorn M, Verkasalo M, Raivio T (2008) Bone turnover and metabolism in paediatric patients with inflammatory bowel disease treated with systemic glucocorticoids. Eur J Endocrinol 159: 693-698.

73. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC (1998) Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest 102: 274-282.

74. Giustina A, Wehrenberg WB (1992) The role of glucocorticoids in the regulation of Growth Hormone secretion: mechanisms and clinical significance. Trends Endocrinol Metab 3: 306-311.

75. Jux C, Leiber K, Hügel U, Blum W, Ohlsson C, et al. (1998) Dexamethasone impairs growth hormone (GH)-stimulated growth by suppression of local insulin-like growth factor (IGF)-I production and expression of GH- and IGF-I-receptor in cultured rat chondrocytes. Endocrinology 139: 3296-3305.

76. Kundhal P, Zachos M, Holmes JL, Griffiths AM (2001) Controlled ileal release budesonide in pediatric Crohn disease: efficacy and effect on growth. J Pediatr Gastroenterol Nutr 33: 75-80.

77. Lee JJ, Essers JB, Kugathasan S, Escher JC, Lettre G, et al. (2010) Association of linear growth impairment in pediatric Crohn's disease and a known height locus: a pilot study. Ann Hum Genet 74: 489-497.

78. Hood HC, Cohen LE, Lee JJ (2011) Late adolescent linear growth pattern in pediatric-onset inflammatory bowel disease. J Pediatr Gastroenterol Nutr 53: 246-249.

79. Ludvigsson JF, Krantz M, Bodin L, Stenhammar L, Lindquist B (2004) Elemental versus polymeric enteral nutrition in paediatric Crohn's disease: a multicentre randomized controlled trial. Acta Paediatr 93: 327-335.

80. Rodrigues AF, Johnson T, Davies P, Murphy MS (2007) Does polymeric formula improve adherence to liquid diet therapy in children with active Crohn's disease? Arch Dis Child 92: 767-770.

81. Heuschkel RB, Menache CC, Megerian JT, Baird AE (2000) Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr 31: 8-15.

82. Soo J, Malik BA, Turner JM, Persad R, Wine E, et al. (2013) Use of exclusive enteral nutrition is just as effective as corticosteroids in newly diagnosed pediatric Crohn's disease. Dig Dis Sci 58: 3584-3591.

83. Day AS, Whitten KE, Sidler M, Lemberg DA (2008) Systematic review: nutritional therapy in paediatric Crohn's disease. Aliment Pharmacol Ther 27: 293-307.

84. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, et al. (2006) Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol 4: 744-753.

85. Fell JM, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, et al. (2000) Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. Aliment Pharmacol Ther 14: 281-289.

86. Bannerjee K, Camacho-Hübner C, Babinska K, Dryhurst KM, Edwards R, et al. (2004) Anti-inflammatory and growth-stimulating effects precede nutritional restitution during enteral feeding in Crohn disease. J Pediatr Gastroenterol Nutr 38: 270-275.

87. Mingrone G, Greco AV, Benedetti G, Capristo E, Semeraro R, et al. (1996) Increased resting lipid oxidation in Crohn's disease. Dig Dis Sci 41: 72-76.

88. Beattie RM, Schiffrin EJ, Donnet-Hughes A, Huggett AC, Domizio P, et al. (1994) Polymeric nutrition as the primary therapy in children with small bowel Crohn's disease. Aliment Pharmacol Ther 8: 609-615.

89. Beattie RM, Camacho-Hübner C, Wacharasindhu S, Cotterill AM, Walker-Smith JA, et al. (1998) Responsiveness of IGF-I and IGFBP-3 to therapeutic intervention in children and adolescents with Crohn's disease. Clin Endocrinol (Oxf) 49: 483-489.

90. Knight C, El-Matary W, Spray C, Sandhu BK (2005) Long-term outcome of nutritional therapy in paediatric Crohn's disease. Clin Nutr 24: 775-779.

91. Cameron FL, Gerasimidis K, Papangelou A, Missiou D, Garrick V, et al. (2013) Clinical progress in the two years following a course of exclusive enteral nutrition in 109 paediatric patients with Crohn's disease. Aliment Pharmacol Ther 37: 622-629.

92. Vasseur F, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, et al. (2010) Nutritional status and growth in pediatric Crohn's disease: a population-based study. Am J Gastroenterol 105: 1893-1900.

93. Papadopoulou A, Rawashdeh MO, Brown GA, McNeish AS, Booth IW (1995) Remission following an elemental diet or prednisolone in Crohn's disease. Acta Paediatr 84: 79-83.

94. Lambert B, Lemberg DA, Leach ST, Day AS (2012) Longer-term outcomes of nutritional management of Crohn's disease in children. Dig Dis Sci 57: 2171-2177.

95. Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, et al. (1996) Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut 38: 543-548.

96. Belli DC, Seidman E, Bouthillier L, Weber AM, Roy CC, et al. (1988) Chronic intermittent elemental diet improves growth failure in children with Crohn's disease. Gastroenterology 94: 603-610.

97. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F (2000) A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology 119: 895-902.

98. Panés J, López-Sanromán A, Bermejo F, García-Sánchez V, Esteve M, et al. (2013) Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology 145: 766-774.

99. Punati J, Markowitz J, Lerer T, Hyams J, Kugathasan S, et al. (2008) Effect of early immunomodulator use in moderate to severe pediatric Crohn disease. Inflamm Bowel Dis 14: 949-954.

100. Fuentes D, Torrente F, Keady S, Thirrupathy K, Thomson MA, et al. (2003) High-dose azathioprine in children with inflammatory bowel disease. Aliment Pharmacol Ther 17: 913-921.

101. Wahed M, Louis-Auguste JR, Baxter LM, Limdi JK, McCartney SA, et al. (2009) Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine /mercaptopurine. Aliment Pharmacol Ther 30: 614-620.

102. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, et al. (2000) A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med 342: 1627-1632.

103. Aloi M, Di Nardo G, Conte F, Mazzeo L, Cavallari N, et al. (2010) Methotrexate in paediatric ulcerative colitis: a retrospective survey at a single tertiary referral centre. Aliment Pharmacol Ther 32: 1017-1022.

104. Turner D, Grossman AB, Rosh J, Kugathasan S, Gilman AR, et al. (2007) Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. Am J Gastroenterol 102: 2804-2812.

105. Uhlen S, Belbouab R, Narebski K, Goulet O, Schmitz J, et al. (2006) Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. Inflamm Bowel Dis 12: 1053-1057.

106. Ruemmele FM, Lachaux A, Cézard JP, Morali A, Maurage C, et al. (2009) Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis 15: 388-394.

107. Caspersen S, Elkjaer M, Riis L, Pedersen N, Mortensen C, et al. (2008) Infliximab for inflammatory bowel disease in Denmark 1999-2005: clinical outcome and follow-up evaluation of malignancy and mortality. Clin Gastroenterol Hepatol 6: 1212-1217.

108. Hyams JS, Lerer T, Griffiths A, PfefferkornM, Kugathasan S, et al. (2009) Long-term outcomeof maintenance infliximab therapy inchildren with Crohn's disease. Inflamm Bowel Dis 15: 816-822.

109. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, et al. (2007) Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 132: 863-873.

110. Borrelli O, Bascietto C, Viola F, Bueno de Mesquita M, Barbato M, et al. (2004) Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Dig Liver Dis 36: 342-347.

111. Baldassano R, Braegger CP, Escher JC, DeWoody K, Hendricks DF, et al. (2003) Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. Am J Gastroenterol 98: 833-838.

112. Assa A, Hartman C, Weiss B, Broide E, Rosenbach Y, et al. (2013) Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. J Crohns Colitis 7: 369-376.

113. Peake ST, Bernardo D, Mann ER, Al-Hassi HO, Knight SC, et al. (2013) Mechanisms of action of anti-tumor necrosis factor Î± agents in Crohn's disease. Inflamm Bowel Dis 19: 1546-1555.

114. Walters TD, Gilman AR, Griffiths AM (2007) Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. Inflamm Bowel Dis 13: 424-430.

115. Malik S, Wong SC, Bishop J, Hassan K, McGrogan P, et al. (2011) Improvement in growth of children with Crohn disease following anti-TNF-Î± therapy can be independent of pubertal progress and glucocorticoid reduction. J Pediatr Gastroenterol Nutr 52: 31-37.

116. Cezard JP, Nouaili N, Talbotec C, Hugot JP, Gobert JG, et al. (2003) A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe pediatric crohn disease. J Pediatr Gastroenterol Nutr 36: 632-636.

117. Gouldthorpe O, Catto-Smith AG, Alex G, Simpson D (2013) Loss of response to long-term infliximab therapy in children with Crohn's disease. Pharmaceuticals (Basel) 6: 1322-1334.

118. Malik S, Ahmed SF, Wilson ML, Shah N, Loganathan S, et al. (2012) The effects of anti-TNF-α treatment with adalimumab on growth in children with Crohn's disease (CD). J Crohns Colitis 6: 337-344.

119. Pichler J, Hanslik A, Huber WD, Aufricht C, Bidmon-Fliegenschnee B (2014) Paediatric patients with inflammatory bowel disease who received infliximab experienced improved growth and bone health. Acta Paediatr 103: e69-75.

120. Crombé V, Salleron J, Savoye G, Dupas JL, Vernier-Massouille G, et al. (2011) Long-term outcome of treatment with infliximab in pediatric-

onset Crohn's disease: a population-based study. Inflamm Bowel Dis 17: 2144-2152.

121. Sinitsky DM, Lemberg DA, Leach ST, Bohane TD, Jackson R, et al. (2010) Infliximab improves inflammation and anthropometric measures in pediatric Crohn's disease. J Gastroenterol Hepatol 25: 810-816.

122. Walters TD, Kim MO, Denson LA, Griffiths AM, Dubinsky M, et al. (2014) Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. Gastroenterology 146: 383-391.

123. DiFedele LM, He J, Bonkowski EL, Han X, Held MA, et al. (2005) Tumor necrosis factor alpha blockade restores growth hormone signaling in murine colitis. Gastroenterology 128: 1278-1291.

124. Vespasiani Gentilucci U1, Caviglia R, Picardi A, Carotti S, Ribolsi M, et al. (2005) Infliximab reverses growth hormone resistance associated with inflammatory bowel disease. Aliment Pharmacol Ther 21: 1063-1071.

125. Eivindson M, Grønbaek H, Skogstrand K, Thorsen P, Frystyk J, et al. (2007) The insulin-like growth factor (IGF) system and its relation to infliximab treatment in adult patients with Crohn's disease. Scand J Gastroenterol 42: 464-470.

126. Deboer MD, Steinman J, Li Y (2012) Partial normalization of pubertal timing in female mice with DSS colitis treated with anti-TNF-α antibody. J Gastroenterol 47: 647-654.

127. Franchimont N, Putzeys V, Collette J, Vermeire S, Rutgeerts P, et al. (2004) Rapid improvement of bone metabolism after infliximab treatment in Crohn's disease. Aliment Pharmacol Ther 20: 607-614.

128. Veerappan SG, O'Morain CA, Daly JS, Ryan BM (2011) Review article: the effects of antitumour necrosis factor-α on bone metabolism in inflammatory bowel disease. Aliment Pharmacol Ther 33: 1261-1272.

129. Barrena S, Martínez L, Hernandez F, Lassaletta L, Lopez-Santamaria M, et al. (2011) Surgical treatment of chronic inflammatory bowel disease in children. Pediatr Surg Int 27: 385-390.

130. Nicholls S, Vieira MC, Majrowski WH, Shand WS, Savage MO, et al. (1995) Linear growth after colectomy for ulcerative colitis in childhood. J Pediatr Gastroenterol Nutr 21: 82-86.

131. Davies G, Evans CM, Shand WS, Walker-Smith JA (1990) Surgery for Crohn's disease in childhood: influence of site of disease and operative procedure on outcome. Br J Surg 77: 891-894.

132. Griffiths AM, Wesson DE, Shandling B, Corey M, Sherman PM (1991) Factors influencing postoperative recurrence of Crohn's disease in childhood. Gut 32: 491-495.

133. Baldassano RN, Han PD, Jeshion WC, Berlin JA, Piccoli DA, et al. (2001) Pediatric Crohn's disease: risk factors for postoperative recurrence. Am J Gastroenterol 96: 2169-2176.

134. Blackburn SC, Wiskin AE, Barnes C, Dick K, Afzal NA, et al. (2014) Surgery for children with Crohn's disease: indications, complications and outcome. Arch Dis Child 99: 420-426.

135. Heyman MB, Garnett EA, Wojcicki J, Gupta N, Davis C, et al. (2008) Growth hormone treatment for growth failure in pediatric patients with Crohn's disease. J Pediatr 153: 651-658, 658.

136. Calenda KA, Schornagel IL, Sadeghi-Nejad A, Grand RJ (2005) Effect of recombinant growth hormone treatment on children with Crohn's disease and short stature: a pilot study. Inflamm Bowel Dis 11: 435-441.

137. Wong SC, Hassan K, McGrogan P, Weaver LT, Ahmed SF (2007) The effects of recombinant human growth hormone on linear growth in children with Crohn's disease and short stature. J Pediatr Endocrinol Metab 20: 1315-1324.

138. Wong SC, Kumar P, Galloway PJ, Blair JC, Didi M, et al. (2011) A preliminary trial of the effect of recombinant human growth hormone on short-term linear growth and glucose homeostasis in children with Crohn's disease. Clin Endocrinol (Oxf) 74: 599-607.

139. Denson LA, Kim MO, Bezold R, Carey R, Osuntokun B, et al. (2010) A randomized controlled trial of growth hormone in active pediatric Crohn disease. J Pediatr Gastroenterol Nutr 51: 130-139.

140. Chen K, Nezu R, Inoue M, Wasa M, Iiboshi Y, et al. (1997) Beneficial effects of growth hormone combined with parenteral nutrition in the management of inflammatory bowel disease: an experimental study. Surgery 121: 212-218.

141. Mason A, Wong SC, McGrogan P, Ahmed SF (2011) Effect of testosterone therapy for delayed growth and puberty in boys with inflammatory bowel disease. Horm Res Paediatr 75: 8-13.