World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i37.13219

World J Gastroenterol 2014 October 7; 20(37): 13219-13233
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Crohn's disease and growth deficiency in children and adolescents

Marco Gasparetto, Graziella Guariso

Marco Gasparetto, Graziella Guariso, Department of Women's and Children's Health, Unit for Pediatric Gastroenterology, Digestive Endoscopy, Hepatology and Care of Children with Liver Transplants, Padova University Hospital, 35128 Padova, Italy
Author contributions: Gasparetto M and Guariso G both made substantial contributions to the article's conception and design, data acquisition, manuscript drafting, critical revision for important intellectual content, and final approval of the version submitted for publication.
Correspondence to: Marco Gasparetto, MD, Department of Women's and Children's Health, Unit for Pediatric Gastroenterology, Digestive Endoscopy, Hepatology and Care of Children with Liver Transplants, Padova University Hospital, Via Giustiniani 3, 35128 Padova, Italy. markgasp@gmail.com
Telephone: +39-49-8213509 Fax: +39-49-8215430
Received: September 22, 2013 Revised: April 22, 2014
Accepted: June 12, 2014
Published online: October 7, 2014

Abstract

Nutritional concerns, linear growth deficiency, and delayed puberty are currently detected in up to 85% of patients with Crohn's disease (CD) diagnosed at childhood. To provide advice on how to assess and manage nutritional concerns in these patients, a Medline search was conducted using "pediatric inflammatory bowel disease", "pediatric Crohn's disease", "linear growth", "pubertal growth", "bone health", and "vitamin D" as key words. Clinical trials, systematic reviews, and meta-analyses published between 2008 and 2013 were selected to produce this narrative review. Studies referring to earlier periods were also considered if the data was relevant to our review. Although current treatment strategies for CD that include anti-tumor necrosis factor-α therapy have been shown to improve patients' growth rate, linear growth deficiencies are still common. In pediatric CD patients, prolonged diagnostic delay, high initial activity index, and stricturing/penetrating type of behavior may cause growth deficiencies (in weight and height) and delayed puberty, with several studies reporting that these patients may not reach an optimal bone mass. Glucocorticoids and inflammation inhibit bone formation, though their impact on skeletal modeling remains unclear. Long-term control of active inflammation and an adequate intake of nutrients are both fundamental in promoting normal puberty. Recent evidence suggests that recombinant growth factor therapy is effective in improving short-term linear growth in selected patients, but is of limited benefit for ameliorating mucosal disease and reducing clinical disease activity. The authors conclude that an intense initial treatment (taking a "top-down" approach, with the early introduction of immunomodulatory treatment) may be justified to induce and maintain remission so that the growth of children with CD can catch up, ideally before puberty. Exclusive enteral nutrition has a key role in inducing remission and improving patients' nutritional status.

Key words: Bone health; Enteral nutrition; Growth; Height; Pediatric inflammatory bowel disease; Pediatric Crohn's disease; Linear growth; Pubertal growth; Vitamin D; Weight loss

Core tip: This review focuses on current evidence for managing growth issues in children diagnosed with Crohn's disease. Long-term control of active inflammation and an adequate intake of nutrients are both essential in promoting puberty. Exclusive enteral nutrition has a key role, as it induces disease remission and improves nutritional status. The early introduction of immunosuppressants or biologics may be justified in children to achieve disease remission and enable their growth to catch up, ideally before puberty. Recent evidence suggests that recombinant growth factor therapy is effective in improving short-term linear growth.

Gasparetto M, Guariso G. Crohn's disease and growth deficiency in children and adolescents. *World J Gastroenterol* 2014; 20(37): 13219-13233 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i37/13219.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i37.13219

INTRODUCTION

Crohn's disease (CD) is a global health concern and a condition that significantly affects patients' quality of life, as well as placing a heavy financial burden on the community[1]. CD is currently without a cure, and its incidence is rising not only in Western countries, but also in most developing countries. It manifests in childhood or adolescence in up to 25% of cases[2].

The microbial ecosystem colonizing the human bowel is influenced by diet, which prompts metabolic processes essential to bowel metabolism[3-7]. Genetic susceptibility, intestinal microbiota, lifestyle and environmental factors are amongst the potential mechanisms involved in the pathogenesis of inflammatory bowel diseases (IBD)[3]. Prolonged diagnostic delays, high initial activity indexes, and stricturing/penetrating behavior patterns may predict subsequent complications and the need for surgery, thus justifying a resort to early intensive therapy. The early introduction of immunomodulatory therapy favorably affects the course of IBD[8-12]. Growth failure and impaired nutritional status are seen in 65%-85% of children and adolescents diagnosed with CD, and 15%-40% of these patients continue to suffer from growth deficiency throughout the course of their disease[1,13]. Exclusive enteral nutrition has become a key treatment strategy for inducing disease remission in pediatric CD, offering the advantage of improving patients' nutritional status as well as enabling the mucosa to heal at much the same rate as is achievable with corticosteroids[1,14-17].

GROWTH ISSUES IN PEDIATRIC CROHN'S DISEASE

Growth deficiency can severely affect quality of life for children and adolescents with CD, and complicate their management[18-20]. It occurs in a significant proportion of patients (up to 85%), and may even precede any clinical evidence of bowel disease. Abraham *et al*[21] recently conducted a systematic review focusing on understanding the long-term risks of growth deficiency, disease reclassification and extension, hospitalization, cancer, and death among patients with childhood IBD[21] (Table 1): in 41 studies considered, concerning 3505 patients with CD, 2071 with ulcerative colitis (UC) and 461 with non-IBD colitis, growth failure was identified more often in CD (10%-56%) than in UC (0%-10%) or non-IBD controls. Growth improved after surgical resection in patients with CD[21].

Among IBD sufferers, male patients are more vulnerable to growth deficiencies than females of the same age because the male growth spurt in puberty is greater, occurs later, and lasts longer than in females[22]. Vasseur *et al*[23] examined a total of 261 pediatric patients with CD registered in the EPIMAD registry in northern France. At diagnosis, 25 children (9.5%) had a height more than 2 standard deviations below the norm, and the same applied to the weight of 70 children (27%), and the BMI of 84 children (32%). At maximal follow-up, 18 children (6.9%) had a growth deficiency and 40 (15%) suffered from malnutrition. Nutritional status was more severely impaired in children with stricturing disease. Growth and nutritional deficiency at diagnosis, young age, male gender, and extraintestinal manifestations at diagnosis were indicators of a poor prognosis. The authors concluded that young boys with substantial inflammatory manifestations of CD are at higher risk of subsequent growth failure, especially when their growth is already deficient at diagnosis[23].

Assessing growth in IBD patients of a developmental age is so important that it was included among the key points in the Paris classification of pediatric CD, which replaced the previous Montreal classification[24]. The following factors are implicit in the physiopathology of growth deficiency in pediatric IBD[22]: (1) chronic calorie insufficiency: these patients' malnutrition is due to a lower intake, protein malabsorption, abnormal intestinal losses, and anorexia correlating with the pathological picture [tumor necrosis factor-α (TNF-α) also has a direct influence at the hypothalamic level]. Inflammatory mediators trigger an increase in basal metabolism too, coinciding with a further deterioration in nutritional status; (2) direct cytokine effects: insulin-like growth factor (IGF)-1 is produced in the liver and is the principal mediator of the effects of growth hormone (GH). Patients suffering from CD have significantly reduced IGF-1 blood levels, irrespective of their GH levels. TNF-α and interleukin (IL)-6 also have a direct inhibitory effect on GH. Other pathways independent of IGF-1 inhibition by means of which the inflammatory cytokines inhibit the linear growth rate have recently been identified as well; (3) effects of chronic treatment with corticosteroids: these drugs induce a central suppression of GH production and reduce IGF-1 synthesis in the liver, as well as interfering with its peripheral receptor activity; (4) effects of IBD on endocrine growth mediators: delayed puberty gives rise to a sex hormone deficiency that may be involved in growth deficiencies; and (5) genetic factors: polymorphisms of NOD2/CARD15 and other already-identified genes appear to generate a cytokine pattern capable of contributing to pediatric IBD patients' growth deficiency; promoter regions of the gene coding for TNF-α and IL-6 also seem to be involved.

NUTRITIONAL CONCERNS IN PEDIATRIC CROHN'S DISEASE

Nutritional issues are often associated with CD, especially in pediatric cases, with underweight and stunting

Table 1 Summary of the main studies that were reviewed on nutritional concerns in pediatric Crohn's disease

Ref.	Type of study	Patients	Results	Conclusion
Vaisman *et al*[25], *Nutrition* 2006	Prospective cohort study	16 pts with CD; Age 19-57 yr Remission of disease (CDAI Activity Disease Index < 150); 2 groups (BMI 18.5 kg/m^2 as a cutoff point)	Subjects with lower BMIs tended to have less lean body mass (P = 0.006), less bone mineral density (P = 0.006), and lower resting energy expenditure (P = 0.003); No correlation between BMI and energy intake, although percentage of malabsorption negatively correlated with BMI (P = 0.07)	In the presence of similar energy intake, resting energy expenditure does not seem to contribute to lower BMI, although nutrient malabsorption is higher in malnourished patients with CD in remission; Malabsorption should be evaluated in patients with CD who fail to gain Wt during disease remission, to establish their extra caloric requirements
Gupta *et al*[28], *Inflamm Bowel Dis* 2013	Retrospective review	43 IBD pts (mean age 12.8 yr; range 5.1-17.4 yr) 67% M 33% F	Reductions in erythrocyte sedimentation rate (P < 0.0001) and C-reactive protein (P < 0.02), and increases in albumin (P < 0.03); Mean PCDAI score 26.9 at baseline and 10, 2 at follow-up (P < 0.0001); Induction of remission achieved in 65% and response in 87% at a mean follow-up of 2 mo (1-4 mo)	Novel protocol for enteral nutrition (80%-90% of patient's caloric needs) seems to be effective for the induction of remission in CD children; The protocol may result in improved EN acceptance and compliance and will be evaluated prospectively
Wiskin *et al*[29], *J Hum Nutr Diet* 2012	Prospective cohort study	46 IBD children	No children scored low risk with STAMP, STRONGkids or PNRS; 23 children scored low risk with PYMS; Good agreement between STAMP, STRONGkids, and PNRS (K > 0.6); Modest agreement between PYMS and the other scores (K = 0.3); No agreement between the risk tools and the degree of malnutrition based on anthropometric data (K < 0.1)	Relevance of nutrition screening tools for children with chronic disease is unclear; There is the potential to under recognize nutritional impairment (and therefore nutritional risk) in children with IBD
Valentini *et al*[30], *Nutrition* 2008	Prospective, controlled, multicentric study	94 pts with CD (CDAI 71 +/- 47) 61 F 33 M 50 UC (UCAI 3.1 +/- 1.5) 33 F 17 M 61 healthy control subjects 41 F 20 M from centers in Berlin (Germany), Vienna (Austria), and Bari (Italy) 47 well-nourished patients with IBD pair-matched to healthy controls by BMI, sex, and age	74% IBD patients were well-nourished according to the SGA, BMI, and serum albumin; Body composition analysis demonstrated a decrease in BCM in patients with CD (P = 0.021) and UC (P = 0.041) compared with controls; Handgrip strength correlated with BCM (r = 0.703, P = 0.001) and was decreased in patients with CD (P = 0.005) and UC (P = 0.001) compared with controls; Lower BMC in patients with moderately increased serum CRP levels compared with patients with normal levels	In CD and UC, selected micronutrient deficits and loss of BCM and muscle strength are frequent in remission and cannot be detected by standard malnutrition screening
Chan *et al*[31], *Am J Gastroenterol* 2013	Prospective cohort study	300724 participants (recruited into the European Prospective Investigation into Cancer and Nutrition study) 177 UC and 75 CD	No associations with the four higher categories of BMI compared with a normal BMI for UC (P trend = 0.36) or CD (P trend = 0.83); Lack of associations when BMI analyzed as a continuous or binary variable (BMI 18.5 kg/m^2 *vs* ⩾ 25 kg/m^2); Physical activity and total energy intake not associated with UC (P trends 0.79-0.18) or CD (P trends 0.42-0.11)	Obesity as measured by BMI not associated with the development of incident UC or CD; Alternative measures of obesity required to further investigate the role of obesity in the development of incident IBD
Werkstetter *et al*[32], *J Crohns Colitis* 2012	Prospective cohort study	39 IBD children in remission; 27 CD, 12 UC 24 M; 39 healthy age-sex-matched controls	IBD pts *vs* controls: Lower Z-scores for phase angle α [-0.72; 95%CI: (-1.10-0.34)] Lower grip strength [-1.02 (-1.58-0.47) Lesser number of steps per day [-1339 (-2760-83)] Shorter duration of physical activity [-0.44 h (-0.94-0.06)], particularly in F and patients with mild disease. Quality of life and energy intake did not differ between patients and controls	In spite of quiescent IBD, lean body mass and physical activity were reduced; Interventions to encourage physical activity may be beneficial in this lifelong disease

Gerasimidis *et al*[33] *Inflamm Bowel Dis* 2013	Prospective cohort study	184 new pediatric IBD Dg 139 one year follow-up IBD children 84 children treated with EEN	72% anemic at Dg; Anemic children with CD had shorter diagnosis delay, lower BMI, lower Dg delay ($P < 0.001$) and BMI Z-score, $P = 0.003$) than non-anemic patients; Extensive colitis associated with severe anemia in UC; After EEN, severe anemia decreased (32%-9%, $P < 0.001$) and hemoglobin concentration increased by 0.75 g/dL	Anemia is frequent at Dg and follow-up and should receive more attention from the clinical team; The focus should remain suppression of inflammatory process in active disease

Dg: Diagnosis; pt/pts: Patient/patients; CD: Crohn's disease; UC: Ulcerative colitis; IBD-U: Unclassified IBD; rhGH: Recombinant growth factor; ESR: Erythrocyte sedimentation rate; BMC: Body cell mass; BMI: Body mass index; Ht: Height; Wt: Weight; BMD: Bone mineral density; DXA: Dual-energy X-ray absorptiometry; EEN: Exclusive enteral nutrition; GH: Growth hormone; (P)CDAI: (Pediatric) Crohn's disease activity index; PUCAI: Pediatric ulcerative colitis activity index; M: Male; F: Female.

commonly seen at presentation, as well as linear growth retardation and delayed puberty developing later on[1]. Undernutrition has been reported in 65%-75% of patients with CD[25] (Table 1), and recent weight loss is one of the triad of clinical manifestations of the disease. Although medical treatment can soon restore body weight, this is not reflected in concomitant changes in body composition. Children with CD have the features of nutritional cachexia, with normal fat stores but depleted lean mass. Poor bone health, delayed puberty, and growth failure are other possible features complicating their clinical management[26].

As growth impairment is mainly secondary to disease activity, all available pharmacological steps to induce remission in a given patient (depending on their disease phenotype) should have a positive effect on growth as well. Exclusive enteral nutrition has been used as a therapeutic approach to CD because it can improve patients' nutritional status and induce remission (mucosal healing) as quickly as corticosteroids[1,27]. Exclusive enteral nutrition has thus become a fundamental option at many centers treating pediatric CD[1]. A recent retrospective review by Gupta *et al*[28] (Table 1) assessed the efficacy of enteral nutrition (EN) in delivering 80%-90% of patients' calorie needs with a view to inducing remission in pediatric patients with CD. This approach allowed for patients to ingest the remainder of the calories they needed from a normal diet, and so it differs from the standard practice of providing EN to cover 100% of patients' calorie needs. The sample's mean Pediatric Crohn's Disease Activity Index score (PCDAI) at the baseline was 26.9 and it dropped to 10.2 at follow-up ($P = 0.0001$). Remission was induced in 65% of cases and response in 87% after a mean 2 mo of follow-up (1-4 mo). The authors concluded that this novel EN protocol seems to be effective in inducing remission in pediatric patients with CD, helping to increase their weight and improve their laboratory markers. This protocol may also make EN more readily acceptable to patients and improve their compliance[28].

There has recently been increasing interest in the use of nutrition risk assessment tools in children to identify those needing nutritional support[29] (Table 1). Four screening tools that are not disease-specific [the Screening tool for the assessment of malnutrition in pediatrics (STAMP), the screening tool for risk on nutritional status and growth (STRONGkids), the pediatric Yorkhill malnutrition score (PYMS), and the simple pediatric nutrition risk score (PNRS)] were applied by Wiskin *et al*[29] to 46 children with IBD. The degree of malnutrition was measured by anthropometry alone using the World Health Organization's International Classification of Diseases (ICD-10) criteria. There was a good agreement between STAMP, STRONGkids, and PNRS ($K > 0.6$), but only a modest agreement between PYMS and the other scores ($K = 0.3$), and no agreement between the risk tools and the degree of malnutrition based on anthropometric data ($K < 0.1$). The authors concluded that the relevance of nutrition screening tools for children with chronic intestinal disease is unclear, and there is a risk of their failing to recognize nutritional impairment (and consequent nutritional risk) in children with IBD[29].

A study by Vaisman *et al*[25] (Table 1) focused on identifying the relative contribution of factors causing malnutrition in a sample of 16 patients with CD in remission (age 19-57 years). Resting energy expenditure (REE) was studied by indirect calorimetry and body composition by dual-energy X-ray absorptiometry. Subjects with lower BMIs tended to have less lean body mass ($P = 0.006$), a lower bone mineral density ($P = 0.006$), and lower REE ($P = 0.003$). No correlation emerged between BMI and energy intake, although the percentage of malabsorption correlated negatively with BMI ($P = 0.07$). The authors concluded that nutrient malabsorption is more severe in malnourished patients with CD in remission, and consequently suggested that malabsorption should be assessed in CD patients who fail to gain weight while in remission in order to establish their extra calorie needs[25].

A prospective, controlled, multicentric study by Valentini *et al*[30] (Table 1) considered nutritional status (subjective global assessment [SGA], BMI, albumin, trace elements), body composition (bioelectrical impedance analysis, anthropometry), muscle strength, and quality of life in 94 patients with CD and 50 with UC, all in clinical remission, and 61 healthy controls. Most patients with IBD (74%) were well-nourished according to their SGA, BMI, and serum albumin levels, but body composition analysis demonstrated a lower body cell mass (BCM) in patients with CD ($P = 0.021$) and UC ($P = 0.041$) than in

controls. Handgrip strength correlated with BCM (P = 0.001) and was again lower in patients with CD (P = 0.005) and UC (P = 0.001) than in controls. These differences were seen even in patients classified as well-nourished. BCM was lower in patients with moderately increased serum C-reactive protein levels than in patients with normal levels. The authors concluded that selected micronutrient deficits and loss of BCM and muscle strength are frequent in CD and UC in remission, and go undetected in standard malnutrition screening[30].

Obesity is associated with a pro-inflammatory state that may be involved in the etiology of IBD. Chan *et al*[31] (Table 1) conducted the first prospective cohort study to identify any association between obesity and the onset of incident IBD in a sample of 300724 participants recruited for the European Prospective Investigation into Cancer and Nutrition study. At recruitment, anthropometric measurements were taken of patients' height and weight, and their physical activity and total energy intake were recorded using validated questionnaires. The cohort was monitored and 177 participants developed incident UC, while 75 developed incident CD. No associations emerged vis-à-vis UC or CD between the four higher BMI categories and a normal BMI level. Physical activity and total energy intake (factors influencing BMI) also revealed no association with UC or CD. The authors concluded that obesity, as measured by the BMI, is unassociated with the onset of incident UC or CD. Alternative obesity measures are needed to further clarify the role of obesity in the onset of incident IBD[31].

Physical activity is important for muscle and bone strength in growing children and may be limited in pediatric IBD patients, even when their disease is quiescent[32]. A recent study by Werkstetter *et al*[32] (Table 1) compared 39 IBD patients (27 CD, 12 UC) in remission (or with only mild disease activity) with 39 healthy age- and sex-matched controls. The patients had lower Z-scores for phase angle α and lower handgrip strength than controls. They tended to take fewer steps per day and engage in shorter periods of physical activity, particularly among females and patients with mild disease. The authors concluded that, even with quiescent disease, IBD patients have reduced levels of lean body mass and physical activity. Action to encourage them to engage in physical exercise may therefore be beneficial in this lifelong disease[32].

Low concentrations of plasma micronutrients are commonly reported in IBD patients, but may be difficult to interpret in the presence of an acute phase response, and other body store adequacy indices are needed. Anemia is a common extraintestinal manifestation in IBD children: these are primarily cases of iron-deficiency anemia, with anemia of chronic disease coming second[33]. A study by Gerasimidis *et al*[33] (Table 1) explored the epidemiology of anemia and associated factors in children with IBD at the time of their diagnosis, after 1 year, and during treatment with exclusive enteral nutrition (EEN). At diagnosis, 72% of the children were anemic. Children with CD who were anemic had a shorter diagnostic delay and a lower BMI than those who were not (P = 0.003). Extensive colitis was associated with severe anemia in UC. After EEN, the cases of severe anemia decreased (32%-9%; P = 0.001), and hemoglobin concentrations increased by 0.75 g/dL. The authors concluded that children with IBD are highly likely to have anemia at diagnosis, and that this matter should receive more attention during their follow-up, even though clinicians should focus on suppressing the inflammatory process in cases of active disease[33].

Deficiencies in the liposoluble vitamins A-D and E, and zinc are also possible features of IBD patients[34-36].

Vitamin D

Vitamin D is a key factor not only for its role in the mineralization of bone and teeth, but also because of its other metabolic functions and its protective role in immune-mediated diseases and allergies[37-39]. Vitamin D status is assessed by testing its metabolite 25-hydroxy-vitamin D (25-OH-D) in plasma or serum, which reflects the amount of vitamin D converted in the skin through sunlight exposure and ingested in the diet[37]. Poor vitamin D status may have detrimental consequences for the future health of a child, so an optimal vitamin D status is a crucial public health goal. Vitamin D levels are classed as severely deficient for levels < 37 nmol/L, insufficient for levels < 50 nmol/L, and suboptimal for levels of 50-75 nmol/L[37]. Exposure to sunlight is generally the most important source of vitamin D3, while the contribution of vitamin D from foods and supplements is fundamental in populations living at latitudes with limited hours of sunlight[37]. Obesity is a risk factor for vitamin D deficiency because a greater proportion of the body's vitamin D remains stored in adipose tissue[37].

Current national recommendations suggest a daily intake of 7.5 mcg of vitamin D[37]. Foods containing large amounts of vitamin D include oily fish and eggs. Vitamin D is produced endogenously in the skin by the photo-reduction of 7-dehydrocholesterol by ultraviolet light. Human exposure to sunlight is limited throughout their lives and some foods are fortified with vitamin D (*e.g.*, milk, some juices, breads, and cereals). Children with chronic diseases are consequently at risk of vitamin D deficiency. The Institute of Medicine recommends a vitamin D intake of 600 IU/d in individuals 1-70 years of age, plus 700-1300 mg/d of calcium (depending on age) to promote healthy skeletal growth[40]. Vitamin and mineral deficiencies have been described in patients with IBD and are attributed to gut mucosa inflammation and a reduced oral intake[34]. Cranney *et al*[41] conducted a systematic qualitative review of 167 eligible studies (112 randomized controlled trials (RCTs), 19 prospective cohort studies, 30 case-control, and 6 before-after studies). The largest body of evidence on vitamin D status and bone health concerned older adults, while few studies focused on infants, children, and adolescents. There was inconsistent evidence of an association between circulating 25(OH)D levels and bone mineral content in infants. In adoles-

cents, there was a fair amount of evidence for an association between 25(OH)D levels and changes in BMD. There was solid evidence of the use of foods fortified with vitamin D (11 RCTs) consistently increasing serum 25(OH)D in both young and older adults. In short, the studies generated fairly good evidence of an association between circulating 25(OH)D concentrations and some bone health outcomes (established rickets, PTH, falls, BMD). When compared with a placebo, vitamin D(3) (> 700 IU/d) with calcium supplementation reportedly had a small beneficial effect on BMD and reduced the risk of fractures and falls, although this benefit may be confined to specific subgroups[42]. A recent retrospective study performed by Alkhouri *et al*[34] in the US investigated the prevalence of vitamin and zinc deficiencies in 61 children (age 1-18 years) with newly-diagnosed IBD from 2006 to 2010 (80% with ileal inflammation) by comparison with a control group of 61 age- and sex-matched individuals. While none of the IBD patients had folate or vitamin B12 deficiency, 62% of them had vitamin D deficiency (*vs* 75% in the control group), 16% had vitamin A deficiency, 5% had vitamin E deficiency (*vs* 8% in the control group), and 40% had zinc deficiency (*vs* 19% in the control group). The authors concluded that vitamin B12 and folate deficiencies are rare in children with newly-diagnosed IBD in the United States, so there is no reason to support their routine monitoring. On the other hand, vitamin A and zinc deficiencies were statistically more prevalent among the IBD cases than in controls, so their levels should be assessed at the time of their diagnosis to enable enteral supplementation to be started[34]. Vitamin D deficiency was common in the population tested, so routine screening for this deficiency and supplementation are warranted. These results contrast with previous studies by Yakut *et al*[43] and Chowers *et al*[44].

To sum up on vitamin D, there is still no strong evidence in the literature of an association between circulating 25(OH)D concentrations and bone health outcomes, and an improvement in BMD in particular. Only partial benefits of administering vitamin D(3) (> 700 IU/d) and calcium supplementation have been seen in terms of BMD and a lower risk of fractures and falls, and only in specific subgroups[41]. Supplementing vitamin D in pediatric patients is nonetheless generally recommended when its levels are found to be depleted, given its action not only on bone metabolism but also in terms of immunomodulation[37,40].

BONE HEALTH AND PEDIATRIC CROHN'S DISEASE

Although current treatment strategies for CD that include therapy against TNF-α have been found to speed up growth, linear growth deficiencies persist even with optimized therapy[22]. Children with CD continue to suffer from short stature and slow growth, and several studies have indicated that children with IBD may fail to achieve optimal bone mass[45-47]. Children with CD have multiple risk factors for impaired bone accrual[48]. The skeleton is a highly dynamic tissue regulated by local, systemic, and environmental clues that modify osteoblastic (bone formation) and/or osteoclastic (bone reabsorption) activities. IBD affects bone regulation at all levels: environmentally through intestinal barrier breaks and/or a microbial composition in the gut; systemically with the circulation of gut immune cells and cytokines throughout the body; and locally by causing inflammation of extra-intestinal organs (such as the bone marrow)[49].

Bone formation and reabsorption are significantly involved in bone health and growth. In children with CD, both of these processes are impaired, so bone growth is ultimately suboptimal[49]. Factors contributing to this derangement are inflammation, delayed growth and puberty, lean mass deficiencies, and the use of glucocorticoids[50,51]. A recent study by Irwin *et al*[52] examined the effect of experimental IBD on bone health. Interleukin-10-deficient animals infected with *Helicobacter hepaticus* (*H. hepaticus*) were used as a murine model of colitis, and the molecular and histological properties of their bone and intestine were examined to identify the immunopathological consequences of colitis in mice. Six weeks after they were infected, male (but not female) mice revealed significant trabecular bone loss in the distal femur and vertebrae. The authors concluded that the severity of *H. hepaticus*-induced colitis and the associated bone loss are gender-related, possibly as a result of gender-specific effects on *H. hepaticus* colonization in the mouse gastrointestinal tract and the consequent immunopathological responses[52].

A prospective study by Kim *et al*[45] (Table 2) aimed to examine the risk factors and extent of bone mass reduction and to analyze the impact of IBD developing early, before bone mass has peaked (*i.e.*, before the maximal bone mineral density has been reached during development). Bone mineral density (BMD) was assessed in the lumbar spine and hip bone in 44 IBD patients (21 of them < 30 years old). Younger patients had a significantly more severe bone mass reduction in the lumbar spine than patients aged > 30 years (multivariate analysis showed a hazard ratio of 3.96, $P = 0.06$)[45]. On the other hand, a recent prospective cohort study by Tsampalieros *et al*[53] (Table 2) suggested that younger age provides a window of opportunity for skeletal recovery. The aim of their study was to examine changes in BMD and cortical structure after CD had been diagnosed, and to identify associations with growth, glucocorticoids, and disease activity. The authors concluded that CD was associated with a persistently low trabecular BMD, although younger participants showed a greater potential for recovery. A greater linear growth was associated with a greater recovery of cortical dimensions, especially among participants with less glucocorticoid exposure and inflammation. So, although glucocorticoids and inflammation inhibit bone formation, their impact on skeletal modeling is still not clear[53].

Another longitudinal study performed by Schmidt *et al*[51] (Table 2) on a total of 144 patients with IBD (including 83 with UC and 45 with CD) concluded that IBD

Table 2 Summary of the main studies that were reviewed on growth issues and bone health in pediatric Crohn's disease

Ref.	Type of study	Patients	Results	Conclusion
Abraham *et al*[21] *J Clin Gastroenterol* 2012	Systematic review	3505 CD, 2071 UC, and 461 IBD-U (age at onset < 18 yr)	Growth failure was reported in CD (10% and 56%) more often than UC (0%-10%) or non-IBD controls; Improvements in growth occurred after surgical resection in CD pts; Increase in disease reclassification over time from UC and IBD-U Dg to CD; CD pts had higher number of hospitalizations and hospital days per year *vs* UC pts in most studies; The reported surgery rates in CD ranged between 10% and 72%; the colectomy rates in UC ranged between 0% and 50%	Childhood-onset IBD pts had growth failure reported in pts with CD more often than those with UC, and had a reclassification of disease type to CD over time; Higher rates of surgery and hospitalizations were found with CD than with UC
Kim *et al*[45] *Clin Endosc* 2013	Prospective cohort study	44 IBD (21 aged < 30 yr; 23 aged > 30 yr)	Significant bone mass reduction at the LS in IBD patients aged < 30 yr *vs* patients aged > 30 yr (BMD $P < 0.01$; T-score $P < 0.01$; Z-score $P < 0.01$); Multivariate analysis: risk factor of bone mass reduction for patients < 30 yr → HR = 3.96, $P = 0.06$	Bone mass reduction is more severe in patients diagnosed with IBD before the age of 30 yr
Schmidt *et al*[51] *J Pediatr Gastroenterol Nutr* 2012	Longitudinal cohort study	144 IBD pts 83 UC, 45 CD	Children with UC and CD had significantly lower mean BMD Z-scores for the LS at baseline and after 2 yr; The reduction in BMD was equally pronounced in patients with UC and CD; Neither group improved their Z-score during the follow-up period; Significantly lower mean BMD Z-scores for the LS were found at baseline in M ($P < 0.001$), but not in F; Lowest BMD values in the group of patients ages 17 to 19 yr in M and in F	The entire group of pediatric patients with IBD showed permanent decreases in their BMD Z-scores for the LS; however, afflicted children have the potential to improve their BMD by the time they reach early adulthood
Tsampalieros *et al*[53] *J Clin Endocrinol Metab* 2013	Prospective cohort study	CD (age 5-21)	Disease activity improved over the study interval ($P < 0.001$); Trabecular BMD-Z improved over the first 6 mo; Increases associated with improved disease activity ($P < 0.001$), younger age ($P = 0.005$), and increases in vitamin D levels ($P = 0.02$); Greater increases in tibia length associated with greater increases in cortical area-Z ($P < 0.001$); Greater glucocorticoid doses and disease activity significantly associated with failure to accrue cortical area, and more pronounced with greater linear growth (interaction $P < 0.05$); Mean ± SD trabecular BMD and cortical area Z-scores significantly reduced at the final visit	CD was associated with persistent deficits in trabecular BMD; Younger participants demonstrated greater potential for recovery; Greater linear growth associated with greater recovery of cortical dimensions, especially among participants with lesser glucocorticoid exposure and inflammation; Younger age and concurrent growth provide a window of opportunity for skeletal recovery
Malik *et al*[54] *J Crohns Colitis* 2012	Prospective cohort study	36 children with CD (Male 22)	28 (78%) CD children treated with adalimumab went into remission; Overall 42% of children showed catch-up growth, which was more likely in: Pts who achieved remission ($P = 0.007$); Pts who were on immunosuppression ($P = 0.03$); Pts whose indication for adalimumab was an allergic reaction to infliximab ($P = 0.02$); Pts who were on prednisolone when starting adalimumab, ($P = 0.04$)	Clinical response to adalimumab is associated with an improvement in linear growth in a proportion of children with CD; Improved growth is more likely in patients entering remission and on immunosuppression but is not solely due to a steroid sparing effect
Malik *et al*[55] *Arch Dis Child* 2012	Retrospective cohort study	116 CD children; 68 M; Mean age at diagnosis 10.8 yr (range 4.9-15.5); Mean age at maximum follow-up of 15.4 yr (9.4-19.3)	At T0, mean height SD score was -0.5 (-3.3-2.6) compared to a mid-parental mean height SD score of 0.2 (-2.0-1.4) ($P = 0.002$); At T1, T2, T3, and maximum follow-up, mean height SD score was -0.6 (-4.8-7.8), -0.6 (-2.9-2.2), -0.7 (-3.6- 2.5) and -0.5 (-3.5-2.9), respectively; Mean Ht velocity SDS at T1, T2, T3 and maximum follow-up was -1.4 (-7.4-7.4), -0.6 (-7.5-6.1), -0.1 (-6.6 -7.6) and 0.6 (-4.8-7.8), respectively ($P < 0.05$)	In final models: Mean Ht velocity SDS was associated negatively with the use of prednisolone ($P = 0.0001$), azathioprine ($P = 0.0001$), methotrexate ($P = 0.0001$), and weight SDS (WtSDS) $P = 0.0001$); Mean Ht velocity SDS was associated positively with age ($P = 0.0001$) and Wt SDS ($P = 0.01$); ΔHt SDS was associated negatively with use of prednisolone ($P < 0.02$)

Laakso *et al*[56] *Calcif Tissue Int* 2012	Cross-sectional Cohort Study	80 IBD pts (median age 14.9 yr, range 5-20), median disease duration 3.4 yr; 51 UC, 26 CD, and 3 IBD-U	IBD pts had lower bone age-adjusted LS and whole-body areal BMD ($P < 0.001$ for both) and whole-body composition adjusted for Ht ($P = 0.02$) than controls; Lean mass and fat mass Z-scores did not differ between the groups, but IBD patients had lower whole-body composition relative to muscle mass ($P = 0.006$); Vitamin D deficiency in 48%, despite vitamin D supplementation; In IBD cumulative weight-adjusted prednisolone dose > 150 mg/kg for the preceding 3 yr increased the risk for low whole-body areal BMD (OR = 5.5, 95 %CI: 1.3-23.3, $P = 0.02$). Vertebral fractures found in 11% of patients and in 3% of controls ($P = 0.02$)	IBD in childhood was associated with low areal BMD and reduced bone mass accrual relative to muscle mass; The risk for subclinical vertebral fractures may be increased; Careful follow-up and active preventive measures are needed
Ahmed *et al*[60] *J Pediatr Gastroenterol Nutr* 2004	Prospective cohort study	47 CD and 26 UC (median age of 13.5 yr - range, 5.5-18.2 yr)	Pts with CD were shorter than those with UC ($P < 0.05$); Median ppBone Area for LS and total body for the whole group was 85% and 81%, respectively; ppBone Area at both sites was directly related to height SDS and BMI SDS ($r > 0.5$; $P < 0.005$); Median BMD SDS for LS and total body was -1.6 and -0.9, respectively; Median ppBMC for LS and total bone was 98% and 101%, respectively; ppBMC showed no relationship to ppBone Area ($r = 0.1$, NS); Children with osteopenia 22% after adjustment for bone area	Children with IBD often have small bones for age because they have growth retardation; When DXA data are interpreted with adjustment for bone size, most children have adequate bone mass; Correct interpretation of DXA is important for identifying children who may be at a real risk of osteoporosis
Burnham *et al*[61] *J Bone Miner Res* 2004	Prospective cohort study	104 children and young adults with CD 233 healthy controls (age 4-26)	CD pts had significantly lower Ht Z-score, BMI Z-score, and lean mass relative to Ht compared with controls (all $P < 0.0001$); After adjustment for group differences in age, Ht, and race, the ratio of BMC in CD relative to controls was significantly reduced in M (0.86; 95%CI: 0.83-0.94) and F (0.91; 95%CI: 0.85-0.98) with CD; Adjustment for pubertal maturation did not alter the estimate; addition of lean mass to the model eliminated the bone deficit; Steroid exposure was associated with short stature but not bone deficits	Importance of considering differences in body size and composition when interpreting DXA data in children with chronic inflammatory conditions; Association between deficits in muscle mass and bone in pediatric CD
Boot *et al*[62] *Gut* 1998	Prospective cohort study	55 pts (34 M 21 F, age range 4-18 yr) 22 CD, 33 UC	Mean SDS of LS BMD and total body BMD were significantly lower than normal (-0.75 and -0.95, both $P < 0.001$); Height SDS and BMI SDS were decreased. The decrease in BMD SDS could not be explained by delay in bone maturation; The cumulative dose of prednisolone correlated negatively with LS BMD SDS ($r = -0.32$, $P < 0.02$); BMI SDS correlated positively with total body BMD SDS ($r = 0.36$, $P < 0.02$); CD pts had significantly lower LS and total BMD SDS than UC pts, even after adjustment for cumulative dose of prednisolone; In the longitudinal data cumulative dose of prednisolone between the measurements correlated negatively with the change in LS and total BMD SDS; Lean tissue mass measured by dual X-ray absorptiometry had a strong correlation with lean body mass measured by bioelectrical impedance analysis ($r = 0.98$)	IBD children have a decreased BMD; CD children have a higher risk of developing osteopenia than UC children; Corticosteroid therapy and nutritional status are important determinants of BMD in IBD pts

Dg: Diagnosis; pt/pts: Patient/patients; CD: Crohn's disease; UC: Ulcerative colitis; IBD-U: Unclassified IBD; rhGH: Recombinant growth factor; ESR: Erythrocyte sedimentation rate; BMC: Body cell mass; BMI: Body mass index; Ht: Height; Wt: Weight; BMD: Bone mineral density; DXA: Dual-energy X-ray absorptiometry; EEN: Exclusive enteral nutrition; GH: Growth hormone; (P)CDAI: (Pediatric) Crohn's disease activity index; PUCAI: Pediatric ulcerative colitis activity index; M: Male; F: Female.

children have the potential to improve their BMD by the time they reach early adulthood. Children with UC and CD had significantly lower mean BMD Z-scores for the lumbar spine (LS), both at the baseline and after 2 years. Sub-analyses of the different age groups at the baseline found the lowest BMD values for patients aged 17 to 19 years, be they boys or girls; at follow-up, these patients' BMD had significantly improved, however[51].

A recent study by Malik *et al*[54] (Table 2) assessed the frequency of short stature and poor growth, and how they correlated with the course of the disease and the therapy administered in children with CD. The anthropometric and treatment details regarding 116 children showed that mean height SDS was negatively associated with the use of prednisolone ($P = 0.0001$), azathioprine ($P = 0.0001$), or methotrexate ($P = 0.0001$) and with weight SDS (Wt SDS) ($P = 0.0001$)[54]. Another study by Malik *et al*[55] (Table 2) focused on growth and disease activity over 12 mo in 36 children with CD who started taking adalimumab. Disease remission was achieved in 78% of these cases, and an overall 42% of the children caught up in terms of their growth. This was more likely to happen for those in remission, taking immunosuppressants, and those starting adalimumab therapy due to an allergic reaction to infliximab. An increase in growth rate was also seen in 15 children who were on prednisolone therapy when they started taking adalimumab. The authors concluded that clinical response to adalimumab therapy is associated with an improvement in linear growth in some children with CD, and that this is more likely for patients entering remission and on immunosuppression, although the effect is not due to a steroid-sparing effect alone[55].

Another recent cross-sectional cohort study by Laakso *et al*[56](Table 2) compared the skeletal characteristics of 80 children and adolescents suffering from IBD with 80 healthy controls matched for age and gender. The IBD patients had a lower bone age (BA)-adjusted lumbar spine, total body bone area BMD ($P < 0.001$ for both), and whole-body bone mineral content (BMC) than controls, after adjusting for height ($P = 0.02$). Lean mass and fat mass z-scores did not differ between the groups, but IBD patients had a lower whole-body BMC relative to muscle mass ($P = 0.006$). Despite 48% of the IBD patients receiving vitamin D supplementation, deficiencies of this vitamin were common. In the IBD group, a cumulative weight-adjusted prednisolone dose > 150 mg/kg for the preceding 3 years increased the risk of low whole-body aBMD ($P = 0.02$). Vertebral fractures (VFs) were found in 11% of patients and 3% of controls ($P = 0.02$). The authors concluded that IBD in childhood is associated with a low aBMD and reduced bone mass accrual relative to muscle mass; the risk of subclinical VFs may increase. These observations warrant careful follow-up and active preventive measures[56].

There is a well-established relationship between the long-term use of glucocorticoids for any disease indication and a higher risk of osteoporosis and fractures[57-59], but the relationship between CD or UC and bone loss remains controversial. Inability to achieve peak bone mass when the disease starts in childhood, malnutrition, immobilization, low BMI, smoking, and hypogonadism may all have a part to play in the pathogenesis of bone loss. Although evidence is sparse on the topic of bone health in children and adolescents with IBD, most authors recommend bone health screening, monitoring growth parameters and pubertal development, checking vitamin D status and vitamin D and calcium intake, and prescribing exercise and nutritional support[30]. Bone health status should be assessed systematically in patients treated for more than 6 mo, particularly during puberty[50].

Assessing BMD with dual energy X-ray absorptiometry (DXA) generally involves a comparison with age- and gender-matched reference ranges, and such studies show a high prevalence of osteopenia in children with IBD[60]. A recent study by Ahmed *et al*[60] (Table 2) aimed to compare the prevalence of osteopenia using two interpretation methods, one adjusted for age and gender, the other adjusted for bone size and gender. Forty-seven patients with CD and 26 with UC were considered, and the former were found shorter than the latter (median height, SDS, - 0.9 *vs* 0, $P < 0.05$). The authors concluded that children with IBD often have small bones for their age because they have a growth deficiency. When DXA data were interpreted after adjusting for bone size, most of the children were found to have an adequate bone mass. It is therefore important to interpret DXA findings correctly to identify children who may be at real risk of osteoporosis[60].

A study by Burnham *et al*[61] (Table 2) was designed to assess BMC relative to growth, body composition, and maturation in CD cases compared with controls. Whole-body BMC and lean mass were assessed by DXA in 104 CD subjects and 233 healthy controls. CD was associated with significant deficits in BMC and lean mass, relative to height. Individuals with CD had significantly lower z-scores for height and BMI, and a lower lean mass relative to height than controls ($P < 0.0001$). After adjusting for group differences in age, height, and race, males and females with CD had a significantly lower BMC than controls. Steroid exposure was associated with short stature but not with bone deficits. This study pointed to the importance of considering differences in body size and composition when interpreting DXA data in children with chronic inflammatory conditions, as well as showing an association between deficits in muscle mass and bone in pediatric CD[61].

A study by Boot *et al*[62] (Table 2) assessed BMD, nutritional status, and determinants of BMD in 55 children with IBD (34 boys and 21 girls, age range 4-18 years; 22 years with CD, 33 years with UC). The mean SDS for lumbar spine BMD and total body BMD were significantly lower than normal (both $P < 0.001$). The SDS for height and BMI were low as well. The decrease in BMD SDS could not be explained by any delay in bone maturation. The cumulative dose of prednisolone correlated negatively with lumbar spine BMD SDS ($P < 0.02$). Patients with CD had significantly lower lumbar spine and total body BMD SDS than patients with UC, even after adjusting for the cumulative dose of prednisolone. The authors concluded that: children with IBD have a reduced BMD; children with CD are at higher risk of osteopenia than children with UC; and corticosteroid therapy and nutritional status are important determinants of BMD in these patients[62].

A very interesting report from Whitten *et al*[63] sup-

ported the role of enteral nutrition in improving bone metabolism. The authors enrolled 23 children with newly-diagnosed CD and 20 controls. Children with CD were treated for 8 weeks with EEN, and inflammatory markers, nutritional markers (height, weight), bone markers [C-terminal telopeptides of Type-1 collagen (CTX), and bone-specific alkaline phosphatase (BAP)] were measured before and after the treatment. At diagnosis, children with CD had higher serum CTX than controls ($P = 0.0003$). After the period of EEN, their CTX levels fell significantly ($P = 0.002$), and their serum BAP levels ($P = 0.07$) increased significantly ($P = 0.02$), both normalizing to control levels. This evidence indicates that, as well as reducing inflammation, decreasing disease activity, and improving nutrition in children with newly-diagnosed CD, EEN therapy also normalizes serum markers of bone turnover, suggesting an improvement in bone health[63].

To sum up, although current therapy for CD is associated with a better growth rate for the first few years, a substantial proportion of children with CD remain short. Depending on the population considered, the prevalence of osteoporosis has been variably reported to range from 12% to 42% in patients with IBD[13]. While prospective studies suggest sustained bone loss at both trabecular and cortical sites in long-term glucocorticoid users with IBD[57], a decrease in bone mass is also seen in patients with active CD not using glucocorticoids[49,50]. Be that as it may, it is strongly recommended that excessively long periods of corticosteroid therapy be scrupulously avoided, particularly for patients of developmental age, and enteral nutrition should be used (whenever possible) as an alternative front-line therapy because it helps to contain the need for corticosteroids and thus limits their unwanted effects on growth, as well as cosmetic issues (which are very important in adolescence)[22]. Data on vertebral fractures are scarce and there is no agreement about the risk of non-vertebral fractures in patients with CD, though it has been suggested that patients with IBD may carry a 60% higher risk of non-vertebral fractures. The main question is whether all patients with CD should be treated with bone-protecting agents on the assumption that they could all potentially develop osteoporosis, or whether these agents should be used only in patients clearly at risk of osteoporosis and fractures (providing such patients can be identified)[49].

PUBERTY-RELATED ISSUES IN PEDIATRIC CROHN'S DISEASE

Many nutritional, inflammatory, immunological, and endocrine factors affecting patients suffering from IBD and influencing their growth also have an important impact on the initiation and progression of puberty. The onset of IBD before puberty is frequently associated with an underdeveloped stature and weight, and with patients having a significantly slower growth rate and lower final height by comparison with the parental target. This is more evident in children with CD than in cases of UC[64,65]. Other correlations include delayed puberty and menarche, an extended duration of the pubertal phase, and secondary amenorrhea[64]. Potential causes of late puberty in patients developing IBD in pre-pubertal and pubertal age include[64]: (1) malnutrition: this correlates mainly with a delay in menarche and sexual maturity. A link has been suggested between late puberty and reduced fat mass, which is normally rich in the aromatases that induce the conversion of androgens into estrogens and the consequent active production of female hormones; and (2) interactions between proinflammatory cytokines and the endocrine system: endocrine functions seem to be disrupted in IBD patients, also due to a direct effect of proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, on hormonal feedback mechanisms.

A recent retrospective study by Mason *et al*[66] (Table 3) aimed to ascertain the impact of CD and UC on the pubertal growth spurt. Pubertal growth was assessed by calculating peak height velocity (HV) SDS (PHV SDS), height SDS at diagnosis, height SDS at PHV, and age at PHV in patients with CD (30 boys, 11 girls) and UC (14 boys and 12 girls). Systemic markers of disease activity were also recorded. Altered pubertal growth parameters were apparent in the CD cases by comparison with the normal population, particularly in boys. In the group as a whole, age (PHV) showed an association with erythrocyte sedimentation rate ($r = 0.4$; $P = 0.005$) and an inverse association with BMI ($r = 0.4$; $P = 0.001$)[66].

MANAGEMENT OF GROWTH AND PUBERTAL ISSUES IN PEDIATRIC CROHN'S DISEASE

Healthy children grow at an annual rate of 4-6 cm up until puberty, when their rate of growth doubles for over a year[22]. A declining trend in growth chart percentiles for height and weight arouses the suspicion of growth deficiency vis-à-vis a child's targets for gender and age[22]. An early diagnosis of CD is fundamentally important, but the early signs of IBD vary and can easily go unnoticed, meaning that a statural growth deficiency and concomitant late puberty quite often precede the intestinal manifestations of the disease[22]. It is essential to monitor patients' growth, taking their initial height (as measured before the onset of IBD) for reference and routinely reassessing patients as their disease evolves in order to fully appreciate its impact on their growth[22]. Monitoring patients' growth rate is also important to see how they are responding to therapy over time[22]. Precise serial checkups should always include an assessment of patients' pubertal development, which should be correlated with their statural growth. If any discrepancies come to light, action can be taken without delay: radiology is used to establish patients' skeletal age and thus identify their residual potential for growth[22]. On average, it takes about 12 mo to see any response to treatment in terms of linear growth or pubertal development, so the intervals

Table 3 Summary of the main studies that were reviewed on management of growth and pubertal issues in pediatric Crohn's disease

Ref.	Type of study	Patients	Results	Conclusion
Mason *et al*[66] *Horm Res Paediatr* 2011	Retrospective cohort study	IBD adolescents 41 with CD, 30 M 11 F 26 with UC, 14 M 12 F	Altered parameters of pubertal growth observed in the CD groups compared to the normal population: In the CD M group, median Ht at Dg was -0.56 (P = 0.001) and median age at peak Ht velocity was 14.45 yr (P = 0.004) In the CD F group, median Ht at Dg was -1.14 (P = 0.007) and Ht at peak Ht velocity was -0.79 (P = 0.039). Individually, 8/30 CD M cases had one or more parameter affected: In the whole group, age at peak Ht velocity showed an association with ESR (r = 0.4; P = 0.005) and an inverse association with BMI (r = 0.4; P = 0.001)	Disorders of pubertal growth are more likely to occur in CD (particularly M)
Tietjen *et al*[69] *Turk J Gastroenterol* 2009	Prospective cohort study	40 pts with CD 26 M, 14 F mean age 16,7 yr (median: 17 yr, range: 4-29 yr)	Urinary GH levels were found as normal in CD; Corticosteroid therapy did not appear to be the most responsible factor for growth failure in CD	Growth failure in patients with CD is not caused by GH deficiency; A high PCDAI score has an important impact on impaired growth in children and adolescents with CD
Wong *et al*[70] *J Pediatr Endocrinol Metab* 2007	Retrospective data analysis	7 pts with CD 5 M	Median chronological age and median difference between chronological age and bone age was 15.9 yr (range, 13.0-17.9 yr) and 1.7 yr (-0.7-3.3 yr), respectively; Median dose of rhGH at T+0 was 0.23 mg/wk (0.15-0.31); Pubertal status remained unchanged in 6/7 patients; Median albumin and C-reactive protein were similar at T+0 and T+6; Median height SDS at T+0, T+6 and T+12 was -2.2 (-4.0 to -1.5), -1.9 (-4.1 to -0.8), -1.9 (-4.1 to -0.7), respectively (NS). Median Ht velocity SDS at T+0 and T+6 was -2.5 (-4.8-1.4) and -0.9 (-5.3 to 3.4), respectively (NS); Positive correlation between percentage change in Ht velocity SDS at T+6 and dose of rhGH at T+0 (r = 0.8, P = 0.03)	Introduction of rhGH therapy was associated with a cessation in the deterioration in linear growth; An improvement in Ht SDS was not observed over the period of the study
Wong *et al*[71] *Clin Endocrinol* (Oxf) 2011	Randomized controlled trial in 2 tertiary Children's Hospitals	22 children with IBD 21 with CD	Median Ht velocity increased from 4.5 (range, 0.6-8.9) at baseline to 10.8 (6.1-15) cm/year at 6 mo (P = 0.003) in the rhGH group, whereas in the Ctrl group, it was 3.8 (1.4-6.7) and 3.5 cm/yr (2-9.6), respectively (P = 0.58); Median percentage increase in Ht velocity after 6 mo in the rhGH group was 140% (16.7%-916.7%) compared with 17.4% (-42.1%-97.7%) in the Ctrl group (P < 0.001). No significant differences in disease activity and proinflammatory cytokines at baseline and 6 mo in both groups	rhGH can improve short-term linear growth in children with CD; The clinical efficacy of this therapy needs to be further studied in longer-term studies of growth, glucose homeostasis, and disease status

Dg: Diagnosis; pt/pts: Patient/patients; CD: Crohn's disease; UC: Ulcerative Colitis; IBD-U: Unclassified IBD; rhGH: Recombinant growth factor; ESR: Erythrocyte sedimentation rate; BMC: Body cell mass; BMI: Body mass index; Ht: Height; Wt: Weight; BMD: Bone mineral density; DXA: Dual-energy X-ray absorptiometry; EEN: Exclusive enteral nutrition; GH: Growth hormone; (P)CDAI: (Pediatric) Crohn's disease activity index; PUCAI: Pediatric ulcerative colitis activity index; M: Male; F: Female; NS: Not significant.

between follow-up assessments should never be less than six months[22].

To prevent and manage growth deficiencies in pediatric IBD patients, we must first establish the most appropriate nutritional, pharmacological, and surgical treatment for their underlying disease: managing their chronic inflammatory status and providing adequate nutrition are two synergically interacting aspects of the same approach[22]. Ensuring long-term control of active inflammation and administering an adequate intake of nutrients are both fundamental to promoting normal puberty[64]. Controlled clinical trials have documented a significant correlation between enteral nutrition, a reduced mucosal production of cytokines, and endoscopic healing. Enteral nutrition is potentially capable of inducing remission and achieving a nutritional recovery. Trials have also established that the effect of exclusively enteral nutrition on the inflammatory picture is influenced by factors such as the disease being localized in the small intestine or of recent onset, whereas the age factor appears to be less influential[22]. Immunomodulators other than corticosteroids used for pediatric IBD include the thiopurines (azathioprine and 6-mercaptopurine), which are used to maintain remission and have no demonstrated side-effects on growth, and biologics (infliximab and adalimumab), which potentially improve growth velocity by inducing and maintaining disease remission. Artificially-inducing puberty with the aid of estrogens and testosterone carries the risk of causing early growth cartilage calcification, giving rise to statural deficiencies[64].

Role of treatment with recombinant growth factor for pediatric Crohn's disease

Current treatment strategies for CD that include therapy against TNF-α have been found to improve growth velocity, but linear growth deficiencies persist even with optimized therapy[67]. Through complex mechanisms that include reducing IGF-1 levels and inducing systemic and hepatic GH resistance, cytokines such as TNF-α and IL-6 - which are commonly elevated in active CD - are important mediators of linear growth delay[68]. The potential for linear growth impairment as a complication of chronic intestinal inflammation is unique to pediatric CD patient populations[67]. IGF-I, produced by the liver in response to GH stimulation, is the key mediator of GH effects on the growth plate of bones. There is a well-known association between impaired growth in children with CD and low IGF-I levels. Early studies emphasized the role of malnutrition in suppressing IGF-I production. The direct, growth-inhibiting effects of pro-inflammatory cytokines have been increasingly recognized and explored. The role of non-cytokine factors (such as lipopolysaccharides) and their potential for negatively influencing the growth axis have also been investigated[67]. Recent evidence suggests that recombinant growth factor (rhGH) therapy is effective in improving short-term linear growth in selected patients[2], but is of limited benefit as a therapy for improving mucosal disease or reducing clinical disease activity[67]. A clinical analysis was performed by Tietjen *et al*[69] (Table 3) on 40 children, adolescents, and young adults with CD to see whether their growth failure was caused by impaired GH secretion. To assess growth hormone excretion, the authors measured urinary growth hormone with an in vitro immunoradiometric assay in three morning urine samples. They found normal urinary growth hormone levels in CD, concluding that growth failure in patients with CD is not caused by GH deficiency. Corticosteroid therapy did not appear to be the main culprit responsible for growth failure in CD either[69]. A retrospective data analysis was conducted by Wong *et al*[70] (Table 3) on 7 patients with CD treated with rhGH, after which the deterioration in their linear growth came to a stop, but no improvement in their height SDS was observed during the study period[70]. Another randomized controlled trial at two tertiary children's hospitals on 22 children with IBD (21 being cases of CD)[71] (Table 3) investigated the effects of rhGH on HV and glucose homeostasis over a 6-mo period. The median HV increased from 4.5 (range 0.6-8.9) at the baseline to 10.8 (6.1-15) cm/year at 6 mo (P = 0.003) in the rhGH group, while in the control group it was 3.8 (1.4-6.7) and 3.5 cm/year (2.0-9.6), respectively (P = 0.58). The median percentage increase in HV over 6 mo was 140% (16.7-916.7) in the rhGH group and 17.4% (42.1-97.7) in the control group (P < 0.001). There were no significant differences in disease activity or pro-inflammatory cytokines at the baseline or after 6 mo in either group, and the change in bone age for chronological age was also similar in the two groups[71]. This was the first randomized controlled trial on rhGH in children with IBD and growth retardation, and it showed - albeit over a brief period of 6 mo - that a dose of 0.067 mg/kg per day of rhGH improves linear growth. The authors also emphasized the continuing need to optimize the child's disease status (*i.e.*, to induce and maintain remission of IBD activity), as they found a greater growth response to rhGH in patients in biochemical remission. In short, although these data provide evidence of the efficacy of rhGH treatment in terms of height velocity over a short- to medium-term follow-up, patients treated with GH experienced no significant improvements in disease activity and pro-inflammatory cytokines by comparison with controls; and long-term follow-up data are lacking. In conclusion, based on currently-available evidence, the efficacy of rhGH in treating growth failure associated with CD is still unclear, and future studies should explore the use of higher doses of rhGH in CD[70].

CONCLUSION

Despite current treatment strategies for CD including anti-TNF-α medication, short stature and slow growth are still encountered in children with CD. Several studies have shown that children with IBD may not achieve optimal bone mass[25], and those with CD have multiple risk factors for impaired bone accrual[22]. A declining trend in growth chart percentiles for height and weight with respect to a patient's targets for gender and age should arouse the suspicion of a growth deficiency[22]. An early diagnosis is fundamentally important, but signs of the onset of IBD vary and can easily go unnoticed, meaning that statural growth deficiencies and concomitant late puberty quite often precede the intestinal manifestations of the disease[64].

Nutritional concerns are common in pediatric CD patients, who are often underweight at presentation[1]. Undernutrition has been reported in up to 65%-75% of such patients[25], and a low dietary intake due to poor appetite and aversion to food is a major cause of undernutrition in pediatric IBD, though the systemic release of proinflammatory cytokines also contributes significantly[26]. Although medical treatment can quickly restore body weight, this does not reflect concomitant changes in patients' body composition, which is characterized by normal fat stores but depleted lean mass. Poor bone health, delayed puberty, and growth failure may also complicate these patients' clinical management[26]. Vitamin and mineral deficiencies have been described in patients with IBD and are attributed to mucosal inflammation in the gut and a low oral intake. Although 25(OH) vitamin D levels have yet to be convincingly demonstrated to correlate with BMD[56], poor vitamin D status may have detrimental consequences for any child's future health, so an optimal vitamin D status still represents a crucial public health goal[37]. Corticosteroid therapy and nutritional status are important determinants of BMD in CD patients[49].

It is indispensable to monitor CD patients' growth, taking their initial height as a reference and routinely reassessing them as their disease evolves in order to fully appreciate its impact on their growth[22]. Monitoring patients' growth rate is also essential to enable their response to therapy to be assessed over time[22]. Precise serial check-ups should always include an assessment of patients' pubertal development, which should be correlated with their statural growth, so that action can be taken without delay in the event of any discrepancies coming to light. A radiological examination of patients' skeletal age enables their residual potential for growth to be identified[22]. Recent evidence suggests that rhGH therapy is effective in improving short-term linear growth for a selected group of CD patients, but is of limited benefit as a therapy for improving mucosal disease and reducing its clinical activity[70]. Exclusive enteral nutrition is a potentially effective option for treating CD because it can improve patients' nutritional state as well as inducing disease remission (mucosal healing) just as quickly as corticosteroids[1,27].

REFERENCES

1 **Alhagamhmad MH**, Day AS, Lemberg DA, Leach ST. An update of the role of nutritional therapy in the management of Crohn's disease. *J Gastroenterol* 2012; **47**: 872-882 [PMID: 22699323 DOI: 10.1007/s00535-012-0617-9]

2 **Vortia E**, Kay M, Wyllie R. The role of growth hormone and insulin-like growth factor-1 in Crohn's disease: implications for therapeutic use of human growth hormone in pediatric patients. *Curr Opin Pediatr* 2011; **23**: 545-551 [PMID: 21900782 DOI: 10.1097/MOP.0b013e32834a7810]

3 **Neuman MG**, Nanau RM. Inflammatory bowel disease: role of diet, microbiota, life style. *Transl Res* 2012; **160**: 29-44 [PMID: 22687961 DOI: 10.1016/j.trsl.2011.09.001]

4 **Haller D**. Nutrigenomics and IBD: the intestinal microbiota at the cross-road between inflammation and metabolism. *J Clin Gastroenterol* 2010; **44** Suppl 1: S6-S9 [PMID: 20535026 DOI: 10.1097/MCG.0b013e3181dd8b76]

5 **Nanau RM**, Neuman MG. Metabolome and inflammasome in inflammatory bowel disease. *Transl Res* 2012; **160**: 1-28 [PMID: 22687960 DOI: 10.1016/j.trsl.2011.08.006]

6 **Macfarlane S**, Steed H, Macfarlane GT. Intestinal bacteria and inflammatory bowel disease. *Crit Rev Clin Lab Sci* 2009; **46**: 25-54 [PMID: 19107650 DOI: 10.1080/10408360802485792]

7 **Gentschew L**, Ferguson LR. Role of nutrition and microbiota in susceptibility to inflammatory bowel diseases. *Mol Nutr Food Res* 2012; **56**: 524-535 [PMID: 22495981 DOI: 10.1002/mnfr.201100630]

8 **Kovács J**, Nagy A, Szabó A, Lorincz M. [To grow up with Crohn's disease]. *Orv Hetil* 2011; **152**: 546-554 [PMID: 21436017 DOI: 10.1556/OH2011.29074]

9 **Vermeire S**, van Assche G, Rutgeerts P. Review article: Altering the natural history of Crohn's disease--evidence for and against current therapies. *Aliment Pharmacol Ther* 2007; **25**: 3-12 [PMID: 17229216]

10 **Van Assche G**, Vermeire S, Rutgeerts P. The potential for disease modification in Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 79-85 [PMID: 20134489 DOI: 10.1038/nrgastro.2009.220]

11 **Sninsky CA**. Altering the natural history of Crohn's disease? *Inflamm Bowel Dis* 2001; **7** Suppl 1: S34-S39 [PMID: 11380042]

12 **Ricart E**, García-Bosch O, Ordás I, Panés J. Are we giving biologics too late? The case for early versus late use. *World J Gastroenterol* 2008; **14**: 5523-5527 [PMID: 18810770]

13 **Shamir R**. Nutritional aspects in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009; **48** Suppl 2: S86-S88 [PMID: 19300135 DOI: 10.1097/MPG.0b013e3181a15ca0]

14 **Berni Canani R**, Terrin G, Borrelli O, Romano MT, Manguso F, Coruzzo A, D'Armiento F, Romeo EF, Cucchiara S. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. *Dig Liver Dis* 2006; **38**: 381-387 [PMID: 16301010]

15 **Rubio A**, Pigneur B, Garnier-Lengliné H, Talbotec C, Schmitz J, Canioni D, Goulet O, Ruemmele FM. The efficacy of exclusive nutritional therapy in paediatric Crohn's disease, comparing fractionated oral vs. continuous enteral feeding. *Aliment Pharmacol Ther* 2011; **33**: 1332-1339 [PMID: 21507029 DOI: 10.1111/j.1365-2036.2011.04662.x]

16 **Heuschkel R**. Enteral nutrition should be used to induce remission in childhood Crohn's disease. *Dig Dis* 2009; **27**: 297-305 [PMID: 19786755 DOI: 10.1159/000228564]

17 **Day AS**, Whitten KE, Sidler M, Lemberg DA. Systematic review: nutritional therapy in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2008; **27**: 293-307 [PMID: 18045244]

18 **Shamir R**, Phillip M, Levine A. Growth retardation in pediatric Crohn's disease: pathogenesis and interventions. *Inflamm Bowel Dis* 2007; **13**: 620-628 [PMID: 17262806]

19 **Heuschkel R**, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. *Inflamm Bowel Dis* 2008; **14**: 839-849 [PMID: 18266237 DOI: 10.1002/ibd.20378]

20 **Griffiths AM**. Growth retardation in early-onset inflammatory bowel disease: should we monitor and treat these patients differently? *Dig Dis* 2009; **27**: 404-411 [PMID: 19786772 DOI: 10.1159/000228581]

21 **Abraham BP**, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol* 2012; **46**: 581-589 [PMID: 22772738 DOI: 10.1097/MCG.0b013e318247c32f]

22 **Walters TD**, Griffiths AM. Growth impairment in pediatric inflammatory bowel disease. Pediatric Inflammatory Bowel Diseases. In: Mamula P, Markowitz JE, Baldassano RN, editors. New York: Springer, 2008: 103-104

23 **Vasseur F**, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, Merlin B, Lerebours E, Savoye G, Salomez JL, Cortot A, Colombel JF, Turck D. Nutritional status and growth in pediatric Crohn's disease: a population-based study. *Am J Gastroenterol* 2010; **105**: 1893-1900 [PMID: 20145606 DOI: 10.1038/ajg.2010.20]

24 **Crombé V**, Salleron J, Savoye G, Dupas JL, Vernier-Massouille G, Lerebours E, Cortot A, Merle V, Vasseur F, Turck D, Gower-Rousseau C, Lémann M, Colombel JF, Duhamel A. Long-term outcome of treatment with infliximab in pediatric-onset Crohn's disease: a population-based study. *Inflamm Bowel Dis* 2011; **17**: 2144-2152 [PMID: 21287665 DOI: 10.1002/ibd.21615]

25 **Vaisman N**, Dotan I, Halack A, Niv E. Malabsorption is a major contributor to underweight in Crohn's disease patients in remission. *Nutrition* 2006; **22**: 855-859 [PMID: 16928471]

26 **Gerasimidis K**, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. *J Hum Nutr Diet* 2011; **24**: 313-326 [PMID: 21564345 DOI: 10.1111/j.1365-277X.2011.01171.x]

27 **Soo J**, Malik BA, Turner JM, Persad R, Wine E, Siminoski K, Huynh HQ. Use of exclusive enteral nutrition is just as effective as corticosteroids in newly diagnosed pediatric Crohn's disease. *Dig Dis Sci* 2013; **58**: 3584-3591 [PMID: 24026403]

28 **Gupta K**, Noble A, Kachelries KE, Albenberg L, Kelsen JR, Grossman AB, Baldassano RN. A novel enteral nutrition protocol for the treatment of pediatric Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 1374-1378 [PMID: 23567777 DOI: 10.1097/MIB.0b013e318281321b]

29 **Wiskin AE**, Owens DR, Cornelius VR, Wootton SA, Beattie RM. Paediatric nutrition risk scores in clinical practice: children with inflammatory bowel disease. *J Hum Nutr Diet* 2012; **25**: 319-322 [PMID: 22591201 DOI: 10.1111/j.1365-277X.2012.01254.x]

30 **Valentini L**, Schaper L, Buning C, Hengstermann S, Koernicke T, Tillinger W, Guglielmi FW, Norman K, Buhner S, Ockenga J, Pirlich M, Lochs H. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. *Nutrition* 2008; **24**: 694-702 [PMID: 18499398 DOI: 10.1016/j.nut.2008.03.018]

31 **Chan SS**, Luben R, Olsen A, Tjonneland A, Kaaks R, Teucher B, Lindgren S, Grip O, Key T, Crowe FL, Bergmann MM, Boeing H, Hallmans G, Karling P, Overvad K, Palli D, Masala G, Kennedy H, vanSchaik F, Bueno-de-Mesquita B, Oldenburg B, Khaw KT, Riboli E, Hart AR. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol* 2013; **108**: 575-582 [PMID: 23318483 DOI: 10.1038/ajg.2012.453]

32 **Werkstetter KJ**, Ullrich J, Schatz SB, Prell C, Koletzko B, Koletzko S. Lean body mass, physical activity and quality of life in paediatric patients with inflammatory bowel disease and in healthy controls. *J Crohns Colitis* 2012; **6**: 665-673 [PMID: 22398103 DOI: 10.1016/j.crohns.2011.11.017]

33 **Gerasimidis K**, Barclay A, Papangelou A, Missiou D, Buchanan E, Tracey C, Tayler R, Russell RK, Edwards CA, McGrogan P. The epidemiology of anemia in pediatric inflammatory bowel disease: prevalence and associated factors at diagnosis and follow-up and the impact of exclusive enteral nutrition. *Inflamm Bowel Dis* 2013; **19**: 2411-2422 [PMID: 23899546 DOI: 10.1097/MIB.0b013e31829ed855]

34 **Alkhouri RH**, Hashmi H, Baker RD, Gelfond D, Baker SS. Vitamin and mineral status in patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2013; **56**: 89-92 [PMID: 22832510 DOI: 10.1097/MPG.0b013e31826a105d]

35 **Vagianos K**, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* 2007; **31**: 311-319 [PMID: 17595441]

36 **Kuwabara A**, Tanaka K, Tsugawa N, Nakase H, Tsuji H, Shide K, Kamao M, Chiba T, Inagaki N, Okano T, Kido S. High prevalence of vitamin K and D deficiency and decreased BMD in inflammatory bowel disease. *Osteoporos Int* 2009; **20**: 935-942 [PMID: 18825300 DOI: 10.1007/s00198-008-0764-2]

37 **Öhlund I**, Silfverdal SA, Hernell O, Lind T. Serum 25-hydroxyvitamin D levels in preschool-age children in northern Sweden are inadequate after summer and diminish further during winter. *J Pediatr Gastroenterol Nutr* 2013; **56**: 551-555 [PMID: 23274340 DOI: 10.1097/MPG.0b013e3182838e5b]

38 **Carpenter TO**, Herreros F, Zhang JH, Ellis BK, Simpson C, Torrealba-Fox E, Kim GJ, Savoye M, Held NA, Cole DE. Demographic, dietary, and biochemical determinants of vitamin D status in inner-city children. *Am J Clin Nutr* 2012; **95**: 137-146 [PMID: 22170368 DOI: 10.3945/ajcn.111.018721]

39 **Cranney A**, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *Am J Clin Nutr* 2008; **88**: 513S-519S [PMID: 18689393]

40 **Ross AC**, Taylor CL, Yaktine AL, Del Valle HB. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy. Prakut M, Ustun Y, Kabacam G. Serum vitamin B (12) and folate status in patients with inflammatory bowel diseases. *Eur J Intern Med* 2012; **21**: 320-323

41 **Cranney A**, Horsley T, O'Donnell S, Weiler H, Puil L, Ooi D, Atkinson S, Ward L, Moher D, Hanley D, Fang M, Yazdi F, Garritty C, Sampson M, Barrowman N, Tsertsvadze A, Mamaladze V. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess* (Full Rep) 2007; **(158)**: 1-235 [PMID: 18088161]

42 **Heaney RP**, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003; **22**: 142-146 [PMID: 12672710]

43 **Yakut M**, Ustün Y, Kabaçam G, Soykan I. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. *Eur J Intern Med* 2010; **21**: 320-323 [PMID: 20603044 DOI: 10.1016/j.ejim.2010.05.007]

44 **Chowers Y**, Sela BA, Holland R, Fidder H, Simoni FB, Bar-Meir S. Increased levels of homocysteine in patients with Crohn's disease are related to folate levels. *Am J Gastroenterol* 2000; **95**: 3498-3502 [PMID: 11151883]

45 **Kim HJ**, Hong SJ, Jeon YW, Han JP, Han SH, Kang JH, Tae JW, Lim HS, Kim HK, Ko BM, Lee MS. The early onset of disease may be a risk factor for decreased bone mineral density in patients with inflammatory bowel disease. *Clin Endosc* 2013; **46**: 71-76 [PMID: 23423611 DOI: 10.5946/ce.2013.46.1.71]

46 **Frei P**, Fried M, Hungerbuhler V, Rammert C, Rousson V, Kullak-Ublick GA. Analysis of risk factors for low bone mineral density in inflammatory bowel disease. *Digestion* 2006; **73**: 40-46 [PMID: 16543736]

47 **Jahnsen J**, Falch JA, Mowinckel P, Aadland E. Bone mineral density in patients with inflammatory bowel disease: a population-based prospective two-year follow-up study. *Scand J Gastroenterol* 2004; **39**: 145-153 [PMID: 15000276]

48 **van Hogezand RA**, Hamdy NA. Skeletal morbidity in inflammatory bowel disease. *Scand J Gastroenterol Suppl* 2006; **(243)**: 59-64 [PMID: 16782623]

49 **Pappa H**, Thayu M, Sylvester F, Leonard M, Zemel B, Gordon C. Skeletal health of children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011; **53**: 11-25 [PMID: 21694532 DOI: 10.1097/MPG.0b013e31821988a3]

50 **Pappa HM**, Langereis EJ, Grand RJ, Gordon CM. Prevalence and risk factors for hypovitaminosis D in young patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011; **53**: 361-364 [PMID: 21613964 DOI: 10.1097/MPG.0b013e3182250b3e]

51 **Schmidt S**, Mellström D, Norjavaara E, Sundh V, Saalman R. Longitudinal assessment of bone mineral density in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2012; **55**: 511-518 [PMID: 22688562 DOI: 10.1097/MPG.0b013e31825817a0]

52 **Irwin R**, Lee T, Young VB, Parameswaran N, McCabe LR. Colitis-induced bone loss is gender dependent and associated with increased inflammation. *Inflamm Bowel Dis* 2013; **19**: 1586-1597 [PMID: 23702805 DOI: 10.1097/MIB.0b013e318289e17b]

53 **Tsampalieros A**, Lam CK, Spencer JC, Thayu M, Shults J, Zemel BS, Herskovitz RM, Baldassano RN, Leonard MB. Long-term inflammation and glucocorticoid therapy impair skeletal modeling during growth in childhood Crohn disease. *J Clin Endocrinol Metab* 2013; **98**: 3438-3445 [PMID: 23690309 DOI: 10.1210/jc.2013-1631]

54 **Malik S**, Ahmed SF, Wilson ML, Shah N, Loganathan S, Naik S, Bourke B, Thomas A, Akobeng AK, Fagbemi A, Wilson DC, Russell RK. The effects of anti-TNF-α treatment with adalimumab on growth in children with Crohn's disease (CD). *J Crohns Colitis* 2012; **6**: 337-344 [PMID: 22405171 DOI: 10.1016/j.crohns.2011.09.004]

55 **Malik S**, Mason A, Bakhshi A, Young D, Bishop J, Garrick V, McGrogan P, Russell RK, Ahmed SF. Growth in children receiving contemporary disease specific therapy for Crohn's disease. *Arch Dis Child* 2012; **97**: 698-703 [PMID: 22685044 DOI: 10.1136/archdischild-2011-300771]

56 **Laakso S**, Valta H, Verkasalo M, Toiviainen-Salo S, Viljakainen H, Mäkitie O. Impaired bone health in inflammatory bowel disease: a case-control study in 80 pediatric patients. *Calcif Tissue Int* 2012; **91**: 121-130 [PMID: 22729560 DOI: 10.1007/s00223-012-9617-2]

57 **Tsampalieros A**, Gupta P, Denburg MR, Shults J, Zemel BS, Mostoufi-Moab S, Wetzsteon RJ, Herskovitz RM, Whitehead KM, Leonard MB. Glucocorticoid effects on changes in bone mineral density and cortical structure in childhood nephrotic syndrome. *J Bone Miner Res* 2013; **28**: 480-488 [PMID: 23044926 DOI: 10.1002/jbmr.1785]

58 **De Nijs RN**. Glucocorticoid-induced osteoporosis: a review on pathophysiology and treatment options. *Minerva Med* 2008; **99**: 23-43 [PMID: 18299694]

59 **van Brussel MS**, Bultink IE, Lems WF. Prevention of glucocorticoid-induced osteoporosis. *Expert Opin Pharmacother* 2009; **10**: 997-1005 [PMID: 19351276 DOI: 10.1517/14656560902868225]

60 **Ahmed SF**, Horrocks IA, Patterson T, Zaidi S, Ling SC, McGrogan P, Weaver LT. Bone mineral assessment by dual energy X-ray absorptiometry in children with inflammatory bowel disease: evaluation by age or bone area. *J Pediatr Gastroenterol Nutr* 2004; **38**: 276-280 [PMID: 15076625]

61 **Burnham JM**, Shults J, Semeao E, Foster B, Zemel BS, Stallings VA, Leonard MB. Whole body BMC in pediatric Crohn disease: independent effects of altered growth, maturation, and body composition. *J Bone Miner Res* 2004; **19**: 1961-1968 [PMID: 15537438]

62 **Boot AM**, Bouquet J, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. *Gut* 1998; **42**: 188-194 [PMID: 9536942]

63 **Whitten KE**, Leach ST, Bohane TD, Woodhead HJ, Day AS. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol* 2010; **45**: 399-405 [PMID: 19957194 DOI: 10.1007/s00535-009-0165-0]

64 **Kirschner BS**, Rich BH. Puberty and pediatric-onset inflammatory bowel disease. Pediatric Inflammatory Bowel Diseases. In: Mamula P, Markowitz JE, Baldassano RN, editors. New York: Springer, 2008: 133-139

65 **Newby EA**, Croft NM, Green M, Hassan K, Heuschkel RB, Jenkins H, Casson DH. Natural history of paediatric inflammatory bowel diseases over a 5-year follow-up: a retrospective review of data from the register of paediatric inflammatory bowel diseases. *J Pediatr Gastroenterol Nutr* 2008; **46**: 539-545 [PMID: 18493209 DOI: 10.1097/MPG.0b013e3181596efd]

66 **Mason A**, Malik S, Russell RK, Bishop J, McGrogan P, Ahmed SF. Impact of inflammatory bowel disease on pubertal growth. *Horm Res Paediatr* 2011; **76**: 293-299 [PMID: 22024935 DOI: 10.1159/000329991]

67 **Walters TD**, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 513-523 [PMID: 19713986 DOI: 10.1038/nrgastro.2009.124]

68 **D'Mello S**, Trauernicht A, Ryan A, Bonkowski E, Willson T, Trapnell BC, Frank SJ, Kugasathan S, Denson LA. Innate dysfunction promotes linear growth failure in pediatric Crohn's disease and growth hormone resistance in murine ileitis. *Inflamm Bowel Dis* 2012; **18**: 236-245 [PMID: 21337672 DOI: 10.1002/ibd.21689]

69 **Tietjen K**, Behrens R, Weimann E. Growth failure in children and adolescents with Crohn's disease. *Turk J Gastroenterol* 2009; **20**: 13-19 [PMID: 19330730]

70 **Wong SC**, Hassan K, McGrogan P, Weaver LT, Ahmed SF. The effects of recombinant human growth hormone on linear growth in children with Crohn's disease and short stature. *J Pediatr Endocrinol Metab* 2007; **20**: 1315-1324 [PMID: 18341091]

71 **Wong SC**, Kumar P, Galloway PJ, Blair JC, Didi M, Dalzell AM, Hassan K, McGrogan P, Ahmed SF. 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) 2011; **74**: 599-607 [PMID: 21470283 DOI: 10.1111/j.1365-2265.2011.03977]

P- Reviewer: Afzal NA, Day AS, Maric I **S- Editor**: Qi Y
L- Editor: Rutherford A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327