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Gut-bone Cross Talks and Implications in Celiac Disease

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Abstract Metabolic bone disease is a frequent extra-intestinal co-morbidity in newly diagnosed, mostly adult patients who have 70% low bone mineral density. Musculoskeletal signs and symptoms, osteopenia, osteoporosis and fractures are the most frequent manifestations. The etiology is multifactorial, however, micronutrient malabsorption, mainly of calcium and vitamin D, secondary hyperparathyroidism and inflammation are the main driving forces. The diagnosis is based on signs and symptoms, biochemical and endocrinologic laboratory evaluation and imaging by dual x-ray absorptiometry. Treatment of low bone mineral density in CD comprises: a gluten free diet, coverage of nutritional deficiencies (including calcium and vitamin D), changes in life style and if necessary, pharmacologic and hormonal replacement therapy. The cost effectiveness of those therapy methods were barely assessed. Understanding the pathophysiology of bone loss in celiac disease might bring new therapeutical strategies for the patient's benefit.

Keywords: *celiac disease, bone, osteopenia, osteoporosis, calcium, vitamin D, mineral density*

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1. Introduction

1.1. Celiac Disease

Celiac disease (CD) is a life-long autoimmune condition [1] mainly of the gastrointestinal tract, affecting the small intestine of genetically susceptible individuals. Gluten, which is the storage protein of wheat and its alcohol soluble gliadins are the offending inducers of the disease and together with structurally related molecules are found in barley and rye. Nevertheless, environmental factors like infections might play a role in CD induction [2]. Many additional factors were suggested: breast feeding, time and amount of gluten consumption, intestinal permeability, the microbiome/dysbiome, mode of delivery, early vaccination or early consumption of antibiotics and geoepidemiological influences [3,4,5,6,7]. However, cause and effect relationships are far from being elucidated. Tissue transglutaminase (tTG) is the autoantigen against which the abnormal immune response is directed to [8,9] and the two main auto antibodies, anti-endomysium and anti-tTG, are the most useful serological markers to screen for the disease [10,11]. Recently, two additional autoantibodies, namely antideaminated gliadin peptide and anti-neo-epitope tTG, were found to be reliable for CD screening [12,13,14]. As yet, HLA-DQ2 and HLA-DQ8 molecules are the most important known predisposing genetic factors. A lot is known on the pathogenesis of the disease. The sequential chain of events operating in the disease was recently unraveled and gives hope for future therapeutic strategies [15]. Furthermore, its epidemiology, prevalence, and clinical presentation are changing constantly, and with time, new clinical presentations are depicted and widen the plethora of clinical variability of CD [16]. It has been shown that the classical intestinal clinical picture is disappearing, and the extra-intestinal presentation is emerging. Skin, endocrine, hepatic, skeletal, rheumatic, geriatric, hematological, gynecological, infertility, dental, hypercoagulability, cardiac, and behavioral abnormalities are often described [16-22]. With the growing awareness of family practitioners, hematologists and gastroenterologists, and now gynecologists and neurologists, and other subspecialties, the diagnosis of CD is increasingly being made during the whole life-span. In fact, about 20% of newly diagnosed cases occur in patients who are older than 60 years of age. One of the growing domains is the extra-intestinal presentation of CD affecting the bone, presenting as osteopenia or osteoporosis, fractures, and falls [23-33]. The present review will concentrate, expand and update on the multiple faces of the gut-bone axis in celiac disease.

1.2. Skeletal Health Physiology

Bone homeostasis involves multiple but coordinated cellular and molecular events [34]. It is a dynamic tissue that undergoes continual adaption during vertebrate life to attain and preserve skeletal size, shape, and structural integrity and to regulate mineral homeostasis. Two processes, remodeling and modeling, underpin development and maintenance of the skeletal system. The two main types of cells responsible for bone metabolism are: osteoblasts (which secrete new bone), and osteoclasts (which break bone down). The structure of bones as well as an adequate supply of calcium requires close cooperation between these two cell types and other cell populations (osteocytes, hematopoietic precursors, macrophages, T-cells, natural killer cells and adipocytes) present at the bone remodeling

sites, or in the bone marrow space. [35] Bone metabolism relies on complex signaling pathways and control mechanisms to achieve proper rates of growth and differentiation. These controls include the action of several hormones, including parathyroid hormone (PTH), vitamin D, growth hormone, steroids, and calcitonin, as well as several bone marrow-derived membranes and soluble cytokines and growth factors like M-CSF, RANKL, decoy receptor inhibitor osteoprotegerin, VEGF, IL-6 family, cardiotrophin-1, sphingosine-1-phosphate and ephrinB2. The process is regulated by mechanically-induced stressors. In this way the body is able to maintain proper levels of calcium required for the above mentioned physiological processes.

Subsequent to appropriate signaling, osteoclasts move to resorb the surface of the bone, followed by deposition of bone by osteoblasts. Together, the cells that are responsible for bone remodeling are known as the basic multicellular unit, and the temporal duration of the BMU is referred to as the bone remodeling period [36].

Before delving into CD, defining the major bone density abnormalities is worthwhile.

Osteoporosis involves a reduction in bone mass below -2.5 standard deviations of peak bone mass. Osteopenia is defined when those values are located between -1 to -2.5 SD. Severe osteoporosis exists when the lower bone mass is associated with fracture.

2. Epidemiology of Bone Abnormalities in CD.

The intestine plays a critical role in bone homeostasis in the normal population as well as in various gastrointestinal disorders, including CD. An increased prevalence of CD in the osteoporotic population was reported, and serological screening was recommended [37]. Others casted doubt on the association and opposed routine CD screening [38]. It is estimated that by the time childhood CD is diagnosed, one-third of affected children have osteoporosis, one-third have osteopenia and only the remaining third retain a normal BMD [39]. Once the gluten free diet is instituted, most of them accelerate their rate of bone mineralization, so that most achieve normal peak bone mass by the time bone growth is completed. An opposite situation exists in adulthood once the peak bone mass has been achieved. Among these adult CD patients, the prevalence of osteoporosis is at least twice that of the unaffected population in the same age range [39,40]. More than half of asymptomatic coeliac patients with positive serological and digestive tract markers may have bone disease at the time of diagnosis [39,41]. This even includes those with minimal to moderate intestinal damage, stages 1 and 2 of the revised Marsh classification criteria. A recent literature review reported low BMD affects up to 75% celiac patients, independently of the serological status or digestive symptomatology [39]. Due to substantial differences in the experimental designs, a wide variability in the frequency of low BMD in CD exist. However, it is clear that increased prevalence exists in celiac patients, compared to the general adult population, which generally range around 40% [39]. Due to this common complication of CD, the question of screening the celiacs for BMD or the osteoporotic for CD serology, is apparent. Despite a lack of definitive consensus, most of the opinion-leaders and societies favor screening the adult osteoporotic populations. It should be noticed that the frequency of CD is 10x higher than expected in the later ones. A most recent study recommended not to routinely screen patients with idiopathic osteoporosis for CD, unless celiac or gastrointestinal related symptom exist [42]. Even in postmenopausal women, there is no justification to routinely screen for CD [43,44].

3. Etiology and Pathogenesis of Low BMD in CD

Table 1 summarizes the etiologies of low BMD in the CD patients.

Table 1. The etiologies of low BMD in the CD patients (Adapted from reference [39,45]) GFD-gluten free diet, BMI-body mass index.

Mechanism	etiology	Parameters
Pathological	malabsorption	Proteins, Calcium, Vitamins: D, A, K, E, C, B12, folic acid, B6. Trace elements: Fe, Ca, P, Cu, Zn, Boron, Fluorine
Endocrine	Hyperparathyroidism	secondary
Nutritional	Lower intake, GFD	Dairy products, lactose
inflammatory	Pro inflammatory mediators	TNF-α, IL-1-β, IL-6, ϒINF, RANK, RANKL, osteopreotegerin.
Risk factors:		
epidemiological	Advanced Age, reduced BMI, drugs	Decreased bone density
Genetic	Family history	Allele IL1B-511T
Life style	Smoking, low physical activity, increased alcohol consumption	
endocrine	menopause	Woman>50y

The main mechanisms underlying low BMD in CD are osteomalacia due to calcium and vitamin D malabsorption and secondary hyperparathyroidism, resulting in inadequate bone deposition and net loss.

Several discrepancies should be addressed. As mentioned, at least in children, GFD can reverse the bone abnormalities associated with CD. On the other hand GFD is low in vitamins and minerals [46,47]. Surveying CD children in Brazil, Sdepanian VL et al reported that 76% to 88% of children and 85% of adolescents with CD adhering to a GFD have inadequate calcium intake. Additionally, naturally gluten-free products are often low in calcium, iron, zinc, magnesium, vitamins B and D and fiber. Very few gluten-free products are enriched in

calcium as their wheat containing counterparts [45]. The second debatable question is the routine supplementation of calcium and vitamin D, in view of their contribution to the etiology. A recent review on the subject recommended that due to the fact that exclusion of gluten from the diet does not always normalize bone mineral density, in these cases, supplementation of vitamin D and calcium is recommended [48]. We investigated vitamin D status in Israeli and Spanish CD children and their parents and concluded that it is not recommended to routinely supplement the children with vitamin D, since the problem of low BMD is an age dependent phenomenon. [31]. Being a "common denominator' of bone and the gut [45], calcium is an essential ion necessary to maintain the functionality of the circulatory, neuromuscular, endocrine, immune and the enzymatic systems. Despite its pivotal roles, calcium supplementation is not recommended routinely for CD patients unless, the intake or absorption are compromised or losses or bone pathologies are depicted.

4. Recommendations for Assessment and Follow up of Bone Health in CD Patients

There is no consensus or accepted policy between the professional CD associations, concerning assessment, diagnosis or follow-up of bone status in CD patients. Reality is more complex due to the multiple subspecialties involved in bone health. At least in the CD domain, gastroenterologists, nutritionists, dieticians, endocrinologists, gynecologists, orthopedics on one hand and internal medicine, general practitioners, pediatricians and geriatric physicians, on the other hand, are involved. Due to the complexity and the multifaceted reality, the position statement, published in the Can J Gastroenterol, in 2012 is exposed [49]. For clarity and simplicity, only level I of evidence (at least one properly conducted randomized controlled trial, systemic review or meta-analysis), is mentioned (Table 2). The bone mineralization bio-markers, serological markers and imaging technics that can be used in the diagnosis of CD are summarized in Table 3.

Table 2. Recommendations for diagnosis and follow-up of patients with CD with regard to skeletal health (Adapted from ref [49]) CD-celiac disease, GFD-gluten free diet, BMD-bone mineral density, tTg-tissue transglutaminase, EMA-endomysial antibodies

Indication for	Clinical presentation	Timing	Test to perform
BMD testing	Adult classic CD	Following diagnosis	BMD measurement
	Asymptomatic/silent adult CD	One year on GFD	BMD measurement
	Asymptomatic/silent adult CD	>1 year after diagnosis if:	Peri/postmenopausal Men>50 years Family history of fractures High titer of Cd serology GFD non-adherent children
BMD follow-up, adults	If oesteopenic/porotic at diagnosis	1 year on GFD	BMD measurement
Biochemical assessment and follow-up	CD serology as indicator of intestinal damage		IgA-tTg, IgA-EMA

Table 3. The bone mineralization, serological markers and imaging that can be used in the diagnosis of CD. (Adapted from [13,14,32,45,49,50]). PTH-parathyroid hormone, DXA-dual x-ray absorptiometry, tTg-tissue transglutaminase, DGP-delaminated gliadin peptide, EMA-endomysial antibodies.

Category	Parameter
Endocrine	PTH
Biochemical	25(OH)D_3
	Bone-specific alkaline phosphatase
	Calcium correlated to albumin
	Osteocalcin
	Carboxy-terminal propeptide of type I collagen
	Urinary collagen cross links
	Urinary hydroxyproline
Serological	IgA-tTg, IgA-EMA, anti DGP, anti neo-epitope tTg
	osteoprotegerin autoantibodies
Imaging	DXA
	Bone quantitative ultrasound

5. Therapy for Bone Loss in CD

5.1. Gluten Free Diet

GFD is very effective for bone health when CD was diagnosed during childhood or adolescence, but the compliance for the gluten restrictive diet is age dependent, to the point that more than 50% of adults don't adhere [15]. Pediatric longitudinal studies reported that after 1 y on GFD, BMD became normal [51,52]. On the contrary, despite being the most rational treatment in adult CD, GFD rarely normalizes BMD [45,53]. Therefore, the nutritional options should considered to improve BMD.

5.2. Nutritional Supplementations

The nutrient supplementations in question are calcium and vitamin D. There are few studies performed on the cost effectiveness of such therapy to improve BMD in the CD patients. In post- menopausal women it failed, while partially effective in pediatric CD patients [54,55].

5.3. Hormonal Therapy

Facing a situation of severe or complicated osteoporosis, hormonal replacement therapy, especially for post-menopausal women, estrogens should be considered. Most recently, transdermal estradiol has been shown to increase bone mineral density, in post-menopausal women. Safety studies of transdermal estradiol have shown a decreased risk in cardiovascular disease as compared with oral estrogen therapy [56].

5.4. Pharmaceutical Therapy

Bisphosphonates have been found to be useful in post-menopausal osteoporosis and secondary hyperparathyroidism,

but it is not clear whether bisphosphonates are useful in younger CD patients with low BMD. Lately, administration of zoledronic acid (bisphosphonate) was not found to be better than GFD alone in increasing BMD in CD patients with low BMD in a pilot study [57].

5.5. Lifestyle Modifications

Several behavioral suggestions in life style can be offered to the low BMD, CD patients. A well balanced diet with adequate dairy, lactose containing products, can enhance calcium intake and absorption. Adapting a daily exercise program, smoking cessation, decreased alcohol consumption, can be beneficial. Above all, as in other extra intestinal manifestations of CD, increased knowledge and education, integrated with a team work of professionals, including dietitian, is the name of the game.

6. Conclusions

It can be concluded that low BMD is a frequent extra-intestinal manifestation of CD, mainly in adults and in post-menopausal woman. Like most of the asymptomatic or hyposymptomatic or vague presenting symptoms of childhood CD, bone abnormality remains unnoticed, unless looked for. The early detection of a low BMD is potentiated since it is completely/partially reversible early/late in life, respectively. GFD with adequate nutrition to cover the nutritional deficiencies, with dairy products and supplementation with calcium and vitamin D, when needed, increase the probability to improve BMD, thus avoiding unnecessary skeletal complications.

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