Nutrition in paediatric Crohn's disease

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Abstract

Inflammatory bowel disease (IBD) such as Crohn's disease (CD) results from the interaction between an individual's immune response and precipitant environmental factors, which generate an anomalous chronic inflammatory response in those who are genetically predisposed. Protein-energy malnutrition (PEM) is a frequent consequence of CD. Macrophage products such as Tumour Necrosis Factor-α (TNF-α) and interleukins 1 and 6 may be the central molecules that link the inflammatory process to derangements of homeostasis. CD is associated with frequent nutritional deficiencies, the pattern and severity of which depends on the extent, duration and activity of the inflammation. Nutritional support is especially important in childhood CD as an alternative to pharmacological treatment, especially steroids. Current treatment regimens limit the use of corticosteroids, by using immunomodulatory drugs, recommend the use of enteral nutrition, and, if necessary, consider surgery for intestinal complications of localised CD. Biologic agents with the potential for mucosal healing hold promise of growth enhancement even among children whose growth remained compromised with previously available therapies. For all treatment modalities, there is a window of opportunity to achieve normal growth before puberty is too advanced.

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Crohn's disease CD manifests during childhood or adolescence. Protein-energy malnutrition (PEM) is a frequent consequence of CD.[1–3] PEM in childhood and adolescence leads to failure to thrive and deficit in final height. According to different studies and to diagnosis delays, linear growth is reduced in one to two third of affected children at the time of diagnosis. However, comparison between populations is difficult because the definition of growth retardation varies according to different studies.[1–3] Protracted PEM with subsequent failure to thrive is associated with an impairment in the achievement of the final target size. In addition, protracted use of steroids and/or insufficient control of the disease activity may further impair growth and body composition.

Primary therapy for CD, has two aims, namely i) the control of the inflammatory process, as assessed by the the paediatric Crohn's disease activity index (PCDAI) as well as ii) the correction or the prevention of malnutrition and failure to thrive. One of the "peculiarities" of CD is the ability of nutritional therapy to achieve both of them. Growth is fundamental to the practice of paediatrics, so by taking growth as the primary outcome measure in this chronic inflammatory disease, an important issue is addressed for the patients and their families as well as for paediatricians.

Factors inducing malnutrition and failure to thrive

Several associated factors are responsible for PEM, including poor oral intake, intestinal malabsorption, increased gut losses from protein losing enteropathy, increased nutrient requirements, increased protein turn over, and drug nutrient interactions (Table I).[4–11] Energy and protein substrates are diverted into the inflammatory process, thus weight loss, and linear growth as well as pubertal development in children are notably retarded. There is considerable controversy about nutritional needs during phases of active and inactive disease. It is, for example, often assumed that in acute illness a child requires increased nutritional support, however the precise relationship between illness severity and energy expenditure is uncertain. Measurement of resting energy expenditure (REE) and

Table I: Causes of malnutrition in Crohn's disease

Reduced oral intake
Disease induced anorexia
Restrictive diet/iatrogenic
Intestinal malabsorption
Decreased absorptive surface (mucosal injury)
Bile salt deficiency (ileal disease)
Intraluminal bacterial overgrowth
Increased intestinal losses
Protein-losing enteropathy
Blood loss
Electrolytes, minerals, trace elements (fistula)
Increased requirements
Increased energy expenditure (sepsis, fever, tissue repair)
Impaired protein metabolism (inflammation, cytokines)
Drug-nutrient interactions
Corticosteroids (calcium, protein)
Cholestyramine (fat, fat soluble vitamins)
Sulphasalasine

its relationship with disease activity in children with inflammatory bowel disease has provided conflicting results.[6–9]

Macrophage products such as Tumour Necrosis Factor-α (TNF-α) and interleukins 1 and 6 may be the central molecules that link the inflammatory process to derangements of homeostasis.[12,13] An association between impaired growth in children with CD and low IGF-I levels is well recognised. Early studies emphasised the role of malnutrition in the suppression of IGF-I production. Insulin-like growth factor I (IGF-I), produced by the liver in response to growth hormone (GH) stimulation, is the key mediator of GH effects at the growth plate of bones.[14] However, a simple nutritional hypothesis fails to explain all the observations related to growth in children with CD. The direct, growth-inhibitory effects of pro-inflammatory cytokines are increasingly being recognised and explored. In rats with trinitrobenzenesulphonic acid-induced colitis, 40% of growth impairment was attributable to inflammation, with the rest being due to undernutrition.[15] In transgenic mice without inflammation, raised IL-6 retards growth and suppressing insulin-like growth factor (IGF)-I.[16]

Steroid dependency and their side effects when used for a long period, justify the need to limit their use. The permanent height deficit documented in children with CD seems to be directly linked to the duration of steroid treatment and to the age of diagnosis or the localisation of the disease.[17,18] Whatever the consequences on the final height, which vary from one study to another, the consideration of the quality of the bone mineralisation has now become of a greater concern in relation to both the degree and the persistence of inflammation as well as the long-term use of steroids.[19]

Enteral feeding

CD is associated with frequent nutritional deficiencies, the pattern and severity of which depends on the extent, duration and activity of the inflammation. Nutritional support allows these deficiencies in energy, macro- and micro-nutrients to be corrected. Enteral feeding (EF) is a primary therapy for CD, as it allows the inflammatory activity to be controlled and the patient to be kept in remission. Nutritional support is especially important in childhood CD as an alternative to pharmacological treatment, especially steroids. O'Morain et al were the first to perform a controlled study in acute CD showing that EF based on an elemental diet was as effective as steroids, with remission rates of 81 and 80%, respectively.[20] Subsequent prospective controlled trials have confirmed the therapeutic efficacy of EF, even if the published meta-analyses of EF as primary therapy in CD reported only a modest advantage for steroids.[21–24] However, the value of nutritional support in the correction and maintenance of nutritional status is widely accepted.[25]

Enteral feeding (EF) has been traditionally proposed in the proximal localisation of the disease where its efficacy has been documented. However, many cases with disease involving the colon have been reported.[26,27] The therapeutic effect of EF is multifactorial (Table II). Whether or not the type of enteral feeds is elemental, oligopeptides (protein hydrolysate) or whole protein may influence the result of EF still remains the subject of debate.[28,29] Intriguingly, there is also increasing evidence that an aggressive nutritional programme may in itself be sufficient to reduce the mucosal inflammatory response. EF alone may reduce many pro-inflammatory cytokines to normal, and allow mucosal healing.[30,31] In addition, specific nutritional components, such as n-3 polyunsaturated fatty acids, may have an anti-inflammatory effect as they may alter the pattern of leukotrienes generated during the immune response.[32] Several other factors have also been thought to determine the response to EF (Table II). Recent studies have emphasised the role of anti-inflammatory cytokine such as transforming growth factor-beta (TGFb) present in the diet. A polymeric diet (Modulen IBD®, Nestlé®) rich in tTGFb2 is now widely used as a single nutrient and has been shown to induce remission in children with active CD.[33] We have recently reported the beneficial effects of this diet in children regardless of the route of administration orally or by gastric tube feeding.[34] Moreover, Lionetti et al studied intestinal microbiota in children receiving full EF using Modulen IBD® for 8 weeks.[35] In 8 out of 9 children, the exclusive EF alone induced disease remission. In 1 child, steroids were added to achieve remission. In all children, analysis of gel band distribution revealed profound modification of the intestinal microbiota after exclusive EF. These data suggest that a possible mechanism of action of EF in inducing disease remission in CD is the capacity of modification of intestinal microbiota. Possible explanations of such capacity are both low residue and prebiotic properties of the polymeric liquid formula. In another study, exclusive EF was shown to reduce bacterial diversity and to initiate a sustained modulation of all predominant intestinal bacterial groups.[36] Exclusive EF may reduce inflammation through modulating intestinal Bacteroides species. The implications of these results for exclusive EF therapy and CD pathogenesis has became an important area of research.

Table II: Mode of action of enteral feeding in Crohn's disease

- Bowel rest
- Reduced intestinal secretions
- Low antigenic load
- Decreased intestinal permeability
- Anti-inflammatory effect of diet (transforming growth factor-beta (TGFb2)
- Modification of intestinal microbiota
- Trophic nutrients
- Improved nutritional status

Phenotype as well as genotype of the disease have been thought to influence the response to EF. Buchanan et al reported an 8-week course of primary exclusive EF in 114 children, median age at diagnosis was 11.6 years.[37] Disease phenotype was assigned using published classifications. Inflammatory markers and anthropometry (Z-scores) were calculated before and after treatment. Fifty-seven children (51.8%) were fed orally whilst 53 (48.2%) were fed by tube. Eighty-eight children (80%) achieved remission. Patients in remission had comparative improvements in weight and BMI Z-scores by the end of treatment. Individuals with isolated terminal ileal disease ($N = 4$) had lower remission rates than children in whom CD affected other locations ($P = 0.02$). No other significant differences in remission rates for any other disease locations were found. The authors concluded that EF nutrition induced clinical remission, normalisation of inflammatory markers and improved weight/BMI Z-scores in most patients. This study demonstrated that disease phenotype should not influence clinicians when commencing patients on exclusive EF.[37]

It has also been recently reported that the response to treatment with systemic steroids, AZA/6-MP and infliximab are not related to NOD2/CARD15 mutations, age of diagnosis and disease behaviour. Patients with colonic disease seem to have higher rates of steroid dependency.[38]

Although the totality of the evidence is not consistent, available data suggest that EF may be useful for maintaining remission in patients with CD. Large randomised controlled trials are necessary to assess definitively the efficacy of EF in the maintenance of CD remission.[39]

Parenteral nutrition

In the early 1970s, it was postulated that "bowel rest" achieved by the administration of parenteral nutrition (PN) might be of primary importance in the treatment of CD. Many trials since then examined this theory, but the results were difficult to interpret because of major methodological flaws. Greenberg et al achieved a prospective, controlled trial to compare directly the efficacy of TPN with continuous EF as a primary therapy in patients with CD[40] and found similar short term remission rates and long-term outcomes in patients receiving either treatment.[41–43]

The role of intraluminal nutrients and the preservation of the intestinal mucosal barrier function seems very important and makes the use of TPN questionable. Thus, TPN can no longer be regarded as having a role in the primary treatment of active uncomplicated CD. Its use in complicated disease remains, but probably in an adjunctive rather than a therapeutic role (Table III).

Table III: Indications for parenteral nutrition

- Severe fulminant enterocolitis
- Enteral feeding or steroid resistance
- Complication
  - *intestinal stenosis*
  - *fistula*
- Severe anoperineal disease
- Perioperative management

Immunosuppressive therapies influencing growth

Early forms of CD in children are usually severe because of the diagnostic challenges, the extent of the lesions and CD's duration. In the adolescent or the young adult it is now possible to predict the outcome of the disease based on the extent and severity of the lesions at the time of the first CD episode. [44] CD can be considered to be a lifetime disease with a major risk of extension and growth impairment. Childhood CD therefore requires a therapeutic approach, even more so when discovered early, which aims to limit long-term use of steroids and surgery. In a long term therapeutic strategy CD cases in very young children might justify the wider and earlier use of immunosuppressive drugs such as azathioprine, 6-mercaptopurine or methotrexate in view of the documented efficacy of these drugs in maintaining remission in serious and/or steroid dependent CD cases in adults as well as in children.[45–48]

The efficacy of infliximab as maintenance therapy in patients with otherwise chronically active CD is well established. Data concerning linear catch up growth following anti-TNF therapy are now available. In a cohort of 32 children and adolescents (63% males; mean age 13.4 years, range 4.7–17.3) with chronically active CD, despite immunomodulatory and prior corticosteroid therapy, were commenced on infliximab therapy. [49] Growth parameters standardised for age, gender, and pubertal development prior to and following infliximab therapy were compared. In all, 28 of 32 patients tolerated and responded to the induction regimen and 27 responders continued to receive infliximab via regularly scheduled infusions (n = 22) or episodically (n = 5) for a median of 26 months. Mean standard deviation score (SDS) for height at the time of initiation of infliximab therapy was -1.15 +/- 1.2 and had declined despite the use of other therapies from -0.44 +/- 1.1 at initial diagnosis. Increases in height velocity and stature during infliximab therapy were limited by pubertal stage: Tanner I-III: DeltaSDS for height velocity was +3.94, for height +/-0.50, ($P < 0.001$); Tanner IV, V: DeltaSDS for height velocity +0.22, for height +/- 0.02, (P = NS). The authors concluded that height velocity improved and height centile increased during infliximab therapy provided patients were treated prior to or in early puberty. These data support the use of infliximab in young patients with otherwise refractory disease, and suggest that ultimate height in this subset of children with severe CD may be less compromised than with previous therapies.[49] A recent prospective study involved 176 children (mean age 10.1 years; 65% male) younger than 16 years old at diagnosis and Tanner I to III during the study. They had mild (33%) or moderate/severe (67%) disease at diagnosis. [50] Clinical and growth data were prospectively obtained during the study. First-year treatments included immunomodulators (60%), corticosteroids (77%), 5-aminosalicylates (61%), anti-TNF (15%), and EF (10%).Disease activity at one year was inactive/mild (89%) or moderate/severe (11%). By two years, 86% had received immunomodulators and 36% anti-TNF. Mean height Z-scores at diagnosis, one year, and two years were -0.49 +/- 1.2 standard deviations (SDs), -0.50 +/- 1.2, and -0.46 +/- 1.1, respectively. Of the subjects, 10%, 8%, and 6.5% had height Z-scores less than -2 SD at diagnosis and 1 year, and 2 years of treatment respsectively. A height velocity Z-score less than -1SD was seen in 45% of subjects at one year and 38% at two years. The mean height velocity Z-score, however, increased between one and two years from -0.71 to 0.26 ($P < 0.03$). Duration of corticosteroid use longer than six months in the first year of treatment was associated with abnormal height velocity at one year. Interestingly, no statistically significant effect on height velocity Z-scores was noted when comparing those receiving or not receiving infliximab. The persistent growth delay despite improved disease activity and the frequent use of immunomodulators and biologics suggests that additional strategies are needed to improve growth outcomes. Although surgery has been shown to improve growth velocity, it does not prevent relapse.[51] Thus surgery should be used only in refractory and limited CD resistant to anti-TNF treatment.

Introduction of rhGH therapy in children was associated with a cessation in the deterioration in linear growth. However, an improvement in height SDS was not observed over the period of the study.[52] Future studies should explore the efficacy of a higher dose of rhGH in CD. Because of the unfavourable cost and side effects of rhGH considerations, it is now probably preferable to avoid long term steroid treatment and/or to use nutritional therapy whose efficacy has been documented in children.[53]

Conclusions

The severity and course of the cases diagnosed before the age of 10 must be taken into account in the therapeutic strategy. Current treatment regimens limit the use of corticosteroids, by using immunomodulatory drugs, recommend the use of enteral nutrition, and, if necessary, and consider surgery for intestinal complications of localised CD. Biologic agents with the potential for mucosal healing hold promise of growth enhancement even among children whose growth remained compromised with previously available therapies. Treatments, such as anti-TNF, are now becoming more widely used and may offer advantages in promoting growth. There remains, however, a need for large, multi centre studies of the different treatment options in paediatric CD. One should emphasise the importance of using standardised measurements of growth, such as height velocity standard deviation scores and height standard deviation scores as outcome measures to monitor progress in response to treatment. For all treatment modalities, there is a window of opportunity to achieve normal growth before puberty is too advanced.

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