

Evaluation and management of skeletal health in celiac disease: Position statement

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OBJECTIVE: To review the evaluation and management of skeletal health in patients with celiac disease (CD), and to make recommendations on screening, diagnosis, treatment and follow-up of low bone mineral density (BMD) in CD patients.

METHODS: A multidisciplinary team developed clinically relevant questions for review. An electronic search of the literature was conducted using the MEDLINE and EMBASE databases from 1996 to 2010. All original studies, reviews and guidelines, both pediatric and adult, were included. A document summarizing the results of the review and proposed recommendations was prepared and underwent multiple revisions until consensus was reached.

RESULTS: At diagnosis, approximately one-third of adult CD patients have osteoporosis, one-third have osteopenia and one-third have normal BMD. Children with CD have low bone mass at diagnosis. Adult and pediatric CD patients are at increased risk of fractures.

DISCUSSION: For adults, serum calcium, albumin, 25(OH) vitamin D₃, parathyroid hormone and 24 h urine calcium testing should be performed at diagnosis; patients with 'classic' CD and those at risk for osteoporosis should undergo a dual x-ray absorptiometry scan. An abnormal baseline dual x-ray absorptiometry scan should be repeated one to two years after initiation of a gluten-free diet (GFD). For children, BMD should be assessed one year after diagnosis if GFD adherence is not strict. A GFD is the most important treatment for bone loss. Supplemental antiresorptives may be justified in those who remain at high fracture risk (eg, postmenopausal women, older men) after implementation of a GFD.

CONCLUSION: Current evidence does not support the screening of all CD patients for low BMD at diagnosis. Follow-up BMD assessment should be performed one to two years after initiation of a GFD.

Key Words: Bone; Celiac disease; Osteoporosis

Celiac disease (CD) is an autoimmune enteropathy that occurs in genetically susceptible individuals (human leukocyte antigen [HLA]-DQ2 and HLA-DQ8) as a result of an immune response to gluten (1).

The clinical presentation of CD is heterogenous, ranging from the classic features of malabsorption, weight loss and steatorrhea, to clinically asymptomatic forms that probably represent two-thirds of CD patients today (2,3).

More than 10 years ago, Ferguson et al (3) likened the CD population to an iceberg, with only the tip visible over the waterline (the classically symptomatic patients), and the main body remaining underwater (the asymptomatic patients). Among the asymptomatic patients, silent cases are defined as those with abnormal mucosal changes on biopsy that return to normal on a gluten-free diet (GFD). Latent CD patients are defined as those with a normal jejunal biopsy but test positive for immunoglobulin (Ig) A endomysial antibody (EMA) and/or IgA-tissue transglutaminase (tTG) (4).

L'évaluation et la prise en charge de la santé squelettique en cas de maladie cœliaque : un document de principes

OBJECTIF : Analyser l'évaluation et la prise en charge de la santé squelettique des patients ayant une maladie cœliaque (MC) et faire des recommandations sur le dépistage, le diagnostic, le traitement et le suivi d'une faible densité minérale osseuse (DMO) chez des patients ayant une MC.

MÉTHODOLOGIE : Une équipe multidisciplinaire a préparé des questions pertinentes sur le plan médical à analyser. Elle a procédé à une recherche électronique des publications de 1996 à 2010, dans les bases de données MEDLINE et EMBASE. Toutes les études originales, les analyses et les lignes directrices, pour les groupes pédiatriques et adultes, en faisaient partie. Un document résumant l'information et proposant des recommandations a été préparé et modifié à de multiples reprises jusqu'à l'atteinte d'un consensus.

RÉSULTATS : Au diagnostic, environ le tiers des patients adultes ayant une MC présente une ostéoporose, un tiers, de l'ostéopénie et un tiers, une DMO normale. Les enfants ayant une MC ont une faible masse osseuse au diagnostic. Les patients des groupes pédiatriques et adultes ayant une MC sont plus vulnérables aux fractures.

EXPOSÉ : Au diagnostic des adultes, il faudrait vérifier le calcium sérique, l'albumine, la 25(OH) vitamine D₃, la parathyroïde et la calciurie des 24 heures; les patients ayant une MC « classique » et ceux qui sont vulnérables à l'ostéoporose devraient subir une absorptiométrie biénergétique à rayons X. Lorsque les résultats de départ sont anormaux, il faudrait reprendre cette absorptiométrie de un à deux ans après le début d'un régime sans gluten (RSG). Chez les enfants, la DMO devrait être évaluée un an après le diagnostic si la compliance au RSG n'est pas rigoureuse. Le RSG est le principal traitement de perte de densité osseuse. Des inhibiteurs de la résorption osseuse d'appoint peuvent être justifiés chez les personnes qui présentent un risque élevé de fracture (p. ex., femmes post-ménopausées, homme âgés) après la mise en œuvre du RSG.

CONCLUSION : Les données probantes actuelles n'étaient pas le dépistage de tous les patients ayant une MC afin de diagnostiquer une faible DMO. Une évaluation de suivi de la DMO devrait être effectuée de un à deux ans après le début du RSG.

The reported prevalence of CD has increased over the past 10 years; recent systematic reviews report a CD prevalence, measured by screening unselected populations of European ancestry, of nearly 1% (5), with similar figures reported in North America (6).

Fifty per cent of adults are diagnosed after 50 years of age (7), and population-based studies suggest that 50% to 90% of people with CD remain undiagnosed (8,9). Metabolic bone disease in CD patients has been reported in the literature for more than 70 years (10-12), with greater malabsorption leading to greater bone loss. Even subclinical or silent cases have lower bone mineral density (BMD) than healthy controls (13,14).

Many longitudinal studies have confirmed that BMD improves in adult patients who adhere to a GFD (13,15-19).

Given this information, the need for an evidence-based approach to the management of bone disease in patients with CD was recognized. Our objective is to provide recommendations on which CD patients should be screened for low BMD, the extent of biochemical

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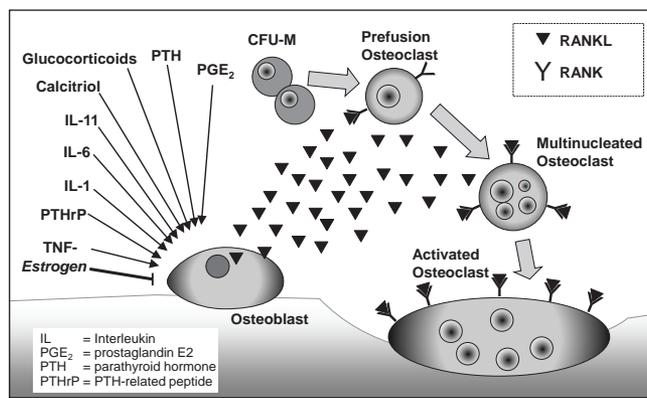


Figure 1 The pathogenesis of bone loss is attributable to increased bone resorption without sufficient corresponding bone formation and mineralization. This may be due to the following: increase in parathyroid hormone (PTH) levels; increase in inflammatory and immunological markers including interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-alpha; increase in the receptor activator of nuclear factor kappa (RANK)-B ligand (RANKL)/osteoprotegerin (OPG) ratio, which causes increased activation and differentiation of osteoclasts; and hypogonadism, particularly in women, with decreases in the levels of circulating estrogen, which also contributes to bone loss. CFU-M Colony-forming unit – Megakaryocyte

assessment that is necessary, appropriate follow-up and management based on BMD and fracture risk.

METHODS

A multidisciplinary team, including experts in gastroenterology, adult and pediatric endocrinology, metabolic bone disease, rheumatology and nutrition, developed key clinical questions addressing skeletal health in individuals with CD. The team reviewed the literature and addressed key clinical questions in optimizing skeletal health and reducing the risk of fracture. The work of the team was supported by the Calcium Disorders Clinic at St Joseph's Healthcare, McMaster University (Hamilton, Ontario).

The key clinical questions addressed were as follows:

- Which CD patients should be offered BMD tests?
 - All CD patients?
 - Only CD patients who have a high risk of fragility fractures?
- What is the role of more extensive biochemical assessment (eg, parathyroid hormone (PTH), 25-hydroxycholecalciferol (25[OH]D₃)?
 - Should it be offered to all CD patients?
 - Should it be offered only to CD patients with an abnormal dual x-ray absorptiometry scan (DXA)?
 - How extensive should the biochemical assessment be in assessing bone mineralization and adequacy of calcium, vitamin D and phosphate absorption (ie, include 25[OH]D₃, PTH concentrations and 24 h urine calcium)?
- How should CD patients be followed with respect to skeletal health?
 - If initial BMD is normal?
 - If initial BMD shows osteopenia or osteoporosis?
 - How frequently should the BMD by DXA be repeated?
 - How frequently should biochemical tests be repeated?
 - What is the relevance of strict adherence to a GFD for skeletal health?
- What treatments have been proven to prevent fractures in CD patients?

Data sources

An electronic search of the medical literature relevant to the key clinical questions was conducted using the MEDLINE and EMBASE databases from 1996 to 2010 without language restriction. The search strategy included the following terms: “celiac disease”, “osteoporosis”, “osteopenia”, “low bone mineral density (low BMD)”, “vitamin D”, “fractures”, “parathormone (PTH)”, “metabolic bone diseases”, “serological markers for celiac disease” and “bone markers”. References from relevant articles and clinical guidelines were also reviewed.

Study selection

All original studies, reviews and clinical guidelines potentially relating to skeletal complications of CD, and with the association between the severity of CD and biochemical and serological markers in both pediatric and adult populations, were considered for inclusion. If non-English language articles were selected, only the abstracts in English were reviewed; no studies were excluded based on design or methodological quality.

Data extraction

Fifty studies on BMD and fractures in CD patients were retrieved and summarized by the first author (MF) in the form of evidence tables, which were circulated to all of the team members. An additional 60 articles were reviewed, and a manuscript was drafted by the first author (MF) based on the information gathered and recommendations were proposed. The recommendations were graded according to the levels of evidence adopted from the Canadian Task Force on Preventive Healthcare (20) (Appendix 1). The draft was revised by each team member until consensus was reached.

RESULTS

What causes bone loss in CD?

Pathophysiological aspects: The main mechanisms underlying low BMD in adult CD are secondary hyperparathyroidism and osteomalacia due to calcium and vitamin D malabsorption (21). Markers of bone resorption, such as telopeptides of type I collagen, urinary collagen cross links and urinary hydroxyproline, are increased in the presence of secondary hyperparathyroidism. The resulting effect is net bone loss (13,17,22,23).

Bone health in youth with CD is determined by factors that influence both bone mineral accrual and bone loss. At the conclusion of puberty, growth of the skeleton and bone mass reaches its peak. Studies on bone metabolism in youth with CD indicate that the PTH-vitamin D levels are not affected (24,25). Similarly, serum levels of calcium and phosphate, when compared with laboratory reference ranges, are reported to be within normal limits (24,26). There are few pediatric studies that have measured markers of bone formation and bone resorption. Limited data indicate that depressed bone formation rates and enhanced bone resorption may contribute to reduced bone mass in children with CD (26,27).

Immunological and inflammatory changes also contribute to bone mass reduction (Figure 1). Production of proinflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumour necrosis factor-alpha, has been detected in the intestinal mucosa of adult CD patients (28), and increased serum levels of IL-1 and IL-6 have also been observed (29,30). In untreated adult CD patients, serum IL-6 levels correlate inversely with lumbar BMD (29) and directly with serum PTH and N-telopeptide of type I collagen levels (30). Along with decreased levels of the inhibitory cytokines IL-12 and IL-18, these cytokine imbalances cause bone loss by virtue of direct effects on osteoclastogenesis and osteoblast activity (31-33).

Untreated adult CD patients have been found to have an increased receptor activator of nuclear factor kappa-B ligand/osteoprotegerin ratio, leading to enhanced bone resorption secondary to increased formation, function and survival of osteoclasts (31). Clinical and subclinical hypogonadism in women can also contribute to bone loss (34,35). Similar findings have not been confirmed in men (30).

Bone mineralization and serological markers in CD: PTH levels

TABLE 1
Bone mineral density (BMD) in untreated celiac disease (CD) in published studies

Author (reference), year	Country	Study type	Participants, n	DXA site	Outcomes	Percentage with					
						Z score		Z score			Other results
					Mean	Median	≤-2.00	Osteoporosis	Osteopenia		
Molteni et al (68), 1990	Italy	Cross-sectional	22 CD children, 29 adults	SPX	Forearm BMD						Untreated children and young untreated adults had significantly lower BMD than controls (P<0.01)
Mora et al (54), 1993	Italy	Cross-sectional	33 CD, 255 control	Radial, BMC	BMC						BMC increased significantly after 1 year GFD
Mazure et al (14), 1994	Argentina		28	Lumbar	BMD, total skeleton			50			Symptomatic and treated had more bone disease than asymptomatic and treated patients
Valdimarsson et al (49), 1994	Sweden	Cross-sectional	288 CD, 13 persistent villous atrophy, 17 normal mucosa after 4 years GFD	SPX, DXA	Forearm, F						BMD reduced at all sites in patients with persistent villous atrophy
Corazza et al (22), 1995	Italy	Cross-sectional	17 untreated, 14 treated, 24 control	DXA	Total body		z-score significantly lower in untreated and lower in treated compared with control				PTH higher in untreated with lower 25(OH)D ₃ and higher 1,25 vitamin D ₃ as well as bone remodelling markers
Gonzalez et al (72), 1995	Argentina	Cross-sectional	20	Lumbar	LS, total skeleton	-2.5		70			All patients showed improvement in BMD and serum levels of bone indices and mineral metabolism
McFarlane et al (51), 1995	England	Case control, longitudinal	45 male, 10 female	DXA	LS, FN				47 male, 50 female		Lower BMI and lower calcium intake in the low BMD group
Pistorius et al (50), 1995	England	Cross-sectional	81 CD, 230 control	DXA	LS, FN						BM lower in LS and FN in CD group
Walters et al (55), 1995	England	Cross-sectional	34 CD treated, 10 new	Lumbar, F	LS, F	-1.85 (women), -0.95 (men)					Suboptimally treated and newly diagnosed more prone to have osteopenia
Corazza et al (13), 1996	Italy	Cross-sectional	14 silent, 10 classic	Lumbar, lumbar	LS	-1.3, -2.6		21, 80			In both groups vs control higher 1,25 vitamin D ₃ and lower 25(OH)D ₃ and higher levels of bone remodelling markers
Leiva et al (73), 1996	Chile	Cross-sectional	17 CD, (6-12 years), 48 control	DXA	LS, FN, total body						Lower bone mass in CD despite good compliance on GFD
McFarlane et al (15), 1996	England	Case control, longitudinal	21 CD, 21 control, mean age 27 years	Lumbar, F	LS, FN, biopsy done			43, 19			Significant gain in year on GFD, LS 16.6%, FN 15.5%
Rea et al (74), 1996	Italy	Case control	23 CD, mean age 4.7 years	Forearm	BMC, forearm	-0.76					Baseline z-score -0.76 with 0.71 change in 1 year
Valdimarsson et al (16), 1996	Sweden	Prospective cohort	63 CD, 680 control, mean age 53.5 years	LS, FN				14, 8			After 1-year treatment ↑LS 5%, ↑FN 8%

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TABLE 1 – CONTINUED

Bone mineral density (BMD) in untreated celiac disease (CD) in published studies

Author (reference), year	Country	Study type	Participants, n	DXA site	Outcomes	Z score		Percentage with			Other results
						Mean	Median	<-2.00	Osteoporosis	Osteopenia	
Bai et al (75), 1997	Argentina	Longitudinal	25 CD, 151 control, mean age 45 years	Lumbar	LS total body	-1.8 -2.2		56		72 LS 84 total skeleton	84% ↑BMD LS (mean ↑12% in first year)
Ciacci et al (19), 1997	Italy	Retrospective cohort	41 CD, mean age 34.3 years	Lumbar, F	LS, FN						↑14% in LS ↑10.4% in FN after GFD 1 year, pretreatment BMD predicted response to GFD
Corazza et al (18), 1997	Italy	Prospective case control	20 CD, 15 control	Lumbar, F	LS, FN	-2.0, -2.0					
Mautalen et al (17), 1997	Argentina		14	Lumbar	LS	-1.3		29		79	
Scotta et al (46), 1997	Italy	Cross-sectional	66 CD, 76 control	Lumbar							LS DXA was the only parameter influenced by age at diagnosis and duration of GFD. BMD LS significantly lower in early diagnosed patients and/or diet for <12 months
Fornari et al (29), 1998	Argentina	Longitudinal	16	Lumbar	LS		-1.6		44	19	
Mora et al (45), 1998	Italy	Longitudinal, cross-sectional	144 CD (2.58 -20.42) 177 control	Whole skeleton	LS total body						Lumbar spine and whole body BMD significantly lower at baseline and improves after 1 year with no difference from control
Di Stefano et al (76), 1999	Italy		16	Lumbar, F	LS, F	-1.70, -1.93		44, 38			
Kemppainen et al (56), 1999	Finland	Cohort	28, mean age 48.6 years (male); 44 years (female)	Lumbar, F	LS, F				33, 0	49, 54	BMD ↑ or remained stable in LS 69%, FN 67%. A high PTH found in 6 patients, normalized in 5 after 1 year
Kemppainen et al (36), 1999	Finland	Cross-sectional	77: 28 newly diagnosed 49 previously diagnosed	LS, FN	LS FN				26		35% had low BMDs for age at LS (compared with 17% controls), 31% had z score ≤ -1 at FN (compared with 16% controls)
Mora et al (27), 1999	Italy	Longitudinal cohort	30 CD, 240 control, mean age 11.4 years	LS, whole skeleton	Lumbar and total body						BMD normalized on GFD as well as bone turnover marker
Mustalahti et al (17), 1999	Finland	Cross-sectional	19 CD asymptomatic, mean age 45 years, 30 CD symptomatic, mean age 44 years	Lumbar, FN	LS FN						Significantly increased LS (8/19) and FN (10/19) in silent mean T-score LS -1.9 silent LS -0.9 FN; -1.1 symptomatic -0.8
Valdimarsson et al (77), 1999	Sweden		29	Lumbar	LS		-1.120				
Bardella et al (78), 2000		Case control	71 CD 142 control, mean age 27 years	Lumbar	LS						LS BMD significantly lower than control (0.9 g/cm ² vs 1.1 g/cm ²)
Di Stefano et al (52), 2000	Italy		21 silent 18 classic	Lumbar, F	LS, F	-1.1 silent, -2.5 classic, -1.2 silent, -2.5 classic					

TABLE 1 – CONTINUED
Bone mineral density (BMD) in untreated celiac disease (CD) in published studies

Author (reference), year	Country	Study type	Participants, n	DXA site	Outcomes	Z score		Percentage with			Other results
						Mean	Median	≤-2.00	Osteoporosis	Osteopenia	
Sategna-Guidetti et al (57), 2000	Italy	Longitudinal	8611 asymptomatic, mean age 29 years	Lumbar, LS, FN; F	LS, FN; biopsy done	-1.5, -1.8			26	40	83.7% ↑ by 1 year, ↑ 5.3% LS
Valdimarsson et al (37), 2000	Sweden	Prospective cohort	105 CD, 942 Control	Lumbar, LS; F	LS; T Hip; biopsy done		-0.72 -0.79				27% ↑ PTH with lower BMD and lower 25(OH) _D ₃ . Also more than one-half of those remained with low BMD and atrophic mucosa
Vazquez et al (62), 2000	Argentina		51	Lumbar	LS		-1.3				
Kalayci et al (79), 2001	Turkey	Prospective cohort	32 CD children, 82 control	Lumbar							Osteopenia found more in those with recent diagnosis than those started on GFD; one-year GFD was not enough in many to correct osteopenia
Meyer et al (44), 2001	USA	Prospective	128 mean age 56 years	Lumbar	LS and FN FN RA				34 27 36	38 44 32	
Mora et al (80), 2001	Italy	Longitudinal	19 CD, 211 control, mean age 14.2 years	LS,	whole skeleton						BMC, bone area and BMD improved with GFD as well as bone turnover markers
Carvalho et al (81), 2003	Brazil	Cross-sectional	30 CD (children + adolescents), 23 control	Lumbar	LS					38	BMD of adolescents lower than control but no difference in BMD of children vs control
Kavak et al (47), 2003	Turkey	Prospective cohort	62 CD, 64 control (children)								BMD lower in untreated vs treated and control. Untreated also had significantly higher PTH and lower serum calcium. GFD improved BMD in 1 year
Barera et al (82), 2004	Italy	Longitudinal	22 CD, mean age 10.5 years, 428 control, mean age 11.3 years								BMD significantly lower in untreated cases vs control and increased gradually over 1 year on GFD
Lewis and Scott (83), 2005	England	Case control	43 CD biopsy proven	Lumbar	LS; F		-0.26, 0.22 (women) -1.16 (men) 0.04 0.22 (women)- 0.43 (men)	5	14	40	
Pazianas et al (84), 2005	USA	Prospective cohort	24 CD male, 20 control	Not stated	LS whole body trochanter						BMD significantly lower in treated vs control with inverse correlation between PTH and FN or whole body BMD as well as PTH and duration of GFD
Deressa et al (85), 2006	Norway	Case control	118 CD, median age 42.5 years								BMD significantly reduced (P<0.001) at all sites
Tau et al (24), 2006	Argentina	Prospective longitudinal	24 CD children, mean age 4.9 years								BMC BMD spine, axial BMD reverted to normal or most in under 4 years following GFD

↑ Increase; BMC Bone mineral content; BMI Body mass index; DXA Dual x-ray absorptiometry; F Femur; FN Femoral neck; GFD Gluten-free diet; LS Lumbar spine; PTH Parathyroid hormone; vs Versus

TABLE 2
Lumbar bone mineral density (BMD) in celiac disease (CD) patients at diagnosis compared with controls

Author (reference), year	Age range,	Lumbar spine BMD, g/cm ²		P
	years	CD group	Control group	
Kemppainen et al (36), 1999	23–69	1.06±0.19	1.13±0.16	0.03
Pistorius et al (50), 1995	20–70	1.076±0.186	1.155±0.143	<0.001
Mora et al (45), 1998	2–20	0.708±0.034	0.749±0.017	0.015
Kavak et al (47), 2003	2–16	0.447±0.144	0.537±0.080	0.006

Data presented as mean ± SD unless otherwise indicated

at CD diagnosis are predictive of bone mineralization status in adult patients. Patients with higher PTH levels are more likely to have lower BMD (36-39) and less likely to normalize their BMD after three years on a GFD (37). These data suggest that PTH levels at CD diagnosis may be a useful prognostic factor for bone disease in CD patients.

Several studies also indicate that serum osteocalcin and bone-specific alkaline phosphatase levels correlate negatively with BMD (18,37,38), while in adults, 25(OH)D₃ levels correlate positively with BMD (18,36,37).

Adults who respond to a GFD have lower levels of bone-specific alkaline phosphatase and osteocalcin, and higher levels of 25(OH)D₃ than patients with refractory disease or persistent villous atrophy (17,39). Baseline levels of carboxy-terminal propeptide of type I collagen have been reported to correlate best with an increase in BMD following a GFD (18).

Based on these studies, it appears reasonable to measure 25(OH)D₃, calcium corrected for albumin and PTH levels in newly diagnosed adult CD patients, to assess the extent of bone loss at diagnosis and to estimate the likely effect of a GFD in restoring bone density.

Other serological markers that correlate with BMD include tTG antibodies and IgA EMA. A study by Agardh et al (40) showed that in women 50 to 64 years of age, high tTG antibody levels (>17 U/mL) were correlated with lower BMD (0.41±0.08 g/cm² versus 0.44±0.08 g/cm²; P=0.001), a higher prevalence of osteoporosis (13.4% versus 6.5%; P=0.008) and a higher fracture frequency (32.2% versus 18.8%; P=0.009). A study by Duerksen et al (41) confirmed that women who were seropositive for tTG and/or EMA had lower BMD at all measured sites than the seronegative control group. The prevalence of osteoporosis among seropositive patients was 67.7% versus 44.8% for seronegative patients. Recommended cut-off values for commercial tTG kits are <20 U/mL (normal), 20 U/mL to 100 U/mL (mid-range), and >100 U/mL (high). Using these cut-offs and a known IgA status, the sensitivity and specificity of tTG as a screening test has been shown to be 0.980 and 0.972, respectively (42).

A study by Blazina et al (43) compared BMD in children and adolescents who were on a strict GFD with patients who had occasional gluten intake. Compliance with a GFD was monitored by EMA status. Patients who were EMA positive at any time during the study were classified as not strictly compliant, whereas those who were EMA negative throughout the study were classified as strictly compliant. The results showed that 71% of patients who were EMA positive had total body BMD Z-scores below -1.0 compared with 38% in the strictly compliant group (P=0.03). However, it is important to note that calcium intake and vitamin D levels were below recommendations within both groups. The authors proposed that because BMD is affected both by impaired absorption of calcium and vitamin D in the bowel, as well as by the presence of inflammatory cytokines and auto-antibodies, patients with occasional gluten ingestion remain seropositive and are thus at an increased risk of reduced BMD even if intestinal absorption is not significantly affected.

How common is skeletal disease in CD patients?

BMD: BMD at diagnosis of CD: Studies evaluating the mean BMD at the time of CD diagnosis are summarized in Table 2. The absolute prevalence of osteoporosis/osteopenia in CD patients is unclear due to the

TABLE 3
Mean lumbar bone mineral density (BMD) in celiac disease patients at diagnosis and after one year on a gluten-free diet (GFD)

Author (ref), year	Age group, years	Lumbar BMD*, g/cm ²		P	Increase after 1 year, %
		Basal	After 1 year on GFD		
Kemppainen et al (36), 1999	23–66	1.07±0.19	1.11±0.13	≤0.001	3.7
Ciacchi et al (19), 1997	18–68	0.795 ±0.177	0.907±0.180	<0.001	14
Sategna-Guidetti et al (57), 2000	19–67	0.886±0.15	0.933±0.14	<0.0001	5.3
Mora et al (45), 1998	2–20	0.683±0.036	0.745±0.042	0.03	9.0

*Data presented as mean ± SD unless otherwise indicated. GFD has a significant effect on improving BMD and is an important component of managing low BMD in celiac disease patients. ref Reference

small numbers of patients studied and the varied study populations. However, data from two studies involving adult CD patients suggest that approximately one-third have osteoporosis, one-third have osteopenia and one-third have a normal BMD at presentation (36,44).

Low BMD is detected in children and adolescents with newly diagnosed CD (45-47). One study conducted in Edmonton, Alberta, observed lumbar spine BMD Z-scores ≤-2 SDs in 16% of pediatric CD patients, Z-scores below -1 SD but above -2 SDs in 19%, and a Z-score ≥-1 SD in 65% (48). In another study that assessed bone mineral content (BMC) in children with CD (26), whole body and lumbar spine BMC were identified to be lower in children with CD than in healthy controls by 1.0 g (lumbar spine) and 38.7 g (whole body). In 24 children ranging in age from one to 11 years at diagnosis, lumbar spine BMD measurements expressed as Z-scores were reported to be low (-1.36±1.20) and 17% had Z-scores that were >2 SDs below the population mean (25).

The risk of low BMD among newly diagnosed adult CD patients is higher with increased age, lower body mass index and years after menopause (16,36,44, 49-52).

Effect of GFD on BMD: Studies evaluating the BMD response to a GFD are summarized in Table 3.

In 2003, the American Gastroenterological Association (53) concluded that, among newly-diagnosed CD patients, osteoporosis was found in 28% when measuring the lumbar spine and 15% when measuring the hip. Adults and children had a similar prevalence of low BMD at diagnosis, but children normalized their BMD after initiation of a GFD (45,54,55). Adults had the greatest increase in BMD (approximately 5%) in their first year on a GFD, but remained below average thereafter (15,56,57). Children diagnosed with CD before two years of age, who were on a GFD for at least 24 months, tended to attain greater bone mass than older patients (46). Patients having persistent abnormal small bowel morphology have the lowest BMD (55).

The American Gastroenterological Association proposed broader screening of family members of patients with CD and those with type 1 diabetes mellitus, Addison disease and other polyglandular diseases because low BMD does not seem to be fully reversible in adults, and because early diagnosis and treatment for asymptomatic CD patients may optimize skeletal health and prevent fracture development.

Fracture risk

BMD is only one of the factors associated with increased fracture rates in CD patients. Bone quality, microarchitecture, geometry, bone cell function, mineralization and collagen fibre strength, as well as neuromuscular function, all determine the risk of fracture and bone strength. This was best highlighted in a study by Moreno et al (58), who did not find a significant difference between T-scores and Z-scores of CD patients with or without fractures. The study found that patients with a classical presentation of CD had a higher fracture risk (47%)

compared with controls (15%) (OR 5.2 [95% CI 2.8 to 9.8]; $P < 0.0001$). Fractures in subclinical/silent cases were not different from their controls (20% versus 14%; OR 1.7 [95% CI 0.7 to 4.4]; P not significant). Multivariate analyses did not show any one single characteristic to be highly predictive of fracture risk.

Studies evaluating the risk of fracture in CD patients are conflicting, with some showing no significant increase in fractures (59,60), and others reporting a higher risk (27,61,62). RRs for fractures of any type range from 0.94 (95% CI -0.71 to 1.24) (46) to 7.0 (63), and for hip fractures, range from 0.66 (95% CI -0.05 to 9.50) (64) to 1.9 (95% CI -1.2-3.02) (65).

In the largest study to date on the incidence of fractures in CD population, Ludvigsson et al (63) used a Swedish National Registry to estimate the risk of hip fractures and fractures of any type in a large general population cohort study. The hazard ratio (HR) for a hip fracture was 2.1 (95% CI 1.8 to 2.4) in adults, and 2.6 (95% CI 1.1 to 6.2) in children. It is important to note that hip fractures are rare in children; the increased HR was based on six hip fractures per 100,000 patient years for pediatric CD patients compared with two per 100,000 patient years among reference individuals. The HR for fractures of any type for all ages was 1.4 (95% CI 1.3 to 1.5), with a marginal statistical significance of $P = 0.052$. Although a GFD allows for improvement in BMD, adult patients do not regain their peak bone mass and their BMD remains lower than in healthy controls (70). As a result, CD patients remain at an increased risk of fractures 20 years after diagnosis even if they adhere to a GFD (63).

The studies above conclude that both adult and pediatric CD patients have a significant increase in the risk of hip fractures and fractures of any other type, regardless of whether the fracture occurred before or after the diagnosis of CD. The duration after diagnosis of CD did not notably influence the risk of hip fractures and, therefore, no evidence was found in the study by Ludvigsson et al (63) that a GFD lowers the risk of hip fractures. The positive association between CD and hip fractures was independent of sex and age (63). The study also showed increased risk of subsequent hip fractures in individuals with CD diagnosed in childhood (HR 2.6 [95% CI -1.1 to 6.2]).

Moreno et al (58) showed that peripheral fractures are more common in adult CD patients than in age- and sex-matched controls. CD patients with a classic clinical course (eg, chronic diarrhea and malabsorption) had a significantly higher prevalence of fractures in the peripheral skeleton (OR 5.2 [95% CI 2.8 to 9.8]) compared with patients with subclinical or silent CD, and to age- and sex-matched controls. Vazquez et al (62) also showed that adult CD patients had a higher prevalence of peripheral fractures (25%) compared with sex- and age-matched controls (8%). Other studies (64,67,68) reported trends toward an increased fracture risk that were not statistically significant.

A recent systematic review of case control and cohort studies (64) reported that the fracture risk was 43% greater in adult CD patients than in controls (OR 1.43 [95% CI -1.15 to 1.78]), although there was significant, unexplained, quantitative and qualitative heterogeneity among the studies, possibly attributable to differences in subject selection, small sample sizes and differences in methodologies used to assess and define fractures, and lack of information on disease duration and therapeutic interventions. Nonetheless, the results of the systematic review, supplemented by the results of two case control studies (Table 4) confirm that adult CD patients have a significantly increased risk of fracture. Additional research is needed to identify which CD patients are at a higher risk of fracture so that clinicians can implement screening, risk stratification and treatment strategies more effectively.

Who should undergo BMD testing?

Based on the available data, there is no indication to perform a BMD test in the pediatric age group if they are compliant with a GFD because data confirm full recovery. The International Society for Clinical Densitometry guidelines do not include CD as an indication to perform a DXA scan on children and adolescents (69). On the other hand, symptomatic adults with classic malabsorption (weight loss, diarrhea, etc) should have their BMD tested at diagnosis and ensure that malabsorption of calcium,

phosphate and vitamin D are corrected. The asymptomatic/silent group represent a 'grey zone' with conflicting data and no consensus, but it would seem prudent to treat them with a GFD and perform a DXA scan one year later when the need for further management can be assessed.

The recent British guidelines (70) recommend that BMD testing be completed in all patients at the time of diagnosis in recognition of the potential impact of chronic malabsorption.

Compston et al (67) suggest BMD assessment be restricted to the minority of individuals in whom short-term fracture risk (five to 10 years) is probably high. In adult CD patients, risk factors may include nonadherence to a GFD, failure to respond to a GFD, corticosteroid treatment, untreated hypogonadism, old age, low body mass index and previous fragility fractures, as well as menstrual irregularity and subclinical hypogonadism in premenopausal women, unexplained iron deficiency anemia and low vitamin D status (indicated by low vitamin D levels and/or low 24 h urinary calcium). Based on this, Corraza et al (71) proposed DXA assessment in peri- and postmenopausal women with CD and male CD patients >50 years of age.

A repeat DXA scan after one year on a GFD is recommended in the presence of osteoporosis/osteopenia at diagnosis (13,15,16,57). In the presence of normal BMD at diagnosis, follow-up may be after two to three years on a GFD, based on other clinical risk factors and response to therapy.

The WHO has developed an absolute fracture risk assessment tool ('FRAX') to estimate the 10-year fracture risk in all adults, which is based on the integration of femoral neck bone density, age and other important clinical risk factors (66). Given that one of the risk factors is chronic malabsorption, use of the FRAX tool would be reasonable for CD patients.

Gaps and limitations with future directions

In summary, although there is agreement that adult CD patients have an increased fracture risk, there are important knowledge gaps regarding the prevalence of fragility fracture and relevant risk factors. Prospective population-based fracture data with small bowel biopsy follow-up to clinical presentation and GFD compliance will be very informative. Prevention of osteoporotic fractures should be the main aim when addressing bone health in the adult CD population; restoration of normal bone metabolism, to achieve optimal peak bone mass at the end of puberty, should be the main aim for pediatric CD patients.

Data on management options, other than GFD, for low BMD in CD patients are limited. Supplementation of calcium and vitamin D has been recommended in some studies but not others, and the role of antiresorptive medications on BMD and fracture risk in CD patients is not known (70,71). There is also no agreement regarding the BMD threshold for treatment in CD patients or whether a T-score or Z-score should be used in adult CD patients (70); in this context, the FRAX tool may be more useful for determining the fracture risk and appropriate management. In pediatric CD patients, the only meaningful value is a BMD Z-score to compare unaffected age- and sex-matched populations.

RECOMMENDATIONS FOR DIAGNOSIS, FOLLOW-UP AND TREATMENT OF PATIENTS WITH CD WITH REGARD TO SKELETAL HEALTH

Indications for BMD testing

1. In adults with classic CD, BMD should be evaluated following the diagnosis of CD. (Level I)
2. In adults with asymptomatic or silent CD, BMD should be evaluated after one year on a GFD. (Level I)
In the absence of other risk factors, the fracture risk is probably less than in patients with classic CD, and it may not be significantly higher than in the general population.
3. In adults with asymptomatic or silent CD, early BMD testing <1 year after diagnosis, may be considered if there are other risk factors for low BMD such as the following:
 - a) Peri- or postmenopausal women. (Level I)
 - b) Men older than 50 years of age. (Level I)
 - c) History of fragility fracture. (Level I)

TABLE 4
Risk of fractures in celiac disease (CD)

Author (ref), year	Country	Study type, fracture ascertainment	Participants	Outcomes	Risk estimates (95% CI)	
Vazquez et al (62), 2000	Argentina	Case control, interview	CD, n=165, biopsy proven Malabsorption clinic Control, n=165	Peripheral fractures Spine	OR 3.5 (1.8–7.2), 2.8 (0.7–1.150)	
Fickling et al (59), 2001	United Kingdom	Case control, interview	CD, n=75 Control, n=75	Previous fractures 21% vs 3%	RR 7.0	
Thomason et al (60), 2003	United Kingdom	Case control, self-report data	CD, n=244 biopsy proven Control, n=166	Low trauma Any fracture Wrist fracture Before CD diagnosis	OR 1.0 (0.68–1.02) 1.21 (0.66–2.25) 1.16 (0.65–2.10) 1.24 (0.65–2.39)	
Vestergaard et al (86), 2002	Denmark	Retrospective cohort, administrative databases	CD, n=7774 person years Control, n=23,316 person years	All fractures Spine, rib, pelvis	RR 0.94 (0.71–1.24) 2.14 (0.7–6.57) pre gluten-free diet 1.07 (0.39–2.95) post gluten-free diet	
West et al (65), 2003	United Kingdom	Retrospective cohort, administrative databases	CD, n=4732 Control, n=23,620 No biopsy data	All fractures Hip fractures Ulna/radius	HR 1.3 (1.16–1.46) HR 1.9 (1.2–3.02) HR 1.77 (1.35–2.34)	
Moreno et al (58), 2004	Argentina	Cross-sectional, case control	CD, n=148 Symptomatic, n=78 (53%) Silent, n=17 (11%) Subclinical, n=53 (36%) Control, n=296 Age/sex-matched Biopsy proven	All fractures	Symptomatic group 47% fractures vs control OR 5.2 (2.8–9.8) Subclinical group 20% fractures vs control OR 1.7 (0.7–4.4) Symptomatic group vs subclinical group OR 3.6 (1.7–7.5) No difference among different group premenopausally	
					Original data	Corrected for height, weight
Davie et al (87), 2005	United Kingdom	Case control, questionnaire-based fractures by recall postmenopausal women	CD, n=383 90.3% biopsy proven Control, n=445	Any fracture Any fracture after 50 yrs Any wrist fracture Any wrist fracture after 50 yrs Any nonwrist fracture Any nonwrist fracture after 50 yrs More than one fracture	OR 1.51 (1.13–2.02) OR 2.20 (1.49–3.25) OR 1.65 (1.12–2.44) OR 2.17 (1.22–3.87) OR 1.66 (1.21–2.27) OR 2.34 (1.51–3.63) OR 2.96 (1.81–4.83)	1.55 (1.11–2.18) 2.38 (1.52–3.75) 1.45 (0.92–2.29) 1.80 (0.93–3.49) 1.86 (1.29–2.68) 2.73 (1.64–4.54) 3.36 (1.94–5.83)
Ludvigsson et al (63), 2007	Sweden	Population-based cohort	CD, n=13,724 Control, n=65,627	<u>First hip fracture</u> *First year excluded Any CD 0–15 yrs ≥16 yrs Males Females * First year included <u>Any fracture</u> *First year excluded Any CD 0–15 yrs ≥16 yrs Males Females *First year included	HR 2.1 (1.8–2.4) HR 2.6 (1.1–6.2) HR 2.1 (1.8–2.4) HR 2.2 (1.7–2.9) HR 2.0 (1.7–2.4) HR 2.2 (2.0–2.5) HR 1.4 (1.3–1.5) HR 1.1 (1.0–1.2) HR 1.8 (1.6–2.0) HR 1.4 (1.2–1.5) HR 1.4 (1.3–1.6) HR 1.5 (1.4–1.6)	
Jafri et al (88), 2007	United States	Population-based cohort, administrative databases	CD, n=83 Control, n=166	Any fracture Peripheral Axial Osteoporotic	OR 2.0 (1.0–3.9) OR 2.0 (1.0–3.8) OR 1.7 (0.7–4.1) OR 8.0 (0.9–72)	

Data analysis showing fracture risk in CD. The analysis in this table was first performed in 2008, before the systematic review and meta-analysis by Olmos et al (65) was published. Thus, much of the analysis in this table is similar to the analysis in that study. However, this table has been re-updated to include new data that became available after the Olmos et al (65) systematic review. The Olmos et al (65) article, which includes the first eight studies in this table, showed that fracture risk was 43% greater in adult CD patients than in controls (OR 1.43 [95% CI 1.15 to 1.78]), with significant, unexplained, quantitative and qualitative heterogeneity among the studies, possibly attributable to differences in subject selection, small sample sizes, differences in methodologies used to assess and define fractures, and lack of information on disease duration and therapeutic interventions. ref Reference; vs Versus; yrs Years of age

- d) Unexplained iron deficiency anemia. (Level III)
 - e) Vitamin D deficiency/insufficiency. (Level II)
 - f) High titres for CD serological markers. (Level I)
 - g) In pediatric CD patients, BMD testing should be offered one year after diagnosis if patients do not self-report strict adherence to a GFD. (Level I)
4. In adult CD patients, repeat DXA (or first time DXA) testing should be offered to all groups at menopause and men after 50 years of age. (Level II)
 5. The FRAX tool will be useful to estimate fracture risk and plan management accordingly. (Level II)

Indications for BMD follow-up in adults

1. In the presence of osteopenia/osteoporosis at diagnosis, follow-up BMD should be offered after one year on a GFD. (Level I)
2. In the presence of a normal BMD at diagnosis, follow-up should be after two years on a GFD, particularly if the patient remains symptomatic or is nonadherent to the diet. (Level III)

Indications for biochemical assessment and follow-up

1. In adult CD patients, biochemical profile for the assessment of skeletal mineralization should be offered at the time of CD diagnosis in adults, including serum calcium, albumin, 25(OH)D₃ and PTH levels. (Level II)
2. In adult CD patients, routine 24 h urine calcium testing is not recommended. (Level III)

Comment: Urinary calcium testing may be helpful to assess calcium absorption; however, there are few data to support this recommendation and there other factors, including renal function, that will affect urinary calcium excretion.

3. Biochemical profile could be repeated every six months until normalization. (Level III)
4. Biochemical markers of bone turnover (eg, osteocalcin, procollagen type 1 N-terminal propeptide, urinary collagen

crosslinks [NTx]) should be reserved for research studies. (Level III)

5. Serological CD markers (IgA, tTGA, IgA EMA) can be used as indicators of the severity of CD-related mucosal damage. (Level I).

Comment: The severity of mucosal damage appears to be a predictor of malabsorption and, hence, of the risk of low bone density. Cytokine excess associated with mucosal damage (increased IL-6, decreased IL-12 and IL-18 levels) also contributes to bone loss through increased osteoclast formation, function and survival.

6. Serological CD markers may be used as a screening tool in asymptomatic/silent CD patients to identify those who may benefit from an early DXA to diagnose low bone mass. (Level II)

Treatment

1. GFD adherence is the treatment of choice for normalization of BMD in CD patients. (Level I)
2. Pharmacological intervention with antiresorptive medications can be used to treat osteoporosis in postmenopausal adult CD patients after ensuring that adequate calcium and vitamin D supplementation has been provided. (Level III)

Comment: Other strategies used in the management of postmenopausal osteoporosis may be considered but there are no longitudinal data to support this practice in CD patients.

APPENDIX 1: LEVELS OF EVIDENCE ADAPTED FROM THE CANADIAN TASK FORCE ON PREVENTIVE HEALTHCARE (20)

Levels of evidence

- Level I:** At least one properly conducted randomized controlled trial, systematic review, or meta-analysis.
- Level II:** Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study.
- Level III:** Expert opinion or consensus statement.

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