

# Clinicians' Forum

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

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## Question: Should all 50-year-old women being assessed for skeletal health have vitamin D and parathyroid hormone levels measured?

### Answers:

This question makes the assumption that 50-year-old women are routinely assessed for skeletal health. At this point in the United States, such an inquiry is not mandated for the woman in perimenopause, however desirable that may be.

The most important diagnostic and predictive tool for osteoporosis and fracture risk is the bone density test. The US Bone Mass Measurement Act of 1998 and most of the authoritative bodies that make pronouncements on

this subject agree that women over the age of 65 should have bone mineral density (BMD) testing.<sup>1-4</sup> Women under age 65 are encouraged to have a BMD test if they have other risk factors for osteoporosis.<sup>5</sup> These other risk factors can include family history of osteoporosis, personal history of fracture, use of glucocorticoids, smoking, life-long low calcium intake, excessive thinness, early menopause, and rheumatoid arthritis. There is certainly a good argument to be made for these women to have bone density testing before age 65. More enthusiastic advocates of bone density testing believe that screening for osteoporosis is appropriate for any woman in perimenopause since a state of increased risk due to estrogen deficiency begins at this time.

In my opinion, evaluation of skeletal health in any woman for whom there is concern, whether she is 50 or 65, should include an assessment of vitamin D level. Many recent studies suggest that vitamin D deficiency is common in this country and throughout the world.<sup>6</sup> The metabolite 25-hydroxyvitamin D, the storage form of vitamin D, is the compound that should be measured. The laboratory reference range is generally 10-50 ng/mL. Since vitamin D deficiency is prevalent in the population, the range defined as the laboratory reference includes a substantial number of individuals who are deficient in vitamin D. The best way to define the normal range of vitamin D is by establishing the concentration at which parathyroid hormone (PTH) levels start to rise. The close inverse relationship between 25-hydroxyvitamin D and PTH allows one to sense this point fairly accurately. In most studies this is about 25-30 ng/mL, considerably higher than the lowest limit of the normal laboratory reference range. Studies that have correlated 25-hydroxyvitamin D with a physiological end point, namely calcium absorption, place the concentration somewhat higher, at 30-32

ng/mL. Most experts now consider a value for 25-hydroxyvitamin D less than 30 ng/mL to be insufficient.

Since vitamin D insufficiency is so common in the general population, it is important to ascertain its level in women who are being evaluated for their skeletal health. After menopause, vitamin D insufficiency can compromise a woman's bone density and limit the effectiveness of pharmacologic treatment when it is indicated.

The question related to whether all women should have PTH measured is a bit more complicated. Some physicians do measure PTH routinely. If there is vitamin D deficiency, the PTH may be elevated on that basis. On the other hand, in the vitamin D-deficient woman, the PTH may not be elevated outside the normal range but may be higher than it was when that individual was not vitamin D deficient. Unless the patient has had a previous PTH determination, one cannot know whether or not this is the case. For example, the PTH level in someone whose 25-hydroxyvitamin D level is 20 ng/mL might be 50 pg/mL (normal, 10 pg/mL-65 pg/mL). Although this is technically a normal value, it might have been substantially lower, perhaps 25 pg/mL, if the 25-hydroxyvitamin D level was normal. The PTH level, thus, does not provide any information in this regard beyond what can be obtained by testing the 25-hydroxyvitamin D level alone. However, there is another reason the practitioner might want to measure PTH; namely, to rule out primary hyperparathyroidism, a very common disorder of PTH secretion in postmenopausal women. Such postmenopausal women are at risk for bone loss. It is my opinion that since primary hyperparathyroidism is generally not associated with symptoms in this



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country, and now has been well described in individuals whose serum calcium levels are normal, a complete evaluation of skeletal health in postmenopausal women should include a determination of both 25-hydroxyvitamin D and PTH levels.

—John P. Bilezikian, MD

#### References

1. Raisz LR. Screening for osteoporosis. *N Eng J Med* 2005;353:164-71.
2. Department of Health and Human Services. *Bone health and osteoporosis: a report of the surgeon general*. Rockville MD: Office of the Surgeon General, 2004.
3. National Osteoporosis Foundation. *Physician's guide to prevention and treatment of osteoporosis*, Washington, DC: National Osteoporosis Foundation, 2003.
4. Hodgson SF, Watts NB, Bilezikian JP, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis. 2001 ed, with selected updates for 2003. *Endocr Practice* 2003;9:544-64.
5. Leib ED, Lewiecki MEM, Binkley N, et al. Official positions of the International Society for Clinical Densitometry. *J Clin Densitometry* 2004;7:1-6.
6. Tannenbaum C, Clark J, Schwartzman K, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *J Clin Endocrinol Metab* 2002;87:4431-7.

There is worldwide concern about vitamin D deficiency. It is not an overt problem of severe deficiency and flagrant osteomalacia. Rather, it is an issue of mild deficiency, the kind that is associated with low hip bone density and subsequent fractures, or with lack of muscle strength and increased risk for imbalance and falling. Studies show significant reduction of fracture when vitamin D deficiency is corrected in patients, but little effect is seen in patients who are not deficient. Direct and indirect effects of this deficiency occur. We recognize the undermineralization of the skeleton with deficiency. But we sometimes fail to realize the potentially destructive secondary hyperparathyroid state that vitamin D deficiency triggers.

It is still not clear why this problem arises in as many as 50% of women. Inadequacy of vitamin D is statistically associated with age, race, body mass index,

drugs that interfere with metabolism of vitamin D, degree of vitamin supplementation, exercise, geography, education and absence of physician counseling.<sup>1,2</sup> The consensus is that a serum level of 25-hydroxyvitamin D of approximately 32 ng/mL-36 ng/mL (80-90 nmol/L) maximizes intestinal absorption of calcium, and serum PTH starts to increase below 30 ng/mL. In a recent study, 70%-80% of patients had secondary hyperparathyroidism with serum vitamin D at 10 ng/mL or less, while only about 10% of patients with secondary hyperparathyroidism had levels of 25 ng/mL-29-ng/mL.<sup>3</sup> Hence, serum PTH may not be increased in all degrees of deficiency. Having said this, it is not clear what the optimal serum level for vitamin D should be. Once this is known, deficiency may be better defined and the guidelines noted above will change.

From the clinical perspective, then, taking a serum measurement of 25-hydroxyvitamin D seems reasonable in all postmenopausal women, as opposed to measuring only serum PTH (which may not be increased in all states of mild vitamin deficiency). The assay used for the evaluation of vitamin D is also a point to consider because all assays may not provide an accurate assessment of vitamin levels. Some assays may not detect total serum 25-hydroxyvitamin D, but may only detect one of its components (the vitamin D<sub>2</sub> or vitamin D<sub>3</sub> forms). It may be necessary to ask the laboratory about which assay is used.

Supplementation with vitamin D is commonplace. Most forms are the vitamin D<sub>2</sub> variety. Most patients absorb this form adequately, but there are patients who absorb vitamin D<sub>3</sub> better. Obtaining vitamin D<sub>3</sub> may be a challenge since it is not readily available in all locations. Maintaining the total serum 25-hydroxyvitamin D level over 30 ng/mL and below the particular assay's upper reference limit is the goal. Values above this limit are not usually deleterious because there is endoge-

nous regulation of 25-hydroxyvitamin D conversion to biologically activated 1, 25-dihydroxyvitamin D. The dose of supplement prescribed can be daily or weekly, depending on the degree of deficiency. Mild deficiency may require 1,000 International Units (IU) or less daily, while severe deficiency requires several thousand units daily or weekly until serum levels of vitamin D become normal. Thereafter, 400- to 800-IU tablets daily should usually maintain the correct level of vitamin D. The important point, however, is to monitor serum levels and adjust dosing accordingly.

—Angelo A. Licata, MD, PhD

#### References

1. Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005;90:3215-24.
2. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporosis Int* 1997;7:439-43.
3. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D<sub>3</sub> supplementation in elderly women; confirmation reversal of secondary hyperparathyroidism and hip fracture risk: the Decaloy II study. *Osteoporosis Int* 2002;13:257-64.

The answer to this question is an unequivocal "no." Vitamin D deficiency is associated with calcium malabsorption, secondary hyperparathyroidism, increased rates of bone turnover resulting in bone loss and, at least in older adults, increased fracture risk.<sup>1</sup> Muscle weakness and increased risk of falling are also complications of vitamin D deficiency in the elderly.<sup>2</sup> Recent studies have documented that subclinical vitamin D deficiency (serum levels of 25-hydroxyvitamin D less than 20 ng/mL) or insufficiency (serum levels of 25-hydroxyvitamin D between 20 ng/mL and 30 ng/mL) is much more common than once imagined.<sup>3-5</sup> Reasons for deficiency include few dietary sources of vitamin D (except for fortified cereals, liquid milk or juices), limited outdoor activity

and sun exposure, the use of sunscreen that blocks the UV response to sunlight that is required for vitamin D synthesis in the skin, and large body size.

Despite the realizations that vitamin D deficiency is common and has important clinical implications, a strong case cannot be made for routine measurement of serum 25-hydroxyvitamin D—and especially not for PTH measurements—in healthy young postmenopausal women. Among the reasons for eschewing routine measurements are the following:

1. In older American women with osteoporosis, vitamin D deficiency occurs uncommonly (12%) in women who take at least 400 IU of vitamin D per day.<sup>5</sup> Because the prevalence of vitamin D deficiency increases with advancing age, even fewer healthy women in the 50-year-old age group in the question posed by this forum would have low levels of vitamin D if they took vitamin D supplements. Rather than measuring vitamin D levels to determine who needs supplements, it is clinically prudent to recommend a supplement in those patients who do not consume at least 1 quart of milk daily or who avoid the sun. In the absence of hypercalcemia or granulomatous disorders, doses of vitamin D between 400 IU and 800 IU daily are safe as well as inexpensive.
2. Although severe vitamin D deficiency induces secondary hyperparathyroidism, measurement of serum PTH is an insensitive test for vitamin D deficiency. Most patients with vitamin D deficiency and almost all with vitamin D insufficiency have PTH values within the reference range.<sup>5</sup>
3. Poor calibration and performance of clinically available vitamin D assays further limit the role of routine measurements of vitamin D.<sup>6</sup>
4. The assays are quite expensive. Each costs more than \$100 in my hospital, about the same as the cost of a bone

density test and enough to buy vitamin D supplements for several years.

Measuring vitamin D is appropriate in patients with clinical features suggestive of vitamin D deficiency or with risk factors for low vitamin D serum levels. This would include patients with hypocalcemia, diffuse bone pain or muscle weakness, unexpectedly low bone density or perhaps those who are losing bone density while on an osteoporosis treatment. Specific medical problems associated with vitamin D deficiency, such as use of anticonvulsants or disorders of small bowel function, warrant testing since they may require higher-than-usual doses of vitamin D. Serum PTH testing is useful in patients with hyper- or hypocalcemia but rarely in those with normal serum calcium values and normal renal function.



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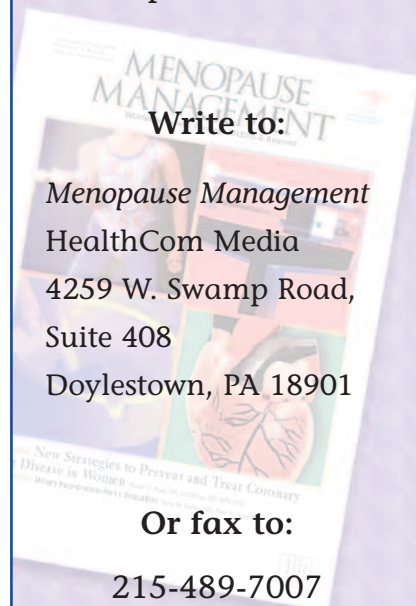
— Michael R. McClung, MD

#### References

1. Sahota O, Munday MK, San P, Godber IM, Lawson N, Hosking DJ. The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. *Bone* 2004; 35:312-19.
2. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997;7:439-43.
3. Holick MF. Vitamin D requirements for humans of all ages: new increased requirements for women and men 50 years and older. *Osteoporos Int* 1998;8:S24-9.
4. Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2000;75:611-15.
5. Holick MF, Siris ES, Binkley N, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab*. 2005;90:3215-24.
6. Binkley N, Krueger D, Cowgill CS, et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. *J Clin Endocrinol Metab* 2004 89:3152-7.

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