Pathophysiology and Management of Abnormal Growth in Children with Chronic Inflammatory Bowel Disease

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Abstract
Many children with a variety of chronic diseases suffer from a variable component of chronic inflammation and often have co-existing growth retardation. The aetiology of this growth retardation may be multifactorial and in a condition such as inflammatory bowel disease it includes the effects of the disease on nutrition as well as the effect of drugs such as glucocorticoids. Growth is primarily regulated through the endocrine and paracrine component of the GH/IGF-1 axis which may be modulated by other factors such as sex steroids. There is increasing evidence that this axis may be affected in children with chronic inflammation. An improved understanding of the GH/IGF-1 axis and how it is affected in chronic inflammation will lead to an improved rationale for developing therapeutic regimens that can improve growth in those children whose growth does not improve despite optimal management of the disease. This review will illustrate these aspects by concentrating primarily on the pathophysiology of growth retardation in inflammatory bowel disease and possible interventions for improving growth.

Inflammation and its adverse effects on skeletal development are observed in a number of chronic diseases such as cystic fibrosis, chronic kidney disease, rheumatological conditions and inflammatory bowel disease (IBD). As the mechanisms that regulate growth in childhood are age and maturity dependent, the effect that these conditions exert on growth will depend on when children develop and clinically present with these conditions. However, whilst it is very likely that there are other condition-specific issues that may also play a major role, inflammation remains a common factor in all these conditions. Given that chronic infection and stunting are commonly encountered in developing countries, inflammation may also play a wider, global role in contributing to poor growth which may, itself, be a marker of the effects of disease on other aspects such as body composition [1]. As an example
of a chronic inflammatory disease that affects a number of growth regulatory mechanisms, IBD occurs in children and adults and its prevalence is estimated at 1 in 500 with about 10,000 affected children in the UK [2]. Growth retardation can be a presenting symptom in over 30% of these children and subsequent short stature in adulthood may occur in over 15% of cases [3]. Both adults and children with chronic inflammatory conditions such as IBD are now living longer and the adverse effects of chronic inflammation on growth and skeletal development have been ranked as one of the top areas by the Crohn’s and Colitis Foundation of America that require further research [4].

**IBD and Puberty**

Children with IBD and, particularly Crohn’s disease (CD), often present during early adolescence and have been reported to display delayed puberty and associated growth retardation [5]. A recent retrospective study which utilized serial height measurements over the period of adolescence in children with IBD showed that an altered pubertal growth spurt is not uncommon in this age group, particularly in boys, and may be related to disease severity and poor nutritional status [6]. In adolescents with IBD, the aetiology of pubertal delay is multifactorial [7] and hypogonadism may encompass a range of abnormalities of the hypothalamic/pituitary/gonadal/end organ axis, including hypogonadotrophic hypogonadism, abnormality of sex steroid synthesis or an abnormality of sex steroid action. In addition, there is a concern that those with CD who present in adolescence may have more profound short stature than expected simply for delayed puberty [5]. Generally, adults with a past history of pubertal delay are often shorter as adults than their predicted height. However, the discrepancy between target height and final height seems to be greater in adults with childhood-onset CD compared to healthy adults with a history of delayed puberty [8, 9]. As sex steroid-induced growth acceleration is dependent on increased GH and IGF-1 production [10], it is possible that the poorer growth and final height may be due to the combined effect of inflammation on the GH/IGF-1 axis as well as puberty.

**Interaction between Inflammatory Cytokines and the GH/IGF-1 Axis**

The GH/IGF-1 pathway is critical for regulating bone growth; circulating GH can act independently of hepatic IGF-1 and directly initiate an increase in growth plate chondrocyte proliferation, matrix production and differentiation as well as stimulate the local production of IGF-1 [11]. Circulating IGF-1 can also rescue the growth in IGF-1 null mice but the levels required are supraphysiological [12]. Although, poor growth may also be secondary to poor nutrition, in experimental models of colitis, 40% of
linear growth impairment may occur as a direct result of inflammation [13]. This may be due to a direct adverse effect of circulating pro-inflammatory cytokines on the systemic hypothalamic-pituitary-growth axis and also due to their effects on the growth plate. In children with chronic inflammation, there is an association between individual circulating concentrations of proinflammatory cytokines and growth but the relationship is not strong especially as individual cytokine concentrations are highly variable at any one time point in children with the same disease [14]. Recent data from our group suggests that the systemic GH/IGF-1 axis is affected to a variable extent in poorly growing children with IBD [15]. Peak GH levels following insulin induced hypoglycaemia were very variable but IGF-1 concentrations were almost universally low. The finding of subnormal GH secretion in some cases is consistent with other studies in this field [16]. Previous investigators have also highlighted the possibility of reduced IGF-1 bioavailability possibly due to an alteration in IGF-binding proteins [17, 18]. Current research suggests that the actions of some proinflammatory cytokines such as TNF-α may be independent of systemic or circulating IGF-1 action and may be exerted directly on growth plate chondrogenesis through local GH/IGF-1-dependent effects as well as independent effects on proteoglycan synthesis and the microarchitecture of the growth plate [19]. On the other hand, in experimental colitis, immunoneutralisation of IL-6 increased both systemic IGF-1 concentrations and linear growth but immunoneutralisation of TNF-α had no effect on systemic IGF-1 concentrations [20]. Furthermore, IL-6 does not seem to generally exert any deleterious direct effects on growth plate chondrogenesis [21, 22]. It is possible that there may also be other mechanisms of how proinflammatory cytokines exert an effect on the GH/IGF-1 axis. There is increasing evidence that proinflammatory cytokines can induce the tissue-specific expression of suppressors of cytokine signalling (SOCS) proteins which are a group of signalling proteins characterised by their ability to downregulate cytokine signalling [11]. SOCS2 is uniquely identified as a primary GH receptor signalling inhibitor in vivo by its overgrowth knockout phenotype in mice which are 30–40% larger than normal littermates and have increased long bone length and these effects seem to be mediated by increased signalling through the JAK/STAT pathway [23]. It is currently unclear whether at the level of the growth plate, the SOCS proteins can alter tissue sensitivity to proinflammatory cytokines [24].

**General Management of Growth Impairment in Children with IBD**

The single most important risk factor for reduced height at diagnosis and follow-up is the time from symptom onset to diagnosis [25]. Early identification of growth deterioration is, therefore, of the utmost importance in the IBD clinic to ensure prompt intervention. This requires regular measurement of height and assessment of puberty. A close working relationship with a paediatric endocrinologist would facilitate appropriate management of these children when there are concerns about growth, puberty
and skeletal development. The first-line management of growth failure in IBD is optimising control of the active disease, which may be occult in parallel with providing adequate nutritional support. In the clinical setting, this should include thorough history and examination to reveal subtle symptoms and signs of disease activity coupled with laboratory investigations for inflammatory markers as well as dietetic assessment. Primary management should also involve correcting poor nutritional status; improving the disease and nutritional status of children with CD has been shown to be associated with beneficial changes in growth and markers of the systemic GH/IGF-1 axis [26] and consideration should also be given to the early introduction of second-line immunomodulating therapy (thiopurines or methotrexate), thereby reducing the use of corticosteroids. In the future, the possibility of using drugs such as selective glucocorticoids receptor modulators which can exert the anti-inflammatory effect but not the growth inhibitory effect holds promise [27]. Significant improvements in height velocity (HV), pubertal progress and IGF-1 levels may also follow surgery for localised disease or resectable disease. Infliximab, a chimeric monoclonal antibody against TNF-α, has been shown to be effective in childhood onset CD and its use has been associated with an improvement in growth [28, 29]. Adalimumab has also recently been reported to be associated with an improvement in disease and growth [30].

Although an evaluation of the GH/IGF-1 axis may be justified in a child who fails to grow despite optimisation of their disease management, the results of pituitary function tests need to be interpreted with caution [15]. There may be a role for growth-promoting agents including treatment with sex steroids and rhGH but these would generally only be considered in conjunction with IBD therapies in a short child who is growing poorly and is out with the target range. The appropriate timing to consider growth-promoting agents is still unclear but it is anticipated that any growth-promoting agent would only be used as an adjunct to aggressive management of the disease process. Although sex steroid treatment is often used and recommended in children with IBD, there are limited data on their effectiveness [31]. Given the possibility that children with IBD may have a concomitant alteration in the GH/IGF-1 axis, the sole use of sex steroids requires careful monitoring and the change in HV needs to be compared with that reported in otherwise healthy children.

Whilst rhGH is a therapeutic possibility in children with IBD who grow slowly, its efficacy remains unclear. Studies of rhGH treatment in children with other inflammatory diseases such as juvenile arthritis have clearly shown a cessation in deterioration of HV and may have added benefits on bone mineral content and body composition [16, 32]. An improvement in growth that is independent of disease activity and steroid dose over a relatively short period of rhGH has also been demonstrated in two randomised controlled trials [33, 34]. There is also a possibility that rhGH treatment may have a beneficial effect on the disease process and, thereby, improve growth [35], but this requires further investigation. Considering that the defect in the GH/IGF-1 axis may be at multiple levels, the role of other forms of growth-promoting agents such as rhIGF-1 needs further investigation [36]. This may be particularly important as patients with
chronic inflammation who receive rhGH may be predisposed to impairment of glucose homeostasis [33, 37] and the use of rhIGF-1 children with chronic disease has been reported to be associated with an improvement in glucose homeostasis [38].

**Conclusion**

The pathophysiology of poor growth in children with IBD is multifactorial and has parallels to many other chronic inflammatory conditions. The assessment of growth is an effective marker of disease itself and in many cases improving disease and nutrition will lead to an improvement in growth. In the small number of cases, where there is persistent growth retardation, there is a need for close involvement of a paediatric endocrinologist with experience in managing children with chronic disease to consider other forms of growth-promoting therapy.

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