Celiac Disease: Its Effects on Bone

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Abstract

Celiac disease (celiac sprue) is a relatively common intestinal disorder, associated with the ingestion of gluten, a protein found in some cereals. In genetically susceptible subjects, gluten ingestion leads to a chronic alteration of the intestinal mucosa, with loss of villi and proliferation of crypt cells. The overt forms of the disease are characterized by steatorrhea, malabsorption and nutritional deficiencies. Atypical or asymptomatic forms of the disease are more common today. The only effective treatment of celiac disease is a strict, lifelong gluten-free diet, as any ingestion of gluten sets off an inflammatory reaction in the small bowel.

Osteoporosis is a frequent long-term complication of untreated celiac disease, and is now also frequently encountered as the presenting manifestation of asymptomatic forms. Bone remodeling seems to be affected by at least two mechanisms, the first related to malabsorption, the second to the release of inflammatory cytokines. A strict gluten-free diet can bring complete bone recovery in young patients, and is a fundamental therapeutic measure in adults. BMD evaluation is still a matter of discussion, and there is no agreement on the advisability of DXA scans at diagnosis or during follow-up, except in high-risk patients.

The aim of this article is to present state-of-the-art knowledge on the bone complications of celiac disease. The need for further, more focused research on specific aspects of bone metabolism in celiac disease (the role of diet, cytokine studies, BMD evaluation, and specific drug therapy) is emphasized, and the specific requirements of young and adult patients are discussed.

Keywords: Celiac disease; Gluten; Gliadin; Malabsorption; Osteopenia; Osteoporosis; Bone density; Cytokines; Hyperparathyroidism

Introduction

Osteoporosis in the absence of obvious risk factors is frequently encountered as the presenting symptom of an otherwise asymptomatic form of celiac disease (also called celiac sprue), an intestinal disorder associated with the ingestion of gluten, a protein found in wheat, rye and barley. The goal of this article is to present state-of-the-art knowledge on the bone complications of celiac disease.

Celiac Disease

Celiac disease is characterized by alterations of the small bowel mucosa, due to an immune reaction to the gliadin fraction of gluten in genetically predisposed subjects (1). It involves the small bowel from the duodenum to the distal ileum, and is characterized by specific histological alterations: more or less severe villous atrophy, crypt hyperplasia, increased
chronic lymphocyte infiltration of the lamina propria and the epithelium (2).

The overt forms of celiac disease are easily recognized because of steatorrhea and other intestinal malabsorption symptoms. Other symptoms (e.g., anemia, weight loss, skin alterations) may be related to deficiency states. However, these symptomatic forms have become uncommon. Today, there is no typical presentation and several different symptoms, often quite confusing ones, may be present. Since the 1980s, a progressive shift towards asymptomatic forms, which can be detected only with specific diagnostic exams (3), has been observed. These forms may go unrecognized for years or even decades, until, for example, the discovery of celiac disease in the family leads to diagnostic screening, or an unexpected osteoporotic fracture occurs.

Celiac disease is now considered an important health problem, because of its prevalence and the possible long-term complications if untreated, among them malignancy and osteoporosis. At present, the only effective treatment is a strict, lifelong gluten-free diet (GFD).

Celiac disease has been the subject of many studies in recent years, and much new knowledge has been gathered. In particular, at least three points are worthy of mention here. First, a diagnosis of celiac disease can be made only upon histological demonstration of compatible mucosal lesions. The decision to perform upper gastrointestinal tract endoscopy is now made simpler by the availability of sensitive and specific serological markers (anti-endomysium and anti-transglutaminase antibodies) which can confirm a clinical suspicion (4). Second, better knowledge of the disease and the greater availability of histological samples have allowed not only demonstration of the large spectrum of mucosal alterations, but also an understanding of why the clinical presentation of celiac disease can be so variable. Third, screening studies found a much higher prevalence of celiac disease than previously thought, up to 1% of the general population in Europe and the USA (5).

Pathogenesis of Bone Alterations in Celiac Disease

Bone and muscle pains, cramps, tetany, rickets, osteoporosis and osteomalacia have been widely described in patients affected by celiac disease. Earlier reports on bone involvement were chiefly based on clinical and biochemical findings (6;7), whereas the more recent availability of bone density measurement has allowed more precise and objective studies. Although decreased bone mass is clearly documented in celiac patients, the underlying pathological processes are still controversial, and at least two main mechanisms should be considered.

In patients with symptomatic celiac disease, low bone mass appears to be directly related to malabsorption: reduced calcium absorption due to atrophy of the intestinal villi, vitamin D deficiency, and secondary hyperparathyroidism are all responsible for the development of osteomalacia and/or osteoporosis (8;9). The link between the increase in parathyroid hormone (PTH) and vitamin D deficiency is not so simple. Persistently high PTH levels have been observed both in the presence and in the absence of vitamin D deficiency (10), and up-regulated parathyroid gland activity appears to persist in celiac patients even after calcium malabsorption has been corrected.

Sophisticated investigations have discovered that vitamin D receptors are still normally present in the duodenal mucosa of celiac patients, even those with mucosal damage and villous atrophy (11). However, the vitamin D-regulated proteins (calbindin and calcium-binding protein) that actively take up calcium from the intestinal lumen are missing in the areas of damaged
mucosa (12), and this is one reason for calcium malabsorption.

In patients without gastrointestinal symptoms, other factors such as a deficiency of growth factors, as yet undiscovered autoimmune deficiencies, or an increased production of cytokines related to the intestinal inflammation could play the main role in reducing bone mass. A decrease in growth stimulating factors is sometimes observed: low circulating levels of IGF-I have been found in untreated patients with celiac disease, and did not increase after one year of GFD (13). Zinc deficiency may be responsible of the low IGF-I levels, since zinc is the earliest and most pronounced nutritional deficiency in celiac disease (14). During a 4-week gluten challenge in children with celiac disease who had been on GFD for at least 12 months, decreased bone AP, IGF-I, IGF-binding protein, and telopeptide of type I collagen were observed. In particular, the decrease in IGF-I and its binding protein was related to the degree of mucosal atrophy (15). It is also interesting to note that patients with asymptomatic celiac disease are often affected by other immunological diseases, such as type-1 diabetes mellitus, autoimmune thyroiditis, or morphea.

A recent study (16) observed altered cytokine levels in patients with celiac disease: increased IL-6 levels (only in patients not on GFD), reduced IL-12 (independently of diet), and reduced IL-18 (only in patients on GFD). The RANKL/OPG ratio was also increased in patients not on GFD. Persistently increased osteoclast numbers were obtained from cultures of peripheral blood mononuclear cells of healthy donors upon incubation with sera of patients not on GFD, with respect to incubation with sera from healthy controls or from patients on GFD. In human osteoblasts from healthy individuals, IL-18 was reduced upon incubation with sera from celiac patients, while OPG expression was lower only with sera from patients not on GFD.

Bone Mass in Celiac Disease at Different Ages

The few studies of pediatric patients affected by celiac disease show either normal (17) or low bone mineral density (BMD) (18;19) at the time of diagnosis. The limited number of studies, little prospective data, and the wide age distribution, from children to young adults, should be taken into account when evaluating these data. Some studies have shown that GFD, followed since an early age, is able to restore BMD to normal in children (19-22) and also to ameliorate disordered vitamin D metabolism (19;21;22). According to these studies, only an early diagnosis of celiac disease, immediately followed by diet, can guarantee the attainment of normal bone mass. Another study (23) drew attention to the very important fact that many patients whose celiac disease was diagnosed in childhood, but who resumed a normal diet during adolescence, may develop bone complications (severe osteopenia) in adult life even if they remained free of intestinal symptoms.

In adult patients, many studies have evaluated bone mass at the diagnosis of celiac disease and after a period of GFD. Most studies involved both men and women, a wide range of ages (including pre- and post-menopausal women) and a different duration of GFD (24-27). The variability of patient populations should be considered when discussing and comparing the results. At the time of diagnosis, a variable proportion of adult celiac patients (18-40%) were found to have osteopenia. This variability was related to the analysis of different skeletal sites as well as to the
different age at diagnosis or, for women, menopausal status (24-27). One of these studies (27) also found a high prevalence of osteoporosis, in 34% of patients at lumbar spine and in 27% at femoral neck. Men were more severely affected than women. Some studies also found osteopenia in suboptimally treated patients, subclinical patients and asymptomatic patients (28-30).

It is agreed that GFD can also improve bone parameters in post-menopausal women and in patients with incomplete mucosal recovery (31;32). However, bone density does not revert to normal in most cases in which the diagnosis of celiac disease is made, and the GFD is started, in adult age. It should also be remarked that, notwithstanding the strong evidence of low bone density in celiac patients, there is still no consensus about the optimal timing for densitometric evaluation, at diagnosis or during follow-up.

Celiac disease can be associated not only with osteopenia and osteoporosis, but also with osteomalacia, although this was more commonly observed in the past. Since osteomalacia is now rare in developed countries, finding its classical biochemical and clinical signs in any patient should raise the suspicion of celiac disease (33).

**Fragility Fractures in Celiac Disease**

There is little published data on fragility fractures in celiac disease. They are not very consistent, and a series of methodological problems that make evaluation difficult (e.g., sample size; method used to diagnose celiac disease; definition of fracture, especially for vertebral fractures; control sample characteristics) must be taken into account. One study (34) demonstrated that celiac disease-affected patients have a high prevalence of bone fractures in the peripheral skeleton: of 165 patients, 25% had a history of one to five previous fractures, compared with 7% among 165 age- and sex-matched controls. The fact that the majority of these patients were young (only 38 over 50 years) may explain why the wrist and radius were the most common fracture sites. These data were confirmed by another study (35), where fractures were found in 21.3% of 75 patients with celiac disease, a proportion that was significantly higher than that among matched controls (2.7% of 75 subjects). Peripheral fractures (wrist, pelvis, tibia, clavicle) were prevalent also in this study. Two other studies (36;37), however, did not find an increased fracture rate among patients with celiac disease. A recent large cross-sectional study (38) of 383 women with celiac disease (aged over 50 years; 90.3% with a diagnosis of celiac disease confirmed by biopsy) shows a greater prevalence of fractures at various peripheral sites, and a higher number of multiple fractures, in comparison with 445 age-stratified and sex-matched controls.

**Therapy of Bone Loss in Celiac Disease**

In children affected by celiac disease, GFD, strictly followed for a long time, is the therapy of choice for the recovery of bone mass (19-22). Prospective studies with long-term follow-up are still not available, however, and there is no evidence that an optimal peak of bone mass can be achieved, or that it can be maintained as in normal subjects. In adults with a relatively late diagnosis of celiac disease, GFD alone cannot always correct bone alterations, even if, on the basis of the available literature such as the guidelines for osteoporosis in celiac disease by the British Society of Gastroenterology (39), it remains the most rational approach. However, there are still open questions. First, different responses to diet have been observed. A prospective study (31) on adult patients with celiac disease found a normalized BMD after three years of GFD only in the group of patients without secondary hyperparathyroidism, suggesting that the response to treatment may depend on the type of bone metabolism derangement. Second, some controversies still remain regarding vitamin D. According to an old
case report (40), after resolution of intestinal symptoms with GFD, and notwithstanding vitamin D supplements, a patient developed osteomalacia. This was resolved only with oral 25-OH vitamin D3, indicating that an active metabolite may be needed to overcome the vitamin D deficiency. This finding has also been confirmed by another study, in which an increase in BMD was found in patients after a year on GFD, only if supplemented with calcium and 25-OH vitamin D (41). In contrast, a study on a small number of patients (42) showed that adding calcium (1 g/day) and vitamin D2 (32,000 IU once a week) gives no additional benefit over GFD alone. However, serum 25-OH vitamin D levels did not increase in the subjects who received the vitamin, in comparison to those who did not, suggesting that too low a dose was used. Considering the very small sample as well, these results must be taken cautiously. No studies have investigated the calcium requirements in celiac disease and the type and dose of vitamin D supplements on adequately sized samples to verify whether these therapies can guarantee a greater increase in BMD than GFD alone. The little data available and our knowledge of vitamin D metabolism in celiac disease would suggest 25-OH vitamin D as the best choice. Third, there are no systematic data on the efficacy of the drugs commonly used for osteoporosis, such as bisphosphonates, in patients with celiac disease. Other factors may be especially important in evaluating and treating bone problems in celiac disease. For example, one study (43) focused on low body mass index, dietary calcium intake and early menopause. In our experience (44), there is an increased risk of bone loss in case of late diagnosis of celiac disease, lapses from GFD, persistently active disease, lactose intolerance, and low BMI (malnutrition). Patients with such risk factors require careful assessment and individually tailored treatment.

Osteoporosis as a Marker of Celiac Disease

Osteoporosis may be a sign of subclinical celiac disease, and, conversely, celiac disease is now considered one of the risk factors for osteoporosis. There are conflicting reports, however. A study of Swedish patients (45) found that the prevalence of antibodies against gliadin was higher in a population with an apparently idiopathic osteoporosis than in a larger population without osteoporosis: 12% of the former had high IgA antibody levels, with respect to only 3% of controls. Another study (46) did not show any increase in the prevalence of celiac disease in patients with low BMD. A study on premenopausal women with osteoporosis reported that 10% of patients were positive for anti-endomysium antibodies (47). In a recent study, the prevalence of silent celiac disease (confirmed by biopsy of small bowel) was found to be progressively increased in patients with osteopenia or osteoporosis compared with normal BMD (48). Another recent American study found that the prevalence of biopsy-proven celiac disease was 17-fold higher in a group of 266 osteoporotic patients (3.4%) than in a group of 574 non-osteoporotic patients (0.2%), and the authors suggest that all individuals with osteoporosis should undergo serologic screening for celiac disease (49).

Some authors also suggest that, even in the absence of gastrointestinal symptoms, celiac disease should be considered in the differential diagnosis of patients with unexplained hypocalcemia, or hyperparathyroidism with low or normal calcium levels (44). Another important aspect is that the appearance or persistence of osteopenia in celiac patients on GFD may be a sign that the mucosa of the small intestine has not fully reverted to normal, thus suggesting poor compliance to the diet or another complication (50).

Conclusion

Bone fragility fractures and small bowel lymphoma are the major long-term
complications of untreated celiac disease and the main reasons for insisting on the strict adherence to GFD even in asymptomatic patients. The risk of these complications diminishes significantly with the diet.

Many points are still controversial. The advisability of mass screening for celiac disease is debated. It seems more prudent to screen high-risk groups, such as individuals affected by autoimmune diseases commonly associated with celiac disease, those with a family history of celiac disease, or those with osteoporosis or iron-deficiency anemia (51). Moreover, the finding of severe osteoporosis (especially if unexpected for age, sex or menopausal status, or poorly responsive to standard therapy) should be considered as the possible expression of asymptomatic celiac disease. BMD evaluation in patients with celiac disease is still a matter of discussion, and there is no agreement on the advisability of a DXA scan at diagnosis in adults, except in high-risk patients. There are open questions also for children: the available data are not sufficient to state that GFD is adequate to solve the problem of bone density acquisition in all younger patients. The actual gain in bone density cannot be estimated reliably, especially at the age of the transition, and considering also the problem of compliance to GFD.

Future research on the etiology of celiac disease will probably offer new insights into the role of cytokines and their effects on bone cells. Regarding therapy, some fundamental aspects - such as the correct calcium intake, the type and dose of vitamin D metabolites, and the use of drugs against osteoporosis - have not been studied on adequately large samples, and further investigation is urgently needed, particularly in adults.

**Conflict of Interest:** The authors report that no conflicts of interest exist.

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