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Review

Inflammatory bowel diseases, celiac disease, and bone

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ABSTRACT

The article summarizes the current knowledge on the pathogenesis, clinical aspects and treatment of bone problems in the major inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and celiac disease. It presents the physiological relationship between intestine and bone as well as the alterations determined by disease-disrupted intestinal integrity. Two hypotheses about the pathogenetic mechanisms of bone metabolism derangements and bone loss are discussed: the classical one, that indicates calcium malabsorption as the main culprit, and the new one, that emphasizes the role of inflammation. The article summarizes the available epidemiological data about osteopenia/osteoporosis and fragility fractures in these chronic intestinal diseases and presents the state-of-the-art treatment options.

Introduction

The relationship between bone and chronic intestinal diseases is not immediately evident. However, the presence of altered bone metabolism in these diseases was first reported many years ago, when studies on bone involvement in Crohn's disease and celiac disease described some cases of overt osteomalacia as a consequence of severe malabsorption [1,2].

More recently, the earlier diagnosis of chronic bowel diseases and the new therapeutic approaches also modified the picture of bone alterations: osteomalacia progressively disappeared and osteoporosis became the most frequent complication [3].

Many factors are involved in the pathogenesis of bone derangements in chronic bowel diseases. This article will present the state-of-the-art knowledge on the pathogenesis, clinical aspects and treatment of such derangements in the major inflammatory bowel diseases (IBD)[1] – Crohn's disease and ulcerative colitis – and celiac disease.

The first question may be why IBD and celiac disease should be treated together, as they have different pathogenesis, clinical presentation and evolution, and require different therapies. The reason is that both IBD and celiac disease can induce more or less severe malabsorption, depending on the disease severity, and both are characterized by the presence of intestinal inflammation. This was initially recognized only in IBD, but recent studies indicate that pro-inflammatory cytokines are also activated in celiac disease [4–6].

A brief presentation of chronic bowel diseases

Inflammatory bowel diseases

Crohn's disease is a chronic, relapsing, transmural inflammatory disease of the gastrointestinal mucosa that can affect the entire gastrointestinal tract, from mouth to anus. Distal ileum and colon are more commonly affected. The lesions begin as crypt inflammation, abscesses and ulcers. Then the inflammation spreads transmurally, with complications such as fibrotic strictures, abscesses, or fistulas. Anatomically, the affected bowel regions are clearly demarcated from the adjacent normal segments.

Ulcerative colitis is a chronic, relapsing, non-transmural mucosal inflammatory disease restricted to the colon. Two different forms are encountered: a less severe distal form, limited to the rectum and sigmoid colon, and an extended form that may involve the entire colon [7–10].

In most cases, IBD occur in young adults, but they may also occur in children. The peak incidence is between the ages of 10 and 40 years. Any age may be affected, however, and 15% of the diagnoses are made in people over 60 years old [9,10].

IBD are characterized by an intermittent course, with periodic exacerbations and remissions. The acute phases of exacerbation

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[1] *Abbreviations used:* IBD, inflammatory bowel diseases; GCs, glucocorticosteroids; BMC, bone mineral content; BMD, bone mineral density; sIgA, secretory immune globulins A; GFD, gluten-free diet; VDR, vitamin D receptors; PTH, parathyroid hormone; BMI, body mass index; pQCT, peripheral quantitative computed tomography.

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can be physically and socially disabling. IBD are associated with an increased risk of gastrointestinal cancer [9–13].

The symptoms of Crohn's disease are quite variable, the most common being chronic diarrhea, recurrent abdominal pain, fever, anorexia and weight loss. Fistulas and bowel obstruction due to stenotic segments or adhesions may be a complication. In children, extraintestinal manifestations (such as fever, anemia, arthritis or growth failure) are often predominating. With correct management, most patients can function normally and maintain an acceptable quality of life. At least 50% of patients require surgery within the first 10 years after diagnosis and about 70–80% during their whole lifetime. The overall mortality of Crohn's disease is slightly higher than normal, and is highest in the first two years after diagnosis or if the upper gastrointestinal tract is involved.

Ulcerative colitis is characterized by episodes of bloody diarrhea separated by asymptomatic intervals. Systemic symptoms (fever, anemia, anorexia, weight loss) occur in severe cases. When proximal colon is involved, feces are loose or even watery, and may contain mucus, blood and pus. In severe attacks, blood loss can be life-threatening. Fulminant colitis and toxic megacolon are also life-threatening acute complications. Ulcerative colitis is a severe disease that in the past was characterized by major morbidity and high mortality. With current medical and surgical management, there is still a slightly higher mortality in the first two years after diagnosis, but after that, there is almost no difference from the normal population [9–16].

IBD affect approximately 3.6 million people in Europe and North America. The incidence of Crohn's disease is around 5–10 per 100,000 per year with a prevalence of 50–100 per 100,000. The incidence of ulcerative colitis is approximately 10–20 per 100,000 per year, and the prevalence 100–200 per 100,000. Recently, a significant increase of IBD has been observed in areas once considered as low-incidence areas, such as Asia [17–22].

IBD frequently develop in patients with primary immune deficiencies. Genetic and animal studies elucidated – at least in part – the pathogenetic mechanisms of these diseases. A genetic predisposition alters some components of the innate and adaptive immune systems that are normally active against intestinal microbes, misdirecting them to attack the bowel mucosa [23,24]. The pathogenesis of IBD seems to depend on complex interactions among susceptibility genes, involving the environment on the one side, and both autoimmune and immune-mediated reactions on the other [25,26]. Pathogenic microbes or epithelial barrier failure activate dendritic cells that trigger effector CD4+ and CD8+ T lymphocytes [27] and there is an increased production of IL-1, TNF-alpha, IFN-gamma, IL-12, IL-6, and IL-18 cytokines [28]. In Crohn's disease, preferential production of Th1 cytokines is observed, and recent data suggest that Th17 cells have a key role in the intestinal inflammation [27–29].

The current standard of therapy for IBD is rapidly evolving, with many new biologic agents under investigation. The therapy of IBD is based on aminosalicylates, glucocorticosteroids (GCs), azathioprine, 6-mercaptopurine, methotrexate, and infliximab, and in some cases also mycophenolate mofetil, cyclosporine and tacrolimus have been used. Unfortunately, long-term use of all these drugs may cause severe side effects and complications, including bone complications [9,10,30].

The main characteristics of IBD are summarized in Table 1.

Celiac disease

Celiac disease is a chronic intestinal disorder characterized by an immune reaction to the gliadin fraction of gluten, a protein found in wheat, rye and barley. Its ingestion causes villous atrophy and inflammatory alterations of the mucosa of the small bowel, from the duodenum to the distal ileum. Celiac disease occurs in genetically predisposed subjects of any age, and is often familial. Large screening studies have demonstrated a much higher prevalence of celiac disease than previously thought: up to 1% of the general population in Europe and the USA seems to be affected [31,32].

In the past, celiac disease was almost always recognized because of steatorrhea and other malabsorption symptoms. Anemia, weight loss, vitamin and trace element deficiency, and skin alterations were also commonly observed [33]. Today, the presentation of celiac disease tends to be atypical both in adults and in children, with confusing symptoms or no symptoms at all [33]. Extra-intestinal symptoms are very frequent, even more than the classical intestinal symptoms. The atypical, silent or latent forms may go undiagnosed for many years, and complications like reduced bone mineral content (BMC) and bone mineral density (BMD), once observed only in adults, are now also observed in younger patients [33].

A recent study [34] compared two groups (125 elderly adults aged over 65 years and 149 young adults aged 18–30 years) with a biopsy-confirmed diagnosis of celiac disease. The clinical presentation and duration of symptoms prior to diagnosis were similar, and there was also a similar prevalence of autoimmune diseases. Diarrhea was the main presenting symptom (49% of young adults and 50% of the elderly). The degree of villous atrophy and the prevalence of bone alterations were similar in the young and the elderly patients.

The factors triggering celiac disease remain unclear and need further study. Genetic predisposition is an important risk factor but not all predisposed individuals develop the disease: for example, monozygotic twins are both affected by celiac disease only in 20–50% of cases [35].

These observations indicate that some unknown factor(s) may play a role in the development of celiac disease. One factor seems

Table 1
Essential characteristics of IBD and celiac disease.

		Crohn's disease	Ulcerative colitis	Celiac disease
Age		Young adults, including children; peak 10–29 years	Mainly young adults, including children; peak 10–40 years; 2nd peak (lower incidence) 50–70 years	Any age
Prevalence		50–100/100,000 F:M 1:1	100–200/100,000 F:M 1:1	1/100–150 F:M 2:1
Symptoms	*Adults*	Variable; essentially intestinal	Intestinal; extra-intestinal only in severe forms	Without typical symptoms; rarely limited to intestine
	Children	Intestinal and systemic (for example growth failure)	Intestinal and systemic (for example growth failure)	Intestinal; increasingly also without typical symptoms
Causes		Genetic predisposition; altered response to intestinal microbes	Genetic predisposition; altered response to intestinal microbes	Genetic predisposition; sensitivity to gluten; frequently familial
Treatment		5-Aminosalicylic acid; glucocorticosteroids; immunosuppressors; immunomodulators	5-Aminosalicylic acid; glucocorticosteroids; immunosuppressors; immunomodulators	Gluten-free diet