Endocrine and metabolic manifestations in inflammatory bowel disease

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Abstract
Extraintestinal manifestations from nearly every organ system are common in inflammatory bowel disease (IBD). This review article describes the epidemiology, pathogenesis, diagnosis and management of the main endocrine and metabolic manifestations in IBD, including metabolic bone disease, growth retardation, hypogonadism, pubertal delay, lipid abnormalities and insulin resistance. These clinical problems are commonly interrelated and they share a common basis, influenced by disease-related inflammation and nutritional status. In addition to nutritional support, every effort should be made to achieve and maintain disease remission, thus correcting the underlying chronic inflammation. The criteria for screening and diagnosing osteoporosis are described and treatment options are discussed (lifestyle advice, vitamin D and calcium supplementation, use of bisphosphonates or other specific antiosteoporotic agents, correction of hypogonadism). Chronic glucocorticoid therapy may affect growth as well as predispose to osteoporosis. The diagnosis and management of growth failure, pubertal delay and hypogonadism in IBD are discussed.

Keywords
Inflammatory bowel disease, osteoporosis, growth failure, hypogonadism, lipids, insulin resistance

Introduction
The two main forms of inflammatory bowel disease (IBD) are ulcerative colitis (UC) and Crohn's disease (CD). These disorders are characterized by chronic inflammation of the gastrointestinal (GI) tract and are defined by clinical, endoscopic, pathological and radiographic features [1]. UC and CD commonly follow a relapsing and remitting course and share a number of clinical features such as diarrhea, rectal bleeding and abdominal pain. Accumulating evidence shows that IBD results from an inappropriate inflammatory response to intestinal microbes in genetically susceptible individuals [2]. The inflammation in UC is limited to the mucosa of the large intestine, typically beginning in the rectum and occasionally extending proximally to the sigmoid colon in a continuous fashion or, less commonly, to the entire colon (pancolitis). In contrast, the inflammation in CD involves all layers of the bowel wall and although the disease most commonly affects the terminal ileum and the large bowel, any part of the GI tract from mouth to anus may be affected, not necessarily in a continuous way [1].

Metabolic bone disease

Epidemiology and pathogenesis
The reported prevalence of osteoporosis (defined as T-score < -2.5) in patients with established IBD varies widely from 17 to 41% [9-11] with an overall prevalence of 15% [10]. The prevalence of osteopenia (T-score -1 to -2.5) varies from 22 to 67% [9]. The variation in prevalence rates is a result of differences in population characteristics, age, disease duration, dual energy x-ray absorptiometry (DXA) methodology and study design. Patients with IBD have an estimated 40% higher risk of fracture compared to the general population that increases further with age [10], or if asymptomatic vertebral fractures are taken into account [12].

The causes of reduced bone mineral density (BMD) in IBD are multifactorial; apart from the common risk factors such as age, smoking and low body mass index (BMI), other
factors are glucocorticoid (GC) use, nutritional deficiencies including vitamin D and K, malabsorption of calcium, hypogonadism and finally, disease-related chronic inflammation (Table 1) [13]. In addition to reducing bone formation and increasing bone resorption, GCs have been shown to reduce absorption of calcium in the small intestine and increase excretion of calcium by the kidneys. Vertebral fractures (often asymptomatic) may affect 30-50% of patients on chronic GC therapy; the risk of bone loss and fractures is already considerable in the first few months of therapy due to a phase of early accelerated bone resorption which is then followed by a more progressive phase of impaired osteoblastogenesis. Although fracture risk increases with larger doses and prolonged length of GC treatment, fractures may occur at prednisone equivalent doses as low as 2.5 – 7.5 mg daily [14,15]. Since patients with more severe or active disease are more likely to receive GC treatment, it is difficult to estimate the relative contribution of (a) GC therapy or (b) disease-related inflammation, on BMD.

Vitamin D levels are lower than those of healthy individuals in adult and pediatric patients with IBD [16]. The prevalence of vitamin D deficiency (defined as serum 25-OH vitamin D concentration of ≤15 ng/mL) ranges from 22 to 70% for CD, and up to 45% for UC [16]. The reasons for the reduced vitamin D levels include impaired absorption (especially in CD patients who had small bowel resection) [17], reduced intake [18], lack of exposure to sunlight, altered metabolism [19] and loss through the GI tract when protein-losing enteropathy develops [16]. Serum and bone levels of vitamin K (a cofactor in the carboxylation of osteocalcin, a protein essential for calcium binding to bone) are reduced in patients with IBD and are inversely related to the rate of bone resorption in CD [20,21]. Vitamin K deficiency in IBD may be due to malabsorption or alterations in vitamin K-producing bacterial flora. Finally, calcium absorption may be impaired in IBD patients with steatorrhea, because of calcium binding to intraluminal fat. As a result, patients are predisposed to hyperoxaluria and renal stones, since calcium normally binds oxalate in the lumen facilitating oxalate extraction. When free intraluminal calcium is decreased as a result of steatorrhea, oxalate absorption increases [22].

Although it is clear that all factors described above contribute to osteoporosis in IBD, there are a number of patients with reduced BMD or osteoporosis who have adequate vitamin D levels and were never treated with GCs [23]. These observations, together with evidence from studies in experimental animals [24] suggest that disease-related chronic inflammation may play a role in the development of osteopenia or osteoporosis in adult and pediatric [25] IBD patients. It is possible that cytokines such as interleukin (IL)-6, IL-1 and tumor necrosis factor alpha (TNF-α), directly impair bone metabolism by increasing bone resorption. Interestingly, treatment with infliximab, an anti-TNF agent, has been shown to improve markers of bone metabolism and BMD in IBD patients [26].

Recent evidence suggests that alterations in the RANKL (receptor activator of nuclear factor kappa-B ligand): OPG (osteoprotegerin) ratios may be implicated in IBD-related bone loss [9,27].

### Diagnosis and evaluation

Osteoporosis can be diagnosed either when there is a history or evidence of fragility fractures (regardless of BMD), or according to the BMD as measured by DXA. The American Gastroenterological Association recommends DXA screening of IBD patients with one or more risk factors for osteoporosis and fracture: **history of previous fracture, postmenopausal, male >50 years, corticosteroid therapy for more than 3 months, or hypogonadism** [10]. The British Society of Gastroenterology (BSG) recommends DXA screening of IBD patients with continuing active disease, weight loss >10%, body mass index <20 kg/m², age >70 years, and those <65 years requiring corticosteroids for >3 months [28]. BMD can be expressed as the number of standard deviations (SD) above or below either the mean BMD for young adults (T-score) or the mean BMD for age-matched controls (Z-score). According to the World Health Organization (WHO), osteoporosis in peri- and postmenopausal women or men >50 years of age can be defined as a T-score at the spine or hip of <−2.5 SD [29]. A T-score of between −1 and −2.5 is defined as osteopenia. For premenopausal women or men <50 however, Z-scores, not T-scores should be used; a Z-score ≤−2.0 should be interpreted as “below the expected range for age” [30]. If BMD is within the normal range, DXA should be repeated in 2-3 years’ time. In patients with abnormal BMD measurements, further clinical and laboratory evaluation is required to exclude secondary causes of osteoporosis (such as primary hyperparathyroidism, hyperthyroidism, hypogonadism or Cushing’s syndrome) and to guide treatment. Investigations should include measurement of serum calcium, phosphate, albumin, total protein, creatinine, liver enzymes including alkaline phosphatase, electrolytes, 25-hydroxyvitamin D and complete blood count. When clinically indicated, thyroid stimulating hormone (TSH), free T4, testosterone (in men), estradiol (in women), prolactin, LH and FSH should also be measured. The FRAAX™ (Fracture Risk Assessment Model) is a web-based tool that can help physicians to assess the 10-year probability of major osteoporotic and hip fracture by calculating a score.

### Table 1 Risk factors of reduced bone mineral density in inflammatory bowel disease

| Factor                                |
|---------------------------------------|
| Age                                   |
| Smoking                               |
| Low body mass index, malnutrition     |
| Previous fragility fracture           |
| Chronic glucocorticoid use            |
| Nutritional deficiencies (vitamin D, vitamin K) |
| Malabsorption of calcium              |
| Hypogonadism                          |
| Disease-related chronic inflammation  |
based on a number of clinical risk factors, and may therefore assist in making treatment decisions [31,32].

**Treatment**

The main treatment aim is prevention of fractures. All patients should receive lifestyle-advice on: prevention of falls, adequate calcium and vitamin D intake, avoidance of excess alcohol intake and smoking cessation, regular weight-bearing exercise. An attempt should be made to control the underlying disease and maintain remission. If necessary, calcium and vitamin D supplements should be prescribed to ensure a daily calcium intake of 1000 mg in younger patients and 1200 - 1500 mg in postmenopausal women and men >55 and a daily vitamin D intake of 400 - 800 IU. Larger amounts of vitamin and calcium may be necessary in CD patients with extensive small bowel disease. Hypogonadal patients should receive hormone replacement. Premenopausal women with IBD and amenorrhea are usually treated with combined estrogen-progestin replacement (an oral contraceptive pill or transdermal estradiol plus oral progestin administered cyclically). Because GCs may cause hypogonadism by suppressing gonadotrophins, men who are on long-term GC treatment should have periodic assessments of their morning serum testosterone (and gonadotrophins) and be put on testosterone replacement should they become hypogonadal [33]. GC use should be minimized when possible by using alternative therapies (appropriate/early use of immunomodulators, budesonide [15], elemental or polymeric diet, surgery for resistant disease). All IBD patients receiving GCs should be given calcium and vitamin D supplements. Bisphosphonate prophylaxis should be used (a) for those >65 years at commencement of GC, or (b) for those <65 who are due to receive GCs for more than three months and their T score is <-1.5 [28]. Specific antosteoporotic treatment is indicated for IBD patients with: (a) fragility fractures or a T-score of <-2.5 (b) T-scores of -2.5 to -1.0 plus long-term GC therapy or presence of other additional risk factors (Fig. 1) [10,28]. Most of the evidence regarding treatment options comes from studies conducted in postmenopausal women who did not have IBD or patients on GC-induced osteoporosis. Patients may be treated with an oral bisphosphonate (e.g. weekly alendronate or risedronate) or with 3-monthly intravenous ibandronate or yearly intravenous zoledronic acid for those unable to take oral bisphosphonates or if compliance is an issue. If bisphosphonates are poorly tolerated or ineffective, alternative agents are strontium ranelate, raloxifene in postmenopausal women, teriparatide (by daily subcutaneous injections), calcitonin by intranasal spray and denosumab [10,28]. These agents have not been specifically studied in IBD. In young men and in premenopausal women with osteoporosis (who are not hypogonadal and therefore sex hormone replacement therapy is not indicated) bisphosphonates should be used with caution as there are insufficient efficacy and safety data in this group of patients and there are potential risks during pregnancy [34] and with long-term use (osteonecrosis of the jaw, atypical femoral fractures) [35,36].

**Growth failure**

**Pathogenesis - epidemiology**

In almost 1 of 4 patients with IBD, the disease presents in childhood, mostly during puberty [37]. Only 12% of children with CD have normal height velocity at diagnosis and up to 46% have...
reduced height velocity before the onset of any symptoms [38]. In contrast, a significantly smaller percentage of children with UC (3-10%) have reduced height velocities at the time of diagnosis [39]. Children with IBD often present with delayed puberty, weight loss or inability to gain weight, whereas a decrease in height velocity may occur at a later stage. A significant proportion (19–37%) of patients who had CD during childhood fail to reach their expected adult height [40,41]. The pathogenesis of growth failure in children with IBD is multifactorial, the most important factors being disease-related inflammation, malnutrition, GC use and hypogonadism [42]. The growth hormone (GH) – insulin-like growth factor (IGF)-1 axis is impaired in IBD resulting in a state of relative GH resistance, manifested by low IGF-1 and IGFBP-3 levels and reduced growth [43,44]. This process may be mediated via proinflammatory cytokines such as IL-6 and IL-1β, although other factors such as under-nutrition or the use of GCs may also impair GH secretion and growth plate function [43–45]. Indirect evidence that disease-related inflammation may affect growth comes from studies in children with resistant CD who underwent complete surgical resection of affected bowel segment; following surgery there is an increase in resting energy expenditure and significant catch up growth [45,46]. Apart from surgery, significant improvements in linear growth have been observed following treatment with infliximab [47,48] or exclusive enteral nutrition [37,49]. There is no doubt that malnutrition is a major factor for growth failure and that appropriate nutritional support and management may reverse growth retardation in these children [50]. Factors contributing to malnutrition include reduced intake (cytokine induced anorexia, avoidance of food due to fear of exacerbation of symptoms), increased resting energy expenditure (REE), malabsorption of fat, protein, vitamins and micronutrients, gastritis, esophagitis. Chronic GC therapy may affect growth by impairing a number of processes essential for normal growth such as endogenous GH secretion and action, bone and collagen formation, IGF-1 binding in cartilage and nitrogen retention [41,51]. It is however difficult to estimate the GC effect on growth since disease severity/activity, anatomic location and other clinical parameters are potential confounding factors; hence, not all studies have confirmed an association between GC use and growth failure in IBD [40,52,53].

**Diagnosis of growth failure /Assessment of growth and nutritional status**

Monitoring at regular intervals of growth and nutritional status of children with IBD, is essential and should include a number of anthropometric and other parameters as described in Table 2 [37,54]. Additionally, in children with growth failure, measurement of IGF-1, thyroid hormones, TSH and assessment of bone age are indicated.

**Management**

Attempts to improve growth rate in children with IBD should focus on achieving and maintaining disease remission to minimize disease-related inflammation. Systematic assessment of growth failure is recommended, with the help of a pediatric endocrinologist. The use of long-term GC therapy should be minimized, if possible [37]. In addition, all children should receive appropriate specialist nutritional advice and support. Children with growth failure have increased energy requirements (125-150% of the recommended daily allowance for energy, and 2.4 to 3 g/kg per day of protein) and those with malabsorption may require supplementation of vitamins and minerals [54,55]. Supplemental enteral nutrition in the form of nocturnal feeding via nasogastric tube or exclusive enteral nutrition may be necessary in more severe cases, especially those children with intolerable GC-related side effects and/or growth failure [37,54,56-58]. As already mentioned, several interventions including surgery and immunomodulators such as infliximab, have been shown to have a positive effect on growth in children with IBD [45–48]. In a relatively small study in children with CD, 6-mercaptopurine (6-MP) (whose parent drug is azathioprine) was effective and reduced the need for steroids but had no effect on growth after 18 months compared with conventional prednisone treatment [59]. Growth hormone therapy should be considered in children with severe growth failure when other measures fail, as it has been shown to increase height velocity, improve BMD [60].

**Table 2: Assessment of growth and nutritional status in inflammatory bowel disease**

| Anthropometric data |  |
|---|---|
| Height, weight and body mass index (BMI; weight in kg/height in m2) measurement* |  |
| Documentation of pre-morbid height and weight if possible. |  |
| Calculation of mid-parental height/centiles |  |
| Assessment of bone age at diagnosis and annually, if growth delay |  |
| Calculation of height velocity at 4–6-month intervals |  |
| Calculation of height and weight Z scores for age and BMI |  |

**Dietetic assessment**

| Calorie intake, calcium and vitamin D sources, micronutrients |  |

**Monitoring for anemia, malabsorption and nutritional deficiencies**

| Complete blood count, albumin, 25-OH vitamin D, prothrombin time, vitamin B12, iron, ferritin, and if indicated folate, calcium, magnesium, phosphorus, vitamins A and E, zinc, selenium |  |

*It is important that anthropometric data and growth parameters are plotted and followed longitudinally on appropriate growth charts. BMI, body mass index; DXA, dual energy x-ray absorptiometry; BMD, bone mineral density*
and induce anabolic effects even in GC-dependent children with CD [61]. If GH is to be used, it is generally more effective when administered in the early rather than in the late puberty [44].

**Hypogonadism, pubertal delay and fertility issues**

Hypogonadism is not uncommon in both male and female patients with IBD, and may be the result of (a) a direct effect of inflammation/cytokines on the reproductive axis, ovarian and testicular function [62-64], (b) undernutrition and reduced leptin levels [65] and (c) the effect of chronic GC treatment on gonadotrophin secretion [33] (as already discussed in the paragraph discussing treatment of osteoporosis).

An association between the bone formation marker osteocalcin and testosterone levels in men with CD was reported by Robinson et al in 1998 [66]. A more recent study confirmed lower testosterone and estradiol levels in men with CD compared to controls, but failed to show any association with BMD or markers of bone metabolism [67]. Nevertheless, hormone replacement should be considered in hypogonadal IBD patients with osteoporosis, especially young men and premenopausal women. When IBD presents during childhood, hypogonadism and pubertal delay are common in CD more often than in UC) [68]. These children have reduced linear growth and delayed accretion of lean body mass compared to their healthy peers. Because children with pubertal delay usually have delayed bone age, some catch-up growth is possible after the onset of puberty. Studies report average delays in puberty onset about 1.5 years for girls and 0.8 years for boys [69]. Management involves nutritional support and appropriate treatment of the underlying disease-related inflammation. Boys with CD and pubertal delay may be treated with testosterone therapy; controlled studies of testosterone use in IBD are however needed [68].

Fertility is not generally impaired in men and women with IBD compared to the general population [70]. Sexual dysfunction appears to be mostly related to depression [71]. However, subfertility may be encountered under certain circumstances such as in men who develop impotence following proctocolectomy, men with sulfasalazine-induced oligospermia (reversible, not observed with 5-ASA agents) and women who have undergone surgery [72].

**Lipid abnormalities and insulin resistance**

Although factors associated with atherosclerosis such as inflammation, carotid intima media thickness (cIMT), homocysteine levels and insulin resistance are commonly increased in IBD patients, low density lipoprotein cholesterol and total cholesterol levels are generally low [73]. These changes are more pronounced in CD compared to UC and they are present independently to disease activity, possibly mediated by cytokine production. LDL cholesterol is lower compared to healthy individuals, even after bowel resection. This has been attributed to malabsorption of bile acids leading to parallel stimulation of cholesterol synthesis, cholesterol degradation and LDL receptor expression in the liver, the net effect being a significant reduction in LDL cholesterol [74]. Hypocholesterolemia is a common feature of various types of acute illness such as sepsis, trauma and surgery and has been related to the severity of the illness. In addition, lipoprotein (a) levels are increased and apolipoprotein A-1 and apolipoprotein B-100 are reduced in CD, possibly predisposing CD patients to a higher risk of thrombosis [75].

In a previous study from Italy in patients with IBD during remission, indirect calorimetry was employed to assess the basal metabolic rate and substrate oxidation and the euglycemic hyperinsulenic clamp technique was used to measure insulin sensitivity; these parameters were similar in the study group (inactive CD or UC) compared to healthy controls, whereas basal lipid oxidation was higher in patients with CD compared to both UC and healthy controls [76]. In contrast, during active CD there is increased insulin resistance as well as insulin secretion (based on the plasma insulin response during a 75 g oral glucose tolerance test) [77]. Anti-TNF-α therapy with infliximab did not alter insulin resistance in patients with active IBD whereas it increased total and HDL cholesterol levels and apo-A1 [78]. Despite the recent discovery of numerous shared susceptibility loci/genes, there is no epidemiological evidence to support an association between IBD and either type 2 or type 1 diabetes [79]. *Insulin resistance, hyperglycemia*, and overt diabetes may however be a consequence of GC therapy in IBD. GC-induced hyperglycemia results from an increased rate of hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue, or impairment of insulin action at the receptor and post-receptor level [80]. The risk of developing GC-induced diabetes depends on the dose used, the age, BMI and genetic predisposition. Clinically significant hyperglycemia is generally treated in the same way as it is treated in type 2 diabetes (with dietary modification, oral anti-diabetic agents and/or insulin if needed).

**Conclusion**

Recent evidence suggests that changes in the endocrine milieu play an important role in the pathogenesis of IBD [81-86]. Adipokines such as leptin, adiponectin and resistin are involved in a number of processes that characterize IBD including anorexia, malnutrition, altered body composition and mesenteric white adipose tissue hypertrophy [83]. Animal studies suggest that expression of peroxisome proliferator-activated receptor γ (PPAR γ) in intestinal epithelial cells as well as in macrophages and T cells of mice with experimental IBD, exhibit immunoregulatory actions and may be involved in preventing gut inflammation [84,87]. On the basis of such observations, thiazolidinediones (drugs that have been widely
used to treat type 2 diabetes) have recently been tried in IBD with interesting results [85,88].

It is becoming clear that the endocrine system is involved in the pathogenesis and clinical manifestations of IBD in several ways. The main endocrine manifestations of IBD described in this brief review article (metabolic bone disease, growth failure, hypogonadism, pubertal delay and changes in lipid and carbohydrate metabolism) are interrelated and their multifactorial pathogenesis is influenced by disease-related inflammation and nutritional status. To achieve best results, interventions need to target the underlying mechanisms; it is essential that in addition to nutritional support and specific therapies for osteoporosis, growth failure and hypogonadism, a continuous effort is made to control the underlying chronic inflammation by achieving and maintaining disease remission.

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