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ORIGINAL ARTICLE

Predictors of improvement in bone mineral density after celiac disease diagnosis

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Abstract
Purpose Low bone density is frequently found in patients newly diagnosed with celiac disease (CD), and improvement is variable. This study was performed to assess changes in bone mineral density (BMD) by dual x-ray absorptiometry (DXA) at the lumbar spine, hip, and distal one-third radius as well as clinical predictors of BMD changes after the diagnosis and treatment of CD.
Methods Adult CD patients who had serial DXA at the Celiac Disease Center at Columbia University Medical Center were included ($N = 103$). We assessed within-person changes in BMD with paired *t*-tests. Multiple regression was utilized to assess baseline clinical and laboratory predictors of BMD improvement after diagnosis and treatment.
Results The mean age of our sample was 45.6 years (±SD 15.1) and 60% were female. After a median follow-up of 21 months, lumbar spine BMD increased by $1.7 \pm 5.5\%$ ($p = 0.006$) after CD diagnosis. There was a similar trend at the total hip ($1.6 \pm 6.3\%$, $p = 0.06$), but no change at the femoral neck or distal one-third radius. Lower baseline serum calcium predicted a greater increase in lumber spine BMD ($\beta = -0.0470$ g/cm^2, $p = 0.002$). At the hip, higher baseline creatinine clearance ($\beta = 0.005$, $p = 0.02$) was associated with greater gains in BMD.
Conclusion BMD increases at the lumbar spine after the diagnosis of CD and greater BMD improvement is associated with lower baseline serum calcium. This suggests that those with the lowest calcium, which is likely a surrogate for the greatest malabsorption, may have the greatest potential for improvement in skeletal health after treatment of CD.

Keywords Celiac disease · Bone mineral density · Predictors · Calcium

Abbreviations

BMD	Bone mineral density
CD	Celiac disease
CUMC	Columbia University Medical Center
DXA	Dual x-ray absorptiometry
LS	Lumber spine
PTH	Parathyroid hormone
TH	Total hip
TTG	Tissue transglutaminase.

Introduction

Celiac disease (CD) is an autoimmune disorder characterized by intestinal inflammation in response to gluten, and is known to cause a range of extra-intestinal complications [1]. One such manifestation is low bone mineral density (BMD) measured by dual x-ray absorptiometry (DXA; *T*-score < -1.0) [1–6]. The reduced BMD observed in CD may represent osteopenia or osteoporosis, which are characterized by deterioration of the skeletal microarchitecture

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and reduced bone strength. In some cases, however, low BMD may represent osteomalacia or impaired skeletal mineralization. Overall, low BMD is found in 75% of untreated CD patients [4, 7] and both symptomatic and asymptomatic CD patients can be affected [2, 5, 8, 9]. Decreased BMD is a strong risk factor for fragility fracture [10], with CD patients having a 40% greater risk of fracture compared to those without CD [7, 11, 12].

Malabsorption of calcium and vitamin D, secondary hyperparathyroidism as well as chronic inflammation have been implicated in bone disease of CD, but the exact pathogenesis of low BMD in CD remains incompletely elucidated. Risk factors for low BMD in newly diagnosed patients with CD include the presence of symptomatic CD [8, 13], presence of CD autoantibodies [9], low serum vitamin D (25-OH) [4, 14], elevated alkaline phosphatase [14, 15], older age [14], and postmenopausal status [15]. Studies of CD patients, regardless of time from diagnosis, have corroborated the association between low BMD and low vitamin D (25-OH) [3, 16], postmenopausal status (3), and older age [16, 17], in addition to disease duration [18], male sex [5], low serum calcium [16], and bodyweight or body mass index [3, 19]. Adherence to a gluten free diet (GFD) improves BMD in CD patients [6, 7, 14, 16, 18, 20–23], with most of the recovery taking place in the first year [7, 24]. Nevertheless, GFD adherence may not effectively restore BMD levels [2, 5, 7, 20] and increased fracture risk persists even after many years of treatment [25, 26].

Few studies have assessed which types of patients with CD have the greatest capacity for BMD improvement after treatment with a GFD, and many of these studies have conflicting results. Some data suggest improvement only in symptomatic CD patients [13] while another study showed similar degrees of BMD recovery in these two groups [14]. While one study found greater improvement in BMD in pre vs. post-menopausal CD patients [22], another found no difference [15]. Though some studies have shown an improvement in BMD after GFD initiation in CD individuals of all ages [14, 23], another study found an association between BMD improvement and age at diagnosis [21].

The purpose of this study was to assess whether clinical factors present at the time of CD diagnosis, such as mode of presentation of CD, disease duration, and biochemical factors, predict BMD improvement at the lumbar spine, hip and radius in patients with CD after diagnosis and treatment.

Methods

Design

This is a longitudinal analysis of BMD data obtained in adult patients with CD as part of their care at the Celiac Disease Center at Columbia University Medical Center (CUMC) in New York City, New York. This study was approved by the Institutional Review Board of CUMC.

Participants

We identified CD patients ($N = 103$) from our CD registry who had serial DXA testing at CUMC as part of their clinical care, with the first DXA test at most 2 years from CD diagnosis, and who had no electronic medical record (EMR) of having received medications affecting bone health at any point in their treatment (bisphosphonates, corticosteroids, selective estrogen receptor modulators, denosumab, and teriparatide). All patients had CD confirmed by small intestinal biopsy. Each participant's BMD and sex, as well as age, height, and weight at time of DXA, was downloaded directly from densitometers. Data regarding date of CD diagnosis and disease presentation were available in our registry. We considered the date of diagnosis the date of biopsy because not all CD patients have symptoms and/or the recognition/recollection of the onset of such symptoms is variable. Disease duration was calculated as the time interval between the date of biopsy and first DXA. Biochemical data and race/ethnicity were obtained from the CUMC EMR. We assessed whether CD patients who had serial DXA differed from those who did not have DXA and those who only had one DXA. Those who had serial DXA were slightly older at the time of this analysis compared to those who did not have DXA (mean age 51.1 ± 32.8 vs. 56.8 ± 23.2 $p = 0.02$), but there was no difference in sex. Those who only had one DXA did not differ from those who had serial DXAs (both $p = 0.40$ for comparison of age at time of this analysis and sex).

Dual X-ray absorptiometry

Areal BMD was measured at the lumbar spine L1-L4 (LS), total hip (TH), femoral neck, and the distal one-third radius using a QDR 4500 instrument (Hologic Inc., Waltham, MA). *T*-scores and *Z*-scores were obtained using the manufacturer's reference norms. In vivo precision, determined according to the standard method at this facility is 1.28% at the LS, 1.36% at the hip, and 0.70% for the distal radius (1/3 site) [27]. DXA measurements were made between November 1992 and June 2016. For each participant, we utilized BMD values from the DXA closest in time to the date of their CD diagnosis and the next subsequent follow-up DXA scan. The dates of the first DXA and subsequent follow-up DXA examinations in relation to the date of CD diagnosis were variable and dependent on individual practitioner patterns. Of the baseline scans, 13% were obtained before the diagnosis of CD was made, 2% were acquired on

the day of diagnosis, and 85% were obtained after the diagnosis.

Biochemical data

Biochemical data were retrieved from the CUMC EMR and represent values available from the CUMC clinical core laboratory. Some individuals did not have complete biochemical assessment as part of their evaluation by individual practitioners. Biochemical values within 3 months of the initial DXA scan were utilized for each patient. Serum calcium, phosphate, creatinine, and alkaline phosphatase were measured by auto-analyzer. Parathyroid hormone (PTH) was measured by an immunochemilumometric assay for intact PTH. Serum 25-hydroxyvitamin D was measured using a radioimmunoassay until 2001 and thereafter it was measured using chemiluminescence. Serum 1,25-dihdyroxyvitamin D was measured with radioimmunoassay until 2014 and thereafter it was measured using chemiluminescence. Measurement of serum tissue transglutaminase IgA (TTG IgA) was performed using serum quantitative enzyme-linked immunosorbent assay. Creatinine clearance was calculated using the Cockcroft-Gault Equation.

Statistical analyzes

Baseline characteristics were assessed as means ± standard deviation (SD) or percentages using descriptive statistics. As tissue transglutaminase IgA assays varied, producing different reference ranges of values, we standardized these values by dividing each value by the upper limit of normal before calculating the mean ± SD. Changes in BMD from baseline were assessed with paired *t*-tests at each skeletal site. Multiple regression was used to evaluate independent predictors of BMD at the LS and TH separately. Potential predictors included were age, sex, race, weight, baseline BMD, serum calcium, creatinine clearance, serum alkaline phosphatase at diagnosis as well as disease duration, and presence of diarrheal symptoms at diagnosis. Other possible predictors such as TTG, phosphorus, PTH, and vitamin-D were not available in the majority of participants and for that reason could not be included in our model. The regression analysis was limited to 51 patients who had a complete set of these laboratory values and predictors. For all analyses, a two-tailed $p < 0.05$ was considered to indicate statistical significance. Statistical analysis was performed using SAS, Version 9.4 (Cary, NC) and R version 3.02.

Results

One hundred and three patients with CD (mean age ± SD: 45.6 ± 15.1 years, 60% female) were included in the analysis. 42% reported diarrhea at diagnosis. Average BMI was normal (mean ± SD: 23 ± 5). As shown in Table 1, serum biochemistries, calciotropic hormones, vitamin D metabolites, and renal function were normal, on average. 21% of those who had a vitamin D level assessed had a value <20 ng/ml and 10.7% of those who had alkaline phosphatase (>129) measured had a level greater than the upper limit of normal. Mean tissue transglutaminase IgA was 3.56 (SD ± 3.29) times the upper limit of normal, as expected (range of scores: 1–272) Mean DXA *T*-scores were in the osteopenic range (*T*-score −1 to −2.4) at all skeletal sites (Table 1); *T*-scores in the osteopenic range was found in 49% of patients, while osteoporosis (*T*-score < −2.5) was found in 33% of patients. Mean DXA Z-scores were within normal limits at all skeletal sites. Of our total sample, only five individuals (4.9%) had a fracture, with only two having a fracture after CD diagnosis. Three individuals had fractures before the date of their first DXA scan. The median duration of CD from date of diagnosis to first DXA exam was 132 days (~4.3 months). Median days between the two DXA scans was 641 days (~21.4 months).

Table 1 Baseline Characteristics ($N = 103$)

Variable	Normal range	Mean ± SD or percentage
Race		
White non-Hispanic		73%
Black non-Hispanic		1%
Other race		12%
Unknown race		14%
Height (cm)		167.54 ± 9.08
Weight (kg)		64.09 ± 16.24
BMI (kg/m^2)	18.5–24.9	23 ± 5
Celiac duration (days)		196 ± 237
Diarrhea at presentation (%)		44%
Laboratory values		
Serum calcium (mg/dl)	8.8–10.3	9.0 ± 0.6
Parathyroid hormone (pg/ml)	10–65	50.38 ± 31.06
1,25-dihydroxyvitamin D (pg/ml)	20–79.3	52.84 ± 17.1
25-hydroxyvitamin D (ng/ml)	30–50	31.97 ± 15.92
Creatinine clearance (ml/min)	≥88	101.57 ± 32.41
Phosphorus (mg/dl)	2.5–4.3	4.48 ± 6.94
Alkaline phosphatase (U/l)	35–104	78.83 ± 54.61
Transglutaminase IgA (U/ml), standardized	Times the upper limit of normal	3.56 ± 3.29
DXA values		
Lumbar Spine *T*-score	≥−1.0	−1.50 ± 1.22
Femoral Neck *T*-score		−1.28 ± 1.08
Total Hip *T*-score		−1.43 ± 1.50
Distal one-third radius *T*-score		−1.18 ± 1.56
Lumbar spine *Z*-score	>−2.0	−0.94 ± 1.20
Femoral neck *Z*-score		−0.57 ± 0.99
Total hip *Z*-score		−0.74 ± 1.49
One-third radius *Z*-score		−0.51 ± 1.58

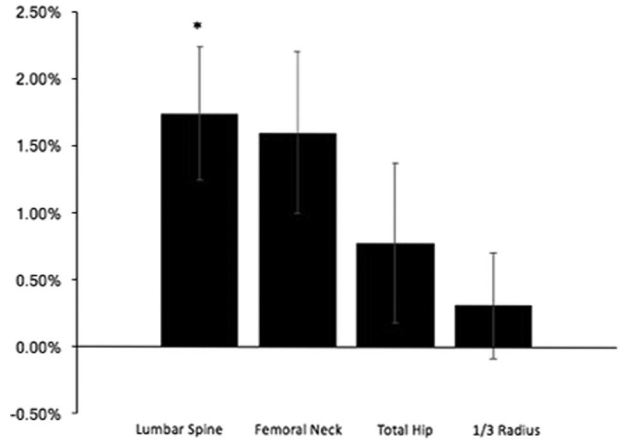

Fig. 1 Change in bone mineral density at each skeletal site after the diagnosis of celiac disease and institution of a gluten-free diet in our sample of 103 patients. Values represent mean ± standard error of the mean. *$p < 0.05$

As shown in Fig. 1, BMD increased significantly by 1.7 ± 5.5% at the predominantly trabecular LS ($p = 0.006$) after the diagnosis of CD and institution of a GFD over a median of 21.4 months between the 2 DXA scans. There was a similar trend at the total hip (1.6 ± 6.3%, $p = 0.06$). BMD changes at more cortical skeletal sites (femoral neck and distal one-third radius) were not statistically significant. As such, predictors of improvement were not assessed at these sites.

In a regression model (Table 2), only baseline serum calcium predicted the change in LS BMD ($p = 0.002$) after diagnosis. The ß-coefficient is interpreted to mean that lower baseline serum calcium is associated with a greater increase in LS BMD. Each 1 mg/dl lower serum calcium is associated with a 0.0470 g/cm^2 increase in BMD after diagnosis. In contrast, baseline age, weight, sex, LS BMD, renal function, and alkaline phosphatase level, as well as race, disease duration, and diarrhea at presentation were not associated with changes in BMD after diagnosis at the LS. Overall, the model explained 40% of the known variance in change in LS BMD. Patients with low baseline serum calcium (calcium <8.8 mg/dl) had lower mean baseline LS BMD compared to patients with normal serum calcium (calcium ≥8.8 mg/dl): 0.84 ± 0.78 vs. 0.92 ± 0.14 g/cm^2, $p = 0.03$.

At the TH (Table 3), higher creatinine clearance ($\beta = 0.005$, $p = 0.02$) was associated with greater gains in BMD after the diagnosis of CD. There was a tendency for men ($p = 0.08$), individuals of lower weight ($p = 0.08$), and those with longer disease duration ($p = 0.06$) to gain more TH BMD after diagnosis. In contrast, baseline age, hip BMD, serum calcium, and alkaline phosphatase, as well as symptomatic disease, and race were not associated with changes in BMD after diagnosis at the TH in the regression model. Overall, the model explained 32% of the known variance in change in total hip BMD.

Discussion

In this analysis, we demonstrate that BMD at the LS improves after the treatment of CD and that greater BMD improvement is associated with lower baseline serum calcium level. A similar BMD trend was seen at the hip, though better kidney function predicted greater improvement in BMD at this site, while male sex, disease duration and weight were of borderline significance. While the magnitude of increase in BMD was small, it exceeded the least significant change in BMD at the lumbar spine at our center. Such a change could be important, particularly in elderly adults, in whom BMD would be expected to decline over the period of follow-up. We also found that CD patients with low serum calcium had lower LS BMD at baseline compared to those without hypocalcemia, suggesting these patients may be at higher risk for osteoporosis and may warrant screening with DXA. To our knowledge, our study is the first performed in the United States to assess predictors associated with improvement in BMD in a population of CD patients over time.

Increased BMD after GFD initiation has been previously reported [6, 13–16, 18, 20, 21, 24, 26, 28], but there were limited data regarding which patients and skeletal sites have the greatest capacity to improve. Several studies indicate improvement in the LS and FN BMD. In the current study, the trabecular lumbar spine improved while sites richer in cortical bone (femoral neck and distal one-third radius) increased less or not at all. As trabecular bone is more metabolically active (i.e., higher remodeling rate) than cortical bone, it follows that recovery of BMD would be observed there first. Consistent with our finding, a recent study using high-resolution peripheral quantitative computed tomography found that the trabecular compartments of the radius and tibia increased more than the cortical compartments in CD patients after one year of a GFD [20].

The mechanisms of reduced BMD in CD and recovery after treatment have not been fully elucidated, but both local and systemic mechanisms have been implicated [29, 30]. The villous atrophy present in CD can impair the intestinal absorption of calcium and vitamin D [2, 29, 30], leading to compensatory secondary hyperparathyroidism and bone resorption, which occurs in order to maintain normal serum calcium levels. Indeed, secondary hyperparathyroidism was present in 28% of patients with CD in one study and PTH level was negatively associated with BMD at the forearm [31]. Osteomalacia may be present in some patients due to prolonged vitamin D deficiency and calcium malabsorption [4]. While bone biopsy data were not available in our study,

Table 2 Predictors of Change in Lumbar Spine BMD ($n = 51$)

	β estimate	Standard error	p-value	Overall model R^2
Intercept	0.3998	0.1773	0.03	$R^2 = 0.40$, $p = 0.001$
Age (per 10 years)	−0.005	0.006	0.4	
Weight (per 10 kg)	0.0041	0.009	0.7	
LS BMD (per 10 g/cm^2)	−0.179	0.740	0.8	
Calcium (per mg/dl)	−0.0470	0.0141	0.002	
Creatinine clearance (per 10 ml/min)	0.002	0.003	0.5	
Alkaline phosphatase (per 10 U/l)	0.002	0.002	0.2	
Male sex	0.01780	0.0175	0.3	
Disease suration (per 10 years)	0.0003	0.0003	0.3	
Diarrhea at presentation	0.0083	0.0137	0.6	
Race- White/Non-Hispanic	0.0185	0.0181	0.3	

Table 3 Predictors of Change in Total Hip Bone Mineral Density ($N = 51$)

	β estimate	Standard error	p-value	Overall model R^2
Intercept	0.0555	0.1257	0.7	$R^2 = 0.32$, $p = 0.01$
Age (per 10 years)	0.006	0.005	0.3	
Weight (per 10 kg)	−0.014	0.007	0.08	
Hip BMD (per 10 g/cm^2)	0.244	0.505	0.6	
Calcium (per mg/dl)	−0.108	0.108	0.3	
Creatinine clearance (per 10 ml/min)	0.005	0.002	0.02	
Alkaline phosphatase (per 10 U/l)	0.002	0.001	0.11	
Male sex	0.0242	0.0134	0.08	
Disease duration (per 10 years)	0.0005	0.0003	0.07	
Diarrhea at presentation	0.0055	0.0102	0.6	
Race-White/Non-Hispanic	0.0195	0.0140	0.17	

the elevated alkaline phosphatase level in a small percentage of our patients suggests that osteomalacia, rather than osteopenia or osteoporosis, may have contributed to low BMD in a minority of patients. Alkaline phosphatase level was not, however, a significant predictor of change in our model.

The second mechanism posits that the underlying autoimmune and inflammatory component of CD increase levels of pro-inflammatory cytokines, such as interleukin 1 and 6, and tumor necrosis factor-alpha, which may increase the ratio of receptor activator of nuclear factor kappa B ligand (RANKL) to osteoprotegerin (OPG) [29, 30, 32]. High RANKL/OPG ratios lead to an increase in the maturation and activation of osteoclasts, which are responsible for bone resorption. There were limited data regarding whether OPG or RANKL levels are altered in patients with CD, though one report indicated that the OPG/RANKL ratio was significantly lower in CD patients than in controls and was positively correlated with BMD at the spine [33]. Another study indicated that neutralizing antibodies against OPG may be present in some patients with CD [34].

Our finding that lower calcium is associated with a greater increase in BMD at the LS suggests that those with the greatest malabsorption may have the greatest potential for improvement in skeletal health with identification and treatment of CD. While lower serum calcium is not diagnostic of malabsorption, in the setting of newly diagnosed celiac disease, malabsorption remains the likely cause. Patients in our study were ambulatory and did not have other conditions that tend to decrease serum calcium (antiresorptive medications, hypoparathyroidism, advanced renal disease, tumor lysis, sepsis, osteoblastic metastases and pancreatitis). It is possible, however, that lower serum calcium indicates general malabsorption, rather than calcium malabsorption per se, as albumin-corrected calcium values were not available nor were more specific indicators of malabsorption (other than diarrheal symptoms) such as fecal fat testing. Fecal studies are not routinely ordered for patients with hypocalcemia in the setting of celiac disease and this analysis, therefore, offers real-world data from prevailing clinical practice.

The tendency for individuals with lower weight and greater disease duration to have the greatest increase in BMD at the TH also supports the concept of malabsorption playing a role in skeletal health in CD. Similar to our study, some prior studies have found an association between

reduced BMD and low body weight [3] and serum calcium [16] in patients with CD. Unfortunately, vitamin D was not included in our regression model as this value was missing from the EMR records of many patients, which is a limitation of our study. Some investigations have found vitamin D levels [3, 14–16] to be associated with low BMD in patients with CD, while other data suggest concomitant vitamin D deficiency and elevated bone alkaline phosphatase at diagnosis did not affect BMD improvement [15].

Diarrhea at CD diagnosis was not a predictor of improved BMD in our study. There are conflicting data regarding this finding [13, 14]. It appears somewhat counterintuitive that signs of malabsorption, such as low calcium and weight, predicted improved BMD in our study, while diarrheal symptoms at diagnosis, which is also a sign of malabsorption, did not. However, the presence of gastrointestinal symptoms correlates poorly with the degree of villous atrophy [35], and in a previous study we found evidence that patients with iron deficiency anemia (evidence of iron malabsorption) had more severe disease than patients presenting with diarrhea [36]. Few studies have looked at the relationship between bone health and villous atrophy in patients with CD. An increased risk of hip fracture has been found among CD patients with persistent villous atrophy [37] and a positive association has been found between normal BMD and duodenal mucosal healing after years of GFD adherence [17]. However, another study found no difference in BMD improvement in patients with persistent villous atrophy compared to those with normal mucosa after 1 year of a GFD [15]. We were unable to assess whether degree of villous atrophy or if mucosal healing was a predictor of BMD improvement but future studies should focus on this variable.

There are conflicting data with regard to the effect of sex upon improvement in BMD following institution of a GFD. In the current study, we found that male sex tended to predict greater gains in BMD at TH after diagnosis. Another study suggests women with CD were more likely to have improvement in BMD than men [21]. The reason for this difference is not entirely clear, but the previous study was limited to patients with asymptomatic CD, while ours included both symptomatic and asymptomatic patients. It is also possible that menopause status influenced results in women in our cohort. Though one study found no significant difference in degree of BMD improvement between pre and post-menopausal women with CD after a GFD [15] another found greater improvement in those who were premenopausal [22]. Data regarding menopausal status were not available and we therefore could not assess whether this factor influenced BMD recovery. In addition, men appear to have more severe disease at CD presentation compared to women, consistent with greater opportunity for overall improvement [38].

No other study has explored if renal function influences BMD or BMD changes in CD patients. Renal dysfunction is well known to be associated with bone loss and an increase in fracture risk in patients without CD [39]. Our findings extend our knowledge regarding the effect of renal function on BMD recovery in patients with CD and indicate that better renal function at baseline leads to greater improvement. Further studies on this topic are warranted.

This study has several limitations. Our sample represents a convenience sample of patients who had serial DXA at our center and the design is retrospective. As might be expected, older patients were more likely to have DXA and our results may not be applicable to younger patients. Secondly, since bone recovery varies with length of GFD adherence [24], and the DXA measurements used in this study were obtained at variable intervals after diagnosis, it is possible that we did not capture the full extent of BMD changes. However, the median follow-up in this study was 21 months and available data suggest that the largest BMD increase occurs within the first year after a GFD is instituted [24]. We do not have information regarding additional life style changes impacting bone health, such as vitamin D and calcium supplementation which could have been taken without a prescription. However, we did exclude patients with a medical record of taking prescription medications that would interfere with bone metabolism. Additionally, information about the extent to which patients were compliant with the GFD was not available, though all individuals were instructed to adhere to the GFD. We could not determine whether a GFD reduces the risk of fracture as the number of fractures occurring after diagnosis was small and we did not have a comparator group that continued to consume gluten. Because this study retrospectively obtained laboratory data from our medical record, some predictors (such as TTG IgA, mucosal healing, etc.) were missing or not available in some patients, and were therefore not included in our regression analyses.

Despite these limitations, our study also has several strengths. We assessed BMD at multiple skeletal sites including the distal one-third forearm. Our cohort of 103 patients is larger than most previously published longitudinal studies assessing skeletal health in CD. Most published studies have sample sizes of 24–86 participants [13–16, 18, 20–23]. To our knowledge, ours is the first longitudinal study in the United States to determine predictors of BMD improvement in CD patients from diagnosis. Further, most other studies were performed at least a decade ago [13–15, 21, 25]. Our study is also unique in that it is the first to include weight, disease duration, and multiple biochemical factors as possible predictors.

Our findings suggest that CD patients with low serum calcium are at risk for low BMD. Further, the greatest improvement in skeletal health after CD diagnosis occurs in

those with the lowest serum calcium, which is likely a surrogate for greatest malabsorption or disease severity at diagnosis. We feel the results of this study are important as they may aid physicians in counseling newly diagnosed CD patients about their risk for low BMD as well as their chances of skeletal recovery. Future studies should investigate whether degree of intestinal villous atrophy and elevated serology at time of CD diagnosis predict BMD improvement.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This analysis was approved by the Institutional Review Board of Columbia University (IRB-AAAR0254).

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