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REVIEW

Bone in celiac disease

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Abstract
Summary Chronic inflammation and malabsorption in celiac disease (CD) can cause bone metabolism alterations and bone mineral loss in children and adults. Bone status before and after gluten-free diet, epidemiology of fractures, and possible treatment options for CD-related osteoporosis are presented. Controversial aspects of this complication of CD are discussed.

The relationship between bone derangements and celiac disease (CD) was recognized almost 50 years ago, but many questions are still open. We are now aware that osteoporosis is a relatively frequent atypical presentation of CD, especially in adults, and that undiagnosed CD can be the cause of osteoporosis and related fractures. Chronic inflammatory intestinal diseases, including CD, can affect bone and mineral metabolism because of alterations in both systemic and local regulatory factors. The pathogenetic processes are still controversial, but two main mechanisms seem to be involved: intestinal malabsorption and the presence of chronic inflammation. This review analyzes the published data on bone involvement in children, adolescents, and adults either before or after a gluten-free diet. Special attention is paid to the epidemiology of fractures in celiac patients, considering that fractures are a major complication of osteoporosis and an important problem in the management of a chronic disease like CD. The usefulness of screening osteoporotic patients systematically for CD is still an open question, but some rules can be given. Finally, the current treatment options for children and adults are discussed. Recommendations for future clinical research are proposed.

Keywords Bone density · Celiac disease · Cytokines · Gluten · Hyperparathyroidism · Osteoporosis

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Introduction

Celiac disease (CD), also called celiac sprue, 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. CD occurs in genetically predisposed subjects, and is often familial. Large screening studies have demonstrated a much higher prevalence of CD than previously thought: up to 1% of the general population in Europe and the USA is affected [1, 2].

As a rule, the clinical manifestations of CD are related to the extent and severity of the intestinal damage. In the past, CD was almost always recognized because of steatorrhea and other malabsorption symptoms. Anemia, weight loss, vitamin and trace element deficiency, skin alterations (mainly dermatitis herpetiformis, but also psoriasis, urticaria, vitiligo, oral lichen planus, porphyria, ichthyosiform dermatoses, alopecia areata) were also commonly observed. Today, the presentation of CD tends to be atypical, with confusing symptoms or no symptoms at all [3]. Dyspepsia, bowel disturbances, abdominal pain, iron deficiency anemia, osteoporosis, infertility, recurrent miscarriages, alone or in various combinations, may be the presenting symptoms. The

reason why the presentation of the disease has changed in the recent years is not completely understood: increased duration of breastfeeding and delayed exposure to gluten in infancy have been proposed as possible causal factors. In addition, the availability of sensitive and specific serologic markers, and the wider availability of upper gastrointestinal endoscopy and biopsy certainly increased the doctors' awareness of atypical manifestations and the appreciation of early signs and symptoms of the disease well before its full clinical expression.

Screening studies of first-degree relatives of celiac patients and other risk groups (e.g., patients with various autoimmune diseases) have demonstrated that serious intestinal damage may be present without any symptoms (silent CD) [4]. These atypical forms can be detected only with specific diagnostic exams and may go unrecognized for years or even decades. It is interesting to note that patients with asymptomatic CD are often affected by other immunological diseases, such as type-1 diabetes mellitus, autoimmune thyroiditis, or morphea [5].

A diagnosis of CD is strongly suggested by the presence of sensitive and specific serological markers (anti-endomysium and anti-transglutaminase antibodies). However, upper gastrointestinal tract endoscopy is usually required, since a definitive diagnosis can be made only by the histological demonstration of compatible intestinal mucosal lesions [6–8].

In recent years, significant advances in the knowledge of this disease have been made, and the greater availability of histological samples has demonstrated the presence of different degrees of mucosal alterations, such as more or less severe villous atrophy, crypt hyperplasia, increased chronic lymphocyte infiltration of the lamina propria and the epithelium [9]. On the basis of these findings a standardized histological classification has been approved and is widely used.

Presently, the only effective treatment of CD is a strict, lifelong gluten-free diet (GFD), although the response to treatment is poor in up to 30% of the patients, mainly because of low adherence to the dietary restrictions [10–12].

Osteoporosis, intestinal T-cell lymphoma and other malignancies are the most common long-term complications of untreated CD, and the discovery of osteoporosis in a person without apparent risk factors should raise a strong suspicion of asymptomatic CD.

Celiac disease and bone

The earlier reports on bone involvement in CD were chiefly based on clinical and biochemical findings [13, 14]. Since the late 1980s, single and dual X-ray absorptiometry (DXA) have provided more precise quantitative bone data [15]. More recently, some epidemiological studies have brought to light the increased risks of fractures in celiac patients.

Chronic inflammatory intestinal diseases, including CD, can affect bone and mineral metabolism because of alterations in both systemic and local regulatory factors. Calcium and phosphate malabsorption, hormones, and local factors (e.g., growth factors, cytokines) may all be involved in determining the loss of bone minerals.

Low bone mineral density (BMD) is frequently found in celiac patients, affecting up to 70% of celiac subjects according to some studies [16]. However, notwithstanding the high frequency of low bone density, there is still no consensus about the optimal timing for densitometric evaluations in celiac patients, whether at diagnosis or during the follow-up.

The pathogenetic processes are still controversial, but two main mechanisms are thought to be involved. The first is an impaired intestinal absorption of nutrients, which can lead not only to calcium deficiency, but also to general malnutrition and a reduced BMI. The second is related to the presence of inflammation and the chronic release of proinflammatory cytokines.

In patients with symptomatic CD, low bone density appears to be directly related to the intestinal malabsorption. Osteomalacia or osteoporosis are secondary to the reduced calcium absorption, caused by atrophy of the intestinal villi, and/or to a vitamin D deficiency, leading to secondary hyperparathyroidism [17, 18]. High parathyroid hormone (PTH) levels have been observed not only, as usual, in the presence of vitamin D deficiency but also with normal vitamin D levels [19]. Moreover, in celiac patients on long-term GFD, a persisting up-regulation of parathyroid gland activity, with PTH levels in the upper normal range, has been described long after the disappearance of calcium malabsorption [20].

With regard to this point, some essential notes on the interaction between PTH and vitamin D may be useful. PTH and 1,25-dihydroxy vitamin D exert complex, coordinated activities to maintain normal serum calcium levels. In the presence of low calcium (for example caused by vitamin D deficiency, malabsorption or steatorrhea), the parathyroid glands increase the secretion of PTH, which in turns increases the circulating levels of 1,25-dihydroxy vitamin D, by stimulating the renal production of 1alpha-hydroxylase, the enzyme responsible for the conversion of 25-hydroxy vitamin D (the main circulating metabolite of vitamin D) to the final hormone 1,25-dihydroxy vitamin D. For this reason, increased 1,25-dihydroxy vitamin D levels may be observed in CD. Moreover, since 1,25-dihydroxy vitamin D is also involved in the catabolism of 25-hydroxy vitamin D, a sustained increase in serum 1,25-dihydroxy vitamin D may lead to an accelerated depletion of vitamin D stores, and to a worsening of vitamin D deficiency [21].

Vitamin D receptors are normally expressed in the duodenal mucosa of celiac patients, notwithstanding mucosal damage and atrophy of the villi [22]. However, in the

areas of damaged mucosa, there is a lack of calbindin and calcium-binding protein, the vitamin D-regulated proteins that actively take up calcium from the intestinal lumen [23]. No difference in the frequency of VDR genotypes between celiac patients and controls has been found, so that low bone density seems unrelated to a specific VDR genetic pattern in celiac patients [24].

A decrease in growth stimulating factors, like IGF-I, is sometimes observed in osteoporotic patients: untreated celiac patients may have low IGF-I levels, and GFD for one year seems unable to normalize them [25]. Zinc deficiency has been suggested as a cause of low IGF-I levels, because zinc is the earliest and most pronounced nutritional deficiency in CD [26], and can be normalized only after the complete repair of intestinal mucosa with GFD. A decrease in alkaline phosphatase (AP), due to a reduction of its bone isoforms, as well as a decrease in IGF-I, IGF-binding protein, and the telopeptide of type I collagen, have been observed with a 4-week gluten challenge in 54 celiac children (aged 2–9.3 years), who had been on a GFD for at least 12 months [27]. This decrease in growth factors and bone markers correlated with reduced body weight and increased intestinal mucosa inflammation. In particular, the decrease in IGF-I and its binding protein was related to the degree of mucosal atrophy. This could be an explanation for the stunted growth observed in celiac children without any clinical signs of malabsorption.

In patients with asymptomatic CD, factors related to the chronic intestinal inflammation (deficiency of growth factors, increased production of cytokines, possibly also autoimmune alterations) may be the main factors leading to a reduced bone density [28]. Cytokines are locally active factors involved in the normal communication of signals between cells, particularly in embryogenesis, hematopoiesis, and immune responses. Osteotropic cytokines are involved in both normal and abnormal bone remodeling. Cytokines are released by immunologically competent cells in the response to infection, injury and inflammation. Increased cytokine production in chronic inflammatory diseases is associated with increased bone loss.

Confirming the cytokine involvement in CD osteoporosis, Moreno et al. found that low total body BMD in celiac patients was associated with an allelic variant (IL-1B-511T) of the IL-1 gene, and concluded that "a genetic factor participating in the regulation of the immune response and bone metabolism contributes to CD osteopathy" [29]. A recent study found altered cytokine levels in patients with CD, strongly suggesting that bone loss in these subjects may be related to a cytokine imbalance directly affecting osteoclastogenesis and osteoblast activity [30]. In this study, untreated patients had increased IL-6 levels and an increased RANKL/OPG ratio, while IL-18 was reduced in patients on GFD, and IL-12 was reduced in all celiac patients irrespective of diet. Cultures of peripheral blood mononuclear cells of healthy donors incubated with sera of celiac patients not on GFD gave origin to a persistently increased number (about 40-fold) of osteoclasts, while incubation with sera from healthy controls or from celiac patients on GFD did not have any effect. In human osteoblasts from healthy individuals, IL-18 was reduced upon incubation with sera of celiac patients, while OPG expression was reduced only with sera from celiac patients not on GFD. Proliferation, alkaline phosphatase and nodule mineralization were increased (1.4 to 2.7-fold) in osteoblast cultures containing sera from all celiac patients, either on GFD or not.

Additional risk factors for osteoporosis in celiac disease

Celiac patients have the same major risk factors for osteopenia or osteoporosis (female gender, physical activity, lifestyle) as the general population [31]. However, according to McFarlane et al. [32] some risk factors (low body mass index, dietary calcium intake, early menopause) are especially important in CD. According to our personal experience, special risk factors like diagnosis of CD in adult life, lapses from gluten-free diet, active CD, lactose intolerance, and malnutrition with low BMI may all contribute to increasing the risk of bone loss in these patients and require careful assessment and appropriate treatment.

A recent study [33] showed that patients with persistent small-intestinal mucosal villous atrophy, despite a strict adherence to a gluten-free diet and the absence of symptoms (GFD-non-responders), had a high risk of severe complications: osteoporosis (spine BMD T-score < -2.5, evaluated with DXA) was found in 58% of 13 GFD-non-responder patients and only in 22% of 18 matched GFD-responders (intestinal histological recovery). Even more dramatically, three out of the 13 non-responders developed severe malignancies, and two developed symptomatic refractory CD requiring immunosuppressant therapy.

Bone density in celiac children and adolescents

It is essential to know that the clinical presentation of CD is currently highly variable both in children and in adults, and that extra-intestinal symptoms are very frequent, even more than the classical intestinal symptoms. In a recent review of CD in children, Fasano and Catassi [34] identified four different presentations of CD in these patients: typical cases with classical malabsorption symptoms; atypical cases; silent cases discovered only with occasional serological screening; latent or potential cases, with isolated serological positivity with future development of symptoms. Also in younger

patients, the frequent occurrence of atypical, silent, or latent forms, unrecognized for many years, has determined the appearance of several CD-associated complications once observed only in adults, among them reduced bone density.

There are only few bone studies, mostly cross-sectional and on small numbers of cases, on pediatric patients affected by CD. Lower-than-normal bone mineral content (BMC) has often been found in celiac children, and even more in adolescents, at the time of diagnosis [35–38], although normal values have also been reported [39]. However, these data should be evaluated with prudence, considering the limited number of studies, the fact that prospective data are few, and the wide age ranges included (some studies included also older patients).

Besides CD itself, additional risk factors for a less-than-optimal peak bone mass value in young celiac patients have been recently highlighted. An important aspect is the high prevalence of CD (2.4% to 10.4%) in children with type I diabetes [40]. A recent study in children with type I diabetes found that the presence of celiac autoimmunity is associated with a more reduced bone density [41]. Moreover, celiac children have often a retarded growth. An Italian study found CD in 12 (1.12%) of 1.066 children evaluated for short stature: after 1-year of GFD, only nine of the celiac children showed an increased growth, while in the remaining three an associated growth hormone (GH) deficiency was found [42]. Thus, in children with CD a careful attention to growth is necessary even after starting GFD, and GH secretion should be evaluated in those with a good adherence to diet but without catch-up growth. This aspect is relevant when evaluating BMD in celiac children not only to avoid a misinterpretation of DXA data (apparently reduced BMD due to the short stature), but also because of the major influence of GH on bone density increase.

Another risk factor is related to leptin, a hormone essential for body weight regulation, and also important in bone remodeling. Several studies have suggested that the serum leptin level is correlated with BMD. The action of leptin is very complex and not fully known yet. This cytokine-like hormone, secreted by adipocytes, has both a direct anabolic effect on bone, acting on osteoblasts, and an indirect catabolic effect, via central hypothalamic mechanisms involving the activation of the sympathetic nervous system. The complexity of its action is further demonstrated by its different effects on the remodeling of cortical and trabecular bone [43, 44].

It has been recently discovered that celiac children have reduced serum leptin levels, and that GFD seems to be able to increase them. A significant correlation between leptin levels and BMI was found in these children [45]. Both cross-sectional and longitudinal studies in adults and children have shown that bone density is positively correlated to body weight and BMI. It may be possible that, in CD children on GFD, the increased level of leptin act positively on bone, through both the increased body weight and the hormone's anabolic action on osteoblasts.

There are many evidences that the introduction of GFD can improve bone development and bone density gain, even if the entity of this recovery is widely variable, depending on many factors. Some studies have shown that GFD, started at an early age, can restore BMD to normal in children [35, 36, 46–49] and also correct the altered vitamin D metabolism [49]. According to these studies, only an early diagnosis of CD, immediately followed by diet, can guarantee the attainment of normal bone density.

In a prospective study, Mora et al. [35] followed a small group of 14 celiac children, aged 9.5 ± 5.08 years, for 1.28 years after starting GFD and found that the annual increase in peripheral BMC was greater than in normal children (0.07 vs. 0.05 g/cm), concluding that GFD alone was able to improve bone mineralization and restore BMC to normal. These authors reported similar results in two later studies on slightly larger groups (25 and 30 children respectively): both lumbar spine and total body BMD were completely normalized with long-term GFD [46, 47].

Scotta et al. [36] studied 66 celiac children (33 boys and 33 girls; age 28–227 months), and found a reduced BMC and BMD (spine and total body) only in those who had been on GFD for less than 12 months. Moreover, they found that when a diagnosis was made after 24 months of age, the patients had lower values of body mass index (BMI), fat mass and spinal BMD. These data suggest that only an early diagnosis of CD and a strict GFD allow to obtain a normal bone mass in adulthood. Barera et al. [37] found that total body BMD, fat mass and limb lean mass were lower in 29 children (aged 9.5 ± 3.4 years) at the time of a diagnosis of CD than in a matched control group, but that GFD for 1.2 years normalized the body composition in 20 patients (69%). In an earlier study, Molteni et al. [48] reported similar data in a group of young patients (13–28 years) of both sexes: normalized forearm BMD was only present in those with an early diagnosis and who had constantly followed a GFD since childhood.

There is not much published information on vitamin D metabolism in CD. Challa et al. [49], studying a very small sample of celiac children (2–8 years) and a suitable control group, suggested that vitamin D metabolism can be normalized by GFD. Serum calcium and vitamin D metabolites were measured both at the time of diagnosis of CD, and after GFD for between 2 and 12 months. After GFD, serum calcium remained in the normal range but was significantly increased; 24,25-(OH)2 vitamin D, initially low, was significantly increased; while 1,25-(OH)2 vitamin D, initially high, was significantly decreased, reverting to normal. 25-(OH) was also increased after GFD, although not significantly.

Tau et al. [50] following spine BMC and BMD in 24 children (16 aged less than 4 years) before and after GFD

(average 14 months, from 3 months to 3.9 years) observed that 93% of children starting GFD before age 4 reached a normal spine BMD, while only 50% of children older at the time of diagnosis, and at the start of GFD, did so. The authors noted that "the increment of BMC was two-fold greater than the increment of the area, indicating that GFD treatment increases bone mineralization in addition to the increment due to bone growth".

Finally, Cellier et al. [51] underlined the very important fact that many patients whose CD was diagnosed in childhood, but who resumed a normal diet during adolescence, may develop bone complications (severe osteopenia) in adult life even if remaining free of intestinal symptoms.

Bone density in celiac adults

The bone density in adult patients with CD has been evaluated in many studies, both soon after diagnosis and after a period on GFD. Most studies involved both men and women of a wide age range (including pre-and post-menopausal women) and with different duration of GFD. The variability of the studied populations should be considered when discussing and comparing the results.

For example, according to different studies, a variable proportion of adult celiac patients, ranging from 18% to 75%, has osteopenia (T-score < −1) at the time of diagnosis [16, 52–57]. The variability may depend on the analysis of different skeletal sites as well as on the different age at diagnosis or, for women, menopause.

Valdimarsson et al. [54], in a prospective study of 63 celiac patients (35 women and 28 men, aged 17–79 years), found low forearm, trochanter and spine BMD (Z-score < −2) at the time of diagnosis in respectively 22%, 18% and 15% of the patients [1]. On the contrary, Bardella et al. [55] observed a low BMD (total body) only in women in whom a diagnosis of CD was made in adult age. Pistorius et al. [56] observed low spine and femoral neck bone density in 81 celiac women (age 20–70 years): a comparison with age-matched controls showed that BMD was reduced only at femoral neck in pre-menopausal women, but also at vertebrae in post-menopausal women. Meyer et al. [16] confirmed a similar prevalence of low BMD (38% spine, 44% femoral neck and 32% radius) in 128 North American adults with CD (105 women, 23 men). Osteoporosis (T-score < −2.5) was present at lumbar spine in 34% of the patients, at femoral neck in 27% and at radius in 36%. When compared with age-matched controls, men were more severely affected than women.

Osteopenia was found in unsuspected sub-optimally treated celiac patients [59], subclinical patients [60] and asymptomatic adult patients [61], indicating that bone loss is not simply related to steatorrhea and malabsorption. Moreover, Mustalahti et al. [62], found that in a group of 29 patients (6 women and 23 men, aged 23–69 years), asymptomatic patients had a significantly lower bone density than symptomatic patients (T-score: spine −1.9 vs. −1.1; femoral neck −0.9 vs. −0.8). The appearance or persistence of osteopenia in celiac patients on GFD should also be considered a sign that the mucosa of the small intestine has not completely reverted to normal, perhaps revealing poor dietary compliance or some complication [59]. A recent study observed that men affected by CD not only have a greater malabsorption than women, but also a greater frequency of "female-predominant associated diseases" (e.g., a lower T-score at the radius) [63].

The results obtained by DXA studies were confirmed by a quantitative ultrasonography (QUS) study [24]: in 78 celiac patients (age 15–83 years), a Z-score < −1 was found in 40% for broadband ultrasound attenuation (BUA) and in 47% for speed of sound (SOS), and a Z-score < −2 in 10% and 12%, respectively.

The effects of GFD on the bone density of celiac patients have been studied by many authors [15, 18, 32, 64–67]. Most of them have found that GFD can improve bone density also in post-menopausal women and in patients with incomplete mucosal recovery. However, a complete normalization of bone density seems to be possible only if the diagnosis is made at a young age and a strict GFD is followed thereafter. Otherwise, the BMD can have some increase but it will not attain normal levels. According to a study by Ciacci et al. [68], an increase in BMD was considered possible only if the GFD was started before 25 years of age.

Cellier et al. [51] found severe osteopenia (Z-score < −2) in one-third of 23 asymptomatic adults, who where diagnosed in childhood but abandoned GFD in adolescence: notwithstanding the lack of symptoms, they had severe villous atrophy and a low BMI. This observation is

[1] A short comment, not specific for celiac disease, on the use of the T- or Z-score to evaluate bone density in adults (in adults *only*, since in children and adolescents the Z-score must be used) may be useful at this point, to better understand the differences in bone density reported by different authors. By definition, the Z-score virtually coincides with the T-score in the 25–39 years age range. In older adults, the use of the T-score is universally accepted to define osteoporosis, osteopenia, or normality, according to the recommendations of a WHO Study Group [58]. There are strong scientific evidences of a clear relationship between the decrease of the T-score value and the increase of fragility fractures at any age. Thus, the T-score helps to evaluate the current risk of fractures, as well as the future risk. The Z-score, being the comparison with the mean value of healthy controls matched for both sex and age, is less useful in older adults, because some degree of bone loss is prevalent even among the apparently healthy subjects used as controls. However, the Z-score may help to understand how much the bone density of an individual affected by a disease is different from that of the healthy population of the same gender and age, and this may be the main reason why many studies on celiac patients with a wide age range used the Z-score.

confirmed by a recent retrospective study on a larger number of patients. Sixty-one adult subjects (aged 17–53 years) with CD diagnosed in childhood or adolescence, had first followed a GFD for 1 to 18 years, then had resumed a normal diet (for an average of 10 years, range 2–44 years) and were still asymptomatic at the time of enrollment in the study: in the subgroup without villous atrophy (latent CD) only 11% (1/9) had osteopenia/osteoporosis, while among those with villous atrophy (silent CD) 70% (23/33) had osteopenia/osteoporosis. The authors conclude that "in silent CD patients the increased risk of osteoporosis substantiates the need for a GFD" [69].

A few studies evaluated calcium absorption in celiac patients with the stable strontium test. Ciacci et al. [70] found that the rate of calcium absorption was 45% lower in untreated adult patients with either overt or subclinical CD than in healthy controls. They also found a marked reduction in urinary calcium excretion in both symptomatic and asymptomatic patients, but calcium excretion increased by 52% after six months on GFD. Molteni et al. [71] found that intestinal calcium absorption returned to normal after one year of GFD.

General malnutrition secondary to villous atrophy and malabsorption may also have a role in the reduction of bone density in celiac patients. Corazza et al. [72] found that malnutrition was present at the time of diagnosis in 67% of patients with overt CD and in 31% of those with subclinical CD. This suggests that children and adolescents with undiagnosed CD may suffer from an inadequate intake of calcium, protein and total calories in the years of maximal skeletal development and bone density accrual, so that they will attain a lower than optimal peak bone mass, with a higher risk of osteopenia/osteoporosis in older age.

Finally, it must be remembered that in the atypical forms of CD, as well as in the unrecognized cases, bone and muscle pains, cramps, tetany, rickets and osteomalacia, in addition to osteopenia and osteoporosis, are possible clinical manifestations [73].

Regarding CD and osteomalacia, almost all the published studies are case reports on one or few cases, mainly females. In the 1950s and 1960s, osteomalacia was the first bone alteration described in CD [74]. In those times, it was essentially associated with CD diagnosed in adulthood, and characterized by diarrhea and malabsorption. The usual presentation was pain, proximal muscle weakness, waddling gait, spontaneous fractures (related to a late diagnosis). Today, classical osteomalacia is rarely seen in CD, at least in Western countries, possibly because of the different clinical presentation of the disease and the absence of overt malabsorption. However, it is still reported, mostly in females, in Middle-Eastern countries [73, 75, 76]. Severe proximal lower-limb weakness, associated with disabling pain, is the clinical picture usually leading to a diagnosis of osteomalacia, and eventually, in some patients, to the discovery of CD. So, even today, the discovery of the biochemical and clinical signs and symptoms of osteomalacia in any patient should strongly suggest the possibility of CD [77, 78].

To close this section on a positive note, a study from Finland, where CD is common and the awareness of the disease is generally good, found that the quality of life and the BMD of celiac patients screen-detected from risk groups, after long-term treatment and excellent dietary compliance, were comparable with those of non-CD subjects and the general population [79].

Celiac disease and the risk of fragility fractures

A recent, dramatic case-report [80] of a 78-year old woman confined to a wheel-chair for ten spontaneous axial and peripheral fractures, sustained during 21 years because of undiagnosed osteoporosis-osteomalacia originated by CD, called attention to this severe complication of untreated CD, and to the importance of a careful search for the cause of any spontaneous fracture.

Unfortunately, there are few published data on fragility fractures in CD. Moreover, these data are not very consistent, and there are several methodological problems that must be taken into account and make the evaluation of these studies very difficult.

Important methodological aspects to consider are the reliability of the method used to diagnose both CD and fractures, which clearly affects the required sample size of the studied CD cohort. The characteristics of controls, and especially the estimated fracture rate in controls (very variable in the studies considered), are critical for calculating the sample size, and affect the power of statistical calculations. Other relevant factors are the methods for the collection of fracture data, as each method (personal interviews, self-administered questionnaires, hospital discharge cards, general databases, etc.) has different inner biases. Moreover, most published studies do not consider vertebral fractures, with a likely underestimation of the total fracture rate in CD patients, including the youngest. Finally, when vertebral fractures are considered, the definition of "fracture" and the requirement of X-ray confirmation should be clearly defined, to make possible the comparison of data.

A study [81] found that celiac patients (74 on GFD and 91 untreated or on partial dietary restriction) have a high prevalence of bone fractures in the peripheral skeleton: 41 (25%) of 165 patients had a history of one to five previous fractures, compared with 14 (7%) subjects with fractures among 165 age- and sex-matched controls (odds ratio (OR) 3.5; 95% confidence interval (CI) 1.8–7.2, $p<0.0001$).

Higher risks have been reported, related to the severity of presenting symptoms. The fact that the majority of these patients were young (only 38 were over 50 years) may explain why the wrist and the radius were the commonest fracture sites. These data have been confirmed by other studies. In the first one [82], based only on a reported history of fractures, fractures were found in 16 (21.3%) of 75 patients with CD, a significantly higher proportion than that observed in 75 matched controls (two cases, or 2.7%), a relative risk of 8:1. Peripheral fractures (wrist, pelvis, tibia, clavicle) were more prevalent also in this study. Another study [83], evaluating 148 unselected patients affected by CD and 296 sex-matched controls with functional gastrointestinal disorders, found an increased number of peripheral fractures in symptomatic celiac subjects (47% vs. 15% of controls). Celiac patients had also more fractures due to mild trauma.

On the contrary, two other studies did not find a significantly increased fracture rate among patients with CD. A study from England [84] on 244 celiac patients reported an OR of 1.05; 95% CI 0.65–2.1 for all fractures, with a little higher, but not significant, increase for forearm and wrist fractures (OR 1.21; 95% CI 0.66–2.25). A Danish study [85] on 1,021 celiac patients did not observe a significant increase in fracture risk before and after diagnosis (incidence rate ratio for all fractures: 0.70, 95% CI 0.45–1.09, before diagnosis; 0.94, 95% CI 0.71–1.24, after diagnosis). However, the authors concluded that "the validity of a diagnosis of CD was low (78%) … and the misclassification may have affected the results"; and in any case, the increasing age and a history of fracture before CD diagnosis increased the risk of sustaining a new fracture after CD diagnosis (hazard ratio 2.04; 95% CI 0.49–8.4). Finally, in another UK study on 4,732 patients affected by CD [86], the hazard ratio of fractures seemed not very high, being 1.9 (95% CI 1.2–3.02) for hip fractures, and 1.77 (95% CI 1.35–2.34) for ulna or radius fracture.

These contradictory results may be at least partly explained by the difficulty to organize a good study design (sample size, method of fracture diagnosis, types of fractures considered, selection of the control population). This means that the contradictions should be attributed more to the limitations and different design of the studies than to a lack of association between low BMD and fracture rate in celiac subjects.

In the last three years, four new studies on fractures in CD were published. The high prevalence of fractures was confirmed by a large cross-sectional study [87] on 383 women, aged over 50 years, with CD (confirmed by biopsy in 90.3%). Compared with 445 age-stratified and sex-matched controls, the celiac patients had a greater prevalence of fractures at various peripheral sites (OR 1.51; 95% CI 1.13–2.02) and a higher number of multiple fractures (OR 2.96; 95% CI 1.81–4.83). In another study on 83 celiac patients [88], an increased fracture risk was observed before and after diagnosis (OR 2; 95% CI 1–3.9, p = 0.045 before; and OR 2.5; 95% CI 1.1–5.6.9, p = 0.026 after) and appendicular and axial fractures were 2.5 and 3.2 times more likely. A Swedish general population-based study [89] on 13,724 celiac patients and 65,627 controls concluded that subjects with CD, including children, had an increased risk of hip and any-type fracture, and that the increased risk for hip fracture persisted 20 years after the diagnosis of CD (hip fracture hazard ratio 2.1; 95% CI 1.8–2.4; for children 2.6; 95% CI 1.1–6.2; any-type fracture hazard ratio 1.4; 95% CI 1.3–1.5; for children 1.1; 95% CI 1–1.2).

Finally, Olmos et al. [90] in a meta-analysis essentially based on eight studies [81–87, 89] considered 20,955 celiac patients and 97,777 controls: 1,819 fractures (frequency 8.7%) occurred in the first group, versus 5,955 (6.1%) in controls (pooled OR 1.43; 95% CI 1.15–1.78), confirming a significant association between fractures and CD.

Osteoporosis as a sign of unrecognized celiac disease

Considering the high prevalence of both CD and osteoporosis, their possible connection should always be taken into account: osteoporosis may be a sign of subclinical CD, and, vice versa, CD is now considered a risk factor for osteoporosis.

The current standard of care for CD is not a generalized screening, but an aggressive case finding with an increased awareness of the different presentations of CD, among which osteoporosis is certainly a frequent non-classical presentation [91]. However, the literature exploring the relation between low BMD and CD remains not so clear, since the simple screening based on the presence of typical antibodies is considered insufficient for a definitive diagnosis of CD, which requires a duodenal biopsy.

More than 15 years ago, a study on Swedish subjects [92] found that the prevalence of positive antibodies against gliadin was higher in a population of patients with apparently idiopathic osteoporosis than in a larger population without osteoporosis: 12% of 92 osteoporotic patients, but only 3% of the healthy controls, had high anti-gliadin IgA antibody levels. As none of the patients presented clear intestinal symptoms, CD had never been suspected before the discovery of low bone density. On the basis of this study, CD began to be considered a risk factor for osteoporosis [93].

More recently, Mather et al. [94] found a 7.3% rate of positive anti-endomysium IgA antibodies in 96 asymptomatic subjects with low BMD, but this could not be attributed to the presence of asymptomatic CD, since duodenal biopsies were negative and a diagnosis of CD was

excluded. Another study [95] reported that 17 (19%) of 89 pre-menopausal women with osteoporosis were positive for anti-gliadin antibodies and 9 (10%) also for anti-endomysium antibodies, and suggested to perform a serological screening for CD in all cases of apparently idiopathic osteoporosis. This study, however, did not confirm the diagnosis of CD with biopsy.

These results differ from the conclusions of two earlier studies from Ireland that did not find an increased prevalence of CD in an unselected group of women with reduced BMD [96, 97].

In a recent study [98], on a series of consecutive patients aged below 70 years who had a DXA scan, the authors obtained the consent of 978 subjects (936 F, 42 M) to undergo a screening for CD, first with serological tests (IgG/IgA antigliadin antibodies and endomysial antibodies) and then, in case of positive results, with a small bowel biopsy. Silent CD was discovered in 12 of these patients (1.2%). The prevalence of CD was inversely related to the BMD value: it was 0.7% (2/304) in those with a normal BMD, 1.2% (5/431) in those with osteopenia, and 2.1% (5/243) in those with osteoporosis. Since direct questioning revealed that all patients with unrecognized CD had subtle gastrointestinal symptoms or a history of anemia, the authors suggest that patients without any of these symptoms could be excluded from the screening for CD: excluding these patients in their sample, the observed prevalence of CD would have been of 3.9% for osteoporosis (5/127) and 2.6% for osteopenia (5/191). The authors suggest that routinely questioning the patients undergoing DXA about gastrointestinal symptoms or anemia could be helpful to identify those in need of further screening for CD. Another recent study [99] found that the prevalence of biopsy-proven CD was 17-fold higher in a group of 266 osteoporotic patients (3.4%) than in a group of 574 non-osteoporotic subjects (0.2%), and the authors suggest that all individuals with osteoporosis should undergo serologic screening for CD.

Considering that in a series of 150 consecutive patients affected by osteoporosis, we discovered 5 (3.3%) new cases of CD (one male and four females, age range 49–73 years, diagnosis confirmed by biopsy), in a cost/benefit evaluation, we would not suggest to screen all post-menopausal women with osteoporosis for CD, but to focus on the patients with a more severe BMD reduction than expected for age or years of menopause, or those not responding to conventional therapies, or showing unexpected alterations in laboratory tests.

Finally, some authors have recommended to include CD in the differential diagnosis of patients with unexplained hypocalcemia, or hyperparathyroidism in the presence of low or normal calcium levels, even in the absence of gastrointestinal symptoms [100–102].

Treating bone loss in celiac disease

When a diagnosis of CD is made in children, GFD is considered the sole therapy. If strictly followed for the rest of life, it is effective in resolving the intestinal inflammatory processes and can also make the recovery of a normal bone density possible [36, 46–48]. However, prospective studies with long-term follow-up are still lacking, and there is no evidence that an optimal peak bone mass level can be achieved, or that it can be maintained for many years, as happens in normal subjects.

When a diagnosis of CD is made in an adult, GFD is still considered the most rational treatment approach, even if by itself it cannot always correct the bone alterations [102, 103].

There are still open questions regarding the best treatment of bone problems in these patients. First, different responses to the GFD have been observed. For example, a prospective study [66] on 105 patients initially not on GFD found that, after three years of GFD, BMD was normalized only in the patients without secondary hyperparathyroidism, thus suggesting that the type and severity of bone metabolism derangement can influence the response to treatment.

Second, the role of vitamin D may be quite important. In an old case report, Hepner et al. [104] described a woman who developed osteomalacia notwithstanding supplements of oral dihydrotachysterol (1.2 mg/day) and GFD, that resolved her intestinal symptoms. Muscle strength and biochemical tests normalized only with oral 25-OH vitamin D3 (20 mg/day), suggesting that celiac patients may have a deranged vitamin D metabolism, probably linked to alterations in fat metabolism. This finding was confirmed also by another study [54], in which, after one year on GFD, an increase in BMD was found only in the patients receiving supplements of calcium and 25-OH vitamin D. Increased plasma turnover and fecal excretion of 25-OH vitamin D have been found in celiac patients [104] and this active vitamin D metabolite may be more effective than native vitamin D in correcting the deficiency.

A study [105] on 14 patients (nine women and five men aged 21–73 years) showed a 5% increase in both lumbar spine and total skeleton BMD after one year of GFD. Supplements of calcium (1 g/day) and vitamin D2 (32,000 IU once a week) did not confer additional benefits over GFD alone. However, serum 25-OH vitamin D levels did not increase in the subjects who received the supplement, in comparison to those who did not, suggesting that too low a dose was used. Moreover, considering the very small study sample as well, these results must be taken with caution.

It has been suggested that the daily calcium intake in CD should be higher than the RDA because of latent malabsorption in many patients [106]. Pazianas et al. [107] demonstrated that fractional calcium absorption remained

Table 1 Practical points

What we know	What we don't know
Reduced bone density is frequent in CD	The characteristics of adult patients without a reduced bone density
Osteoporosis and fractures may be a presentation of CD	The real incidence of CD in women and men with osteoporosis
GFD improves BMD, but does not normalize it in all patients	How to identify the patients with high chances of BMD normalization with GFD

BMD = bone mineral density, CD = celiac disease, GFD = gluten-free diet

lower in a small sample of 24 celiac women, after more than 4 years of GFD, than in controls. The authors suggest that increased calcium intake could potentially compensate for the reduced fractional calcium absorption in treated adult celiac patients, but cannot by itself normalize BMD.

However, no studies have investigated the calcium requirements and the type and dose of vitamin D supplements on sufficiently large samples of celiac patients, to verify whether these adjuncts could improve BMD better than GFD alone, and whether 25-OH vitamin D would be a better choice as a supplement than the native vitamin.

Moreover, a diet based on gluten-free products is often low in various vitamins, including vitamin D, and other nutrients, including calcium. Few gluten-free products are enriched or fortified, and some patients suffer from other food sensitivities and intolerances, most commonly to dairy foods, thus increasing the risk of nutritional deficiencies [108].

Finally, there are no systematic data on the efficacy of bisphosphonates or other drugs commonly used for osteoporosis in patients with CD. A recent case report found that in an osteoporotic man, oral alendronate induced symptomatic hypocalcemia, which subsequently led to the diagnosis of a previously unrecognized CD. This suggests that all patients developing symptomatic persistent hypocalcemia under oral bisphosphonates should be screened for CD even in the absence of intestinal symptoms [109].

According to the current guidelines for osteoporosis in CD [103, 110], there is a general consensus on the need for a strict GFD, but the need for calcium and vitamin D supplementation is less stressed and further investigation is needed. Also, how to use bone densitometry in these patients, both at diagnosis and during follow-up, has never been specified, and even the usefulness of a DXA scan in celiac patients at diagnosis has recently been challenged [111].

Concluding remarks

All physicians should bear in mind the possible link between CD and bone alterations: in particular, gastroenterologists and all those treating osteoporosis should be fully aware of the problem, as a low bone mass is a major long-term complication of untreated CD.

The current advice is that dietary adherence is necessary also in patients with minor symptoms to reduce the risk of severe long-term complications, such as osteoporosis and small bowel lymphoma. The risk of these complications diminishes very considerably in patients on GFD [112]. Table 1 presents the state-of-the-art clinical knowledge about bone and CD.

Many points, however, are still controversial.

Table 2 Recommendations for future clinical research

In celiac children and adolescents	In celiac adults
Long-term follow-up studies on the attainment of an optimal PBM	Rational, evidence-based approach to BMD evaluation (when to perform DXA; follow-up)
Epidemiological studies on fractures vs. healthy sex- and age-matched controls	Epidemiological studies on vertebral fractures vs. healthy controls
Evaluation of specific dietary requirements of calcium	Evaluation of specific dietary requirements of calcium (for women and men)
Evaluation of specific requirements of vitamin D	Evaluation of specific requirements of vitamin D (for women and men)
Long-term follow-up studies of subjects on GFD since childhood (evaluation of BMD and fractures in adult and old age)	What is the safest and most effective drug treatment to prevent and improve bone loss (lack of studies of bone specific drugs in CD patients)

All studies must be done on statistically significant samples
BMD = bone mineral density, CD = celiac disease, DXA = dual X-rays absorptiometry, GFD = gluten-free diet, PBM = peak bone mass

First, the advisability of mass screening for CD is debated. It has been recommended to screen the high-risk subjects, such as those with type-1 diabetes mellitus and other autoimmune conditions, osteoporosis, iron-deficiency anemia, or a family history of CD [113]. The forms of osteoporosis that should always be considered as the possible expression of an asymptomatic CD are those particularly severe and unexpected for age, sex or menopausal status, or those poorly responsive to standard therapy [114].

Second, the need of a BMD evaluation in patients with CD is still a matter of discussion, and there is no agreement on the usefulness of a DXA scan at diagnosis in adults, except in high-risk patients.

Third, regarding children, the available data are not sufficient to state that GFD is enough to solve the problem of bone mass acquisition in all young patients, the actual gain in bone density cannot be reliably estimated, especially at the age of the transition, and the thorny problem of the compliance to GFD cannot be ignored.

Finally, regarding therapy, particularly in adults, some basic aspects (such as the correct calcium intake, the use of vitamin D metabolites, and even the use of the bone-specific drugs commonly given for primary osteoporosis) have not been studied on adequately large samples and further investigation is urgently needed.

Recommendations for future clinical research on bone and bone metabolism in celiac disease are presented in Table 2.

Conflicts of interest None.

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