Published in final edited form as:

J Nutr Health Aging. 2013 ; 17(6): 562–565. doi:10.1007/s12603-013-0017-8.

Celiac Disease in Women with Hip Fractures

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Abstract

Objective—Celiac disease is associated with decreased bone density, however, the risk of fractures in celiac disease patients is unclear. We compared the prevalence of celiac disease between a group of women with hip fractures and a group of women undergoing elective joint replacement surgery and the association between celiac disease and vitamin D levels.

Methods—Two hundred eight community dwelling and postmenopausal women were recruited from Boston, MA (n=81) and Baltimore, MD (n=127). We measured tissue transglutaminase IgA by ELISA to diagnose celiac disease and 25-hydroxyvitamin D (25(OH)D) levels by radioimmunoassay in both women with hip fractures (n=157) and the control group (n=51), all of whom were from Boston. Subjects were excluded if they took any medications or had medical conditions that might affect bone.

Results—Median serum 25(OH)D levels were significantly lower ($p < 0.0001$) in the hip fracture cohorts compared to the elective joint replacement cohort (14.1 ng/ml vs. 21.3 ng/ml, respectively). There were no differences in the percentage of subjects with a positive tissue transglutaminase in the women with hip fractures versus the control group (1.91% vs. 1.61%, respectively).

Conclusion—Vitamin D levels are markedly reduced in women with hip fractures, however hip fracture patients did not show a higher percentage of positive tissue transglutaminase levels compared with controls. These data suggest that routine testing for celiac disease among hip fracture patients may not prove useful, although larger prospective studies among hip fracture subjects are needed.

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

Keywords

Celiac disease; hip fracture; vitamin D

INTRODUCTION

Hip fractures are one of the most serious of fractures and are associated with functional impairment and increased mortality among elderly men and women. An estimated 80% of hip fracture patients have a secondary cause associated with their underlying osteoporosis. [1] Data also indicate that up to 85% of women with hip fractures are vitamin D deficient and have a median 25-hydroxyvitamin D [25(OH)D] level that ranges between 10.2 to 14.7 ng/ml.[2–4] Celiac disease is associated with vitamin D deficiency and low bone mass.[5–7] Up to 77% of individuals with celiac disease have below average bone mineral density (BMD) for their age and 26–34% have osteoporosis.[8] The prevalence of celiac disease ranges from an estimated 1 out of 120 to 300 individuals in both Europe and the United States.[9] However, as many as 50% – 90% of individuals with celiac disease are undiagnosed due to an absence or minimal presence of clinical symptoms, such as diarrhea and weight loss.[10]

Sensitive and specific screening tests for celiac disease are available.[11] At present, there are limited data regarding the relationship between celiac disease and vitamin D deficiency in elderly hip fracture patients; vitamin D deficiency can result in an increased risk of hip fractures and osteoporosis and, when severe, symptomatic osteomalacia.[12] Further, it is not known whether these patients should be screened for celiac disease.

In this study, we investigated in a group of women with hip fractures and in a comparison group of women undergoing elective total hip arthroplasties (i.e. controls), the proportion of women with positive tissue transglutaminase antibodies, a test for celiac disease, and the association between antibody status and vitamin D levels.

MATERIAL AND METHODS

Sample Selection

The study subjects include 208 community dwelling women, 81 from Boston, Massachusetts and 127 from Baltimore, Maryland.[2, 3, 13] The Boston cohort of 30 women with hip fractures was part of a larger study of 98 women who had no secondary cause for osteoporosis. The control group of 51 women from Boston admitted for elective hip joint replacement was also selected from this larger study, and did not have osteoporosis. Subjects were excluded if they were taking any other medications, had any disorder or abnormal admission test results that might affect bone, or had any underlying hip disease other than osteoarthritis. Women with high-energy, pathological fractures or not community-dwelling at the time of fracture were also excluded. In Boston, subjects were recruited between 1995 and 1998 for another study, and completed questionnaires regarding lifestyle, reproductive factors, calcium intake, and physical activity.[2, 3, 14] The Baltimore cohort of 127 women with acute hip fractures was part of a larger study of 205 subjects recruited between 1992

and 1995.[3, 13] The subjects experienced either natural or surgical menopause with amenorrhea for at least 12 months; 95% were Caucasian race/ethnicity.

Procedure

To evaluate the contribution of celiac disease to vitamin D deficiency in women with hip fractures, we measured 25-hydroxyvitamin D (DiaSorin RIA: normal 20–57 ng/ml) and tissue transglutaminase IgA (tTG-IgA; ELISA: normal < 1 U). In subjects with normal tTG-IgA, serum total IgA (ELISA: normal 70–400 mg/dl) was determined, and if IgA was low, a tTG-IgG (normal=> 26 U) was determined. The sensitivity and specificity was 95% for these methods. All serum samples were stored at –60°C.

RESULTS

For the Boston and Baltimore hip fracture cohorts, the age (mean $\pm$ SD) was 77.9 ± 9.2 and 80.8 ± 7.9 years, respectively. The age (mean $\pm$ SD) of subjects admitted for elective joint replacement was 64.4 ± 8.1 years.

Median serum 25(OH)D levels were 14.1 ng/ml for the hip fracture cohort, and 21.3 ng/ml for the elective joint replacement cohort ($p < 0.0001$). In the Boston hip fracture group, 3.33% of subjects, or 1 in 30, tested positive for celiac disease. In the Baltimore hip fracture group, 1.57%, or 2 in 127, tested positive. Among the subjects undergoing elective joint replacement, 1.16%, or 1 in 51, tested positive for celiac disease in the Boston group. Including the total number of hip fracture subjects, there were no differences in the percentage of subjects with a positive tissue transglutaminase in the women with hip fractures versus the control group.

DISCUSSION

The results of our study showed no increased prevalence of celiac disease in subjects with hip fractures compared to those without osteoporosis admitted for elective joint replacement. The combined incidence of subjects with celiac disease was 1.91% in the hip fracture cohort versus 1.61% in the elective joint replacement cohort. These results were not statistically significant despite a significantly lower median 25(OH)D levels in women with hip fractures. Although the women with hip fractures in the Boston cohort had a higher percentage of positive tissue transglutaminase levels than the control group (3.3% vs 1.57%, respectively), the number of affected hip fracture subjects was small.

Hypovitaminosis D, or vitamin D deficiency, is common in newly diagnosed individuals with refractory celiac disease and in individuals with elevated serum AGA or TG antibodies. [5, 7] After the introduction of a GFD, vitamin D levels in individuals with celiac disease often become normal and BMD improves within a year of successfully following a GFD, with minimal changes seen thereafter.[7, 15] Through multiple regression analysis in a sample of adults with celiac disease, a study found that a low serum 25(OH)D level was the main factor that contributed to low BMD,[16] but the presence of celiac disease was not correlated with abnormal 25(OH)D levels. Similarly, our study did not find a significant

difference between the occurrence of celiac disease in hip fracture subjects with lower serum 25(OH)D levels and the control group.

Past studies have reported on the relationship between fractures and celiac disease with conflicting results; some show an increased risk of all fractures in patients with celiac disease while others report no association.[17, 18] Several population-based studies have shown increased risk of hip fractures and other fractures in individuals with celiac disease, [19–22] In addition, one cross-sectional, case-controlled study has also reported a positive correlation between fracture prevalence and celiac disease among female s aged 50 years. [23] Factors that may contribute to increased risk of fracture in individuals with celiac disease include, but are not limited to malabsorption of calcium and vitamin D which lead to calcium and vitamin D deficiency, hyperparathyroidism;[24] failure to achieve peak bone mass in young adulthood,[25] lymphoma and other bone related malignancies,[9] and underlying metabolic bone diseases.[24]

Other studies similar to ours have found little to no evidence linking celiac disease to elevated risk of fracture.[26] Some studies show that celiac disease is not an important contributing factor in older hip fracture population with osteoporosis[17] and that there is no increased fracture risk before or after diagnosis.[18]

One limitation of our study was the absence of endoscopic biopsy specimens to further confirm celiac disease in subjects. To determine whether a subject had celiac disease, we used a serological test to measure tissue transglutaminase IgA, which is accurate 78.8% of the time[27] while biopsy is 100% accurate when four biopsies are taken.[28] Endoscopic biopsies, however, are invasive procedures in these elderly subjects. Since individuals with undiagnosed celiac disease or those who do not comply with a GFD have a higher mortality rate,[17, 29] it is possible that there is a low prevalence of celiac disease in hip fracture patients because these subjects may have expired before age 80, the mean age of the hip fracture cohort. Study subjects also did not complete a detailed dietary analysis to determine whether or not they were already on a GFD prior to time of fracture. Individuals on a GFD prior to time of fracture would not have elevated transglutaminase despite diagnosis of celiac disease thus further contributing to the low prevalence of celiac disease in these subjects. Because participation in our study was limited to women only, our results cannot be generalized to men with celiac disease who typically exhibit worse symptoms than women, including greater malabsorption of vitamins and minerals, and a lower BMD than women.[30] Another limitation is that we compared hip fracture patients with an average age of 80 to a group of patients receiving elective arthroplasties with an average age of 64. These groups also are known to differ in other ways such as their health, functional status, physical activity, and exposure to sunlight.

In summary, our study in women with hip fractures did not reveal an increased percentage of subjects with a positive tissue transglutaminase compared with a control group. These data suggest that routine testing for celiac disease among hip fracture patients may not prove useful. Larger prospective studies are warranted to definitively determine whether celiac disease contributes to the high prevalence of vitamin D deficiency in hip fracture patients.

Acknowledgments

We thank Giulia Rinaldi, M.D., Nithya G. Setty, B.S., M.S., and Natalie Glass, B.A., M.A. for their assistance in manuscript preparation.

Dr. Jay Magaziner and Dr. Meryl LeBoff had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

All Funding Sources Funding support, in part by: NIH R01 AG13519, NIH R01 AG 12271, and R01 25015 (MSL, JG), the NCRR, General Clinical Research Center (Brigham and Women's Hospital), and R37 AG009901 and R01 AG18668 CWH (WH, JY, JM). Support also was provided by the Claude D. Pepper Older Americans Independence Center (OAIC) P30 AG028747 (WH, JM).

References

1. Edwards BJ, Langman CB, Bunta AD, Vicuna M, Favus M. Secondary contributors to bone loss in osteoporosis related hip fractures. *Osteoporos Int*. 2008; 19(7):991–999. [PubMed: 18180974]
2. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. *JAMA*. 1999; 281(16):1505–1511. [PubMed: 10227320]
3. LeBoff MS, Hawkes WG, Glowacki J, Yu-Yahiro J, Hurwitz S, Magaziner J. Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures. *Osteoporos Int*. 2008; 19(9):1283–1290. [PubMed: 18373057]
4. Pieper CF, Colon-Emeric C, Caminis J, Betchyk K, Zhang J, Janning C, Shostak J, LeBoff MS, Heaney RR, Lyles KW. Distribution and correlates of serum 25-hydroxyvitamin D levels in a sample of patients with hip fracture. *Am J Geriatr Pharmacother*. 2007; 5(4):335–340. [PubMed: 18179991]
5. Keaveny AP, Freaney R, McKenna MJ, Masterson J, O'Donoghue DP. Bone remodeling indices and secondary hyperparathyroidism in celiac disease. *Am J Gastroenterol*. 1996; 91(6):1226–1231. [PubMed: 8651176]
6. McFarlane XA, Bhalla AK, Reeves DE, Morgan LM, Robertson DA. Osteoporosis in treated adult coeliac disease. *Gut*. 1995; 36(5):710–714. [PubMed: 7797121]
7. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology*. 2003; 124(3):795–841. [PubMed: 12612917]
8. Meyer D, Stavropoulos S, Diamond B, Shane E, Green PH. Osteoporosis in a north american adult population with celiac disease. *Am J Gastroenterol*. 2001; 96(1):112–119. [PubMed: 11197239]
9. Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med*. 2002; 346(3):180–188. [PubMed: 11796853]
10. Armstrong MJ, Robins GG, Howdle PD. Recent advances in coeliac disease. *Curr Opin Gastroenterol*. 2009; 25(2):100–109. [PubMed: 19528877]
11. van der Windt DA, Jellema P, Mulder CJ, Kneepkens CM, van der Horst HE. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. *JAMA*. 303(17):1738–1746. [PubMed: 20442390]
12. Boonen S, Vanderschueren D, Cheng XG, Verbeke G, Dequeker J, Geusens P, Broos P, Bouillon R. Age-related (type II) femoral neck osteoporosis in men: biochemical evidence for both hypovitaminosis D- and androgen deficiency-induced bone resorption. *J Bone Miner Res*. 1997; 12(12):2119–2126. [PubMed: 9421246]
13. Fox KM, Magaziner J, Hawkes WG, Yu-Yahiro J, Hebel JR, Zimmerman SI, Holder L, Michael R. Loss of bone density and lean body mass after hip fracture. *Osteoporos Int*. 2000; 11(1):31–35. [PubMed: 10663356]
14. Magaziner J, Lydick E, Hawkes W, Fox KM, Zimmerman SI, Epstein RS, Hebel JR. Excess mortality attributable to hip fracture in white women aged 70 years and older. *Am J Public Health*. 1997; 87(10):1630–1636. [PubMed: 9357344]
15. Ciacci C, Maurelli L, Klain M, Savino G, Salvatore M, Mazzacca G, Cirillo M. Effects of dietary treatment on bone mineral density in adults with celiac disease: factors predicting response. *Am J Gastroenterol*. 1997; 92(6):992–996. [PubMed: 9177517]

16. Kempainen T, Kroger H, Janatuinen E, Arnala I, Kosma VM, Pikkarainen P, Julkunen R, Jurvelin J, Alhava E, Uusitupa M. Osteoporosis in adult patients with celiac disease. *Bone*. 1999; 24(3): 249–255. [PubMed: 10071918]
17. Fisher AA, Davis MW, Budge MM. Should we screen adults with osteoporotic fractures for coeliac disease? *Gut*. 2004; 53(1):154–155. [PubMed: 14684593]
18. Vestergaard P, Mosekilde L. Fracture risk in patients with celiac Disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark. *Am J Epidemiol*. 2002; 156(1):1–10. [PubMed: 12076883]
19. Ludvigsson JF, Michaelsson K, Ekblom A, Montgomery SM. Coeliac disease and the risk of fractures - a general population-based cohort study. *Aliment Pharmacol Ther*. 2007; 25(3):273–285. [PubMed: 17269989]
20. Jafri MR, Nordstrom CW, Murray JA, Van Dyke CT, Dierkhising RA, Zinsmeister AR, Melton LJ 3rd. Long-term fracture risk in patients with celiac disease: a population-based study in Olmsted County, Minnesota. *Dig Dis Sci*. 2008; 53(4):964–971. [PubMed: 17934823]
21. West J, Logan RF, Card TR, Smith C, Hubbard R. Fracture risk in people with celiac disease: a population-based cohort study. *Gastroenterology*. 2003; 125(2):429–436. [PubMed: 12891545]
22. Agardh D, Bjorck S, Agardh CD, Lidfeldt J. Coeliac disease-specific tissue transglutaminase autoantibodies are associated with osteoporosis and related fractures in middle-aged women. *Scand J Gastroenterol*. 2009; 44(5):571–578. [PubMed: 19255929]
23. Davie MW, Gaywood I, George E, Jones PW, Masud T, Price T, Summers GD. Excess non-spine fractures in women over 50 years with celiac disease: a cross-sectional, questionnaire-based study. *Osteoporos Int*. 2005; 16(9):1150–1155. [PubMed: 15692728]
24. Fickling WE, McFarlane XA, Bhalla AK, Robertson DA. The clinical impact of metabolic bone disease in coeliac disease. *Postgrad Med J*. 2001; 77(903):33–36. [PubMed: 11123392]
25. Mora S, Barera G, Ricotti A, Weber G, Bianchi C, Chiumello G. Reversal of low bone density with a gluten-free diet in children and adolescents with celiac disease. *Am J Clin Nutr*. 1998; 67(3):477–481. [PubMed: 9497193]
26. Compston J. Is fracture risk increased in patients with coeliac disease? *Gut*. 2003; 52(4):459–460. [PubMed: 12631649]
27. Basso D, Guariso G, Bozzato D, Rossi E, Pescarin M, Fogar P, Moz S, Navaglia F, Pelloso M, Gasparetto M, et al. New screening tests enrich anti-transglutaminase results and support a highly sensitive two-test based strategy for celiac disease diagnosis. *Clin Chim Acta*. 412(17–18):1662–1667. [PubMed: 21640087]
28. Pais WP, Duerksen DR, Pettigrew NM, Bernstein CN. How many duodenal biopsy specimens are required to make a diagnosis of celiac disease? *Gastrointest Endosc*. 2008; 67(7):1082–1087. [PubMed: 18308317]
29. Feighery C. Fortnightly review: coeliac disease. *BMJ*. 1999; 319(7204):236–239. [PubMed: 10417090]
30. Bai D, Brar P, Holleran S, Ramakrishnan R, Green PH. Effect of gender on the manifestations of celiac disease: evidence for greater malabsorption in men. *Scand J Gastroenterol*. 2005; 40(2): 183–187. [PubMed: 15764149]

Table 1

Variable	Hip Fracture			Elective Joint Replacement T-score -2.5	P-value
	Boston N=30	Baltimore N=127	Total N=157		
Age (mean $\pm$ SD)	77.9 $\pm$ 9.2	80.8 $\pm$ 7.9	80.3 $\pm$ 8.2	64.4 $\pm$ 8.1	Total Hip Fracture v. Elective Joint Replacement <0.0001
Race (% Caucasian)	91%	96%	95%	97%	NS
Median 25(OH)D (ng/ml)	13.0	14.4	14.1	21.3	<0.0001
Patients with celiac disease	1 (3.33%)	2 (1.57%)	3 (1.91%)	1 (1.61%)	NS