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Review

Pathologic bone alterations in celiac disease: Etiology, epidemiology, and treatment

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ABSTRACT

Low bone mineral density (BMD), osteopenia, and osteoporosis are frequent complications of celiac disease (CD). The etiology of pathologic bone alterations in CD is multifactorial; however, two main mechanisms are involved: intestinal malabsorption and chronic inflammation. A strict gluten-free diet (GFD) is thought to be the only effective treatment for CD; but treating bone complications related to CD remains complex.

The objective of this review is to elucidate the bones problems related to CD and to increase awareness of osteoporosis development, considered as a sign of atypical CD presentation. Currently, a question of whether GFD alone is an effective treatment to correct the bone alterations in patients with CD is under debate. This review presents factors contributing to pathologic bone derangement, recent research on the epidemiology of low BMD, osteoporosis, and fractures, and the treatment of bone problems in patients with CD. The roles of calcium and transport mechanisms are additionally presented.

Introduction

The clinical picture of celiac disease (CD) is highly variable, which complicates accurate diagnosis. In CD, the autoimmune response is mainly targeted at the intestinal mucosa; however, it can manifest itself with a variety of signs and symptoms affecting any organ or tissue. Extra-intestinal symptoms, such as low bone mineral density (BMD), reduced bone mass, and increased bone fragility, leading to an increased prevalence of fractures must be considered as a sign of atypical CD presentation. These bone alternations are the consequence of impaired calcium and vitamin D absorption and secondary hyperparathyroidism resulting principally from the loss of villous cells in the proximal intestine, where calcium is most actively absorbed. Several studies evaluated bone status in CD, both at diagnosis and after gluten-free diet (GFD). Nevertheless, studies focusing on the prevalence of bone derangement in patients with CD are still inconclusive because both old and recent findings are widely incongruous [1].

At present, the only effective treatment for CD is a strict lifelong GFD. However, it is still unknown whether GFD alone is sufficient to correct the bone alterations and whether these metabolic bone diseases are reversible. Exploring the literature concerning the effects of GFD on bone alteration in CD reveals contradictory results. On one side, there are studies that suggest that the risk of low BMD in patients with CD on a GFD is considerably diminished [2,3]. Alternatively, the results of other studies [4] showed that patients with persistent small-intestinal mucosal villous atrophy, despite adherence to a strict GFD and the absence of symptoms, had a high risk for osteoporosis. Undoubtedly, patients with CD and additional bone metabolism alterations and bone mineral loss require appropriate management. Early treatment might in part prevent complications of CD, such as malignancies [5], osteoporosis [6], and autoimmune diseases in general [7]. Considering that most bone mass is acquired during the first 2 decades of life, early diagnosis of CD and adherence to a GFD are fundamentally important to ensure adequate bone metabolism in such cases. Recent clinical trials for some new treatment modalities for CD are still ongoing; however, these therapies are aimed at reduction of the need for a strict GFD by the alteration of dietary food products, decrease of gluten exposure by rapid enzymatic degradation, inhibition of

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small intestinal permeability, or modulation of the immune response [8]. Currently, the human studies concerning the most effective treatment for calcium deficiency and bone problems in patients with CD are still lacking.

Celiac disease: Pathogenesis, prevalence, and mode of presentation

CD is a lifelong intestinal disorder that occurs in genetically predisposed individuals. The disease is characterized by an immune reaction to the gliadin fraction of gluten, a protein component found in wheat, rye, and barley. The tendency of CD to run in families is well recognized. This multigene disorder is strongly associated with the human leukocyte antigen (*HLA*) genes. Approximately 90% to 95% of patients with CD inherit alleles encoding HLA-DQ2, whereas most of the remaining patients have HLA-DQ8 [9,10]. The expression of HLA-DQ2 or HLA-DQ8 is a necessary but not sufficient factor in CD pathogenesis. Studies of identical twins have shown that one twin did not develop CD in 25% of the cases studied [11], supporting the role played by environmental factors in the etiology of this disorder. Breastfeeding and the timing of gluten ingestion commencement [12], infections [13], some drugs [14], and smoking [15] might contribute to disease occurrence.

Until recently, CD was thought to occur rarely in childhood; however, current screening studies have demonstrated a much higher prevalence of CD than previously thought. The occurrence of biopsy-proven CD in Finnish and Italian schoolchildren was reported to be 1:99 and 1:106, respectively [16,17]. Similar rates of prevalence have been reported in adult populations in the United Kingdom (1:87) and the United States (1:105) [18,19]. Such a rate establishes CD as one of the most common diseases, affecting approximately 1% of the world's population at any age, although it is less common in most non-Caucasians and thought to be rare in central Africa and East Asia. Recently, more cases are being diagnosed as a consequence of widespread serological testing and increased awareness, still most people with CD remain undiagnosed as subclinical or atypical presentations are more frequently encountered [20–22]. Adult presentations of CD are more common than pediatric presentations, females predominate over males, and newly diagnosed CD occurs in young adults and patients older than age 60 y.

CD primarily affects the mucosa of the proximal small intestine with damage gradually decreasing in severity toward the distal small intestine, although in severe cases the lesion extends to the ileum and colon [23]. The clinical presentation of CD varies widely and depends on the patient's age, duration and extent of disease, and presence of extra-intestinal manifestations [24]. Patients can be asymptomatic to severely symptomatic. One study [25] defined major CD to be those patients complaining of frank malabsorption symptoms often associated with concomitant autoimmune diseases symptoms. In children, and similarly in adolescents and adults, in addition to diarrhea, abdominal distension, vomiting, constipation, weight loss, weakness, short stature, flatus, muscle wasting and hypotonia, general irritability and unhappiness are observed [26,27]. Hypocalcemia, low vitamin D levels, low bone formation, enhanced bone resorption markers, and low BMD are frequently found among children and adolescents with untreated CD. In minor CD, on the other hand, gastrointestinal (GI) symptoms are absent or not prominent. Instead, patients might report unrelated symptoms such as dyspepsia, abdominal discomfort and bloating, mild or occasional altered bowel habits without malabsorption mimicking irritable bowel syndrome, unexplained anemia, isolated fatigue, cryptic hypertransaminasemia, infertility, peripheral and central neurologic disorders, osteoporosis, short stature, dental enamel defects, or dermatitis herpetiformis [28]. The silent form of CD is marked by small intestinal mucosal abnormalities and in most cases by positive serology, but it is apparently asymptomatic [29]. Most of these individuals are relatives of patients with known CD or members of the general population found to be positive for antiendomysial antibodies or hTTG antibodies [25]. Screening studies of first-degree relatives of patients with CD and other risk groups (e.g., patients with various autoimmune diseases) have demonstrated that serious intestinal damage may be present without any symptoms [30]. Autoimmune and immune-mediated diseases often are reported in association with CD, such as type 1 diabetes mellitus, autoimmune thyroiditis, or morphea [31]. Moreover, patients with Down, Turner, or Williams syndromes also are at increased risk for development of CD [32].

Serological tests used as an initial non-invasive screen for detecting CD include sensitive and specific serological markers, such as anti-endomysial and anti-transglutaminase antibodies [33]. Although positive test results can be supportive for a diagnosis, upper GI tract biopsy is required because a definitive diagnosis can be made only by the histologic demonstration of compatible intestinal mucosal lesions [34]. The diagnosis depends on the finding of characteristic changes including intraepithelial lymphocytosis, crypt hyperplasia, and various degrees of reduced villous height together with symptomatic and histologic improvement when gluten is withdrawn [35]. The pathology of the disease can range from infiltrative lesions characterized by increased intraepithelial lymphocytes with normal architecture to completely flat mucosa [36].

The keystone of CD management is the exclusion of gluten from the diet [37]. It is generally accepted that in a GFD, wheat, barley, and rye must be avoided as their prolamines (gliadin, hordein, and secalin) are the major triggering factors of CD. Clinical improvement is usually evident in the first few weeks after gluten withdrawal, but it can take up to 2 y for complete histologic resolution of the enteropathy [38]. However, some patients show a lack of response to a GFD. Non-responsive celiac disease (NRCD) is a clinical diagnosis defined by the persistence of signs, symptoms, and/or laboratory abnormalities typical of active CD despite treatment with a GFD for at least 6 mo [39]. Among NRCD, the most serious is refractory celiac disease (RCD), which can be complicated by significant morbidity and mortality and carries a poor prognosis due to severe malabsorption, malnutrition, and development of ulcerative jejunitis or enteropathy-associated T-cell lymphoma [40]. The key information concerning CD is summarized in Table 1.

Calcium: A "common denominator" of bone and intestine

Calcium is an essential ion necessary to maintain the proper functionality of the circulatory and neuromuscular systems; it is a cofactor for several hormones and enzymes and influences the immunologic system. In bones and teeth, it plays a structure function and provides mechanical strength. Additionally, calcium is a physiologic link between bone and intestine. Bones, being calcium salt reservoirs, have a metabolic function because calcium is continuously exchanged between bone and blood and can be released from bone to maintain extracellular calcium concentrations, regardless of intake. Wherefore, intestinal calcium absorption is essential to ensure that appropriate concentrations of intra- and extracellular calcium fluids are effectively maintained without bone depletion [41,42].