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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].

Table 1
Essential characteristic of celiac disease

	Coeliac disease
Prevalence	General populations 0.5%–1.26%; Children 0.31%–0.9%
Female:male ratio	Between 2:1 and 3:1
Trigger	Gluten (gliadins and glutenins, hordeins, secalins)
Causation	Genetic predisposition (HLA/Non-HLA genes); Environmental factors (infant-feeding practice, infections, drugs, socioeconomic factors)
Diagnosis	Positive histologic testing (hyperplastic villous atrophy); Positive serologic testing (EMA, TGA antibodies); Clinical remission on a strict GFD
Clinical presentation	Silent–asymptomatic, positive EMA or TGA antibodies; Minor–unrelated symptoms or isolated symptoms of autoimmune diseases; positive EMA or TGA antibodies; Major–frank malabsorption symptoms;
Complications	RCD types I and II EATL
Associated disease	Type 1 diabetes mellitus; autoimmune thyroiditis; autoimmune myocarditis; Sjögren's syndrome; autoimmune hepatitis; primary biliary cirrhosis; selective IgA deficiency; Addison's disease; Down syndrome; Alopecia areata; Sarcoidosis; neurologic abnormalities; asthma and atopy; IBD; systemic and cutaneous vasculitis; psoriasis; inflammatory arthritis; vitiligo
Treatment	GFD; supplementation of identified deficiencies

EATL, enteropathy-associated T-cell lymphoma; EMA, endomysium; GFD, gluten-free diet; IBD, Inflammatory bowel disease; IgA, immunoglobulin A; RCD, refractory coeliac disease; TGA, tissue transglutaminase

Calcium absorption in the intestine, reabsorption from the kidney, and exchange from bones is tightly controlled. To provide calcium homeostasis, the coordinated actions of these three organs and proper hormonal regulation are critical. Calcium balance is regulated through the calciotropic hormones: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D ($1,25[OH]_2D_3$), and calcitonin. A previous study [42] reviewed the role of other hormones on calcium transport mechanisms. PTH and $1,25(OH)_2D_3$ exert complex coordinated activities to maintain normal serum calcium levels. As the extracellular Ca^{2+} concentration decreases, there is a rapid increase in PTH release that promotes bone turnover and cortical bone loss. Hyperparathyroidism is common in patients newly diagnosed with CD (27% in adults; 12%–54% in children) [43–46] and in those with RCD, but is less common in patients who respond to a GFD [47]. High levels of PTH increase the circulating levels of $1,25(OH)_2D_3$ by stimulating the renal production of 1-α-hydroxylase, the enzyme responsible for the conversion of 25-hydroxy vitamin D (25[OH]D) to the final hormone $1,25(OH)_2D_3$. For this reason, increased $1,25(OH)_2D_3$ levels may be observed in CD [48]. Low BMD in adult CD patients are related to secondary hyperparathyroism and osteomalacia due to calcium and vitamin D malabsorption [49]. Vitamin D deficiency occurs in 64% of men and 71% of women with CD [50]. Dietary vitamin D is absorbed through the small intestine as a fat-soluble vitamin along with dietary fat and is incorporated into chylomicrons. The primary etiology of vitamin D deficiency in CD is malabsorption, however, an intestinal mucosal lesion is also a decisive issue of hypovitaminosis D [51].

Of all the endocrine factors involved in calcium transport, $1,25(OH)_2D_3$ is probably the most important and seems to regulate most proteins that are involved in the overall transport process. Regulation of $1,25(OH)_2D_3$ through genomic actions involving the classical vitamin D receptor (VDR) is widely recognized [52], but its non-genomic regulation through a separate membrane receptor, which was identified as the $1,25D_3$-MARRS (membrane-associated, rapid response, steroid hormone-binding) receptor, is also now accepted [53]. VDR are normally expressed in the duodenal mucosa of patients with CD, notwithstanding mucosal damage and atrophy of the villi [54]. No difference in the frequency of VDR genotypes between patients with CD and controls has been found; therefore, low bone density seems unrelated to a specific VDR genetic pattern in patients with CD [55]. However, as normal intestinal mucosa is required for optimal absorption, in the areas of damaged mucosa defective enterocytes have reduced levels of calbindin and calcium-binding protein, the vitamin D-regulated proteins that actively take up calcium from the intestinal lumen [56]. Therefore, they cannot respond to $1,25(OH)_2D_3$, further potentiating calcium loss and secondary hyperparathyroidism.

Calcium in food occurs as salts or is associated with other dietary constituents in the form of complexes of calcium ions (Ca^{2+}). Before it can be absorbed, calcium must be released in a soluble and ionized form. Calcium absorption depends on its chemical form and factors affecting its solubility. Low pH, basic amino acids, lactose, organic acids, bile salts, and adequate calcium/phosphorus ratio increase calcium absorption, whereas higher pH, non-soluble dietary fiber, phytates, and oxalates greatly cause its reduction. Under physiological conditions, the majority of dietary calcium is absorbed in the small intestine, accounting for approximately 90% of overall calcium absorption [57]. Minor amounts of Ca^{2+} ions are absorbed from the stomach and large intestine; the colon accounts for less than 10% of the total Ca^{2+} absorbed. The major contributors to the amount of calcium absorbed are the residence time and the rate of absorption in the particular segments of the GI tract. The order of absorption rate is: duodenum > jejunum > ileum. Extracellular concentrations of unbound calcium are approximately 1 μM, whereas the intracellular free concentration under resting conditions is in the range of 0.1 μM, creating a steep gradient between intra- and extracellular concentrations [41]. Moreover, intracellular calcium can undergo large, rapid changes due to either influx through the cell membrane or release from intracellular stores, whereas extracellular calcium remains relatively constant under normal circumstances [57]. The maintenance of the extracellular Ca^{2+} concentration is of utmost importance for many vital functions of the body. Differences between intra- and extracellular calcium concentrations put severe constraints and demands on the plasma membrane transport mechanism to safeguard the integrity of the intracellular milieu.

In general, calcium transport is mediated by a complex array of transport processes that are regulated by hormonal, developmental, and physiological factors. Its movement across the intestinal epithelium is based on two mechanisms: passive (paracellular) and active (transcellular). The transcellular calcium transport is a three step metabolically energized process, consisting of the apical uptake via the transient receptor potential vanilloid family calcium channel 5 and 6 (TRPV5/6) and L-type calcium channel Cav1.3, cytoplasmic translocation in a calbindin-D9k-bound form, and the basolateral extrusion via the plasma membrane Ca^{2+}-ATPase1b (PMCA1b) and Na^+/Ca^{2+}exchanger 1 (NCX1) [57]. In contrast, the paracellular passive calcium transport is dependent on the transepithelial calcium gradient and is absent when both sides of the epithelium have equal calcium concentration [41]. Paracellular calcium movement is regulated by the tight junction, which contains several charge-selective proteins, particularly claudin-2, claudin-3, and claudin-12, arranged in the arrays of channel-like paracellular pores [58]. Additionally, the integrity of the tight junction is regulated by tight junction proteins, such as the zonula occludens-1 (ZO-1) and occludins [59].

Intestinal Ca^{2+} absorption varies according to the age and physiological conditions of individuals. It is apparent that

paracellular calcium transport is predominant in the small intestine [41]. However, when calcium demand is markedly increased, such as during growth, pregnancy and lactation, high physical activity, and/or when dietary calcium supply is low, passive Ca^{2+} absorption alone would be insufficient to maintain optimal health status. Therefore, the contribution of transcellular transport becomes more significant. Calcitriol is one of the main regulators of active intestinal calcium absorption and increases the gene transcription of several calcium transporters, including TRPV6, Calbindin-D9k, Calbindin-D28k, and PMCA1b [60–62]. However, recent genetic studies question the critical role of TRPV6 and calbindin-D9k in calcitriol-mediated intestinal calcium absorption [63,64]. Indeed, duodenal calcium absorption is not impaired in Trpv6−/− mice and calbindin-D9k/Trpv6 double-null mice fed a normal calcium diet. Lieben et al. [65] indicated that TRPV6 is redundant for intestinal calcium absorption during normal calcium intake, and therefore is not necessary for normal bone volume, morphology, or remodeling when dietary calcium supply is sufficient. Nevertheless, authors demonstrated that TRPV6 does contribute to the energy-dependent pathway of intestinal calcium absorption and is essential to ensure adequate calcium absorption during dietary calcium deprivation, thereby avoiding excessive bone turnover and impaired bone mineralisation. The finding that TRPV6 is not essential for the maintenance of serum calcium levels during normal/high calcium intake indicates that other molecules contribute to active intestinal calcium absorption. These factors may subsequently compensate for the deficiency in TRPV6, providing an explanation for the modest effects of TRPV6 deletion on intestinal calcium absorption. Additionally, results of one study [66] suggested that $1,25(OH)_2D_3$ stimulates intestinal calcium absorption via regulation of the paracellular pathway, at least in vitro.

Etiology of bone alterations in celiac disease

The relationship between bone derangements and CD was recognized many years ago [67,68]. Patients newly diagnosed or inadequately treated for CD often suffer from skeletal disorders, have low BMD, reduced bone mass, and consequently increased bone fragility leading to a high prevalence of bone fractures [69,70]. The etiology of pathological bone alterations in CD is likely to be multifactorial; however, the emphasis should be on the portion of intestine most severely affected by this disease. CD causes inflammation of the mucosa of the small bowel, from the duodenum to the distal ileum; thus, intestinal absorption is frequently altered leading to malabsorption, which is observed in acute CD. Both malabsorption and chronic intestine inflammation negatively affect bone health. The conditions contributing to pathologic bone alterations in CD are presented in the Table 2.

Table 2
Conditions contributing to pathological bone alterations in celiac disease

Factor	Mechanism of action
Hypocalcemia	Malabsorption of calcium: Vitamin D deficiency Intestine mucosa damage (reduction in the active absorption area) Alterations in calcium-transport mechanism (lost of calbindin and calcium-binding proteins) Inadequate calcium intake Reduced consumption of dairy products (lactose intolerance) Steatorrhea
Hypovitaminosis D	Malabsorption of vitamin D: Alterations in vitamin D metablism Decreased level of vitamin D-binding proteins Decreased intake of vitamin D Steatorrhea
Bowel inflammation	Chronic release of proinflammatory cytokines
Hormones	PTH (secondary hyperparathyroidism) Estrogens and androgens (modulation of RANK/RANKL/OPG system)
Corticosteriods	Reduction of intestinal calcium absorption Increase of renal calcium excretion Impairment of osteoblast function Alteration of osteoclast resorption cycle
Additional risk factors	Autoimmune alternations (autoimmune thyroiditis, dermatitis Herpetiformis, type 1 diabetes mellitus) Diagnosis in adult life Lapses from GFD Active disease Low BMI Lifestyle factors (lack of physical activity, smoking)

BMI, body mass index; GFD, gluten-free diet; PTH, parathyroid hormone

Intestinal malabsorption

In CD, a subsequent immune-mediated enterocyte destruction with atrophic intestinal epithelium results in a decreased surface area for absorption leading to not only to several mineral, vitamin, and protein deficiencies (including albumin and immunoglobulins) but consequently to general malnutrition and a reduced body mass index (BMI). Calcium and vitamin D are generally absorbed throughout the small bowel, predominantly in the proximal portion. Calcium malabsorption is a combined result of steatorrhoea, alterations in calcium-transport mechanisms (i.e., reduced levels of vitamin D-dependent calcium-binding proteins), and lack of vitamin D [71]. Dietary vitamin D, absorbed as a fat-soluble vitamin, along with dietary fat, is secreted with bile and reabsorbed in the intestine. Steatorrhoea may impair the reabsorption of 25(OH)D undergoing enterohepatic circulation, thereby contributing to the development of hypovitaminosis D, especially during acute exacerbations of CD. Augmented hypocalcemia and vitamin D insufficiency are associated with increased levels of serum PTH (secondary hyperparathyroidism), which accelerates bone turnover, bone loss, and increases fracture risk [72,73]. In patients with symptomatic CD, low BMD appears directly related to intestinal malabsorption of calcium, vitamin D, and other nutrients essential to bone health. However, low BMD is present even in atypical or asymptomatic CD patients at the time of diagnosis.

Inflammatory and immunologic alterations

Bone alterations were thought to result simple from intestinal malabsorption and steatorrhoea, but now a more complex interaction between cytokines and local/systemic factors influencing bone formation and reabsorption is envisaged. Osteotropic cytokines are involved in bone remodeling because they regulate the differentiation and activation of osteoblasts and osteoclasts. In inflammatory diseases, including CD, the chronic release of proinflammatory cytokines is well known. Interferon (IFN)-γ is the dominant cytokine in the damaged intestinal mucosa. A study [74] describing the involvement of proinflammatory cytokine network in pathogenesis of CD in children pointed out the abundance of IFN-γ in the intestinal mucosa; additionally, the study's researchers linked gluten intake with the production of interleukin (IL)-15, IL-18, and IL-21. Recently, another study [75] reviewed the involvement of tumor necrosis factor (TNF)-α and IFN-γ in bone remodeling and suggested that their enhanced production and release during chronic inflammation is associated with increased bone loss. Higher levels

of serum cytokines that directly trigger osteoclasts (IL-1, IL-6, and TNF-α) have been detected in individuals with untreated CD; at the same time low levels of cytokines that play an inhibitory role (IL-18 and IL-12) was observed [76,77]. High levels of serum IL-6 in active CD correlated inversely with lumbar BMD values [76].

Bone homeostasis is reached by a dynamic balance between bone-reabsorbing activity performed by receptor activator of nuclear factor kappa-B ligand (RANKL) and the effects of its natural decoy receptor osteoprotegerin (OPG). OPG/RANKL ratio was significantly lower in patients with CD with recovery of intestinal mucosa than in healthy controls and that positively correlated with low BMD [78]. Results of one study [77] observed a significant negative correlation between the BMD *Z* score and RANKL/OPG ratio in CD patients. Recently, another study [79] detected auto-antibodies against OPG in a man with CD and severe osteoporosis and demonstrated the potential of the auto-antibodies to block the inhibitory effect of OPG on RANKL. Inversely, in another study [80], antibodies against OPG were not found in the serum of patients with CD. Therefore, the role and a range of auto-antibodies against OPG in the pathogenesis of bone derangement in patients with CD need to be clearly established and other mechanisms should be investigated.

In patients with asymptomatic CD, factors related to chronic intestinal inflammation (i.e., deficiency of growth factors, increased production of cytokines, and possible autoimmune alterations) may be the main factors leading to reduced BMD [81]. Recent research [82] has demonstrated the association between a genetic predisposition and low bone mass in patients with CD. Authors have reported that single-nucleotide polymorphisms in the genes that encode cytokines of the IL-1 family are associated with bone damage: The carriers of allele T of the IL-1b gene (*IL1B-511T*) had a significantly lower bone mass (total body) and a higher prevalence of osteopenia/osteoporosis. This finding supports the postulated inflammation-associated bone loss pathogenesis as one of the causes of bone weakness in CD.

Nutrition

Diet plays an important role in proper bones mineralization. Generally, a diet based on gluten-free products is low in nutrients, vitamins, and minerals, including calcium [83]. Dietary surveys have found that patients with CD who are on a GFD often consume less than the recommended amounts of calcium and vitamin D. One study [84] demonstrated that 76% to 88% of children and 85% of adolescents with CD adhering to a GFD have inadequate calcium intake. Similarly, another study [85] observed an inadequate calcium intake among children and adolescents on GFD.

Calcium supply in the diet of patients with CD is reduced even more due to a decreased intake of milk and dairy products in an effort to avoid lactose. Secondary lactose intolerance resulting from decreased lactase production by the damaged villi is common in patients with CD. Additionally, naturally gluten-free products often are low in calcium, iron, zinc, magnesium, vitamins (B group vitamins and vitamin D) and fiber. Very few gluten-free products are enriched in calcium as their wheat-containing counterparts; however, it is possible to obtain a good-quality calcium-enriched bread of pleasant sensory characteristic and high-calcium content [86,87], which according to the World Health Organization [88] could be considered an excellent source of calcium.

Epidemiology of low BMD, osteoporosis, and fractures in CD

Low BMD and osteoporosis

Several studies have demonstrated low BMD in children and adults with CD [44,50,89]. Skeletal diseases are reported in association with CD as its non-intestinal presentation. In atypical patients with CD, as well as in unrecognized cases, back pain, diffuse musculoskeletal pain, and proximal muscle weakness and osteomalacia are possible clinical manifestations of the disease in addition to osteopenia and osteoporosis [90]. Osteopenia was found in suboptimally treated patients with CD [91], subclinical patients [92], and asymptomatic adult patients [93]. One study [6] found that asymptomatic patients had significantly lower bone density than symptomatic patients. Recent published studies on BMD in adult and pediatric patients with CD are presented in Table 3.

Adults

Early research [50] investigated the BMD and prevalence of osteopenia and osteoporosis in adult patients with CD and found

Table 3
Recent published studies on BMD in adult and pediatric celiac patients

	Country	Participants	BMD	References
In adult CD patients				
2005	England	43 CD	Low BMD in 5%; osteoporosis in 14%; Osteopenia in 40%	Lewis and Scott, 2005 [94]
2005	USA	24 CD 20 control	BMD significantly reduced in treated vs. control	Pazianas et al. 2005 [95]
2006	Norway	118 CD	BMD significantly reduced ($P < 0.001$) at all sites	Deressa et al. 2006 [96]
2009	Brazil	31 CD	Low BMD in 9%	Motta et al. 2009 [97]
2011	Finland	35 CD	Low BMD in 62%	Vilppula et al. 2011 [99]
2012	Italy	70 CD on GFD	Low BMD in 74% (among these: 24% osteoporosis; 76% osteopenia)	Larussa et al. 2012 [80]
In pediatric CD patients				
2003	Brasil	30 CD (17 children; 13 adolescents) 23 control	BMD of adolescents lower than control; no differences in BMD of children vs. control	Sdepanian et al. 2003 [84]
2003	Turkey	62 CD 64 controls	BMD < in untreated vs. treated and control	Kavak et al. 2003 [44]
2004	Italy	22 CD 428 control	BMD < in untreated vs. control	Barera et al. 2004 [102]
2006	Argentina	24 CD	Low BMD and osteopenia (17%) in untreated; axial BMD reverted to normal in most treated children under 4 y	Tau et al. 2006 [45]
2010	Slovenia	74 CD (55 strict GDF; 19 not strict GFD)	BMD higher in CD on strict GFD vs. CD on not strict GFD; BMD below −1.0 in 71% CD on not strict GFD	Blazina et al. 2010 [85]
2012	Greece	81 CD (45 untreated; 36 on GFD)	Increase of BMD after 1 y of GFD; BMD < vs. normal population	Margoni et al. 2012 [103]

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

that 26% had osteoporosis of the lumbar spine. Also, a study [89] analyzing a North American population with CD found that osteoporosis (T score <-2.5) and low bone mass (T score between -1.0 and -2.5) were present in 27% to 36% and in 32% to 44% of patients, at the femoral neck and lumbar spine/radius, respectively, at the time of CD diagnosis. More recent studies indicated significantly reduced BMD in newly diagnosed patients with CD [94–97]. A study that [98] tested bone density (lumbar spine, total hip, trochanter, and femoral neck) in seropositive tissue transglutaminase/immunoglobulin A endomysial antibody–positive women reported a 67.7% prevalence of osteoporosis. Osteopenia or osteoporosis was found in 22 of 35 new biopsy-proven CD patients in another study [99], which resulted in a 62% prevalence of low BMD.

Children and adolescents

Children with CD are at risk for reduced BMD. Markedly reduced bone mineral content (BMC) and BMD have been repeatedly found in children and adolescents with untreated CD, regardless of the clinical presentation [100,101]. A lower BMD, significantly higher PTH, and lower serum calcium was indicated in untreated children with CD in comparison with treated and controls [44]. Also, a previous study [102] showed significantly lower BMD in untreated children with CD. Studies [45] on young children with CD (mean age 4.9 y) showed lowered BMD and even severe osteopenia (17%) at the time of diagnosis. A recent study [103] assessed bone status in children with CD and found BMD significantly lower than expected for the normal population, even after 1 or at least 2 y of GFD.

Additionally, a risk for less-than-optimal peak bone mass acquisition and a retarded growth in CD children must be highlighted. The most rapid gain in bone mass occurs during adolescence. Bone density increases until the end of puberty, when it reaches its peak value. If normal peak bone mass is not achieved, the individual is at a higher risk for developing osteoporosis; thus, the amount of bone accrued during the pediatric years is an important predictor of an individual's future resistance to fractures [104]. The bone metabolism rate can be assessed by biochemical tests performed on blood or urine samples, which mirrors the ongoing bone metabolic processes [105]; however, only a few studies have monitored the bone metabolism rate in young patients with CD [106,107]. The rate of bone metabolism was altered in children with untreated CD, and these alterations may be the cause of osteopathy [102]. Two studies [108,109] in children with CD suggested a need for careful evaluation of growth and growth hormone (GH) secretion in those without catch-up growth. Therefore, when evaluating BMD in children with CD, an association between CD and GH deficiency should be taken into consideration, not only to avoid a false interpretation of the dual-energy X-ray absorptiometry (DXA) data (apparently reduced BMD due to the short stature) but also because of the major influence of GH on BMD increase.

Fracture risk

Bone resorption and osteoporosis, being a well-established extra-intestinal manifestation of CD, calls attention to a possible increase in fracture risk. An earlier study [110] confirmed the significant association between CD and increased fracture risk. A previous study [69] and a more recent study [111] showed a higher prevalence of fractures in the peripheral skeleton before diagnosis that was associated with male sex and classic clinical presentation. However, studies in smaller numbers of selected patients drawn from hospital clinics are likely to overestimate risk and cannot be generalized to the CD population as a whole.

Population-based cohort studies on fragility fractures in individuals with CD, including those diagnosed in childhood, indicated a relative risk for any fracture ranging widely from 0.9 [112] to 7 [113] and from 0.66 [114] to 1.9 for hip fractures [115]. In a general population-based cohort study [116] that included individuals with CD ($n = 14\ 187$) and reference individuals ($n = 14\ 187$), CD was positively associated with subsequent hip fracture (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.8–2.4) and fractures of any type (HR, 1.4; 95% CI, 1.3–1.5). On the other hand, a systematic review with a meta-analysis that pooled 20 995 CD patients and 97 777 controls, from eight studies published between 2000 and 2007, indicated that CD patients have a 43% higher risk for fracture compared with people without CD [117]. One study [118] questioned the rationale for screening for CD in individuals with fractures, as available evidence indicates that the risk for fragility fractures is only slightly increased in CD and that the absolute risk for fracture in the majority of these individuals is low.

Treatment of bone loss in CD

Gluten-free diet

The best treatment of calcium deficiency and bone problems in patients with CD is debated. Nutritional status of these patients depends on the length of time they have lived with active but undiagnosed disease, the extent of damage to the GI tract, and the degree of malabsorption [119]. A strict and lifelong GFD can help recover normal bone density when a diagnosis of CD is made in children and adolescents [100,101]; however, 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 healthy individuals. An early start to treatment for pediatric patients with CD ensures significantly higher bone metabolism rates because the treatment reverses the inflammatory process and prevents impairment of bone mass acquisition during the most important period for its acquisition [44,120]. A longitudinal study [121] in CD children with DXA-assessed low BMD at diagnosis indicated that after 1 y on GFD, BMD became comparable with healthy controls. Similarly, another study [44] in children with CD confirmed that a strict GFD improved bone mineralization even at 1 y. Another study [122] reported that children and adolescents with CD, after being on a GFD for $\geq$3 y, have normal or even higher radius BMD values than controls, but the bone size remained reduced. One group of researchers [84] evaluated BMD in young patients with CD on a GFD and indicated that BMD of adolescents with CD was lower than that of the control children, whereas no difference was found between the BMD of children with CD and that of the control group. The authors attributed these findings to the longer time between symptoms and diagnosis in adolescents, due to which they suffer more malnutrition and more bone damage than children.

In the case of adult CD patients diagnosed with bones disease, a GFD is still considered to be the most rational treatment approach [123,124]. Nevertheless, a GFD rarely normalizes BMD in adulthood [125,126]. A very recent study [80] indicated that despite long-term strict adherence to GFD, 74% of patients displayed low BMD; among these 24% showed osteoporosis and 76% osteopenia. Therefore, nutritional supplementation should be considered for patients with CD.

Calcium and vitamin D supplementation

Some patients with CD may not be able to meet the recommended daily intake level for calcium and vitamin D through GFD alone, and supplements may be indicated [127]. Few studies tested calcium and vitamin D supplementation in patients with CD. One study [89] observed that among postmenopausal women, BMD was not better in patients taking calcium and vitamin D supplements than in those who were not. Whereas, 2 y of calcium (1 g/d) and vitamin D (400 U/d) supplementation increased the BMD of children and adolescents with CD, but it did not reach the sex- and age-matched values for the control population [128]. Another study [129] suggested that the daily calcium intake for people with CD should be higher than the RDA because of latent malabsorption in many patients. Increased calcium intake could potentially compensate for the reduced fractional calcium absorption in treated adult patients with CD [95]. Multiple forms of calcium supplements are available [130]; medical conditions, such as lactose intolerance, impaired gastric acid secretion, and high-risk for kidney stone formation, should be taken into consideration before selection of a calcium supplement. Currently, the dominant anions in the calcium supplement market worldwide are carbonate and citrate [131]. Calcium citrate is better absorbed than calcium carbonate, causing a greater rise in serum calcium and a greater fall in serum parathyroid hormone (PTH) [132,133]. Moreover, calcium citrate is absorbed regardless of gastric acidity; thus, individuals producing less gastric acids or taking drugs that lower acidity in the stomach, like proton pump inhibitors [134], H_2 blockers, antacids, and anticholinergics, may utilize this salt form optimally.

Finally, in some special situations, such as severe osteoporosis, it might be useful to begin treatment with hormone replacement therapy (in postmenopausal women) or bisphosphonates; however, there are no systematic data on the efficacy of bisphosphonates or other drugs commonly used for osteoporosis in patients with CD [70]. Additionally, a well-balanced diet and consumption of dairy products or alternatively low-/free-lactose products need to be encouraged; education on the importance of lifestyle changes, such as regular exercise, smoking cessation, and excessive alcohol intake should be provided; and a dietitian must be part of the health care team to monitor the patient's nutritional status and compliance of a balanced diet.

Conclusions

The reviewed studies allow one to conclude that bone alterations need to be considered as a sign of atypical CD presentation, especially in adults. Recognizing CD, it's possible connection with osteoporosis, and related fractures should always be taken into account. The investigation on increased/corrected calcium intake, the use of vitamin D metabolites, and the drugs commonly given for primary osteoporosis are required.

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