Title

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CLINICAL VIGNETTE

Clues in Identifying an Unexpected Cause of Osteoporosis in a Post-Menopausal Woman: The Importance of Measuring 24-Hour Urine Calcium

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Introduction

Osteoporosis affected nearly 10.2 million people 50 years or older in the US in 2010, of which 8.2 million were women.[1] Primary osteoporosis is the most common etiology in post-menopausal women, as secondary causes are found in only 20-30% of cases in this demographic group. In contrast, secondary causes are found in 30 to 60% of men with osteoporosis and greater than 50% of perimenopausal women with osteoporosis.[2,3] The clinical presentation and laboratory evaluation are useful in distinguishing the etiologies. We present a case of a post-menopausal woman with osteoporosis and hyperparathyroidism who was being evaluated for parathyroidectomy surgery. Investigation of mechanisms for her elevated parathyroid levels with 24 hour urine calcium led to the diagnosis of a secondary cause for bone loss and avoided unnecessary parathyroid surgery.

Case Report

A 59-year-old woman presented with a history of osteoporosis for 6 years without prior fractures. Her risk factors for bone loss included post-menopause status since age 50, with hormone replacement therapy that likely delayed bone loss, a family history of osteoporosis and vitamin D deficiency treated with Ergocalciferol 50,000 IU weekly chronically. Alendronate was started at the time of diagnosis but was discontinued after 1.5 years due to side effects. Her most recent bone density scan, at age 58, demonstrated osteoporosis with a T-score -3.0 at the femoral neck and a T-score of -3.2 at the lumbar spine.

At baseline, she was mildly hypocalcemic without concurrent parathyroid hormone measurement (Figure 1). After initiating a diet that included 3 servings of calcium per day, repeat testing demonstrated normal calcium 8.6 mg/dL (reference range 8.4-10.3 mg/dL) and significantly elevated parathyroid hormone of 212 pg/mL (reference range 14-72 pg/mL). She was referred to endocrinology surgery, who felt parathyroidectomy was not warranted. Instead, calcium citrate 500mg twice daily was initiated and she was referred to endocrinology. On exam, she was a healthy appearing woman, with blood pressure 120/85 mmHg, heart rate 79 bpm, weight 172 lb, and BMI 29.5 Kg/m^2, and unremarkable multisystem examination. A 24-hour urine calcium was less than 5mg/24 hour while she was receiving calcium supplementation and had adequate dietary calcium intake (estimated 900mg daily). The finding of very low urinary calcium despite robust oral calcium intake was suggestive of calcium malabsorption. She did not have diarrhea, flatulence, abdominal pain, nor weight changes. Celiac disease was investigated as possible cause for calcium malabsorption, and further testing demonstrated an elevated IgA Transglutaminase of 1849.6 CU (normal <20.0 CU), elevated IgA Gliadin of 1201.4 CU (normal <20.0 CU) and Endomysial titer of 1:320. On upper endoscopy, the mucosa of the duodenum and jejunum had a scalloped and nodular appearance (Figure 2). Celiac disease was confirmed by jejunal and duodenal biopsies, which demonstrated crypt hyperplasia, villous atrophy and intra-epithelial lymphocytosis.

She started a gluten-free diet, continued on vitamin D supplementation with Ergocalciferol 50,000 IU every 7 days, and calcium supplementation was progressively increased to 4,000 mg elemental calcium per day in divided doses. Approximately 7 months after initiation of a gluten-free diet, her parathyroid hormone level normalized to 51 pg/mL (normal 14-64 pg/mL) and she maintained normal serum calcium and normal vitamin D levels (Figure 3). Bone density scan will be repeated one year after treatment initiation.

Discussion

This post-menopausal woman with osteoporosis was found to have secondary hyperparathyroidism. Subsequent investigation identified celiac disease, in the absence of gastrointestinal symptoms. This highlights the importance of obtaining 24-hour urine calcium during the investigation of osteoporosis, particularly when parathyroid hormone levels are elevated. It also demonstrates that secondary hyperparathyroidism contributing to bone loss can be reversed with calcium supplementation and a gluten free diet in patients with celiac disease.

Elevation of parathyroid hormone associated with normal calcium levels may occur in mild (normocalcemic) hyperparathyroidism or in secondary hyperparathyroidism. Primary hyperparathyroidism due to parathyroid adenoma or parathyroid hyperplasia results in autonomous production of parathyroid hormone that causes bone calcium reabsorption and subsequent hypercalcemia. In the early stages of primary hyperparathyroidism, calcium may be in the normal-high reference range, i.e. normocalcemic primary hyperparathyroidism. Secondary hyperparathyroidism is characterized by increased production of parathyroid hormone due to

perceived low blood calcium levels due to physiological feedback regulation of PTH. The most common causes of secondary hyperparathyroidism are vitamin D deficiency and low dietary calcium intake (Figure 4).[4] Neither of these factors were present in our patient with normal vitamin D levels and estimated calcium intake of 1900mg daily. The recommended calcium requirement in post-menopausal women is 1200mg daily. Normocalcemic primary hyperparathyroidism and secondary hyperparathyroidism may be differentiated by the measurement of 24-hour urine calcium in patients with normal calcium intake, normal vitamin D level and who are not on a thiazide diuretic that lowers urinary calcium. The measurement of 24-hour urine calcium in combination with serum calcium, serum parathyroid hormone level and thyroid function tests in patients treated with thyroid hormone, leads to the detection of secondary causes in as many as 85% of postmenopausal women with osteoporosis.[5] A 24-hour urine calcium <150 mg/day is the most sensitive threshold for diagnosing calcium malabsorption, while a level <100 mg/day is the most specific threshold. A 24-hour urine > 150 mg/day has high negative predictive value, excluding calcium malabsorption.[6]

Our patient was diagnosed with secondary hyperparathyroidism due to calcium malabsorption based on her elevated parathyroid hormone level accompanied by normal-low serum calcium, and very low 24h urine calcium despite adequate oral calcium intake. Low urine calcium levels ruled out normocalcemic primary hyperparathyroidism. Familial hypocalciuric hypercalcemia due to a mutation in the calcium sensing receptor is associated with elevated PTH level, mild hypercalcemia and low urinary calcium. This was ruled out due to the normal-low calcium and absence of a personal or family history of hypercalcemia.

A systematic review and meta-analysis estimated the prevalence of biopsy-proven celiac disease in patients with osteoporosis is 1.6% (ranging between 0 and 3.4% in the 8 studies included).[7] This raises the question, which patients with osteoporosis should be screened for secondary causes. The American Association of Clinical Endocrinologists/American College of Endocrinology Medical Guidelines recommends evaluation for secondary causes of osteoporosis in all post-menopausal women who have osteoporosis, while testing for celiac antibodies is recommended when there is clinical or biochemical evidence of malabsorption.[8] They recommend complete blood count, comprehensive metabolic panel, 25 hydroxyvitamin D, parathyroid hormone, phosphate, 24 hour urine testing for calcium, sodium and creatinine. The National Osteoporosis Foundation recommends a similar evaluation for secondary causes, but also recommends thyroid testing and bone turnover markers in the initial evaluation of all women, with consideration of celiac antibody testing (tissue trans-glutaminase IgA and IgG) in selected patients.[9] Among patients with osteoporosis, the presence of fecal incontinence (but not other gastrointestinal symptoms), low vitamin D level, and high parathyroid hormone levels occurred more often in patients with celiac disease compared with control population.[10-12] These factors should be considered when deciding which patients to screen for celiac disease.

Treatment of osteoporosis due to celiac disease, as in our patient's case, consists of a gluten-free diet, calcium and vitamin D repletion. A systematic review demonstrated that most, though not all, patients on a gluten free diet had improvement in bone density.[13] There was an average bone mineral density improvement of approximately 5% after 1 year on a gluten free diet, although the final bone density may still be below the normal range.[13] Fractional calcium absorption in patients with celiac disease can also remain persistently lower than normal despite following a gluten free diet.[14,15] Although there is no established recommendation on the specific dose of calcium and vitamin D supplementation, this suggests that patients with celiac disease may require more calcium intake than the recommended daily allowance.[14.15] In these patients, attaining a normal PTH level is likely a good marker of adequate calcium and vitamin D absorption.

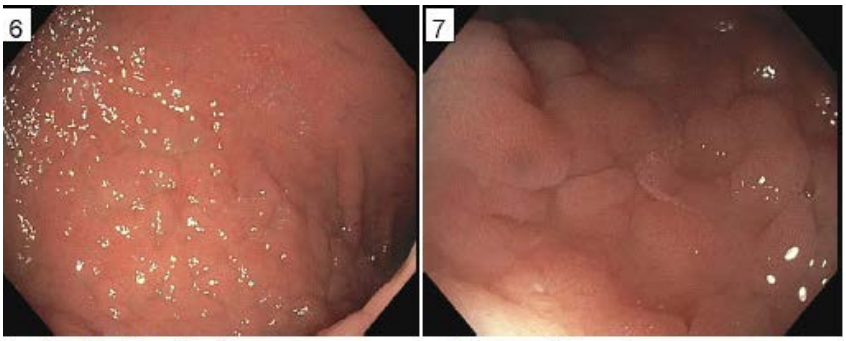
Conclusion

This case highlights the importance of screening for secondary causes of osteoporosis. Basic investigation should include 24-hour urine calcium, especially if parathyroid hormone levels are elevated after adequate vitamin D and calcium supplementation. Celiac disease, although a rare cause of secondary osteoporosis, should be considered in patients with hypocalciuria and secondary hyperparathyroidism. Bone density typically improves with a gluten free diet. Vitamin D and calcium supplementation are also important components of treatment of patients with celiac disease, and higher doses than the recommended daily allowance are often required due to latent malabsorption despite adherence to gluten-free diet.

Figure 1: Baseline laboratorial results.

Lab (normal range)	Baseline	1 month later
Serum Calcium (8.4-10.3 mg/dL)	8.3	8.6
Albumin (3.7-5.0 g/dL)	4.2	-
Intact PTH (14.0-72.0 pg/ml)	-	212.7
25 OH Vitamin D (30-100 ng/mL)	40	44
Phosphorous (2.6-4.5 mg/dL)	-	4.2
Creatinine (0.40-1.20 mg/dL)	0.62	-
Alkaline Phosphatase (<135 U/L)	91	-
TSH (0.350-5.500 uIU/mL)	3.1	-

Figure 2: 1. Small bowel enteroscopy findings showing nodular, blunted appearance to the duodenal and jejunal mucosa.



duodenal bulb noduarity nodular small bowel mucosa

Figure 3: Parathyroid hormone levels declined with duration of gluten-free diet, and with increasing doses of oral calcium supplementation. Dashed line indicates upper limit of reference range for parathyroid hormone level.

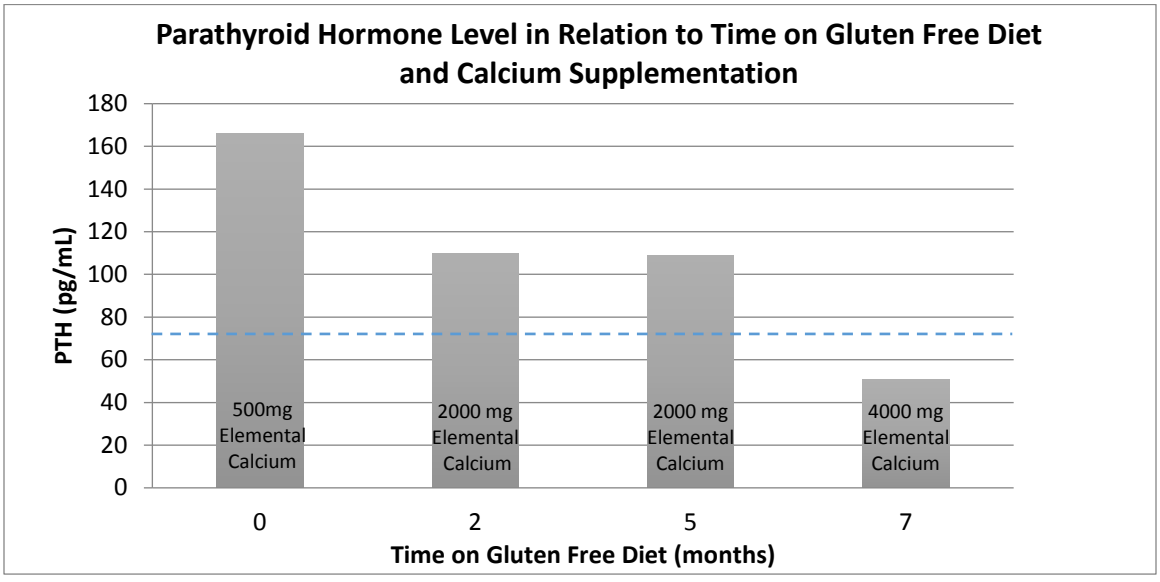


Figure 4: Causes of secondary hyperparathyroidism.

Causes of Secondary Hyperparathyroidism
Insufficient calcium intake/absorption: • *Vitamin D deficiency (poor sun exposure, diet, anti-epileptics, chronic liver disease) • *Low dietary calcium • Gastrointestinal malabsorption: Celiac disease, Inflammatory bowel disease, Gastric bypass surgery, pancreatic insufficiency, cystic fibrosis, lactose intolerance, older age
Chronic kidney disease
Medications: Bisphosphonates, loop diuretics
Pseudohyperparathyroidism
Metastatic prostate cancer
"Hungry bone" syndrome
Rhabdomyolysis
Sepsis
Bone growth
Lactation
Idiopathic hypocalciuria

*Indicates the most common causes

Adapted from Fraser WD. Hyperparathyroidism. Lancet. 374(9684):145-58; 2009 (4)

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