Osteoporosis in Celiac Disease

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Impaired bone mineral density (BMD) is a frequent complication of adult-onset celiac disease (CeD). This is usually due to malabsorption of nutrients, changes in bone metabolism in association with inflammation, and to a lesser extent, decreased overall physical health and mobility. Optimal dietary treatment and an adequate supply of calcium and vitamin D are the cornerstones for the reduction in fracture risk in patients with CeD. In adults with low BMD or fragility fractures, CeD needs to be considered and specifically approached. When osteoporosis is documented, start treatment with an antiresorptive agent; these agents are proven to result in a long-term reduction in fracture risk in high-risk individuals. In patients with persisting diarrhea and malabsorption, parenteral medications may be preferable.

celiac disease osteoporosis bone mineral density prevention malabsorption

1. Celiac Disease

Celiac disease (CeD) is a life-long gluten-related enteropathy triggered by gluten ingestion in susceptible subjects. [1][2]. Genetic background is an essential prerequisite for the development of the disease (HLA-DQ2/DQ8 positivity and non-human leukocyte antigen (HLA) genes), but the contribution of other non-genetic factors such as viral infections and gut dysbiosis might also be important [3][4]. It has been suggested that gut permeability and dysbiosis play a key pathogenic role in CeD through an impaired expression of zonulin.

CeD is considered a global burden since its prevalence reaches almost 1% worldwide, making it one of the most common autoimmune disorders [5]. CeD is diagnosed in females 2–3 times more often than in males. The diagnosis of CeD may be made at all ages, even in the elderly; more than 70% of cases are diagnosed above the age of 20 years [6].

Although CeD is readily treatable with a gluten-free diet (GFD), patients need a structured follow-up to detect and avert long-term complications and achieve a good quality of health.

Non-adherence to a GFD is a notable cause of continuing gut inflammation and a decrease in quality-of-life [7]. The spectrum of CeD symptomatology is broad, ranging from asymptomatic disease detected at screening to a clinical condition characterized by wasting, undernutrition and steatorrhea to several selective deficiencies of nutrients, potentially resulting in extra-gastrointestinal features such as impaired bone mineral density (BMD) and vertebral and non-vertebral fractures [5].

CeD has a benign course in the majority of patients; however, almost <0.5% of adult celiac patients are refractory to GFD. Severe malnutrition, nutritional deficiencies and impaired bone health are regularly found in this subgroup [8].

2. Osteoporosis in Celiac Disease

Osteoporosis is a skeletal disorder characterized by reduced BMD, deteriorated microarchitecture, and reduced strength of bone, with susceptibility to fragility or low-impact fractures [9][10]. Generally, osteoporosis remains an underdiagnosed and undertreated condition, which represents a substantial health care problem [11]. There are high annual direct costs of osteoporosis and the mortality following a hip fracture in the elderly is as high as 24% [12]. Pelvic and/or humeral low-energy fractures are frequent in association with osteoporosis and contribute to high rates of morbidity and mortality [13]. Psychosocial complaints, in particular depression, are usual consequences of fracture, because of pain, limitation of physical activities, and deprivation of independence. About, 60% of survivors of hip fractures do not attain a pre-fracture level of physical independence, and 20% of them will be nursing home residents. Therefore, timely diagnosis of osteoporosis and taking measures to prevent fractures are vital to decreasing mortality and preserving the independence of people at risk for fragility fracture [14].

Osteoporosis might be the sole presentation of undiagnosed CeD without gastrointestinal symptoms or even detected later in the course of the disease [15][16][17]. The prevalence of osteoporosis in adults diagnosed with celiac disease is highly variable, probably depending, among other factors, on the severity and the duration of the condition when diagnosed. Decreased BMD is reported in >50% of newly diagnosed adult celiac patients [16]. CeD is found to be associated with decreased BMD in children and adults and is a recognized risk factor for osteoporotic fractures in men aged ≥40 years [18]. A meta-analysis by Ganji et al. reported an osteoporosis prevalence of 14.4% in CeD and 39.6% in osteopenia [18].

Studies, on the other hand, have found an increased prevalence of CeD in people with low BMD [19][20]. An appropriate estimation of CeD prevalence is 2–3% in those individuals with low BMD, in comparison with about 1% in the general population.

Multiple skeletal sites are affected by low BMD in CeD, particularly the neck of the femur and the lumbar spine. The trabecular bones are usually the sites of bone deterioration as compared to the cortical bone, which is less metabolically active [21]. CeD women have lower BMD and abnormal bone microarchitecture in comparison with non-celiac premenopausal women of similar age, body mass index, ethnicity, and race [22].

Celiac disease-related osteoporosis is associated with being underweight, age over 45 years, and male gender (in those younger patients) [23]. It is also with more severe intestinal histopathological changes [24].

Low BMD in pediatric celiac patients responds to GFD [25]. The same might be seen in adults after adequate treatment with GFD [25][26].

The change in BMD seems to happen particularly in the first year after starting a GFD [27]. In a prospective study, Newnham et al. [27] showed that bone mass improved in celiac patients over the first year after starting GFD and the degree of improvement was related to the T-score measured at diagnosis. The change was seen in those patients having osteopenia or osteoporosis, but no change was witnessed in those with normal BMD. Positive BMD changes improved the classification in 14% of individuals, with a shift from osteoporosis to osteopenia and then to a BMD in the normal range. At the assessment five years later, the changes were still significant. Therefore, mucosal improvement and healing as a consequence of adherence to GFD are linked with continuing improvement of the reduced bone mass. However, there is an important variability in response between individuals, and in most cases, BMD does not achieve normality. This is not unexpected because about 97% of peak bone mass is gained in the first two decades of life [28][29].

Studies dealing with the assessment of fracture risk in CeD patients had conflicting outcomes, depending on the duration of follow-up, degree of dietary compliance, analysis of fracture history, and mucosal status. In patients with CeD, the fracture risk varied from 1.3 to 10-fold more than that in the general population [30][31][32][33][34].

Jafri et al. [17] studied long-term fracture risk in CeD and reported that CeD is associated with an increased fracture risk both before and after diagnosis. Before the diagnosis, the fracture rate is twice that of controls, and the rate is 2.5-fold greater after the date of diagnosis. This applies to both appendicular and axial fractures.

Ludvigsson et al. [35] concluded that CeD was associated with subsequent hip fracture (hazard ratio = 2.1; 95% confidence interval (CI) = 1.8–2.4) and fractures at all sites (hazard ratio = 1.4; 95% CI = 1.3–1.5). This increased risk remains even 20 years after the diagnosis of CeD.

One study reported a 0.38% prevalence of biopsy-proven CeD in patients with fractures; 0.19% of them had a new CeD diagnosis. This lies within the range of prevalence in the Western European population (0.33–1.5%) [36].

3. Physiology and Pathophysiology of Alterations of Bone Health in Celiac Disease

The pathophysiology of decreased bone mineral density in CeD is multifactorial, including local and systemic mechanisms [21]. These can be summarized as follows:

Mucosal villous atrophy in CeD causes decreased calcium absorption, resulting in hypocalcemia and consequently secondary hyperparathyroidism [37]. The latter stimulates osteoclast-mediated bone resorption; which may lead to osteopenia or osteoporosis. Parathyroid hormone (PTH) is essential for the maintenance of serum calcium levels within narrow limits by actions on the kidneys and bone, and also by effects on the gastrointestinal tract. PTH is released tonically in a pulsatile fashion by the parathyroid gland. One of the important mechanisms through which PTH regulates calcium homeostasis is related to its stimulatory role in bone remodeling. PTH stimulates both bone resorption and formation, with the final outcome depending on the dose and periodicity of the PTH signal. Continuous PTH release has catabolic effects on the skeleton; on the other hand, intermittent PTH doses have an

anabolic effect [38]. Vertebral fractures are common in hyperparathyroidism, even at higher BMD than in patients with osteoporosis. This might be explained by microarchitectural changes caused by the parathyroid hormone, which cannot be detected by BMD measurement [39].

Magnesium deficiency, which may occur in gluten-sensitive enteropathy, is known to impair the secretion and action of parathormone, resulting in osteopenia and increased skeletal fragility [40].

Concomitant hypogonadism, low insulin growth factor-1, zinc deficiency, and malnutrition contribute to bone loss by increasing bone resorption.

Systemic, chronic, low-grade inflammation: In CeD, there is a low-grade systemic inflammatory response with hypersecretion of inflammatory cytokines. These cytokines increase bone resorption and promote bone loss [41][42]. Furthermore, hypovitaminosis D is found to often be associated with systemic low-grade inflammation [43].

Tissue transglutaminase, a key immunological component in CeD, might be an important factor in bone metabolism by regulating receptor activator of nuclear factor kappa B (RANKL) and the differentiation of osteoblasts [44]. More research work is needed to explore this hypothesis.

Vitamin D contributes in many ways to bone mineralization, predominantly by maintaining calcium and phosphate homeostasis. It regulates intestinal calcium intake through the vitamin D receptor.

Vitamin D is activated by the renal enzyme 1-alpha-hydroxylase upon stimulation by PTH. In CeD, this process will lead to an increase in intestinal absorption of calcium by an increase in vitamin D-dependent active calcium transport [45][46]. Paradoxically, high levels of 1,25-vitamin D may cause bone resorption. Vitamin D_3 (cholecalciferol) is the principal vitamin D from dietary sources, present mainly in foods of animal origin. However, the majority of vitamin D_3 (estimated at 80%) is from endogenous production by the action of ultraviolet light on the skin. Diet may contain 25-hydroxy cholecalciferol ($25OHD_3$) and also small quantities of dihydroxy cholecalciferol ($1,25(OH)_2D_3$) [46].

At low dietary concentrations, vitamin D uptake is principally protein-mediated, but there is also passive absorption when vitamin D is given at pharmacological doses [47]. The absorption of vitamin D is reduced in the presence of villous atrophy, in part due to the malabsorption of fat. Furthermore, fatigue and decreased activity, coinciding with a diminished nutritional condition, may result in decreased sun exposure with consequent vitamin D deficiency [16].

Calcium homeostasis is controlled by hormones (parathyroid hormone PTH, 1,25-dihydroxyvitamin D, and calcitonin) and organs: the small bowel, which regulates absorption; bone, which serves as a calcium reservoir; and the kidneys. When blood calcium concentration decreases, there will be a rapid increase in PTH release that promotes bone turnover and cortical bone loss. Thus, calcium malabsorption in CeD plays a pivotal role in the induction of a series of events that lead to bone demineralization. Hyperparathyroidism is frequent and should be detected in newly diagnosed patients as it is responsible for the acceleration of bone turnover. Calcium

malabsorption is a consequence of steatorrhea, deficiency of vitamin D and defective vitamin D-dependent calcium absorption [45].

Deficient BMD in CeD may occur independently of gastrointestinal symptoms [48][49]. Additionally, at diagnosis, the severity of the histopathological changes could predict the occurrence of low BMD, which carries a risk of developing osteoporosis if left unaddressed [24][50].

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