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Osteoporosis in a North American Adult Population With Celiac Disease

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OBJECTIVE: Osteoporosis, common in European and South American adults with celiac disease, has not been reported in those patients with celiac disease residing in North America. We therefore evaluated bone density in a group of patients from the United States.

METHODS: Patients (105 women and 23 men) with celiac disease, who had completed a questionnaire and had bone mineral density (BMD) measured by dual energy x-ray absorptiometry, were evaluated. The patients were an average age of 56 yr old (range 21–83 yr) and had been on a gluten-free diet from 0 months to 46 yr (mean 7.5 yr).

RESULTS: Osteoporosis (T score < -2.5) was present in 34% of the patients at the lumbar spine, 27% at the femoral neck, and 36% at the radius. Low bone mass (T score between -1.0 and -2.5) was present in 38% at the lumbar spine, 44% at the femoral neck, and 32% at the radius. When compared to age-matched controls, men were more severely affected than women. BMD did not differ between those on a gluten-free diet and those who had not begun therapy. BMD was remeasured 16 ± 2 months after beginning a gluten-free diet in 5 patients; it increased by 7.5% at the femoral neck ($p < 0.02$). In 16 patients who had followed a gluten-free diet for an average of 12 yr, BMD remained stable over an additional 2 yr of observation.

CONCLUSIONS: Osteoporosis and low bone mass often affect North American adults with celiac disease, whether or not they are on dietary therapy. Routine screening for osteoporosis is indicated in patients with celiac disease. (Am J Gastroenterol 2001;96:112–119. © 2001 by Am. Coll. of Gastroenterology)

INTRODUCTION

Celiac disease, or gluten-sensitive enteropathy, is caused by intolerance to gluten, occurring in genetically predisposed individuals (1). While celiac disease is common in Europe (2, 3), it is considered to be a rare disease in the United States (4). The reasons for this discrepancy are unclear, particularly since a recent study of healthy blood donors in Baltimore, MD found the prevalence of endomysial antibodies to be similar to that observed in Europe (5). This suggests that celiac disease may be underdiagnosed in the United States, either because of a low index of suspicion in American physicians (6, 7, 8) or because of a shift to a more silent form of the disease in which gastrointestinal symptoms are not prominent (9).

Within the past 10 yr, dual energy x-ray absorptiometry (DXA), a relatively inexpensive, accurate, and reproducible technique, has become available to physicians for measuring bone mineral density (BMD) (10). Several European and South American studies have now reported that bone mass is reduced in both treated and untreated adults and children with celiac disease (11, 12, 14–20). There are no published data on bone density in patients with celiac disease who reside in the United States. In an effort to determine the extent of skeletal demineralization associated with celiac disease in this country and whether they resembled celiac patients in other countries, we surveyed a group of adults with celiac disease.

MATERIALS AND METHODS

Study Design

We mailed a survey to 300 adults who had biopsy-proven celiac disease as identified from a databank at Columbia-Presbyterian Medical Center (21). In responding to a previous questionaire, these individuals had indicated that they had at least one BMD determination. Survey questions included: age, gender (and menopausal status), race, height, and weight; information on celiac disease, including age at diagnosis, symptoms at presentation (specifically, diarrhea), duration of gluten-free diet, presence of lactose intolerance, and thyroid disease; risk factors for osteoporosis, including alcohol, caffeine, and tobacco exposure; medications (use and duration of thyroid hormone replacement, calcium, and vitamin D supplements); estimated daily consumption of dairy products; timing of the BMD measurement relative to age at diagnosis of the disease and duration of the gluten-free diet. Of the questionnaires returned, 128 subjects included a complete BMD performed by DXA, either based in

This study was approved by the Institutional Review Board of Columbia-Presbyterian Medical Center.

Table 1. Demographic, Anthropomorphic, and Clinical Characteristics of 128 Patients With Celiac Disease

Characteristic	Men	Premenopausal Women	Postmenopausal Women
Number of patients	23	26	79
Age (yr)	59 ± 15	39 ± 9*	61 ± 9
Age at diagnosis (yr)	52 ± 18	39 ± 9†	51 ± 12
Duration of gluten-free diet (yr)	4 ± 9	3 ± 4	9 ± 10‡
Height (cm)	174.1 ± 9.1§	161.8 ± 6.6	163.5 ± 7.2
Weight (kg)	72.2 ± 13.0§	57.5 ± 10.2	60.7 ± 8.4
Body mass index (kg/m^2)	23.9 ± 4.4	22.0 ± 3.8	22.7 ± 3.4
Classical/asymptomatic presentation	20/2	22/4	69/8
History of lactose intolerance (%)	5 (22%)	5 (19%)	21 (27%)
History of thyroid disease (%)	3 (13%)	3 (12%)	25 (32%)

* $p < 0.001$ compared to men and postmenopausal women.
† $p < 0.0001$ compared to men and postmenopausal women.
‡ $p < 0.01$ compared to men and premenopausal women.
§ $p < 0.0001$ compared to premenopausal and postmenopausal women.

their community hospitals (n = 97) or at Columbia-Presbyterian Medical Center (n = 31). These 128 individuals are the subject of this report. There was no significant difference in the sex distribution or age of those subjects who did not respond to the questionaire or were excluded because of lack of data, compared to the 128 subjects included in the study. The majority (n = 78) had their BMD performed on a Hologic QDR bone densitometer (Hologic Inc., Waltham, MA). BMD was performed on a Lunar densitometer (Lunar, Inc., Madison, WI) in 50 subjects. BMD was expressed as standard deviation scores, which compare individual BMD determinations to those of young (T) and age-matched (Z) normal populations of the same gender and race (22). All femoral neck T and Z scores were compared to the National Health and Nutrition Examination Survey (NHANES) database (23, 24). World Health Organization (WHO) criteria for postmenopausal women (22) define T scores above −1.0 as normal, those between −1.0 and −2.4 as osteopenia or low bone mass, and those equal to or below −2.5 as osteoporosis. The majority had BMD measurements of the lumbar spine (n = 125) and femoral neck (n = 120). BMD of the distal one-third site of the nondominant radius was available in 37 subjects.

Statistical Analysis

All continuous data are presented as mean ± standard deviation and all categorical data as percent or number (n). Distributions of continuous variables were tested for normality and descriptive statistics calculated. Differences between groups were analyzed using both parametric (*t* tests) and nonparametric (Wilcoxon rank score) tests. Since the results of these analyses were the same, we have chosen to report the results from the *t* test analyses. Linear regression analysis was used to assess the relationships between BMD and demographic or anthromorphic characteristics. All inferential tests use a 5% type I error rate.

RESULTS

Study Population

The study group (Tables 1 and 2) included 23 men, 26 premenopausal women, and 79 postmenopausal women, predominantly (n = 128) Caucasian. The average age was 56 yr (range, 21–83 yr). All claimed to adhere to a gluten-free diet (mean duration 9 ± 10 yr). The premenopausal women were approximately 2 decades younger than the men and postmenopausal women. Average age at diagnosis was

Table 2. Medication and Supplement Use in 128 Patients With Celiac Disease When Bone Density Was Measured

Characteristic	Men	Premenopausal Women	Postmenopausal Women
Number of patients on 1-thyroxine	2	4	21
Duration of 1-thyroxine (yr)	2 ± 2	14 ± 11	14 ± 14
Postmenopausal women on estrogen, n (%)	N/A	N/A	50 (63%)
Duration of estrogen use	N/A	N/A	9 ± 8
Estimated dietary calcium intake (mg/day)	417 ± 386	381 ± 356	369 ± 295
Supplemental calcium intake, mg/day (n)	1352 ± 779 (18)	1206 ± 651 (15)	1001 ± 456 (64)
Estimated total calcium intake (mg/day)	1476 ± 751	947 ± 727*	1396 ± 771
Duration of calcium supplements (yr)	2 ± 2	3 ± 3	6 ± 6
Number of patients on vitamin D (%)	15 (65%)	10 (39%)	49 (62%)
Dose of vitamin D (IU/day)	663 ± 488	1343 ± 2595	864 ± 1511
Duration of vitamin D (yr)	1 ± 1	3 ± 3	6 ± 7

N/A = not applicable.
* $p < 0.02$ compared to men and postmenopausal women.

48 yr (range 6 months–83 yr), although the premenopausal women were diagnosed at a significantly younger age. Only 2 patients were diagnosed before age 20. Although the men were taller and heavier than the women (data not shown), BMI did not differ between them. The majority of the patients had presented with classical symptoms of celiac disease (diarrhea); 11% had no gastrointestinal symptoms. Lactose intolerance was reported by 24%. Thirty-one subjects, predominantly (81%) postmenopausal women, reported a history of goiter or hypothyroidism. Of these, 27 were currently receiving l-thyroxine. Fifty postmenopausal women (63%) had taken estrogen replacement therapy for an average of 9 ± 8 yr. The majority of the patients were taking supplemental calcium (80%) and vitamin D (58%).

Bone Mineral Density

The proportion of subjects with low bone mass and osteoporosis is shown in Figure 1. T scores between −1.0 and −2.5 (low bone mass) were present in 38% of the patients at the spine, 44% at the femoral neck, and 32% at the radius. Osteoporosis (T score <−2.5) was present in 34% at the spine, 27% at the femoral neck, and 36% at the radius. Per WHO criteria (23), only 28% had normal spine BMD, 29% had normal femoral neck BMD, and 32% had normal radial BMD. The proportion of subjects with osteoporosis and low bone mass was similar regardless of the manufacturer of the densitometer or whether BMD had been measured in a research (CPMC) or community setting.

BMD was next examined according to gender and menopausal status (Fig. 2). When compared to a young normal population, the spine T scores of men and postmenopausal women (−2.403 ± 1.45 and −2.008 ± 1.48, respectively) were similar and within the range of low bone mass (Fig. 2A). In contrast, the average T score of the premenopausal women was normal (−0.823 ± 1.13), significantly higher than that of the men and postmenopausal women ($p <$ 0.001). Similarly, the femoral neck T scores of both the men and postmenopausal women were consistent with low bone mass (−1.981 ± 1.10 and −1.878 ± 1.08, respectively) and lower ($p < 0.0001$) than that of the premenopausal women, which was normal (−0.676 ± 1.27; Fig. 2C).

When compared to age-matched controls (Z score), a different pattern emerged. At the spine (Fig. 2B), both groups of women were only half a standard deviation below average for their age (−0.507 ± 1.14 and −0.605 ± 1.27, respectively). In contrast, BMD of the men was markedly reduced relative to age-matched norms, significantly lower than that of both groups of women (−1.852 ± 1.42; $p <$ 0.001). A similar pattern was apparent at the femoral neck (Fig. 2D).

Low bone mass and osteoporosis was significantly less common in premenopausal women than in men and postmenopausal women (Fig. 3; χ^2 13.602; $p = 0.009$). Among premenopausal women, 50% had normal spine T scores, 42% had low bone mass, and only 8% had osteoporosis. Among men and postmenopausal women, only 18% and 23% respectively had normal spine T scores. Low bone mass was present in 32% of men and 37% of postmenopausal women, and osteoporosis was present in 50% of men and 40% of postmenopausal women. A similar pattern was apparent at the femoral neck (data not shown; χ^2 11.331; $p = 0.023$).

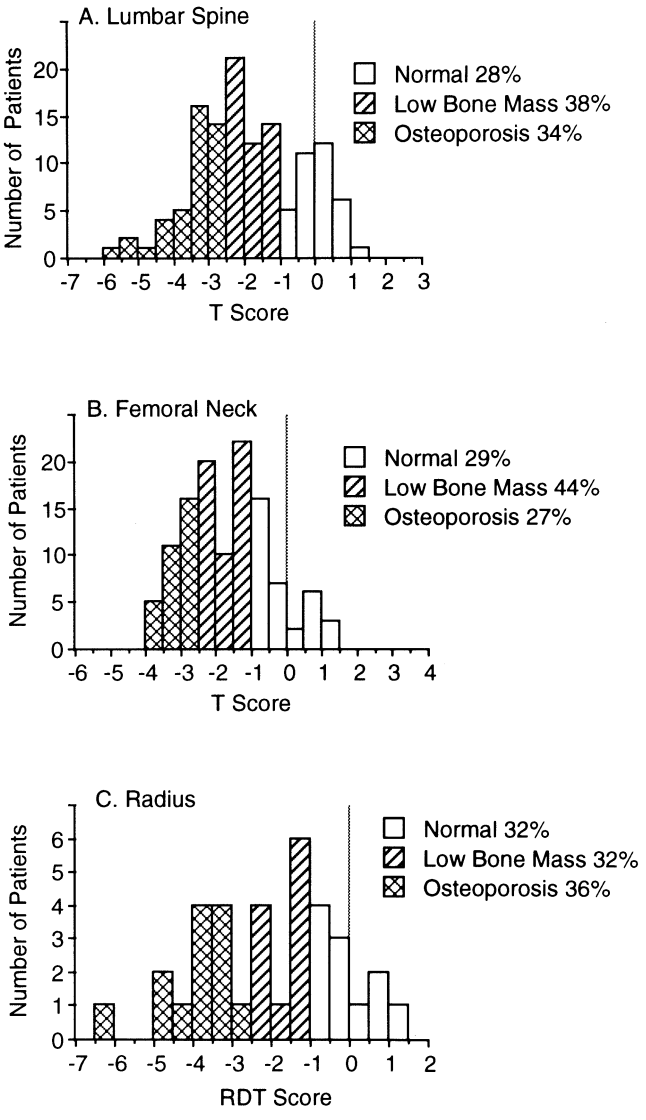

Figure 1. Distribution of bone mineral density measurements of the lumbar spine (*A*), femoral neck (*B*) and one-third site of the radius (*C*) in adults with celiac disease. Data are expressed as T scores, which relate BMD measurements of individual patients to those of a young normal population of the same gender. T score measurements between −1.0 and −2.5 standard deviations below the mean (hatched bars) indicate low bone mass, whereas those more than −2.5 standard deviations below the mean (cross-hatched bars) indicate osteoporosis, and those above −1.0 are normal.

BMD remained unaffected by certain clinical characteristics or medication that had the potential to influence bone and mineral metabolism. Mean lumbar spine and femoral neck T and Z scores did not differ with respect to whether or not patients had typical symptoms of celiac disease,

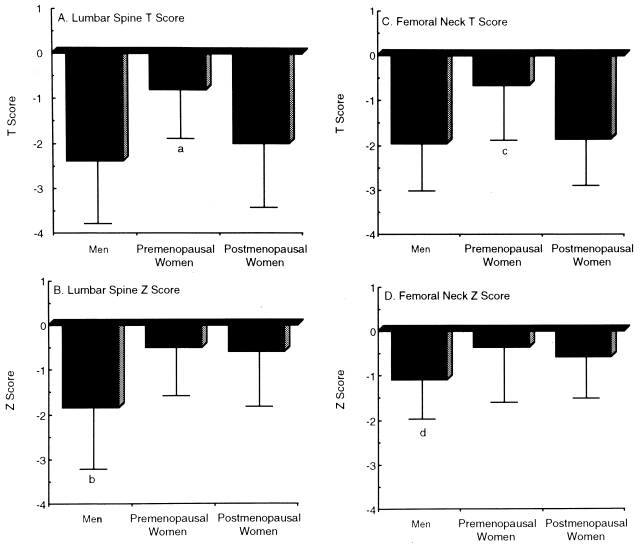

Figure 2. Average bone mineral density in men, premenopausal women and postmenopausal women with celiac disease. In *A* (lumbar spine) and *C* (femoral neck), the data are expressed as T scores, which relate BMD measurements of individual patients to those of a young normal population of the same gender. In *B* (lumbar spine) and *D* (femoral neck), the data are expressed as Z scores, which relate BMD measurements of individual patients to those of a age-matched normal population of the same gender.

lactose intolerance, a history of thyroid disease, or thyroxine therapy. The mean spine T score of the 26 women on estrogen replacement was -2.057 ± 1.41 and the T score of women not taking estrogen was -2.026 ± 1.40; femoral neck T and Z scores were also the same. BMD was not better in patients taking calcium and vitamin D supplements than in those who were not. Mean lumbar spine T score was significantly lower in patients with a history of fracture (-2.971 ± 1.87 *vs* -1.775 ± 1.41; $p \leq 0.04$).

The relationship between certain demographic, anthropomorphic characteristics, and bone density is presented in Table 3. As expected, since the T score compares individual BMD measurements to peak bone mass at age 30 yr, both lumbar spine and femoral neck T scores demonstrated strong negative correlations with increasing age at the time of bone mass measurement. Age at diagnosis of celiac disease was inversely related to T and Z scores at both sites, although the lumbar spine Z score did not quite reach significance ($p = 0.06$). BMI was the only anthropomorphic parameter directly related to T score, as well as to the lumbar spine. Duration of gluten-free diet bore no relationship to BMD. The patients reporting hypothyroidism or thyroxine supplementation were analyzed separately. No significant difference was found in BMD compared to the group as a whole.

Effect of Gluten-Free Diet on BMD

BMD was also analyzed according to how soon it was performed relative to the diagnosis of celiac disease. Untreated patients (n = 31) had not yet begun a gluten-free diet when BMD was measured. Treated patients (n = 97) had the BMD performed after having been on a gluten-free diet for an average of 9 ± 10 yr. There were no significant differences in T scores at either the lumbar spine or the femoral neck in treated and untreated patients (lumbar spine, -1.584 ± 1.27 *vs* -1.913 ± 1.52; femoral neck, -1.307 ± 1.24 *vs* -1.715 ± 1.19). Treated and untreated patients were similar with respect to age at diagnosis (48 ± 14 *vs* 51 ± 16 yr, respectively) and BMI (23.2 ± 3.7 *vs* 21.5 ± 3.2 kg/m^2,

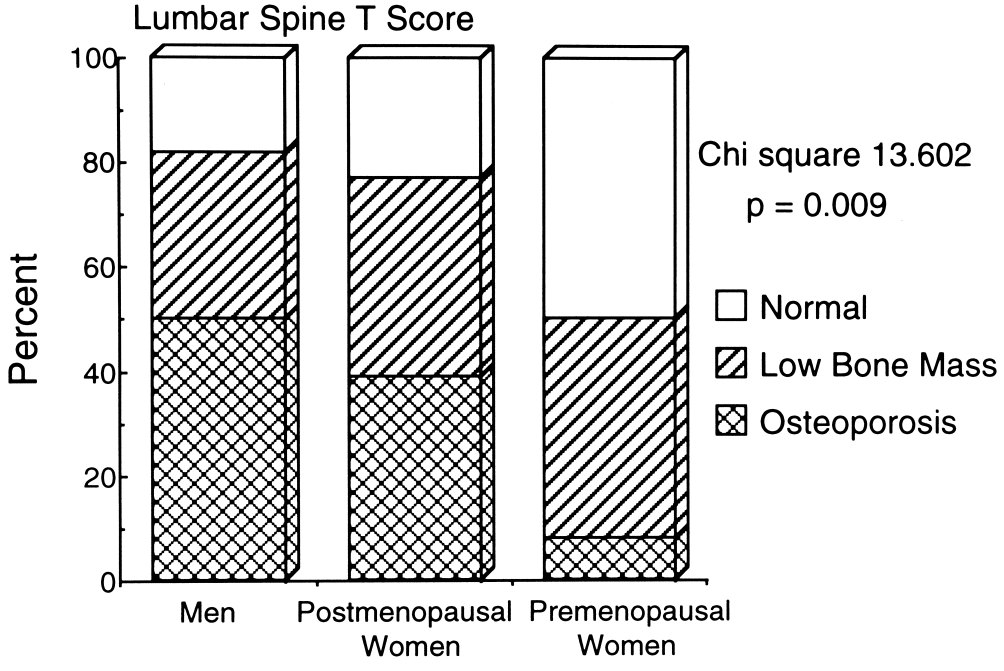

Figure 3. Prevalence of osteoporosis and low bone mass in men, premenopausal women and postmenopausal women with celiac disease.

Table 3. Determinants of Bone Density: Regression Analysis

	Lumbar Spine		Femoral Neck	
	T Score	Z Score	T Score	Z Score
Age	−0.444*	−0.072	−0.535*	−0.109
Age at diagnosis	−0.408*	−0.169	−0.458*	−0.190†
Height	−0.090	−0.203	−0.086	−0.153
Weight	+0.131	+0.027	+0.067	+0.022
Body mass index (kg/m^2)	+0.210†	−0.168	+0.148	+0.138
Duration of gluten-free diet	−0.038	−0.125	−0.027	+0.165

* $p \leq 0.0001$.
† $p \leq 0.05$.

respectively). Treated patients were older than untreated patients (58 ± 12 *vs* 51 ± 16 yr; $p = 0.01$), which could have accounted for the apparent lack of treatment effect, since BMD normally declines with increasing age. However, Z scores were also similar regardless of treatment status (data not shown), suggesting that the lack of an effect of the diet could not be accounted for by a treated patient's older age. There was also no apparent effect of therapy on the proportion of patients with osteoporosis and low bone mass. Osteoporosis was present in 35% of patients scanned at diagnosis and in 34% whose BMD was performed on a gluten-free diet. Low bone mass was present in 31% scanned at diagnosis and 40% of those already on therapy.

Five patients had their BMD measured at diagnosis, and again 16 ± 2 months after beginning a gluten-free diet. At the lumbar spine (Fig. 4A), mean BMD increased by 4.7% (range −2.1–+14.0%), from 0.840 to 0.879 g/cm^2 ($p = 0.18$). There was a significant 7.5% increase (range 2.5%–13.4%) in mean femoral neck BMD (Fig. 4B; $p = 0.024$) over the same period. Fifteen patients in whom BMD was first measured after 12 ± 11 yr (range 20–36 yr) on a gluten-free diet had the measurement repeated 23 ± 4 months later, while maintaining the same diet. In contrast to those patients in whom therapy was recently initiated, mean BMD did not change at either the lumbar spine or femoral neck (data not shown).

DISCUSSION

In this study, BMD, measured predominantly in community-based settings, was evaluated in individuals with celiac disease residing in the United States. We noted, osteoporosis, as defined by the WHO, was common, as was low bone mass or osteopenia. In fact, only 28% of the participants in our study had normal BMD by these criteria. In 75% BMD was below average for their age, and in 46% it was more than one standard deviation below age-matched norms. Because the relative risk of fracture increases by 1.5–2.0 for every one standard deviation decrease in BMD (at least in Caucasian women) (25), patients with celiac disease are likely to be at increased lifetime risk for fracture.

The prevalence of osteoporosis and low bone mass in our subjects is consistent with observations of investigators in Europe (11, 13, 15, 17–20, 26, 27) and South America (14, 16). Virtually every study of adults with celiac disease has found BMD to be significantly reduced.

The severity of the deficit in bone mass varied by gender and menopausal status. Premenopausal women were least likely to have osteoporosis or low bone mass, whereas

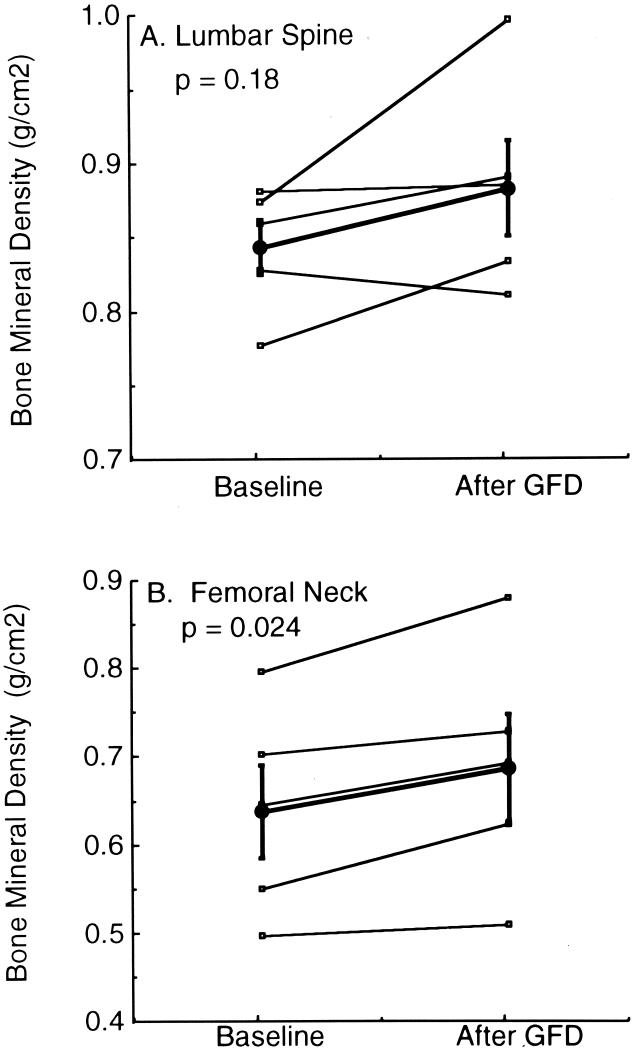

Figure 4. Effect of institution of a gluten-free diet on lumbar spine (*A*) and femoral neck (*B*) bone mineral density. The second bone density measurement was performed 16 ± 2 months after beginning dietary therapy.

postmenopausal women and men were similar in their propensity for both afflictions. However, when compared to age-matched controls, men were more severely affected than either group of women. In fact, our postmenopausal women with celiac disease were only approximately one-half standard deviation lower than normal postmenopausal women, suggesting that the degree of osteopenia they demonstrate is not a great deal more severe than that experienced by other nonceliac women who pass through menopause.

The observation that bone density is lower in adult men than it is in women has not been reported previously. The majority of studies either investigate women only (14, 16, 26), do not analyze results by gender (11, 13, 17–20, 26), or have found similar reductions in age-related BMD in men and women (27). However, in a study of 42 children with treated celiac disease, Bayer *et al*. (20) observed that boys were more severely affected than girls with respect to mean BMD and prevalence of low bone mass. Moreover, while premenarchal girls had low bone mass, postpubertal girls who were estrogen-replete had BMD measurements that were similar to controls. These authors also concluded that male sex may be associated with impaired achievement of peak bone mass in celiac disease. Our data and those of Bayer *et al*. (20) suggest that endogenous estrogen may protect against at least some of the bone loss associated with celiac disease. However, it is also very possible that the low BMD in the men of this study is due to ascertainment bias, since more severely affected men are likely to have bone mass measurements and return questionnaires. It is also important to note that the relevance of the WHO criteria in populations other than postmenopausal Caucasian women (*i.e*., men, premenopausal and perimenopausal women) has not been tested (22). It could be argued that low bone mass, even to osteoporotic levels, may not have the same significance with respect to fracture prediction in men and premenopausal women as it does in an older population of postmenopausal women (25).

The pathogenesis of the low bone mass and osteoporosis in celiac disease is multifactorial. The reduction in surface area of the intestinal mucosa may impair calcium absorption in the proximal jejunum, resulting in secondary hyperparathyroidism, increased bone resorption, and turnover and excessive rates of bone loss (11, 28, 29). Malabsorption of vitamin D may also play a role, particularly in elderly, housebound patients who live in northern latitudes. Patients who are undiagnosed or untreated during childhood and adolescence may never achieve peak bone mass. After institution of a gluten-free diet, intestinal calcium absorption has been demonstrated to improve with resolution of overt biochemical derangements (30). However, subclinical disturbances of bone and mineral metabolism may persist and prevent complete restitution of low bone mass or osteoporosis. For example, levels of the intestinal calcium-binding protein calbindin-D9k, undetectable in biopsies of patients with active celiac disease, are reduced by approximately 75% even in treated patients with normal villous architecture (31). Other authors have observed that serum levels of inflammatory cytokines, elevated in patients with celiac disease, are inversely related to lumbar spine bone density, suggesting that the low BMD observed in patients with celiac disease may be related to the inflammatory process itself (32).

None of the factors that had the potential to influence BMD in patients with celiac disease (lactose intolerance, 1-thyroxine, or estrogen replacement) appeared to affect T and Z scores in our subjects. Similarly, BMD measurements were lower in subjects taking calcium and vitamin D supplements, perhaps because patients with low bone mass or osteoporosis would be more likely to increase their intake of calcium and vitamin D. The only other report to comment on calcium intake and BMD in patients with celiac disease says that patients with lower than average daily calcium intake showed reduced BMD measurements (15). Therefore, we concur with the recommendation that dietary calcium and physiological vitamin D supplementation are rational in patients with celiac disease (33, 34).

Similar to other cross-sectional studies (11, 18, 26, 27), we also found BMD levels to be similar in recently diagnosed adults who had not yet begun a gluten-free diet, as well as in those who had been on therapy for many years. In contrast, Valdimarsson *et al*. (17), in a case-control study, found BMD to be significantly lower in treated adults with persistent villous atrophy, while those with normal villous architecture did not differ significantly from controls. They also detected no correlation between BMD and duration of gluten-free diet. However, at least two studies have reported that patients in whom celiac disease is diagnosed and treated during childhood have normal bone mass, whereas those in whom therapy is begun later in childhood or after adolescence have reduced BMD regardless of therapy (13, 20).

Despite comparable bone mass in treated and untreated patients, our data suggest that BMD may increase during the first years after institution of a gluten-free diet and that patients on gluten-free diet, on average, do not sustain further bone loss. BMD has also been reported to increase significantly during the first years after initiation of dietary therapy in both children (35–37) and adults (17, 37–44). Although BMD may normalize when therapy is begun during childhood (35, 37), most studies of adults suggest that restoration of bone mass is frequently incomplete, with many remaining below comparable control values (38–44). These data, as well as our observation that bone mass is inversely related to age at diagnosis of celiac disease without much effect of gluten-free diet, support the concept that early diagnosis and therapy are critical in permitting patients with celiac disease to achieve normal peak bone mass. They are also consistent with the theory that the increase in BMD observed when therapy is begun during adulthood is the result of mineralization of remodeling space expanded by secondary hyperparathyroidism. If so, BMD should improve for only 2–3 yr and then stabilize, a pattern similar to that observed after initiation of anitresorptive therapy (estrogen,

bisphosphonates, calcitonin) in women with postmenopausal osteoporosis. Remaining deficits in BMD could then be attributed to a lifelong disease which had interfered with attainment of peak bone mass.

There are several limitations to the interpretation of these results. This was a cross-sectional study and therefore subject to all of the well known problems associated with such analyses. Subjects were not randomly selected from a representative sample of patients with celiac disease. Therefore, these results probably reflect the worst cases of gluten-sensitive enteropathy, since there would be a greater likelihood that more severely affected individuals would want their bone densities measured. Inclusion of BMD measurements performed in our research unit and in the community could decrease the reliability of the results. However, average T and Z scores and the proportion of subjects with osteoporosis or low bone mass were the same regardless of where the studies were performed. Finally, the terms osteoporosis and low bone mass or osteopenia as used in this report are meant to quantify bone mineral rather than the pathologic basis of demineralization. Without bone biopsies, it is unclear whether the deficits are due to osteoporosis, osteomalacia, or a mixture of both. However, despite these limitations, the observations reported are of interest and worthy of further investigation.

Despite the fact that celiac disease is probably more occult or "silent" in the United States, our results demonstrate that the prevalence of skeletal demineralization is similar to that observed in patients who reside in Europe and South America. Though institution of a gluten-free diet may be associated with increases in BMD, bone mass is not restored to normal levels in all patients. Finally, because of the high yield of abnormal BMD measurements and the potential for age-related bone loss and fractures, we believe it is reasonable to screen all patients with celiac disease for osteoporosis.

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REFERENCES

1. Marsh M. Gluten, major histocompatibility complex and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ("celiac sprue"). Gastroenterology 1992;102:330–54.
2. Catassi C, Ratsch IM, Fabiani E, et al. Coeliac disease in the year 2000: Exploring the iceberg. Lancet 1994;343:200–3.
3. Johnston SD, Watson RGP, McMillan SA, et al. Prevalence of coeliac disease in Northern Ireland. Lancet 1997;350:1370.
4. Talley NJ, Valdovinos M, Petterson TM, et al. Epidemiology of celiac sprue: A community-based study. Am J Gastroenterol 1994;89:843–6.
5. Not T, Horvath K, Hill ID, et al. Celiac disease risk in the USA: High prevalence of antiendomysial antibodies in healthy blood donors. Scand J Gastroenterol 1998;33:494–8.
6. Ferguson A. Celiac disease, an eminently treatable condition, may be underdiagnosed in the United States. Am J Gastrolenterol 1997;92:1252–4.
7. Fasano A. Where have all the American celiacs gone? Acta Pediatr 1996;4:412–20.
8. Podolsky DK, LaMont JT. So, where are all the celiacs? Gastroenterology 1999;116:237 (editorial).
9. Green PHR, Byfield FC. The diagnosis of celiac disease. Clin Persp Gastroenterol 1998;1:133–9.
10. Johnston CC, Slemenda CW, Melton LJ III. Clinical use of bone densitometry. New Engl J Med 1991;324:1105–9.
11. Keaveny AP, Freaney R, McKenna MJ, et al. Bone remodeling indices and secondary hyperparathyroidism in celiac disease. Am J Gastroenterol 1996;91:1226–31.
12. Shaker JL, Brickner RC, Findling JW, et al. Hypocalcemia and skeletal disease as presenting features of celiac disease. Arch Int Med 1997;157:1013–6.
13. Molteni N, Caraceni MP, Bardella MT, et al. Bone mineral density in adult celiac patients and the effect of gluten-free diet from childhood. Am J Gastroenterol 1990;85:51–3.
14. Mazure R, Vazquez H, Gonzalez D, et al. Bone mineral affection in asymptomatic adult patients with celiac disease. Am J Gastroenterol 1994;89:2130–4.
15. McFarlane XA, Bhalla AK, Reeves DE, et al. Osteoporosis in treated adult coeliac disease. Gut 1995;36:710–4.
16. Gonzalez D, Mazure R, Mautalen C, et al. Body composition and bone mineral density in untreated and treated patients with celiac disease. Bone 1995;16:231–4.
17. Valdimarsson T, Toss G, Ross I, et al. Bone mineral density in coeliac disease. J Gastroenterol 1994;29:457–61.
18. Bode S, Hassager C, Gudmand-Hoyer E, Christiansen C. Body composition and calcium metabolism in adult treated coeliac disease. Gut 1991;32:1342–5.
19. Corazzo GR, di Sario A, Cecchetti L, et al. Bone mass and metabolism in patients with celiac disease. Gastroenterol 1995;109:122–8.
20. Bayer M, Stepan JJ, Sedlackova M, et al. Spinal bone mineral density in children with celiac disease. J Clin Densitometry 1998;1:125–36.
21. Stavropoulos SN, Poneros JM, Das L, et al. Celiac disease: A patient survey. Gastroenterology 1997;112:A44.
22. Kanis JA, Melton LJ, Christiansen C, et al. Perspective. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137–41.
23. Looker AC, Wahner HW, Dunn WL, et al. Proximal femur bone mineral levels of US adults. Osteoporosis Int 1995;5: 385–409.
24. Faulkner KG, Roberts LA, McClung MR. Discrepancies in normative data between Lunar and Hologic DXA systems. Osteoporosis Int 1996;6:432–6.
25. Cummings SR, Black D. Bone mass measurements and risk of fracture in Caucasian: A review of findings from prospective studies. Am J Med 1995;98(suppl 2A):20–4S.
26. Pistorius LR, Sweidan WH, Purdie DW, et al. Coeliac disease and bone mineral density in adult female patients. Gut 1995; 37:639–42.
27. Kemppainen T, Kroger H, Janatuinen E, et al. Osteoporosis in adult patients with celiac disease. Bone 1999;24:249–55.
28. Howdle PD, Losowsky M. Coeliac disease in adults. In: Marsh MN, ed. Coeliac disease. Oxford: Blackwell, 1992:49–80.
29. Selby PL, Davies M, Adams JE, Mawer EB. Bone loss is related to secondary hyperparathyroidism. J Bone Miner Res 1999;14:652–657.
30. Molteni N, Bardella MT, Vezzoli G, et al. Intestinal calcium absorption as shown by stable strontium test in celiac disease

before and after gluten-free diet. Am J Gastroenterol 1995;90: 2025–8.
31. Staun M, Jarnum S. Measurement of the 10,000-molecular weight calcium-binding protein in small-intestinal biopsy specimens from patients with malabsorption syndromes. Scand J Gastroenterol 1988;23:827–32.
32. Forneri MC, Pedreira S, Niveloni S, et al. Pre- and post-treatment serum levels of cytokines IL-1 beta, IL-6, and IL-1 receptor antagonist in celiac disease. Are they related to the associated osteopenia? Am J Gastroenterol 1998;93:413–18.
33. Trier JS. Celiac sprue. New Engl J Med 1991;325:1709–19.
34. Walters JRF. Bone mineral density in coeliac disease. Gut 1994;35:150–1.
35. Mora S, Barera G, Ricotti A, et al. Reversal of low bone density with a gluten-free diet in children and adolexcents with celiac disease. Am J Clin Nutr 1998;67:477–81.
36. Scotta MS, Salvatore S, Salvatoni A, et al. Bone mineralization and body composition in young patients with celiac disease. Am J Gastroenterol 1997;92:1331–4.
37. Rea F, Polito C, Marotta A, et al. Restoration of body composition in celiac children after one year of gluten-free diet. J Pediatr Gastroenterol Nutr 1996;23:408–12.
38. Ciacci C, Maurelli L, Klain M, et al. Effects of dietary treatment on bone mineral in adults with celiac disease: Factors predicting response. Am J Gastroenterol 1997;92:992–6.
39. Smecuol E, Gonzalez D, Mautalen C, et al. Longitudinal study on the effect of treatment on body composition and anthropometry of celiac disease patients. Am J Gastroenterol 1997; 92:639–43.
40. Mautalen C, Gonzalez D, Mazure R, et al. Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. Am J Gastroenterol 1997;92: 313–18.
41. Corazzo GR, Di Stefano M, Jorizzo RA, et al. Propeptide of type I procollagen is predictive of posttreatment bone mass gain in adult celiac disease. Gastroenterology 1997;113:67–71.
42. McFarlane XA, Bhalla AK, Robertson DA. Effect of a gluten-free diet on osteopenia in adults with newly diagnosed coeliac disease. Gut 1996;39:180–4.
43. Corazzo GR, Di Sario A, Cecchetti L, et al. Influence of pattern of clinical presentation and of gluten-free diet on bone mass and metabolism in adult coeliac disease. Bone 1996;18: 525–30.
44. Valdimarsson T, Lofman O, Toss G, Strom M. Reversal of osteopenia with diet in adult coeliac disease. Gut 1996;38: 322–7.