Nutrition and Growth in Inflammatory Bowel Disease

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Abstract
Growth failure is common in children with inflammatory bowel disease (IBD), mainly those with Crohn’s disease (CD). The prevalence of growth failure varies in different cohorts, mainly due to the heterogeneity of the population treated by the reporting centers (primary vs. referral), but can be as high as 40% of the cases. Factors related to growth impairment in CD include low dietary intake, stool loss, increased energy and nutrient requirements, the use of medications (for example, steroids interfere with the IGF-1 axis), disease activity (the effect of inflammation on growth), genetic background (parents height), and physical activity. In animals, malnutrition, genetic polymorphism, elevated pro inflammatory cytokines, and exposure to lipopolysaccharide are involved in growth impairment in IBD, while malnutrition, genetic polymorphism and increased inflammation have been shown to be associated with growth impairment in humans. Exclusive enteral nutrition (EEN) is the preferred first line treatment in CD. EEN induces remission, prolongs remission and affects growth failure via its effect on malnutrition and inflammation. However, similar to drug treatment, EEN effect on growth failure is limited, most probably due to incomplete control of inflammation. Children with IBD should be assessed for growth on diagnosis and on each follow-up visit. New nutritional strategies, identification of genetic polymorphisms that respond to EN, and methods to increase lean body mass (physical activity) are needed in order to improve growth in our IBD patients.

Inflammatory bowel disease (IBD) is a name given to a group of chronic diseases that affect either the large intestine (ulcerative colitis, UC), any part of the intestine the intestine (Crohn’s disease, CD), and cases with large intestinal involvement where UC cannot be definitely diagnosed or excluded (indeterminate colitis, IC). About a fifth of IBD cases are diagnosed in the pediatric age range and in that group, delayed puberty and growth failure are leading causes for concern for physicians and patients alike.
The prevalence of growth failure varies in different cohorts, mainly due to the heterogeneity of the population treated by the reporting centers (primary vs. referral), but can be as high as 40% of the cases [1, 2]. Most of the attention to growth failure is given to CD, since growth failure is much less common in UC compared to CD [2].

It is common to observe that growth failure precedes the diagnosis of CD by many years. This may have an effect on the final height of CD patients, who commonly fail to reach their final predicted height [3]. In that context, short stature (final height below 5th percentile) is seen in up to 30% of the patients [3].

The need to diagnose growth failure early and to treat it is emphasized by a recent publication demonstrating that height predictions were higher by 1.5 cm for girls (p = 0.06) and 2.4 cm for boys (p = 0.02) than measured final adult height [4]. In that study, most patients with IBD attained adult height within normal timing for the population, indicating that the window of opportunity to treat growth failure is narrow and necessitates an immediate action. The need for early and successful intervention is also emphasized by the fact that more than 20% of children with CD continue to have growth velocity lower than –2 SD, 2 years after diagnosis [5].

When assessing growth in CD, one may consider that males may be affected more than females. This was examined in a recent study looking at sex differences in IGF-1 levels in a cross-sectional study of 82 CD patients younger than 21 years (57% males) [6]. In that study, IGF-1 chronological age (CA) z-scores and bone age (BA) z-scores, were significantly lower in males compared to females. Inflammatory markers (erythrocyte sedimentation rate, ESR, and C-reactive protein, CRP) did not differ by gender but were associated with IGF-1 z-scores for CA and BA. In addition, IGFBP-3 levels were significantly lower in males. Finally, IGF-1 BA z-scores were positively associated with height BA z-scores. Altogether, this findings, limited by the cross-sectional design of the study, suggest that lower IGF-1 levels in males may explain sex differences in growth impairment observed in children and adolescents with CD.

Factors related to growth impairment in CD include low dietary intake, stool loss, increased energy and nutrient requirements, the use of medications (for example, steroids interfere with the IGF-1 axis), disease activity (the effect of inflammation on growth), genetic background (parents’ height), and physical activity [1, 7, 8].

Malnutrition has a major impact on growth impairment in CD patients. More than 80% of patients with CD are malnourished on diagnosis. They suffer from reduced energy intake and deficiency of many nutrients including iron and zinc, turning the treatment of malnutrition into a major element of restoring growth in these patients. Caloric restriction inhibits growth in animal models of IBD, however, malnutrition cannot account for all growth impairment. In a rat model of IBD [9], up to 40% of growth impairment was caused by inflammation and was associated with elevated IL-6 levels and lower IGF-1 levels [9]. The importance of IL-6 in impairing growth was shown in a rat model of IBD, anti-IL-6 antibodies given to rats with trinitrobenzenesulphonic acid-induced colitis caused a significant increase
in growth with no effect on energy intake or inflammation [10]. Furthermore, patients with polymorphisms in the IL-6 gene that are associated with higher IL-6 serum levels were found to be more growth retarded than patients with the other IL-6 genotypes [10]. In recent years, few publications related polymorphisms in the genotype of various cytokines with growth impairment. These include the TNF-α genotypes [11], stature related genes and an autophagy susceptibility gene [12] and the combination of NOD2/CARD15 risk allele carriage and the presence of neutralizing GM-CSF antibodies [13]. This last study illustrates the possible importance of bacterial signaling in growth impairment. Further evidence to the importance of bacterial signaling comes from the study by Pasternak et al. [14] where, following trinitrobenzenesulphonic acid administration to mice, serum lipopolysaccharide (LPS) binding protein increased in conjunction with increased serum TNF-α, IL-6, and IL-10, as well as an observed expansion of regulatory T cell numbers. All these observations disappeared in a TLR4-deficient mice model, with concomitant reduction in weight loss.

Finally, Thayu et al. [15], recently showed that males presented with cachexia (only lean body mass deficits) with complete recovery of lean body mass and fat mass upon remission while females presented with wasting (both lean body mass and fat mass deficits) with complete recovery of fat mass but continued low lean body mass. In that study, overall, height-z did not improve; however, greater increases in IGF-1 and decreases in TNF-α, IL-6 and LPS-binding protein levels were associated with increases in height-z, leading the authors to conclude that ‘Immune-mediated mechanisms contribute to growth and body composition deficits in CD’ [15].

Overall, malnutrition, genetic polymorphism, elevated pro-inflammatory cytokines, and exposure to LPS are involved in growth impairment in animal models of IBD, while malnutrition, genetic polymorphism and increased inflammation have been shown to be associated with growth impairment in humans.

Treatment of growth failure in IBD requires early diagnosis and includes nutritional rehabilitation of malnutrition, control of inflammation and induction of remission (exclusive enteral nutrition, immunomodulation, biologic agents and surgery for local disease) and hormonal treatment [1, 2].

From the above, it becomes clear that early induction of remission is essential for treating growth failure in IBD. Thus, nutrition plays another important role, since exclusive enteral nutrition (EEN) is the preferred first-line treatment in CD [16–19]. EEN induces remission as effectively as steroids [20], avoiding the deleterious effects of steroids on growth [21].

Among plausible mechanisms responsible for remission induction, those related to modification of gut flora and reduced mucosal inflammation may provide explanation to the possible effect of EEN on growth. Indeed, mucosal healing and increased mucosal production of pro-inflammatory cytokines has been shown in CD patients in a British and an Italian cohort [22–25]. Furthermore, in an elegant study performed by Bannerjee et al. [26], the anti-inflammatory effects of EEN were observed much
earlier than its effect on nutritional recovery. Of note, there is no evidence for an advantage of any type of formula (elemental vs. polymeric) in the induction of remission [20]. However, limited data suggest that EEN is superior to partial enteral nutrition in inducing remission [27]. Regarding type of formula, it has been suggested that a formula containing high levels of TGF-β protein may provide benefit to patients with IBD [2, 25]. However, this information is supported only by uncontrolled studies with severe methodological limitations.

Limited retrospective data suggest that after remission is achieved using EEN, remission is longer in patients who continue to receive nasogastric supplementation vs. those who do not [28]. Furthermore, chronic intermittent continuous nasogastric infusion increased caloric intake and improved weight and height gain [29].

Two recent cohorts provide long-term follow-up of a pediatric CD cohort in the North of France [30] and 2-year follow-up of a Canadian cohort in Toronto, Canada [31]. The French cohort showed that the prevalence of low BMI and weight z-score was significantly lower at maximal follow-up [30], and the Canadian cohort showed that clinical improvement was associated with improvement in body mass index [31]. Disappointingly, the reduction in the percentage of children having low BMI was not paralleled by reduction in growth failure rates [30]. In the Canadian cohort, improved BMI was mainly related to increased fat mass [31], providing partial explanation to the lack of effect on growth.

In summary, it can currently be concluded that EEN induces remission, prolongs remission and affects growth failure via its effect on malnutrition and inflammation. However, similar to drug treatment, EEN effect on growth failure is limited, most probably due to incomplete control of inflammation.

Children with IBD should be assessed for growth on diagnosis and on each follow up visit. New nutritional strategies, identification of genetic polymorphisms that respond to EEN, and methods to increase lean body mass (physical activity) are needed in order to improve growth in our IBD patients.

References

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