Approach to diagnosing celiac disease in patients with low bone mineral density or fragility fractures

Multidisciplinary task force report

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Abstract

Objective To provide clinicians with an update on the diagnosis of celiac disease (CD) and to make recommendations on the indications to screen for CD in patients presenting with low bone mineral density (BMD) or fragility fractures.

Quality of evidence A multidisciplinary task force developed clinically relevant questions related to the diagnosis of CD as the basis for a literature search of the MEDLINE, EMBASE, and CENTRAL databases (January 2000 to January 2009) using the key words *celiac disease*, *osteoporosis*, *osteopenia*, *low bone mass,* and *fracture*. The existing literature consists of level I and II studies.

Main message The estimated prevalence of asymptomatic CD is 2% to 3% in individuals with low BMD. Routine screening for CD is not justified in patients with low BMD. However, targeted screening for CD is recommended for patients who have T-scores of -1.0 or less at the spine or hip, or a history of fragility fractures in association with any CD-related symptoms or conditions; family history of CD; or low urinary calcium levels, vitamin D insufficiency, and raised parathyroid hormone levels despite adequate intake of calcium and vitamin D. Celiac disease testing should be performed while the subject is consuming a gluten-containing diet; initial screening should be performed with human recombinant immunoglobulin (Ig) A tissue transglutaminase or other IgA tissue transglutaminase assays, in association with IgA endomysial antibody immunofluorescence. Duodenal biopsy is necessary to confirm the diagnosis of CD. Human leukocyte antigen typing might assist in confirming or ruling out the diagnosis of CD in cases where serology and histology are discordant. Definitive diagnosis is based on clinical, serologic, and histologic features, combined with a positive response to a gluten-free diet.

Conclusion Current evidence does not support routine screening for CD in all patients with low BMD. A targeted case-finding approach is appropriate for patients who are at higher risk of CD.

EDITOR'S KEY POINTS

- Patients presenting with osteoporosis, manifested either by low bone mineral density on dual-energy x-ray absorptiometry scans or by fragility fractures, should be evaluated for secondary causes including celiac disease (CD).
- The best available tests are immunoglobulin A tissue transglutaminase and immunoglobulin A endomysial antibody immunofluorescence. The criterion standard test for diagnosing CD is villous atrophy on duodenal biopsy. If serology and histology results are discordant, human leukocyte antigen typing might be useful in diagnosis.
- A T-score of -2.5 or less should prompt a high index of suspicion for CD, as CD is often silent or atypical in adults. A positive family history or any symptoms or conditions associated with CD should prompt screening.

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Celiac disease (CD) is a genetic autoimmune enteropathy caused by an immune response to gluten. Classically, CD presents with chronic diarrhea, abdominal pain, and malabsorption. The small bowel undergoes mucosal atrophy and inflammation, which improve when consuming a gluten-free diet (GFD).[1-4] The clinical spectrum of CD is broad, with marked differences in symptom severity and histology.[1-6] According to a recent systematic review, the prevalence of CD is close to 1% worldwide.[7-12] Children often present with diarrhea, abdominal distention, and failure to thrive; adolescents and adults present more commonly with mild gastrointestinal symptoms for years.[13,14] Celiac disease might also be completely asymptomatic (silent form), detected only by serologic screening or serendipitously during an upper endoscopy.

Patients presenting with osteoporosis, manifested either by low bone mineral density (BMD) on dual-energy x-ray absorptiometry scans or by

fragility fractures, should be evaluated for secondary causes, including CD.[15-17] Celiac disease causes secondary hyperparathyroidism and osteomalacia from calcium and vitamin D malabsorption.[18-20] Markers of bone resorption increase and are not balanced by markers of bone formation, resulting in net bone loss.[21] Chronic inflammation with increased levels of proinflammatory cytokines and decreased levels of inhibitory cytokines causes bone loss owing to direct effects on osteoclastogenesis and osteoblast activity.[22-27] An increased receptor activator of NFκB ligand to osteoprotegerin ratio has also been implicated.[21,28] Hypogonadism associated with CD might also contribute to bone loss.[29]

Patients with CD are at increased risk of fractures, particularly in the peripheral skeleton.[30,31] A recent meta-analysis showed the pooled odds ratios for all fractures in CD patients was 1.43 compared with control groups.[32] Many studies show substantial improvement in BMD after introduction of a GFD.[33-36]

Given the above information, it is plausible that early diagnosis of CD in patients with low BMD could help in fracture prevention. However, no data indicate increased risk of fractures among CD patients detected by screening,[37] and there are no direct studies on the effect of a GFD on fracture risk. Consequently, there is currently no consensus on whether to screen for CD in patients with low BMD. Recognition of the need for evidence-based approaches in this field led to the establishment of a multidisciplinary Canadian task force that was charged with reviewing the relevant literature and providing clinical guidance for the diagnosis of CD in individuals with low BMD or fragility fractures. The initiative was led and supported by the Calcium Disorders Clinic of St Joseph's Healthcare Hamilton at McMaster University in Ontario, in association with members of relevant national societies. The main focus of this review is on the adult population.

Quality of evidence

We conducted a literature search of the MEDLINE, EMBASE, and CENTRAL databases from January 2000 to January 2009 using the key words *celiac disease*, *osteoporosis*, *osteopenia*, *low bone mass*, and *fracture*. All relevant papers on the relationship between osteoporosis and CD, and on CD prevalence and diagnosis were considered for inclusion. International guidelines on CD published after 2000 were reviewed. The quality of evidence was graded according to the Canadian Task Force on Preventive Health Care (**Box 1**).[38] The quality of evidence is good for some questions and fair or nonexistent for others.

How is CD diagnosed? No single test is diagnostic of CD; a definitive diagnosis requires clinical evaluation, serologic tests, and duodenal biopsy, often supplemented by clinical or histologic response to a GFD. Serologic, clinical, and histologic findings are discordant in about 10% of cases.[2] Initial testing should be performed while consuming a full gluten-containing diet, as withdrawal of gluten might lead to false-negative results.

Box 1. Levels of evidence adapted from the Canadian Task Force on Preventive Health Care

Level I: At least 1 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 1 study
Level III: Expert opinion or consensus statement

Adapted from the Canadian Task Force on the Periodic Health Examination.[38]

Serologic tests. Currently, the best available tests are immunoglobulin (Ig) A tissue transglutaminase (tTG) and IgA endomysial antibody (EMA) immunofluorescence. Both have comparable diagnostic accuracy, with a specificity close to 100% and sensitivities between 90% and 98%.[39] Immunoglobulin A tTG testing is preferred because it is automated, less expensive, and quicker. Immunoglobulin A tTG testing has been validated in clinical practice and is an excellent tool for excluding the diagnosis of CD in low- or intermediate-risk populations.[40]

Testing for IgG antibodies of EMA and tTG has generally lower sensitivity,[6,39] being more useful to detect CD in IgA-deficient patients.[41,42]

Antigliadin antibody testing is no longer routinely recommended because of its lower sensitivity (less than 80%) and specificity (80% to 90%).[6,39]

Histologic tests. The criterion standard for diagnosing CD is villous atrophy on duodenal biopsy. A standardized histology report based on the modified Marsh criteria is recommended (**Table 1**).[43-45] As mucosal changes can be patchy, at least 4 to 6 biopsy specimens should be taken to ensure optimal test sensitivity.[46,47] False-negative results might also occur in patients taking immunosuppressants, taking corticosteroids, or consuming a GFD. Histologic findings are characteristic of but not specific for CD; they occur in tropical sprue, HIV enteropathy, *Giardia lamblia* infestation, and common variable immunodeficiency.

Human leukocyte antigen typing. If serology and histology are discordant, human leukocyte antigen (HLA) typing might be useful in diagnosis, as HLA-DQ2 and HLA-DQ8 are present in almost all individuals with CD but only in 30% to 40% of the general population. Thus, the absence of these alleles has a high negative predictive value, virtually excluding the diagnosis of CD.[48] Human leukocyte antigen typing is also useful in selecting what first-degree relatives are at risk of CD and could benefit from longitudinal screening for CD by serology.[2]

Table 1. Histologic grading of duodenal mucosal changes in celiac disease according to modified Marsh criteria

STAGE	MUCOSAL CHANGE	DESCRIPTION
0	Normal	Normal mucosal architecture
I	Infiltrative	Normal mucosal architecture Villous epithelium is infiltrated by lymphocytes (> 30 per 100 enterocytes)
II	Hyperplastic	Crypt hyperplasia with infiltration of inflammatory cells
III	Villous atrophy	
IIIa	• Partial	Shortened blunt villi associated with mild infiltration of lymphocytes and crypt hyperplasia
IIIb	• Subtotal	Clearly atrophic villi but still recognizable Signs of crypt hyperplasia and inflammatory cell infiltration are increased
IIIc	• Total	Nearly total absence of villi Severe atrophic, hyperplastic, and infiltrative lesions
IV	Hypoplastic	Total villous atrophy Crypt hypoplasia Normal intraepithelial lymphocyte count

Adapted from Buchman.[45]

Who should be tested for CD? The role of mass screening for CD remains controversial[45,49,50]; proponents cite the high prevalence of CD, and associated malignancy and fragility fractures. Conversely, opponents cite a lack of knowledge about the progression of asymptomatic CD, poor compliance with diet in individuals whose CD is detected by screening, and impaired quality of life with a lifelong GFD in otherwise asymptomatic patients. It has therefore been proposed that screening be reserved for those at higher risk of CD.[51]

Do patients presenting with low BMD have increased risk of CD? We updated the data from an earlier systematic review on the prevalence of CD diagnosed by screening among patients with low BMD[7] using the same search strategy and inclusion criteria for studies up to June 2008. Eight studies were included and CD prevalence ranged from 0% to 3.4% (**Table 2**).[52-59] Only 4 studies applied the same screening algorithm to patients with low BMD and control groups. They generally showed a higher prevalence of CD among patients with low BMD (**Table 3**).[52,53,57,58] Based on these results, a reasonable estimate of the prevalence of CD is 2% to 3% in low-BMD populations, compared with 1% or less in the general population.

Are specific groups of patients with low BMD at higher risk of CD? Several studies have correlated the severity of CD with the severity of bone loss. It appears that CD is more likely to be diagnosed in patients with low BMD if they have T-scores of -2.5 or less, elevated parathyroid hormone levels, or vitamin D insufficiency[56-58] and unexplained gastrointestinal symptoms.[57,58] However, further research is required to confirm these predictors.

Should all patients with low BMD be screened for CD? To date, there are no studies on the cost effectiveness of routine screening for CD in patients with low BMD. Current data suggest that serologic screening would not be cost effective in this population with low CD prevalence, as it would lead to many false-positive results, requiring additional unnecessary testing. Adding HLA typing to patients with positive serology results would reduce false-positive cases.[48] However, the cost effectiveness of such an approach is unknown. Current evidence does not support routine screening for CD in all

Table 2. Prevalence of CD detected by screening in patients presenting with low bone mineral density

AUTHOR, YEAR, COUNTRY	T-SCORE	SAMPLE SIZE	FEMALE SEX, %	AGE, Y	SCREENING ALGORITHM	BIOPSY CRITERIA	CD PREVALENCE (95% CI), %
Drummond et al,[52] 2003, Ireland	≤ -1.0	366	100	Mean 56 (SD 11.5; range 28-96)	IgA EMA and IgA tTG	NA	2.2 (1.1-4.2)
González et al,[53] 2002, Argentina	< -2.5	127	100	Mean 68 (range 50-82)	1. IgA AGA 2. IgA EMA	Marsh III	0.8 (0.02-4.31)
Lindh et al,[54] 1992, Sweden	NA	92	91	Mean 66 (SD 12)	IgA AGA	NA	3.3 (1.1-9.1)
Mather et al,[55] 2001, Canada	≤ -1.0	96	81	Mean 57 (range 18-86)	IgA EMA	NA	0 (0-3.8)
Nuti et al,[56] 2001, Italy	≤ -2.5	255	100	Mean 66 (SD 8.5)	1. IgA AGA 2. IgA tTG	NA	2.3 (1.1-5.0)
Sanders et al,[57] 2005, United Kingdom	≤ -1.0	674	95	Mean 53 (range 21-69)	IgA AGA and IgA EMA	ESPGHAN	1.5 (0.8-2.7)
Stenson et al,[58] 2005, United States	≤ -2.5	266	90	Mean 57 (SD 12)	IgA EMA and IgA tTG	Marsh III	3.4 (1.8-6.3)
Karakan et al,[59] 2007, Turkey	≤ -1.0	135	90	Mean 57.2 (range 24-81)	IgA EMA	NA	0 (0-2.7)

AGA—antigliadin antibody, CD—celiac disease, EMA—endomysial antibody, ESPGHAN—European Society of Paediatric Gastroenterology, Hepatology and Nutrition, Ig—immunoglobulin, NA—not available, tTG—tissue transglutaminase.

Table 3. Risk of CD in patients with low BMD compared with control groups evaluated by the same screening algorithms

AUTHOR, YEAR, COUNTRY	CHARACTERISTICS OF PATIENTS WITH LOW BMD	CHARACTERISTICS OF CONTROL GROUP	CD PREVALENCE IN PATIENTS WITH LOW BMD, % (CASES/N)	CD PREVALENCE IN CONTROL GROUP, % (CASES/N)	*P* VALUE
Drummond et al,[52] 2003, Ireland	366 women (82% postmenopausal) attending a bone densitometry unit Mean age 56 y (range 28-96 y) T-score ≤ -1.0	89 women (45% postmenopausal) attending the same bone densitometry unit T-score > -1.0	2.2 (8/366)	0 (0/89)	.364
González et al,[53] 2002, Argentina	127 postmenopausal women Mean age 68 y (range 50-82 y) T-score < -2.5	747 women, mean age 29 y (range 16-79 y) attending an obligatory prenuptial examination in the same geographic area	0.8 (1/127)	0.8 (6/747)	> .99
Sanders et al,[57] 2005, United Kingdom	674 individuals (95% women) referred for DEXA scan from primary or secondary care Mean age 53 y (range 21-69 y) Total group: T-score ≤ -1.0	304 individuals of the same population T-score > -1.0	1.5 (10/674)	0.7 (2/304)	.360
	Osteopenia: T-score -2.5 ≤ -1.0		1.2 (5/431)	0.7 (2/304)	.7058
	Osteoporosis: T-score ≤ -2.5		2.1 (5/243)	0.7 (2/304)	.2505
Stenson et al,[58] 2005, United States	266 individuals (90% female, most postmenopausal) attending a university bone clinic Mean age 57 y T-score ≤ -2.5	574 individuals (90% female, most postmenopausal) attending the same clinic Mean age 63.2 y T-score > -2.5	3.4 (9/266)	0.2 (1/574)	< .001

BMD—bone mineral density, CD—celiac disease, DEXA—dual-energy x-ray absorptiometry.

patients with low BMD, although this does not preclude a targeted case-finding approach, as described below.

Screening for CD: targeted case-finding approach. Clinical suspicion of CD increases with CD-associated symptoms, family history, and associated disorders.[1,3,7] **Table 4** describes the prevalence of CD among individuals with these conditions.[3,7,60-66]

Box 2 lists indications for CD screening in patients with low BMD or fragility fractures.[15] We believe it is reasonable to screen patients who present with low urinary calcium, secondary hyperparathyroidism, or vitamin D insufficiency despite adequate daily intake of calcium and vitamin D.[15] We set the screening threshold at a T-score of -1.0 or less instead of -2.5 or less owing to the lack of strong evidence to exclude osteopenic patients from screening. As bisphosphonate malabsorption might occur in CD, it seems reasonable to also consider those who do not respond to bisphosphonate therapy for CD screening.

Study algorithm. **Figure 1** shows a proposed study algorithm for the diagnosis of CD in patients with low BMD (T-score of -1.0 or less) or fragility fractures.

We proposed a cutoff value of 25% to classify patients as being at low or high risk of CD. The reader can estimate the risk (pretest probability) of CD for an individual case, based on the data on prevalence of CD associated with different symptoms and conditions (**Table 4**).[3,7,60-66]

For the high-risk group (CD risk greater than 25%), individuals with dermatitis herpetiformis, chronic diarrhea, or unexplained weight loss have CD prevalences ranging between 25% and 89%.[2,3,7]

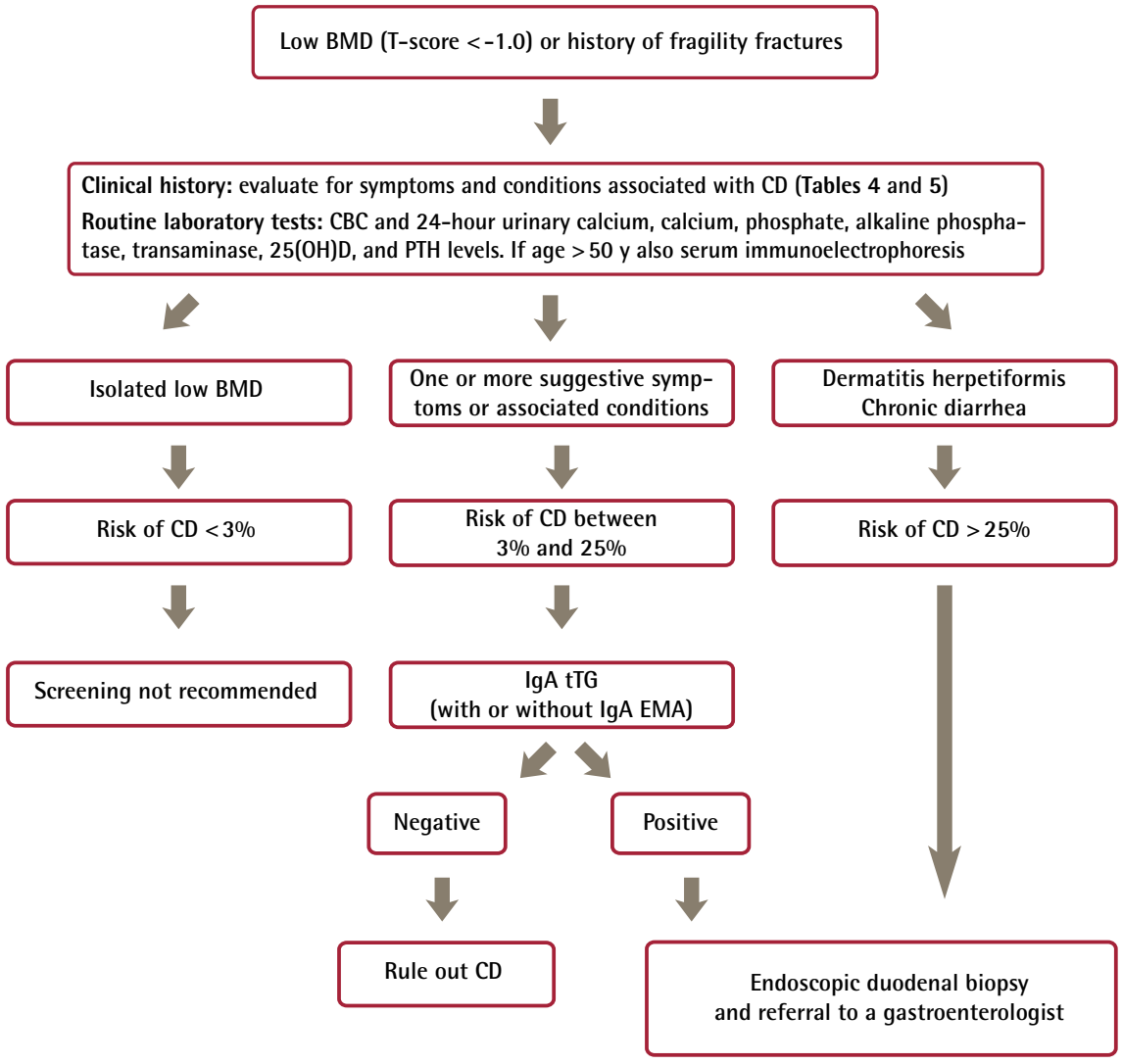
When the prevalence of disease (pretest probability) is high, the negative predictive value of a test decreases (ie, a negative test cannot rule out the diagnosis). As up to 9% of these patients can be seronegative for tTG and EMA, they should undergo intestinal biopsy independent of serology results.[44,67-69]

Most cases fall into the low-risk group (CD risk lower than 25%). These patients have at least 1 symptom or condition associated with CD (**Table 4** and **Box 2**).[3,7,15,60-66] Human recombinant IgA tTG or IgA EMA should be measured. If the serologic test results are positive, then a biopsy should be performed.[70]

Which serologic test should be used? Clinical examples of how serologic tests perform and how to use the likelihood ratio (LHR) monogram are available from **CFPlus**.* Immunoglobulin A tTG and IgA EMA tests have excellent accuracy, with the LHR+ being above 40 and the LHR- close to 0.02. However, they

*Clinical examples of how serologic tests perform and how to use the likelihood ratio monogram are available at **www.cfp.ca**. Go to the full text of the article online and click on **CFPlus** in the menu at the top right-hand side of the page.

Figure 1. Practical algorithm for the diagnosis of CD in adults presenting with low BMD or fragility fractures



25(OH)D—25-hydroxyvitamin D, BMD—bone mineral density, CBC—complete blood count, CD—celiac disease, EMA—endomysial antibody, Ig—immunoglobulin, PTH—parathyroid hormone, tTG—tissue transglutaminase.

perform variably according to the specific assay used. Human recombinant IgA tTG is the best single test for screening asymptomatic people and for excluding CD in symptomatic individuals with a low pretest probability of having CD (ie, <25%).[6,70-72] If this assay is not available, a combination of the IgA tTG assay (or any other assay) and the IgA EMA assay would also be appropriate.[40,73]

Is a confirmatory biopsy always necessary? We recommend that patients with positive serology results undergo a confirmatory biopsy. Although the serologic test has excellent specificity, these results alone are not sufficient, as most cases in the primary care setting have low pretest probabilities (pretest probability of CD has to be greater than 35% for posttest probability to be greater than 95%).[6] Further, the diagnosis of CD has lifelong implications in terms of costs and inconveniences of a GFD.

Conclusion

The prevalence of CD among patients with low BMD is probably higher than in the general population (level I evidence). Routine screening for CD in patients with low BMD is not justified (level III evidence). In adults with low BMD (T-score less than -1.0 at the spine or hip) or fragility fractures, a targeted case-finding approach is recommended. A T-score of -2.5 or less should prompt

Table 4. Conditions associated with increased risk of CD

CONDITION	CD PREVALENCE, %	REFERENCES
Dermatitis herpetiformis*	69.0-89.0	Hopper et al[3]
First-degree relatives of individuals with known CD	4.0-12.0	Dubé et al[7]
Iron deficiency anemia	2.3-8.7	Dubé et al[7]
Unexplained infertility	2.1-4.1	Dubé et al[7]
Unexplained elevation of transaminase levels	1.5-9.0	Dubé et al[7]
Type 1 diabetes	1-11	Dubé et al[7]
Autoimmune liver disease	0.0-6.4	Dubé et al[7]
Autoimmune thyroiditis	1.5-6.7	Dubé et al[7]
Addison disease	1.2-11.0	Betterle et al,[60,61] Myhre et al[62]
Ataxia of unknown cause	1.9-16.0	Bushara[63]
Down syndrome	3.0-12.0	Dubé et al[7]
Turner syndrome	2.0-10.0	Dubé et al[7]
Idiopathic recurrent aphthous ulcers	5.0	Jokinen et al[64]
Alopecia areata	1.0-2.0	Corazza et al,[65] Fessatou et al[66]
Low bone mineral density	0.0-3.4	Discussed in the text

CD—celiac disease.
*Patients with this condition should undergo duodenal biopsy irrespective of whether serologic testing for CD is performed.

a high index of suspicion for CD, as CD is often silent or atypical in adults. A positive family history or any symptoms or conditions associated with CD should prompt screening (level II evidence).

Low urinary calcium level, vitamin D insufficiency, or elevated parathyroid hormone level despite adequate intake of calcium and vitamin D is an indication for CD screening (level II evidence).

Testing for CD should be performed with the patient consuming a gluten-containing diet (level II evidence). Initial CD screening should be performed with human recombinant IgA tTG or other IgA tTG assays in association with IgA EMA assays (level II evidence).

Endoscopy with 4 to 6 duodenal biopsies is necessary as a confirmatory test in most cases (level I evidence). A definitive diagnosis of CD requires consideration of clinical, serologic, and histologic features supplemented, if necessary, by documentation of a positive response to a GFD (level III evidence).

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Contributors
All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Box 2. Indications for serologic screening for CD in patients with low BMD (T-score less than -1.0) or history of fragility fractures

- Low urinary calcium level (< 2.5 mmol/d or < 100 mg/d) in the presence of adequate calcium and vitamin D intake*
- Vitamin D insufficiency (25-hydroxyvitamin D < 50 nmol/L or < 20 pg/mL) in the presence of adequate calcium and vitamin D intake*
- Elevated parathyroid hormone levels in the presence of adequate calcium and vitamin D intake*
- Lack of response to bisphosphonate therapy
- Any of the conditions associated with an increased risk of CD
- Any symptoms suggestive of CD: irritable bowel syndrome or subtle gastrointestinal symptoms, chronic diarrhea with or without malabsorption,† unexplained weight loss,† unexplained iron deficiency anemia†

BMD—bone mineral density, CD—celiac disease.
*Adequate daily intake of calcium and vitamin D as defined by Osteoporosis Canada (vitamin D3 at least 800 IU and 400 IU for individuals older and younger than 50 y, respectively, and elemental calcium ≥ 1000 mg).[15]
†Patients with these symptoms should undergo duodenal biopsy irrespective of whether serologic testing for CD is performed.

Competing interests
None declared

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