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Review

Osteoporosis in Celiac Disease: An Update

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Abstract

Celiac disease (CD) is an autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals. In addition to the typical gastrointestinal symptoms such as diarrhea, bloating, or chronic abdominal pain, CD may also present a wide spectrum of manifestations, including low bone mineral density (BMD) and osteoporosis. This review aims to describe the role of CD in the development of skeletal alterations, underlying important clinical aspects and therapeutic implications. The etiopathology of bone lesions in CD is multifactorial and their management is challenging. Here, we provide gastroenterologists and orthopedics with an up-to-date overview on the link between CD and osteoporosis to improve the management of the CD condition.

Keywords: celiac disease; osteoporosis; osteopenia; bone mass density; malabsorption; calcium; vitamin D

Celiac disease: an introduction

CD is a disorder that involves primarily the proximal small intestine. It is an autoimmune condition triggered by gluten ingestion in susceptible subjects. Genetic background is an essential prerogative for the development of the disease (HLA- DQ2/DQ8 positivity and non-HLA genes), but the contribution of other factors such as viral infections and gut dysbiosis might also play a role.[1]

Many studies[2–4] have reported that gluten is a digestion-resistant protein formed by several immunogenic peptides that can trigger host's immunity responses, increasing both gut permeability and innate and adaptive immune system activation, stimulating IL-8 and TNF- α production.

Until a few decades ago, CD was considered an uncommon disease affecting mainly children and European-native individuals[5], but now it is considered a global burden since its prevalence reaches almost 1% worldwide, making CD one of the most common autoimmune disorders.[6] CD is increasingly diagnosed, in both pediatric population and adults, as described in a recent meta-analysis by *James A. King et al.*[7], especially throughout industrialized countries. The rise in the diagnosis rate seems to be due to true growth in incidence[8]. The "hygiene hypothesis"[9] stating that the better hygienic conditions in western countries and recently lead to a decrease in the incidence of infections and stimulate both allergic and autoimmune disease might be an explanation along with the increase of gluten consumption in our diets[10].

More recently, Fasano suggested that gut permeability and dysbiosis play a key pathogenic role of CD through an impaired expression of zonulin.[11]

CD is diagnosed 2-3 times more frequently in women than men. The disease can occur at any age, from early childhood to the elderly, with two peaks of onset, one shortly after weaning with gluten in the first two years of life and the other in the second or third decades of life.[1]

Accordingly to the 2012 Oslo classification, which is the latest consensus that defines terms related to CD, CD may be classified as classical, non-classical, subclinical, potential and refractory. Signs and symptoms of malabsorption characterize classical form of CD: diarrhea, steatorrhea, weight loss or growth failure and it is more frequent in pediatric population. Non-classical CD is characterized by constipation, alternating bowel habits, osteopenia/osteoporosis,

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recurrent miscarriages. The term “subclinical” is specified to be a form of CD that is below the threshold of clinical detection without signs or symptoms sufficient to trigger CD testing in routine practice. Refractory CD affects patients that present persistent symptoms and/or signs of malabsorption despite a strict gluten withdrawal for at least 12-18 months. The term “potential CD” describes normal small intestinal mucosa with positive CD sierology[12]: these patients are at an increased risk of developing overt CD; however, if it is asymptomatic, GFD is not mandatory.[13]

The European Society for the Study of Coeliac Disease (ESsCD) guidelines suggest that IgA-transglutaminase type 2 (IgA-TG2) antibody is the preferred single test for detection of CD at any age, concurrently with total IgA levels to determine whether IgA levels are sufficient. It is of paramount importance that all serologic testing should be performed while patients are on a gluten-containing diet.[14] In adults, the gold standard for CD diagnosis is the combination of serological test (anti-TG2, anti-endomysium antibodies (EmA), and deamidated gliadin peptide (DGP) antibodies) and mucosal changes detected by duodenal biopsy (described with Marsh-Oberhüber or Corazza and Villanacci classifications).[15] A simple rule by *Catassi* and *Fasano* suggests that the diagnosis of celiac disease is confirmed if at least 4 of the following 5 criteria are satisfied: 1) typical symptoms of celiac disease; 2) positivity of serum celiac disease IgA class autoantibodies at high titer; 3) HLA-DQ2 or DQ8 genotypes; 4) celiac enteropathy at the small intestinal biopsy; 5) response to the GFD (3 out of 4 if HLA is not performed)[16]. To date, the current standard of care is based on these criteria.[1]

Currently, the only effective treatment for CD is following a lifelong strict gluten-free diet (GFD) since it leads to the resolution of intestinal and extraintestinal symptoms, negativity of autoantibodies, and the regrowth of the intestinal villi.[1]

Pathologic bone alterations in celiac disease

Extraintestinal manifestations (EIM) are common in CD and include abnormal liver enzymes, arthralgia/arthritis, dermatitis herpetiformis, alopecia, fatigue, headache, anaemia, stomatitis, myalgias, psychiatric disorders, rashes, seizures, neuropathy, short stature, delayed puberty, and infertility.[17] A well-established relationship between low bone mineral density (BMD) and celiac disease (CD) has been determined.[18] Pathologic bone alterations also include osteopenia and osteoporosis due to malabsorption (especially calcium and vitamin D deficiencies) and chronic inflammation with the secretion of pro-inflammatory cytokines;[18] CD is therefore considered a secondary osteoporosis risk factor.[19]

Osteoporosis is a disease defined by a significant loss of bone mass, causing a lowering in skeletal tissue density, architectural rearrangement, and an increased risk of fractures. Bone loss starts at age 35, but it reaches its peak at late middle life (50> years) and affects mainly women.[20] Osteopenia and osteoporosis lead to an increased prevalence of fractures, as well as an increased morbidity and mortality rate.[21]

A recent metanalysis identifies that 30-60% of newly diagnosed patients with CD show low BMD and 18–35% osteoporosis, despite different definitions and methods might have been used among different studies, underlying that bone alterations are extremely frequent in CD.[22–24] Prevalence of CD in idiopathic osteoporotic fractures has been assessed in several studies. However, there is still lack of univocal conclusion: *Stenson et al.*[25] found a 3.4% incidence of CD in osteoporotic patients compared to 0.2% among general population, while others found increased IgA EmA values in sera of osteoporotic patients but normal intestinal mucosa.[26,27] In some cases, patients could show osteoporosis with elevated serum alkaline phosphatase levels (ALP) and hyperparathyroidism as the sole presentation of CD.[28] *Walker* suggests that forearm bone density measurement, usually not screened when assessing BMD, might be useful to identify osteoporosis. This exam may be performed in addition to hip and lumbar spine BMD evaluation, which alone tend to underestimate the prevalence of osteoporosis.[29]

Mechanisms underlying osteoporosis in celiac disease

Bone is a mineralized tissue that undergoes continuous remodeling, determined by the synergic action of osteoblasts and osteoclasts, regulated by a complex interaction of different mechanisms. It reaches the peak of bone mass around the age of 20-25, and in the third decade of life the process of bone reabsorption begins to exceed bone formation, leading to progressive bone loss. Hormones and nutrition play an important role in this process, and they

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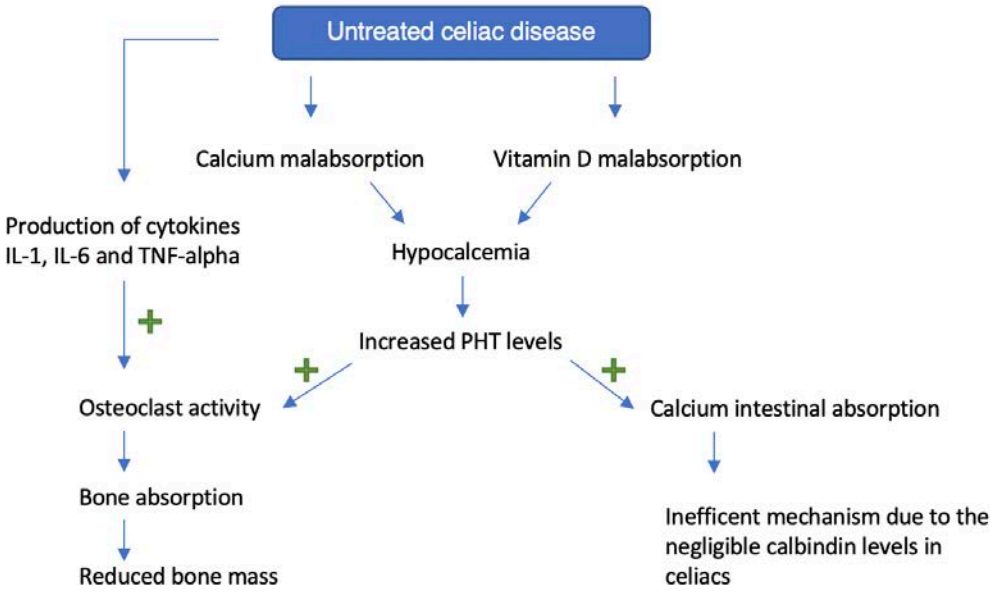
might be impaired in CD. The following scheme (***figure 1***) summarizes the possible mechanisms involved in bone demineralization in untreated CD.[30]

Figure 1. Possible mechanisms involved in bone demineralization in untreated celiac disease



Calcium homeostasis

Industrial gluten-free products could have low levels of minerals, including Calcium (Ca^{2+}), and patients might not assume the recommended daily intake (RDA), suggesting the introduction of fortified gluten-free foods or calcium supplementation.[31] Calcium balance is regulated through a complex coordinating action of hormones (parathyroid hormone PTH, 1,25-dihydroxyvitamin D and calcitonin) and organs: bone, as a calcium reservoir, intestine that regulates the exogen absorption, and kidneys. As blood Ca^{2+} concentration decreases, a rapid increase in PTH release promotes bone turnover and cortical bone loss. Thus, Ca^{2+} malabsorption in CD plays a pivotal role in the induction of a series of events that lead to bone demineralization.[23] Hyperparathyroidism is frequent and should be searched in newly diagnosed patients as it is responsible for the acceleration of bone turnover [32,33]. Impaired Ca^{2+} absorption in CD results from the histological damage of villi in proximal intestinal mucosa, as they absorb the most significant dietary intake of this mineral.[34]

Low calcium intake is a risk factor for osteoporosis and calcium intake at young age is an essential determinant of the peak of bone mass.[35,36] Calcium metabolism defects are common in untreated children with CD, and they returned to normal after GFD.[37] Indeed, adherence to strict GFD for at least 1-2 years is sufficient to normalize Ca^{2+} and vitamin D levels; however, there are some cases (e.g. postmenopausal women) where diet is not sufficient to replenish minerals and vitamins and low BMD is chronic. In these subsets of patients, long-term vitamin D and calcium supplementation is recommended.[38]

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Vitamin D

Vitamin D contributes in many ways to bone mineralization, maintaining calcium and phosphate homeostasis. It regulates intestinal calcium intake through vitamin D receptor (VDR), normally expressed in CD patients, without any significant difference in healthy control group.[39] As vitamin D, (as well as calcium), is absorbed predominantly in the proximal portion of the small bowel, in untreated CD it is often malabsorbed, both due to villous atrophy and to the presence of steatorrhea.[32] Vitamin D is activated by the renal enzyme 1-alpha-hydroxylase upon stimulation by PTH: in CD this step aims to allow increased intestinal absorption of calcium through an increased vitamin D-dependent active transport. However, even if enterocytes have an average number of vitamin D receptors, they contain negligible amounts of vitamin D-dependent calcium-binding protein (calbindin) due to their immaturity, making this effort ineffective. Moreover, high levels of 1,25-vitamin D may, paradoxically, have a negative effect at bone level, being themselves a cause of bone resorption.[22] Furthermore, vitamin D acts directly on immune cells, which play a key role in autoimmune diseases. Clinical studies have demonstrated that vitamin D deficiency is related to morbidity in infectious diseases and the onset or progression of autoimmune diseases, including CD.[40–42]

Vitamin D deficiency is more prevalent in adult and pediatric patients with CD than controls.[43] Insufficient dietary intake and impaired intestinal absorption are considered to be crucial factors in the development of vitamin D deficiency. A study by *Mautalen et al.* found that calcium and vitamin D supplementation did not provide additional benefit to that obtained by diet alone[44], whereas *Barera et al.* evidence only a small positive effect of low dose supplementation with vitamin D, resulting in a rise of the solely vitamin D levels, but no significant changes in BMD.[45]

As for calcium, also for vitamin D strict adherence to GFD normalizes vitamin D levels in most patients.

Some studies claim that most of the patients with intestinal inflammatory diseases (e.g. CD, Crohn's disease, enteropathies) regardless the severity of their condition, have normal intestinal vitamin D absorption but are vitamin D deficient. In contrast, some patients have normal serum vitamin D levels even though their intestinal vitamin D absorption is severely impaired.[46,47] This suggests that other factors such as insufficient light exposure, inflammation and hyperparathyroidism significantly affect vitamin D serum levels.[48]

Treatment and management

GFD is essential to restore mucosal integrity and to allow a proper absorption of micronutrients, including calcium and vitamin D. Calcium, PTH, vitamin D and ALP should be assessed at the time of the diagnosis and a nutritional counseling needs to be provided by a dietician with expertise in GFD in order to guarantee a proper nutrients and micronutrients intake. In case of low serum level or inadequate intake of calcium and/or vitamin D they should be supplemented.[49] Haematological and biochemical profiles should be checked periodically. In addition, education on the importance of lifestyle changes, such as regular exercise, smoking cessation, and reduction of excessive alcohol intake, should be provided.[30]

Both British Society of Gastroenterology Guidelines for the diagnosis and management of CD[50] and ESsCD recommend a Dual-energy X-ray absorptiometry (DEXA) screening in celiac patients especially in patients at high risk of osteoporosis.[14] DEXA should be performed at the diagnosis in high risk patients, in patients with malabsorption, in patients with a long delay in CD diagnosis. If osteoporosis is found in postmenopausal women, they can be offered treatment with hormone replacement therapy (HRT), bisphosphonates (anti-resorption agents), or calcitonin.[51]

Figure 2. Bone health diagnostic work-up (adapted from *"European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders"*[14])

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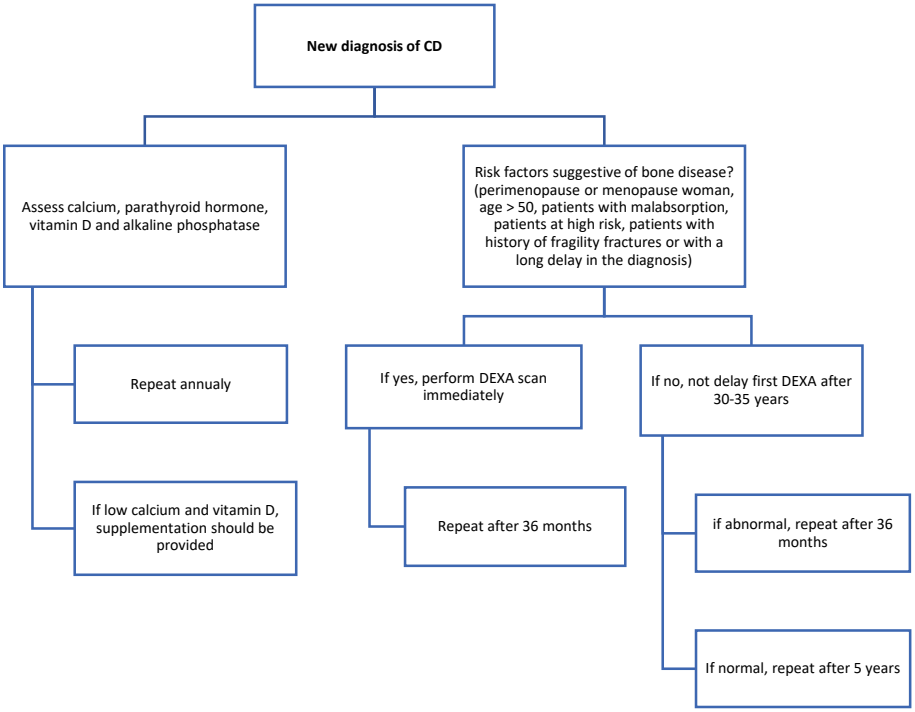

Conclusions

Osteopenia and osteoporosis are conditions frequently associated with CD. Strict adherence to GFD seems to be the only effective treatment to improve BMD in adults and normalize BMD in children,[52] but nutritional status of patients should also be taken into account when it comes to decide whether supplementing calcium and vitamin D. Physicians should be aware of bone conditions linked to CD and they should assess BMD and serum markers of bone health in order to exclude osteoporosis in CD patients and *viceversa*.

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