Impact of Disease and Treatments on Growth and Puberty of Pediatric Patients with Inflammatory Bowel Disease

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Introduction

Approximately one quarter of patients with inflammatory bowel disease (IBD) are diagnosed during childhood and adolescence [1], the majority around pubertal growth spurt. Pediatric IBD patients share the same clinical features and treatments as adults, with one major difference: growth failure and delayed puberty, found in a great proportion of pediatric patients and requiring particular attention [2]. One of the critical aims of pediatric IBD management is therefore optimization of growth, in order to reach target height.

The underlying mechanisms of growth retardation are not fully understood but may be primarily related to malnutrition and the effects of the inflammatory process on the growth hormone/insulin-like growth factor-1 axis or on the growth plate. Therefore, control of disease activity and mucosal healing are paramount to promote growth and adequate pubertal onset. Current therapeutic strategies for maintenance in IBD include anti-inflammatory drugs, immunosuppressives, and, more recently, biologic agents. Although these treatments are efficient in minimizing inflammation and inducing prolonged remission, their long-term effects on growth and final height remain controversial [3, 4].

Current therapeutic strategies for maintenance in IBD include anti-inflammatory drugs (i.e. mesalazine), immunosuppressives (i.e. azathioprine, methotrexate) and more recently biologic agents (i.e. infliximab, adalimumab). Although these treatments are efficient in minimizing inflammation and inducing prolonged remission, their long-term effects on growth and final height remain controversial [5, 6]. Furthermore, it is now well estab-
lished that glucocorticoids adversely impact linear growth [7]. Conversely, exclusive enteral nutrition is efficient in treating pediatric Crohn’s disease (CD) with a positive impact on growth when compared to glucocorticoid treatment [8,9].

The purpose of this review is to report the current knowledge on the effects of IBD and its treatments on linear growth and puberty of pediatric patients.

Growth Failure in Pediatric IBD

Although growth failure can be defined as a static height below the third percentile or a z-score below –2 standard deviations (SD), height velocity, expressed as a percentile or a SD score according to gender and age, appears to be a more accurate and sensitive parameter to identify growth retardation [10].

Most pediatric IBD patients are diagnosed around the pubertal growth spurt [11]. In addition to the expected weight loss, effects on growth and pubertal progression are often observed in up to 85 and 65% of pediatric patients with CD and ulcerative colitis (UC), respectively [12,13]. Subnormal linear growth is already present before the diagnosis in up to 88% of IBD patients [14], and a decrease in height velocity is the first clinical sign of CD in 46% of patients, before the appearance of gastrointestinal symptoms or weight loss [14]. Since many patients manifest their disease at the beginning of puberty before their growth spurt, we could expect an even stronger effect of the disease on growth and pubertal development. Therefore, it is not surprising that decreased adult height can be observed in 11–35% of patients with CD [15–17]. However, many studies did not take into account parental height, a powerful determinant of final height [15,18], which thus renders those results questionable. Conversely, only 3–10% of pediatric UC patients show growth retardation at diagnosis [17,19]. This difference between CD and UC can be explained by a much shorter interval between onset of symptoms and diagnosis in patients with UC. In addition, there is less systemic inflammation in UC and therefore less effect on bone, appetite and nutritional status.

In addition to growth retardation, delayed puberty and development are also frequently observed in pediatric IBD patients, especially those with CD experiencing prolonged active disease and/or frequent relapses [4,20]. Growth retardation and subsequent delayed puberty in children with IBD appears to be multifactorial; the principal determinants are malnutrition and the inflammatory process itself [13], but glucocorticoid therapy also plays a significant role. Malnutrition is mainly due to anorexia and reduced food intake induced by digestive symptoms and pro-inflammatory cytokines, coupled to increased energy expenditure, increased fecal losses, protein-losing enteropathy and malabsorption. However, malnutrition is also found in patients without malabsorption and is probably due to persistent inflammation [21,22]. As shown by several authors [23–25], children with active CD have significantly reduced energy intake, which normalizes during remission. Literature is controversial regarding the effect of IBD on resting energy expenditure (REE) [26–29], probably due to the way results are expressed. Even though REE tends to decrease in anorexia as a sparing mechanism, some authors found an increase in REE, presumably due to inflammation and body composition changes in IBD patients [26–29]. Indeed, increased lipid oxidation with a reduction of fat mass and an increase in percentage of lean mass has been shown in children and adults with CD [30–33]. No relationship between REE and disease activity could be demonstrated in a more recent study [26].

Pathogenesis of Growth Failure and Delayed Puberty in IBD (fig. 1)

Growth Hormone/Insulin-Like Growth Factor

In a colitis-induced rat model, Ballinger et al. [34] showed that, despite nutritional supplementation to restore energy intake and to increase weight gain, inflammation contributed to 30–40% of growth retardation. In rats with colitis, a negative correlation between plasma growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels was found, suggesting inflammation-induced hepatocyte resistance to GH stimulation. De Benedetti et al. [35] had previously suggested a direct effect of the pro-inflammatory cytokine interleukin (IL)-6 on the hypothalamic-pituitary-growth axis. Indeed, transgenic mice expressing high IL-6 levels had significantly reduced circulating IGF-1 levels despite a normal distribution of GH-producing pituitary cells and normal GH levels. Similarly, non-transgenic healthy mice treated with IL-6 also had a significant decrease in IGF-1 levels [35], and immunoneutralization of IL-6 in colitis-induced rats led to increased plasma IGF-1 levels and to improved linear growth [36]. Furthermore, administration of anti-tumor necrosis factor α (TNF-α) antibodies in colitis-induced rats increased linear growth but had no effect on IGF-1, suggesting that TNF-α sup-
presses growth by mechanisms other than a reduction in IGF-1 levels [36].

IGF-1 is mainly produced by the liver in response to GH stimulation. IGF-1 promotes the growth of long bones by stimulating the proliferation and hypertrophy of chondrocytes in the growth plate [37]. Growth retardation in pediatric IBD patients, particularly those with CD, is due to reduction of IGF-1 levels [38, 39]. This reduction is due to a decreased hepatic production as a consequence of the inflammatory process, particularly increased IL-6, and malnutrition [34, 35]. Indeed, in young (age range 8.8–26.1 years) and adult IBD patients [40, 41], IGF-1 levels are inversely correlated with inflammatory markers. Furthermore, chronic glucocorticoid therapy also decreases IGF-1 production [42, 43]. Finally, despite diminished plasma IGF-1 levels, pediatric CD patients have normal GH secretion, suggesting a certain degree of GH resistance [44].

**Growth Plate**

Colitis-induced rats have significantly larger resting and smaller proliferative zones in their growth plates when compared to healthy controls [45]. Colitis-induced rats also present with reduced terminal hypertrophic chondrocytes zone, responsible for matrix production and bone mineralization. These changes suggest an inhibition of proliferation and differentiation of cells responsible for growth. Furthermore, Martensson et al. [46] showed that the combination of TNF-α and IL-1β decreased the proliferation of growth plate chondrocytes and increased the apoptosis of proliferative chondrocytes in fetal rat metatarsal bones.

**Delayed Puberty**

Delayed puberty is a frequent finding in adolescents with chronic disease due to several mechanisms, namely inflammation and malnutrition [4, 20]. Azooz et al. [20] studied the effects of inflammation and malnutrition on puberty in three groups of rats. The first group had induced colitis and developed hypophagia with reduced weight gain. The second group consisted of rats without colitis fed the same amount as the first group (undernutrition), and the third group were healthy controls. Compared to the healthy controls, the females in the colitis-
induced group had their puberty delayed by 6.2 days; similarly, 57% of males also had delayed puberty. Delayed puberty also occurred in the undernutrition group, but to a lesser extent.

The pathogenic mechanisms for delayed puberty are not clearly established. Pro-inflammatory cytokines, such as IL-1α or TNF-α, have been shown to inhibit the production of sex steroids by acting directly on gonads or through the suppression of gonadotropin-releasing hormone (GnRH) secretion \[47, 48\]. Leptin has also been suggested to be a trigger of puberty onset \[49\]. Reduced leptin levels could be a possible pathogenic mechanism for delayed puberty due to inflammation-induced anorexia leading to a decrease in fat mass. However, DeBoer et al. \[50\] showed recently in a colitis-induced rat model that puberty delay is greater than what would be expected from the decrease in body weight and leptin level alone.

**Materials and Methods**

A MEDLINE search was performed for all studies published from 1970 to January 2011 using the Medical Subject Headings and key words: inflammatory bowel disease/Crohn’s disease/ulcerative colitis, growth, glucocorticoids or corticosteroids/budesonide/aminosalicylates or mesalazine/azathioprine or 6-mercaptopurine/methotrexate/infliximab/adalimumab/certolizumab/enteral nutrition/growth hormone, and ‘all child (0–18 years)’. Articles in any other language than English have been excluded. All studies retrieved were considered and data from relevant ones were presented in the text.

**Results**

The effects of the following drug treatments are shown in table 1.

**Glucocorticoids**

Glucocorticoids have a strong anti-inflammatory effect and remain widely used in moderate and severe acute flares in IBD patients, despite their large range of adverse effects, in particular growth retardation and decreased bone mineralization. Although glucocorticoids are very efficient to induce clinical remission, particularly in patients with UC, endoscopic remission only occurs in one third of patients \[51, 52\]. In fact, mucosal healing is observed in only 13–15% of patients with UC after 8 weeks of prednisolone treatment \[53\]. The mechanisms by which glucocorticoids suppress growth are multiple and complex. Children with active IBD already have abnormal bone turnover but glucocorticoid exposure has an acute suppressive effect on osteoblastogenesis, with promotion of osteoblast and osteocyte apoptosis, resulting in reduced bone formation \[54–56\]. This effect ceases with glucocorticoid withdrawal \[55\]. However, recent data suggest that high IL-6 levels in active IBD, despite their stimulating effect on osteoclastic bone resorption, could protect against glucocorticoid-induced suppression of bone formation \[54\]. Glucocorticoids decrease calcium absorption in the gut and increase calcium urinary excretion, with subsequent secondary hyperparathyroidism, further promoting bone resorption. Glucocorticoids mimic a GH deficiency state by interacting with the GH/IGF-1 axis. While in vitro studies show increased pituitary GH production after glucocorticoid exposure, in vivo studies indicate that GH secretion is actually attenuated due to an increase in hypothalamic somatostatin effect and a loss of pulsatile release \[43\]. Glucocorticoids also decrease the expression of hepatic GH receptors, leading to decreased IGF-1 production \[42\]. At the growth plate level, glucocorticoids impair GH receptor expression and IGF-1 production and activity \[57\]. Finally, glucocorticoids inhibit proliferation of chondrocytes and collagen synthesis. Despite all these mechanisms influencing linear growth, it remains unclear to what extent persistent inflammation and absence of mucosal healing are responsible of growth retardation in IBD children treated with glucocorticoids.

Budesonide is a glucocorticoid with a high topical and a low systemic activity (due to a high first-pass hepatic metabolism), resulting in reduced systemic adverse effects and adrenal suppression compared to other glucocorticoids \[58\]. Budesonide, although less effective than prednisone, should only be considered in mild to moderate pediatric CD with terminal ileal and right colonic involvement \[58, 59\]. Kundhal et al. \[60\] assessed the effects on growth of a 6-month administration of pH-dependent controlled ileal release budesonide in 6 prepubertal children with CD of the terminal ileon ± right colon. Despite weight gain and almost absence of gastrointestinal symptoms, linear growth was low in all children and even decreased when compared to the 6-month pretreatment period \[60\]. Currently, it is not possible to assess whether growth retardation under budesonide therapy is due to a glucocorticoid-suppressive effect on growth, an insufficiently controlled inflammation, or both.
Since the early 1980s, 5-aminosalicylates (5-ASA) (sulfasalazine, followed by mesalazine) is widely used to induce and maintain remission in mild-to-moderate UC. Mainly because of transmural inflammation, efficiency of 5-ASA in CD remains controversial, especially for preventing relapse. It exerts its anti-inflammatory effect on intestinal mucosa topically through binding to the nuclear peroxisome proliferator-activated receptor-γ, which inhibits production of cytokines and inflammatory mediators. There are very few trials on 5-ASA use in children with IBD and no data could be found regarding their growth but no direct beneficial effect on growth should be expected from this treatment.

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Immunosuppressives
Converted to their active metabolite, azathioprine and 6-mercaptopurine (6-MP) exert their immunosuppressive effect through interference with the normal metabolism of purines, disrupting DNA or RNA synthesis and lymphocyte function. Used in pediatric IBD since the early 1970s, azathioprine/6-MP is now common as a first-line maintenance therapy for moderate to severe IBD (CD as well as UC), after induction of remission by glucocorticoids or enteral nutrition. Effective, safe and well tolerated, azathioprine is being used in 61 and 80% of children with CD 3 and 12 months after diagnosis, respectively. Despite known adverse effects (hypersensitivity, neutropenia,
thrombocytopenia, pancreatitis, hepatic dysfunction, infection, fever, malignancy), complications requiring drug cessation occur in only 7–18% of patients [68, 71]. There are however several cases of lethal hepatosplenic T-cell lymphoma described in the literature, particularly in young adult men with a treatment combination of azathioprine/6-MP and anti-TNF-α agents [72]. Immunosuppression induced by azathioprine/6-MP allows maintenance of clinical and biological remission and leads to disappearance of mucosal ulcerations in 50% of patients with CD [73]. Therefore these drugs should enable normal growth and puberty of pediatric IBD patients. Furthermore, the use of azathioprine/6-MP is associated with significant reduction in glucocorticoid exposure [69, 71], which could further improve growth. Indeed, comparing duration of glucocorticoid use in 55 randomized children with CD treated with 6-MP versus placebo, Markowitz et al. [69] reported an important decrease in the need for glucocorticoids in the 6-MP group but found no differences in growth parameters in the two groups after 18 months of follow-up. This study should be interpreted with caution because of the small sample size and the high number of early withdrawals from the placebo group. Indeed, and to the best of our knowledge, only one study adequately assessed the effect of azathioprine/6-MP on growth. Fuentes et al. [74] retrospectively assessed growth in 107 children with IBD (CD and UC) treated with high-dose azathioprine (3 mg/kg instead of the usual 2–2.5 mg/kg). Only 10% of children had significant growth retardation (height z-score <-1.64) at time of diagnosis and 36% of the 57 children with CD maintained or improved their height z-score on follow-up. Still, precise data concerning the effect of azathioprine/6-MP on growth are lacking, requiring further studies.

Although high-dose methotrexate (MTX) has well-known antiproliferative and cytotoxic effects through inhibition of several enzymes leading to defective DNA synthesis and apoptosis and/or suppression of T-cell proliferation, the effects of low-dose MTX remain controversial [75–78]. It exerts its immunosuppressive and anti-inflammatory effects through inhibition of proliferative (IL-2) and pro-inflammatory cytokines, increased production of the anti-inflammatory cytokine IL-10 and of adenosine, induction of apoptosis and suppression of cell proliferation. Furthermore, MTX affects adhesion molecule expression and therefore could inhibit lymphocytes recruitment to intestinal mucosa. However, disappearance of mucosal ulcerations has been reported in only 11% of patients [73]. The role of MTX in the treatment of pediatric or adult IBD is not yet established. Trials in adults have shown good efficiency in inducing and maintaining remission in patients with IBD, particularly CD [79, 80]. Although experience of MTX in the pediatric setting is very limited, MTX appears to be a well-tolerated and good therapeutic alternative for children unresponsive or intolerant to azathioprine/6-MP [81–83]. Besides potential well-known serious side effects including severe infection, hematologic complications (anemia, neutropenia, thrombocytopenia) and teratogenicity, drug discontinuation has been reported in 13% of patients [82], mainly due to elevation of transaminases or nausea. The effect of low-dose MTX treatment on growth has been observed retrospectively by Turner et al. [82] in 60 children with CD unresponsive or intolerant to azathioprine/6-MP. Mean height velocity z-score, which was –1.9 the year before MTX initiation, improved to –0.14 the year post-MTX, with, as expected, greater increase in prepubertal subjects. As for azathioprine, MTX enables considerable reduction or cessation of glucocorticoids [82, 83], which could explain its positive effect on growth. However, further studies are needed to better assess the exact mechanism of low-dose MTX on growth in children and adolescents with IBD.

**Biological Treatments**

Use of biologic agents in the treatment of IBD, especially infliximab, a chimeric monoclonal antibody targeting TNF-α, has markedly increased over the last decade. Infliximab inhibits the biological activity of TNF-α by binding directly to it in order to modulate the function of TNF-α-producing cells. Approved by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMEA) for the treatment of CD and UC in adults and children, the efficiency of infliximab in inducing and maintaining prolonged remission in pediatric IBD patients is widely recognized [84–88] and it appears to be a safe and well-tolerated treatment [85, 89]. However, its effect on growth is less obvious. The REACH study [86] showed an improvement of height z-score of 0.5 after 54 weeks of treatment in 112 children with moderate to severe CD, while Diamanti et al. [90] reported no improvement of linear growth despite an increase in weight and BMI in a small sample of 14 subjects. Moreover, Pfefferkorn et al. [5] found no significant improvement of height z-score in 176 children with a Tanner score between I and III but an increase in height velocity z-score after 2 years. Furthermore, height z-score increased more significantly in subjects younger than 9 years and without concomitant glucocorticoid treatment. This sig-

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Significant improvement of growth velocity was also observed in other studies [6, 85, 88, 91, 92].

The mechanisms by which infliximab improves growth are various. Anti-TNF-α agents induce direct mucosal healing with a reduction of mucosal inflammation already after the first infusion [87, 88], independently of its effect on clinical indexes, thus reducing malabsorption and protein-losing enteropathy. Furthermore, by inhibiting the first step of the inflammatory cascade, infliximab reverses suppression of chondrocytes formation, and differentiation induced by pro-inflammatory cytokines. The resulting disease control allows progression of puberty and subsequent growth improvement [5, 6]. Finally, infliximab enables prolonged glucocorticoid withdrawal [84, 86, 87] which has a positive impact on growth. A recent study [91] showed that children who never received glucocorticoids had a better growth improvement than those who did, suggesting a possible adverse priming effect of glucocorticoids on growth. The authors also postulate that glucocorticoid use is associated with a more severe disease.

Other emerging anti-TNF-α agents, such as adalimumab or certolizumab, will improve treatment options in children with IBD. While adalimumab has been approved by both FDA and EMEA for the treatment of CD and UC, certolizumab has been rejected twice by EMEA, though approved by FDA and Switzerland. So far, no data regarding their effect on growth are available.

Exclusive Enteral Nutrition

Nutrition and IBD, especially CD, are intimately related in several aspects. There is still an ongoing debate of a possible relationship between diet and development of IBD, namely a probable pro-inflammatory effect of certain foods [93]. Malnutrition, which is frequently observed in patients with active disease, has always been a major concern to pediatric gastroenterologists [13, 23]. Hypercaloric supplements are often required to counterbalance the insufficient intakes and the possible hypercatabolic state in IBD patients in order to restore or maintain adequate growth.

Introduced in the 1970s, exclusive enteral nutrition (EEN) still has an important place as first-line therapy in active pediatric CD. Probably due to its implications in daily life and possible difficulties to maintain adherence, large geographical variations are observed in the use of EEN, being more popular in Europe and particularly in British and northern countries. Providing all nutritional requirements, EEN is usually administered exclusively for an initial 6- to 8-week course, followed by progressive reintroduction of normal feeding over several weeks. Due to the large amounts of fluids needed, the insertion of a nasogastric feeding tube is sometimes necessary, which may lead to early treatment failure. Initially, elemental amino acid formulas have been used, but polymeric formulas have been shown to be as efficient regarding disease activity control and to be more efficient regarding weight gain [94]. Further, polymeric formulas are more palatable and do not affect adherence but do reduce the need for tube administration [95].

EEN appears to be less efficient than glucocorticoids in inducing clinical remission in adult patients with acute CD [96, 97] and no positive effect of EEN in patients with UC has been shown [98]. Nevertheless, contrarily to what is seen in the adult population, Heuschkel et al. [8] showed in a meta-analysis including 194 children with acute CD, that EEN was as effective as glucocorticoids in inducing remission. Sparing or avoiding glucocorticoids and their adverse effects makes EEN a good choice for children with CD. Conversely, the role of enteral nutrition (EN) in maintaining remission is less obvious. A Canadian study [99] focused on maintenance of remission in pediatric CD patients who achieved remission under EEN. Twenty-eight subjects continued partial EN overnight in addition to normal diet during the day, while 19 children stopped any EN after achieving remission. After 12 months, relapses were significantly higher in the group which stopped EN compared to the group with partial nocturnal EN (79 vs. 43%). However, in a retrospective review [100] of 44 children receiving 1 liter of EN per day in addition to a normal diet for 1–7 years after having achieved clinical remission, 62% showed clinical relapse during the observation period. Still, glucocorticoids could be avoided in half of those patients and postponed in the other half.

No additional beneficial effect of EEN on maintaining remission in adults treated with Infliximab could be demonstrated [101]. However, one could postulate that combination of EEN and infliximab might be an attractive approach to ensure optimal growth in children. Indeed, prolonged EN, even administered intermittently, has clear positive effects on anthropometric parameters, with significant increase in weight and height velocity [8, 9, 102]. Furthermore, children treated with EEN have better growth velocity than those treated with glucocorticoids [25]. In fact, after EEN initiation, a rapid increase in growth factors IGF-1 and IGFBP-3 levels is observed [102–104], which is probably due to a reduction in inflammation rather than to an improvement in nutritional status. Finally, no acceleration in pubertal development and bone age have been described in patients re-
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Conclusions

Regular assessment of weight, height and pubertal stage is essential in children and adolescents with chronic disease, namely IBD. Slowdown of height velocity can be the first sign of IBD onset, even several months before apparition of weight loss and intestinal symptoms; therefore, many pediatric IBD patients, especially those with CD, present with growth retardation and delayed puberty. In order to avoid decreased final height, careful follow-up and aggressive treatment are required in these patients to maintain remission and detect early relapse. Use of glucocorticoids in acute flares should be avoided or at least minimized as much as possible, due to their well-known deleterious effects on growth. Without adverse effect and recognized positive impact on growth, EEN remains an excellent treatment for active pediatric CD and should be tried before considering other therapy. Finally, the relatively new available biologic agents in the pediatric setting have markedly improved the outcome of patients with IBD probably due to their potent effect on mucosal healing, which appears to be the cornerstone of optimal growth. Hence, studies assessing energy metabolism and the effect of newly available treatments have to be performed in order to further optimize catch-up growth.

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