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POINT OF VIEW

Bone mineral density in adult coeliac disease: An updated review

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ABSTRACT

Introduction and objectives: coeliac disease (CD) affects around 1-2 % of the world population. Most patients are now diagnosed when adults, suffering the consequences of an impaired bone mineralization. This review aims to provide an updated discussion on the relationship between low bone mineral density (BMD), osteopenia and osteoporosis, and CD.

Methods: a PubMed search restricted to the last 15 years was conducted. Sources cited in the results were also reviewed to identify potential sources of information.

Results: low BMD affects up to 75 % of celiac patients, and can be found at any age, independently of positive serological markers and presence of digestive symptoms. The prevalence of CD among osteoporotic patients is also significantly increased. Two theories try to explain this origin of low BMD: Micronutrients malabsorption (including calcium and vitamin D) determined by villous atrophy has been related to secondary hyperparathyroidism and incapacity to achieve the potential bone mass peak; chronic inflammation was also related with RANKL secretion, osteoclasts activation and increased bone resorption. As a consequence, celiac patients have a risk for bone fractures that exceed 40 % that of matched non-affected population. Treatment of low BMD in CD comprises gluten-free diet, calcium and vitamin D supplementation, and biphosphonates, although its effects on CD have not been specifically assessed.

Conclusions: up to 75 % of celiac patients and 40 % of that diagnosed in adulthood present a low BMD and a variable increase in the risk of bone fractures. Epidemiological changes in CD make bone density scans more relevant for adult coeliacs.

Key words: Coeliac disease. Osteoporosis. Osteopenia. Bone mineral density. Densitometry.

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INTRODUCTION

A low bone mineral density (BMD) constitutes the first diagnostic criterion for osteoporosis, a skeletal metabolic disease further defined by impaired bone microarchitecture, increased bone fragility and susceptibility to bone fractures. The availability of bone density scan as a non-invasive diagnostic technique uncovered the link between this bone disorder and coeliac disease (CD) relatively few years ago (1,2). By contrast, the association between child osteomalacia and CD has been known since the first descriptions of the latter disease, even before the origin and treatment of CD itself were known (3). Osteomalacia is a disease characterized by low BMD, marked bone deformities and rickets, which, on rare occasions, is part of the initial presentation of CD (4,5).

CD is a highly prevalent disease (6) that affects around 1 % of the world population according to serology-based screening studies (7). While CD has been traditionally considered a childhood-onset disorders predominantly, it is now conclusively demonstrated that most patients are diagnosed when adults, as also corroborated in our country (8,9), among whom both atypical manifestations and a low suspicion index may delay the diagnosis (10). In fact, most CD sufferers are undiagnosed, and women are more frequently diagnosed than men. Many current CD patients lived with their symptoms for years before diagnosis, and were therefore exposed to the consequences of the disease. Furthermore, osteoporosis presents characteristics similar to those of CD in terms of frequency and underdiagnosis. It has been hypothesized that CD could explain part of the considerable "mixed bag" represented by idiopathic

osteoporosis (1,11-13) Therefore, a high rate of suspicion among health professionals treating both diseases (CD and osteoporosis) and using their best knowledge could bring many hidden cases to light, with the benefit of accurate and early treatment.

In adult patients, changes in bone mineralization, osteopenia or osteoporosis represent one of the most common complications of CD, and can affect up to 75 % of patients in some series (1) with a prevalence among coeliac sufferers that is double that of the unaffected population in the same age range (11). Despite this, and the many studies on the subject notwithstanding, a description of how CD - a primarily digestive disorder- can affect bone metabolism has yet to be fully elucidated.

CD in itself causes significant deterioration in quality of life (14-16), which is compounded by the presence of osteoporosis and its clinical manifestation as fractures. These and other factors are reasons for physicians to adopt an interventionist stance and try to prevent its occurrence and/or mitigate its impact.

OSTEOPOROSIS: DEFINITION AND GENERAL CONCEPTS

Osteoporosis is the most common metabolic bone disease. It involves a reduction in bone mass and is responsible for most fractures suffered by adults over 50. It is estimated that 1 in 3 women over 50 in Europe (17) and the United States (18) will suffer an osteoporotic fracture during their lifetimes. Although BMD is considered the major determinant of osteoporosis, there are additional factors that influence bone fragility, which, in recent years, have been brought together under the term "bone quality." These include microarchitecture, the degree of bone turnover, the build-up of lesions or microfractures and the degree of bone mineralization (19).

The World Health Organization establishes different degrees of low bone mass based on bone density scan measurements of any skeletal area in American Caucasian women (20). This strategy establishes a diagnosis of osteoporosis when bone mass values are below -2.5 standard deviations (SD) of peak bone mass (i.e. the maximum BMD value reached by an adult), and osteopenia when those values are located between -1 SD and -2.5 SD. Severe or established osteoporosis is that presenting with a BMD less than -2.5 SD and a current or past fragility fracture (18,21). The results of BMD measurements are expressed as a T-score, which is the number of standard deviations by which BMD measurement differs from bone density measurement in the young population ("peak" BMD) (Table I). Another way of expressing the results is the Z-score, which is obtained by comparing a BMD measurement with reference values for subjects of the same age and gender. It is recommended in some guidelines (22) for men and for premenopausal women.

Table I. World Health Organization (WHO) diagnostic criteria for post-menopausal Caucasian women

Diagnosis	*BMD criteria (T-score)*
Normal	BMD T > - 1 SD
Osteopenia or low bone density	BMD T < - 1 and > -2.5 SD
Osteoporosis	BMD T < - 2.5 SD
Severe osteoporosis	BMD T > - 2.5 SD + fracture

T-score: Comparison with BMD value in average reference population; SD: Standard deviation; BMD: Bone mineral density.

PREVALENCE OF OSTEOPOROSIS AMONG COELIAC DISEASE PATIENTS

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 (12). In any case, once the gluten-free diet (GFD) is instituted, most coeliac children catch up to their height-weight growth curve and accelerate their rate of bone mineralization, so that most achieve normal peak bone mass by the time bone growth is completed. The main problem arises when CD is diagnosed during adulthood, once bone growth is complete and peak bone mass has been reached. Among these patients, the prevalence of osteoporosis is at least twice that of the unaffected population in the same age range (11,23). More than half of asymptomatic coeliac patients with positive serological and digestive tract markers may have bone disease at the time of diagnosis (1,13,24-28). This even includes those without villous atrophy, that is, at stages 1 and 2 of the Marsh-Oberhuber classification for duodenal lesion.

Prevalence studies of bone mass loss among patients with CD reveal widely variable frequencies (2,24,29-36) (Table II); Valdimarsson et al. carried out a prospective study of 63 adult patients and noted a prevalence of

Table II. Studies of BMD in adult patients with coeliac disease before starting GFD (adapted from Scott, 2000) (31)

Parameter	*Mean weighted value*	*Number of studies (number of subjects included)*
Z-score, lumbar spine	-1.3	14 (490)
Z-score, hip	-1.1	7 (239)
T-score, lumbar spine	-1.7	1 (86)
T-score, hip	-1.4	1 (86)
% with lumbar osteoporosis	26	6 (212)
% with hip osteoporosis	11	3 (102)
% with lumbar osteopenia	41	4 (188)
% with hip osteopenia	43	3 (102)

osteoporosis of 22 % in the forearm, 18 % in the hip and 15 % in the lumbar spine (estimated on the basis of Z-scores) (37). Bardella et al. only documented low BMD among women diagnosed with CD during adulthood (38). Meyer et al. found low BMD in the lumbar spine in 38 % and in the hip in 44 % of the adult coeliac patients analysed (36). The wide variability in the frequency of low BMD in these studies may be explained by several factors, including the diagnostic criteria for osteoporosis (T or Z-score), the measurement method, the skeletal location where the measurement was obtained, patient selection, and whether assessment was performed before or after a GFD was started. In any case, the available data confirm a clearly heightened prevalence of low BMD among coeliac patients compared to the general population, which generally ranges around 40 %.

Low BMD has been demonstrated in patients with classic symptoms (14), in sub-clinical cases (39), and even in asymptomatic patients (29). Paradoxically, even greater impairment has been observed among patients without digestive symptoms than among those with classic symptoms (13). Therefore, the type of CD-related symptom does not seem to predict the presence of low BMD, which explains attempts to identify other determinants.

Osteoporosis is therefore a common complication of CD, which suggests that it is appropriate to consider whether or not to screen for CD in patients with idiopathic osteoporosis. Although there is no definitive consensus, the greater weight of opinion is in favour of this strategy (40-43), as the frequency of CD is 10 times higher than expected in patients with osteoporosis; in fact, a similar frequency of CD among type 1 diabetics already justifies universal screening among these patients (44). Moreover, CD screening through specific antibodies in patients with OS has led to diagnosis of between 4 (45) and 17 (43) times more coeliacs.

Results from studies where results were opposed to screen CD patients for osteoporosis can be explained due to the use of low-sensitivity antibodies; in fact, Legroux-Gerot et al. only measured anti-gliadin antibodies, while tissue anti-transglutaminase (AAtTG) was only determined in those with positive titres (46), a strategy that underdiagnoses CD. This same study established the AAtTG positivity threshold at 50 U/ml, well above the 2 U/ml threshold currently recommended for diagnosing adults (47). Other studies suffer from similar limitations: Mather et al. measured antiendomysial antibodies (48), Lindh et al. antigliadin (45), and the positivity threshold for AAtTG in Laadhar's research was set at 10 U/ml (42).

AETIOLOGY AND PATHOGENESIS OF LOW BMD IN CD

The pathogenic mechanisms underlying metabolic bone disease in patients with CD have not been fully elucidated. The origin of osteoporosis in CD has been classically associated with malabsorption caused by intestinal villous atrophy and poor absorption of calcium and vitamin D (49), as well as secondary hyperparathyroidism (50). Low consumption of dairy products (51), failure to ever reach peak theoretical bone mass (29,52-54), higher degree of duodenal injury in biopsies (55), and greater delay in diagnosis (23) have also been directly related to the pathogenesis of low BMD in coeliac patients.

We know that vitamin D deficiency is common among patients with CD, although there are no changes in the expression of vitamin D receptors (56) or a greater number of receptor gene mutations interfering with the metabolism of this vitamin (57) in this population. Restricted milk intake may exacerbate vitamin D deficiency; in fact, co-occurrence of lactose intolerance is common among coeliac patients, and is estimated at 10 %, but may increase to 50 % in presence of obvious symptoms of malabsorption (58-61). However, one must bear in mind that diet only provides 5-10 % of required vitamin D (62), with the rest being obtained from exposure to sunlight. Even so, studies of coeliac patients have failed to establish any clear association between vitamin D levels and bone impairment. This is also the case for other intestinal diseases, such as inflammatory bowel disease (62).

Several authors have suggested that deficits in other fat-soluble vitamins (A, K and E) and even water-soluble vitamins (C, B12, folic acid and B6) or minerals (such as iron, calcium, phosphorus, copper, zinc, boron, fluorine), which are all required for normal bone metabolism (55,63), also result from the intestinal malabsorption exhibited by coeliac patients.

Hyperparathyroidism is another implicated factor; even in patients with normal vitamin D serum levels, high PTH levels have been associated with bone mass loss (50). Indeed, coeliac patients on a GFD frequently exhibit high serum PTH levels (64). Reduced serum levels of IGF-1 (insulin-like growth factor-1 or somatomedin C) (65) constitutes an additional hormonal factor which has been involved in patients with a lower bone mass. This was associated with decreased serum levels of zinc (66), which normalized after introduction a GFD.

Despite the above, the malabsorption theory in and of itself has not been corroborated in some studies (55), while the complex regulation of bone turnover and the effect of the multiple nutritional factors involved, together with the discordant results of various studies, have led to the emergence of new hypotheses for the origin of osteoporosis in CD, such as the link between low BMD and chronic inflammation (67). Indeed, a less well-known function of vitamin D is its role in the activation of T lymphocytes that maintain the integrity of intestinal mucosal immunity, prevent infection (68) and regulate protein binding (69). Accordingly, vitamin D deficiency has long been considered a trigger of autoimmune and inflammatory diseases (70).

Chronic inflammation determines changes in bone metabolism via several proinflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), interleukins

(IL)-1beta, IL-6 or gamma interferon. TNF-related cytokines include the receptor activator of nuclear factor kappa-B (RANK), its ligand (RANKL), and osteopreotegerin (OPG). RANKL is a key molecule in the regulation of bone metabolism; its genetic expression is induced after activation of T lymphocytes and it is secreted by these cells. RANKL has proved to be a survival factor whose primary function is activation of osteoclasts, cells involved in bone resorption (71). Overproduction of RANKL is implicated in a variety of degenerative diseases of bone tissue, such as rheumatoid arthritis or psoriatic arthritis, while RANKL gene inactivation in mice produces severe osteopetrosis caused by a massive osteoclast deficit (72,73). Conversely, OPG (osteoprotegerin, "for bone protection") is an osteoclastogenesis-inhibiting protein, which acts as a decoy receptor homologous to RANK, binds to its ligand RANKL, and thereby neutralizes its action (74). OPG production is stimulated in vivo by oestrogens and by the anti-resorptive drug strontium ranelate (75). IL-6 promotes the expression of both RANKL and OPG, and stimulates both osteoblast formation and bone resorption.

Serum levels of RANKL and OPG are high in patients with CD (76), and the relative relationship established between these cytokines is therefore more important than their actual levels; hence, an imbalance in the OPG/RANKL ratio has been associated with altered bone turnover in patients with different conditions, including renal osteodystrophy (77), rheumatoid arthritis (78), Cushing's disease (79) and primary biliary cirrhosis (80). The OPG/RANKL ratio is directly associated with IL-6 serum levels (79) and lumbar bone mass (81). Thus, adult women with CD have OPG/RANKL ratios significantly lower than controls despite adherence to a GFD; this correlates with a lower lumbar BMD (82). Although the role of high OPG levels in CD has not been fully elucidated, the available evidence suggests that this is a protective mechanism against other factors that cause bone damage. The mechanisms described as direct activators of osteoclastogenesis and subsequent bone mass loss (83) have recently been recognized as potential contributors to osteoporosis among patients with a range of digestive diseases. In fact, patients with CD and inflammatory bowel disease have similar profiles in terms of expression of bone metabolism regulatory cytokines (84-86).

Finally, the aetiology of osteoporosis in CD of course includes factors shared with the rest of the population (87) (family history, age, menopause, physical activity, smoking), as well as other specific factors such as genetic influence, the above-mentioned vitamin deficiencies, hormonal changes and the inflammatory process itself.

Years of exposure to gluten in the diet before diagnosis do not appear to influence BMD significantly (29,35, 36,88,89) nor does early menopause (27). Some studies report an inverse relationship between GFD and calcium intake (90). There is little data on the influence of patient sex on BMD, but most studies show no difference in this respect (27,36,37,91,92). Another factor associated with poor bone condition is a low body mass index (BMI) (14,55,87,93). Patients with persistent villous atrophy despite proper adherence to the GFD (refractory CD) are particularly susceptible to osteoporosis, with a prevalence of 58 % compared to the 22 % reported among GFD-responsive patients (93).

DIAGNOSIS OF LOW BONE MINERAL DENSITY IN CD

All patients in whom there is clinical suspicion of osteoporosis should undergo a thorough history-taking and physical examination so as to identify other risk factors and/or consequences. As for imaging methods, conventional radiography has not proven to be a specific or sensitive method for assessment of changes in bone mass; therefore, osteoporosis studies should be performed using bone density scans. In the case of CD, it has been suggested that all patients diagnosed in adulthood should undergo bone densitometry (14,94), as it is a simple, non-invasive and highly accurate (95) diagnostic method (the margin of error is estimated at only 5-6 %). Its greatest benefit is determining whether there is osteoporosis and the degree of impairment, so that a treatment regimen can be planned. However, some studies, seeing the low risk of bone fracture among coeliac patients, have questioned the utility of routine bone density scan (31,96), as it is considered to have low cost-effectiveness. Other authors suggest using densitometry only in patients with digestive conditions (97), even though this is not a conditioning factor for greater risk (98). In fact, coeliac patients without gastrointestinal symptoms may have low BMD, which increases after start of the GFD (13). Recent studies advocate densitometric assessment in all coeliac patients diagnosed during adulthood who have villous atrophy on duodenal biopsies and/or laboratory values suggestive of malnutrition or malabsorption, regardless of their symptoms (55).

Another issue raised in the literature concerns the optimal timing for bone density scan in coeliac patients -whether at the time of CD diagnosis or after a period of adherence to the GFD. In fact, coeliac children show a great bone recovery capacity after starting a GFD, so no further studies seem to be necessary until their growth period is completed. In any case, the main benefit of BMD testing would be obtained when the introduction of a different treatment rather than the GFD alone are derived from test results.

As development of osteoporosis is determined by multiple risk factors, identifying which of these factors are most relevant, or using a score for the risk of fracture at 10 years, is highly desirable. Markers of bone remodelling (such as the N-terminal telopeptide of procollagen-1, hydroxyproline, and bone alkaline phosphatase) provide additional information on the dynamics of bone turnover that is complementary to densitometry findings. In coeliac patients with osteoporosis, levels of these markers are higher than in coeliacs with normal BMD (55). However, the usefulness

of their determination in the diagnosis of bone diseases is limited, so measurement is not recommended as part of the routine evaluation of patients with osteoporosis.

BONE FRACTURE RISK IN CD

Due to the increased prevalence of osteoporosis, coeliac patients have a high risk of fracture, estimated at between 3.5 to 7 times higher than that of the unaffected population of the same age and gender (14). Furthermore, up to one in four adult CD patients have an established history of fractures (99), which produces significant deterioration in quality of life.

As in other aspects of the relationship between CD and osteoporosis, quantification of fracture risk by different studies shows mixed results. These discrepancies are largely due to the way in which the data were collected -mainly from fracture reports, questionnaires, or hospital admissions. It is therefore possible that the prevalence of fractures (vertebral, hip, and overall) is underestimated in the coeliac population. One of the common issues of fracture risk studies is that they lack proper morphometric assessment of the spine, which underestimates fractures at that level (2), or failure to use validated questionnaires or methods, such as the FRAX® (Fracture Risk Assessment Tool) index proposed by the World Health Organization (100).

To date, nine published studies and one meta-analysis have estimated the incidence or prevalence of bone fractures in the adult coeliac population (31) (Table III). Their heterogeneous methodologies, use of different cut-off points for determination of osteoporosis, and variable diagnostic criteria for CD translate into significant discrepancies in results. A study conducted in Argentina on 165 coeliac patients retrospectively determined a prevalence of peripheral fractures over 3 times higher than that observed in controls (2). The same study showed that the highest prevalence of fractures in the lumbar spine was only present in patients with "classic symptoms" of CD (101). A retrospective study carried out in the UK showed that 21.3 % of coeliac patients had a history of fractures, compared with only 2.7 % of non-coeliac controls, a highly significant difference quantified as a relative risk (RR) of 7.0 (102). By contrast, other studies with large sample sizes in the same geographical region found no major differences (32). Two further researches in Europe, the first with a large number of patients, reported a slight increase in risk of fracture: a study of approximately 13,000 patients and 65,000 controls in Sweden showed a 2.1 % higher risk (95 %CI: 1.8-2.4) of hip fracture and a 1.4 % higher risk (95 %CI: 1.3-1.5) of any type of fracture among coeliacs (34). A recent study of adult coeliacs in Spain, conducted at the time of diagnosis, used the FRAX® tool to estimate the risk of fracture at 10 years. This showed a moderate risk of fracture among patients with duodenal villous atrophy (Marsh stage III), which was 3.5 times that of patients without villous atrophy (Marsh stage I or II) (55).

Finally, the Olmos et al. meta-analysis (104), which included 21,000 coeliac patients and about 100,000 controls, confirmed a 43 % increase in the prevalence of fractures among coeliacs (8.7 *vs.* 6.1 %).

TREATMENT OF LOW BONE MINERAL DENSITY IN PATIENTS WITH CD

The first-line treatment for osteoporosis in CD is GFD itself: Many studies have demonstrated its effect on bone density and calcium absorption (24,26,27,30,35,90-93,105-108). The greatest bone mass gain described in these studies is during the first year (27,37): GFD leads to a 5 % increase in bone mass after 1 year (1), although this is not enough for bone mass to normalise. In clinical practice conditions, the degree of adherence to the GFD also determines the recovery of bone mass, which is generally estimated at around 30 % (109,110). Furthermore, the recovery rate is higher in young coeliac patients (24) than among adults (24,37), which is largely explained by the fact that 97 % of bone mass is gained in the first two decades of life and full recovery is difficult after this time.

BMD loss associated with paediatric CD responds to GFD continuously and gradually, with almost complete restoration of bone mass after about two years' treatment (111). The earlier the age at which the GFD is started, the better and faster the response (29). In fact, it is estimated that an increase in BMD will only take place if the GFD is started before the age of 25 (49). Proper GFD is so important for bone metabolism that lack of improvement in BMD after its introduction has been associated with persistent duodenal lesions (14).

In addition to the GFD, and in accordance with the NIH consensus statement on the treatment of osteoporosis (18), adequate daily intake of calcium and vitamin D should be ensured, as it is a critical factor for bone mass acquisition and maintenance. Untreated adult coeliac patients have shown a 45 % reduction in calcium absorption followed by an improvement of 52 % after 6 months of GFD adherence (112). Regarding vitamin D, at the time of diagnosis, less than 5 % of Spanish adult CD patients had normal serum levels (55). A daily intake of 1,200-1,500 mg calcium and 800 U vitamin D is recommended, and as in all other forms of osteoporosis, this should be supplemented with medications. Adherence to drug therapy, as to the GFD, is a crucial aspect of treatment, so patients must be kept motivated. In fact, these patients will most commonly abandon treatment with calcium and vitamin D, as it must be taken daily, while hormonal therapy and bisphosphonates (which are administered weekly) are usually adhered to correctly (113). Drug treatment would be indicated for patients who do not achieve bone mass recovery goals, and would not differ from that established for other causes of osteoporosis, with bisphosphonates being the recommended first-line therapy. However, the literature is lacking in data on the specific effect of bisphosphonates on CD-associated osteoporosis.

Table III. Available studies on bone fracture risk in adult coeliac disease (adapted from Scott, 2000) (28)

	Country and year	*Study population*	*Design*	*Osteoporosis/fractures diagnostic methods*	*Fractures analysed*	*Risk of fracture*
Vasquez et al. (2)	Argentina, 2000	165 coeliacs and 165 controls with gastrointestinal symptoms	Cross-sectional with retrospective analysis	Dual energy X-ray densitometry, spine radiography	Peripheral Lumbar spine	OR 3.5 (1.8-7.2) OR 2.8 (0.7-11.5)
Fickling et al. (102)	UK, 2001	75 coeliacs with 75 controls matched by age and sex	Cross-sectional with retrospective analysis	Dual energy X-ray absorptiometry (DEXA) of lumbar spine and femoral neck	Any location	21 % among coeliacs, *versus* 3 % in controls
Thomason et al. (32)	UK, 2003	244 coeliacs born after 1950, 161 controls of the same age and sex	Analysis of coeliac population records. Controls paired for age and sex	Lifestyle and general health questionnaire, with specific questions about history of fractures	Any location Forearm	OR 1.05 (0.68-1.62) OR 1.21 (0.66-2.25)
West et al. (99)	UK, 2003	4732 coeliacs (1589 "incidents") and 23620 controls matched by age and sex	Population cohort study from a database	Codified registry of fractures in coeliacs and controls	Any location Hip Ulna, radius	HR 1.30 (1.16-1.46) HR 1.90 (1.20-3.02) HR 1.77 (1.35-2.34)
Moreno et al. (101)	Argentina, 2004	148 coeliacs and 292 controls of the same age and sex with gastrointestinal symptoms	Cross-sectional study of cases and controls	History of fracture based on interview with a predefined questionnaire	Any location	OR 5.2 (2.8 to 9.8) in "classic" CD OR 1.7 (0.7 to 4.4) in "asymptomatic" CD
Vestergaard et al. (34)	Denmark, 2002	1021 coeliacs and 3063 controls matched by age and sex	Computerized registry of all national hospital admissions and discharges	Diagnoses of fractures in cases and controls in the same national registry	Any Lumbar Distal radius (Colles) Neck of femur	RRI 0.7 (0.45-1.09) RRI 2.14 (0.70-6.57) RRI 2.00 (0.58-6.91) RRI 0.71 (0.27-1.89)
Davie et al. (103)	UK, 2005	383 coeliac women over 50 and 445 controls	Cross-sectional study using	Detailed questionnaire about history of fractures	Any location	OR 1.51 (1.13-1.5)
Ludvigsson et al. (34)	Sweden, 2007	13000 individuals with CD (4819 adults) and 65000 controls matched by age and sex	Cross-sectional population cohort study based on hospital discharge records	Records of 1st documented fracture at any location	Any location Hip	HR 1.4 (1.3-1.5) HR 2.1 (1.8-2.4)
García-Manzanares et al. (55)	Spain, 2012	40 patients with a diagnosis of CD in adulthood	Prospective cross-sectional	Dual energy X-ray densitometry, FRAX® tool	Risk of hip fracture Risk of major osteoporotic fracture (lumbar, femoral neck, forearm and shoulder)	3.5 times greater in Marsh III on I-II. 1.34 times greater in Marsh III on I-II

CD: Coeliac disease; OR: Odds ratio; RRI: Relative risk increase; HR: Hazard ratio.

CONCLUSIONS

CD has been associated with low BMD since its very first descriptions. Osteomalacia in children with CD is now an exceptionally rare finding; unfortunately, the same cannot be said for osteoporosis and osteopenia, which occur in 40 % of patients diagnosed in adulthood and determine a variable increase in the risk of bone fracture, leading to lower quality of life. Changes in the epidemiology of CD make low BMD screening by bone density scans more relevant for adult coeliacs. Subjects with villous atrophy or laboratory values suggestive of malnutrition at the time of CD diagnosis may derive greater benefit from bone density scan.

The gluten-free diet is also the basis of low BMD treatment among coeliacs, and is sufficient in younger patients. In adults with low bone mass, however, it must be supplemented with calcium and vitamin D. Although specific studies are lacking, bisphosphonates might also provide an effective first line of treatment for adult coeliac patients with osteoporosis.

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