

Looking Beyond the “Obvious” to Promote Bone Health

ASHP Advantage E-Newsletter

Spring 2010

Update on Bone Health and Osteoporosis Prevention and Treatment: The Experts Answer Questions from Health-System Pharmacists

This e-Newsletter focuses on questions related to vitamin D requirements for bone health and commonly used medications that can potentially increase the risk of fractures, as well as emerging information related to osteoporosis prevention and treatment. The questions were discussed in a live webinar conducted in January 2010 as a follow up to a Midday Symposium on the topic held at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, on December 8, 2009. Questions related to current controversies in osteoporosis screening, prevention, and treatment were described in a previously released newsletter available at www.ashpadvantage.com/bonehealth.

Page 7 of the newsletter lists ways that pharmacists who participated in recent bone health educational activities have incorporated what they learned into practice.

Question: Concerns about inadequate vitamin D intake and an adverse effect on bone health in otherwise healthy people have been in the news lately. What evidence supports increasing vitamin D intake beyond currently recommended amounts?

Vitamin D deficiency and insufficiency are defined as a 25-hydroxyvitamin D concentration less than 20 ng/mL and 20-29 ng/mL, respectively.^{1,2} A level of 30-100 ng/mL is considered sufficient (i.e., normal).

The potential consequences of vitamin D deficiency are as follows¹:

- Bone loss and fractures related to decreased gastrointestinal calcium absorption, increased parathyroid hormone secretion, decreased bone mineralization, and increased bone turnover;
- Falls due to impaired neurologic and muscle function; and
- Increased risk for certain diseases, such as
 - Heart disease,
 - Diabetes mellitus,
 - Autoimmune diseases,
 - Infection, and
 - Selected cancers.

The 20-ng/mL vitamin D level used as the threshold for deficiency is based on clinical evidence. In a randomized, crossover study of 24 postmenopausal

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women, gastrointestinal (GI) calcium absorption was 65% lower when the mean vitamin D level was 20 ng/mL than when it was 35 ng/mL 1 year later.³ In the Women's Health Initiative observational study, there was a 71% higher risk of hip fractures in postmenopausal women whose vitamin D levels were less than 19 ng/mL compared with participants whose levels were above this value.⁴ In a meta-analysis of 12 randomized, double-blind, controlled trials of vitamin D supplementation in elderly patients at least 60 years of age, significant reductions in the risk for hip fractures by 26% and nonvertebral fractures by 23% were associated with the use of vitamin D 700-800 units/day and a vitamin D level of 36-40 ng/mL, but not with vitamin D 400 units/day and lower vitamin D levels.^{5,6} In a dose-ranging, placebo-controlled study of elderly nursing home residents receiving daily vitamin D 200 units, 400 units, 600 units, or 800 units, the incidence of falls was significantly lower compared with placebo only in the group receiving the largest dose, and the vitamin D level in this group was 30 ng/mL.⁷

Current recommendations for daily vitamin D intake from two authoritative sources are listed in Table 1. The recommended daily vitamin D intake is the amount needed to maintain vitamin D levels within the sufficient range in most healthy persons. Patients with vitamin D deficiency or insufficiency require larger doses to build up their stores and achieve levels in the sufficient range. Certain patient populations are at increased risk for vitamin D deficiency (Table 2) and may require larger-than-recommended daily doses to achieve and maintain vitamin D levels in the sufficient range.

In the past, a maximum vitamin D daily intake of 2000 units was recommended.^{8,9} The National Osteoporosis Foundation now suggests that a much larger amount is safe and needed by some patient populations.¹⁰

The daily dose of vitamin D needed to attain a sufficient level of at least 30 ng/mL over a 9-week period was explored in a study of 138 healthy African American and

Table 1. Current Recommendations for Vitamin D Intake in Adults^{8,9}

Age (yr)	Recommended Daily Intake (units)
<i>National Osteoporosis Foundation</i>	
19-49	400-800
≥ 50	800-1000
<i>Institute of Medicine^a</i>	
19-50	200
51-70	400
≥ 71	600

^a Recommendations from the Institute of Medicine were last updated in 1997. An update is expected in mid 2010.

Table 2. Patient Populations at Risk for Vitamin D Deficiency and Possible Mechanisms^{1,8,10,11}

Characteristic	Possible Mechanism for Vitamin D Deficiency
Advanced age	Reduced vitamin D activation in skin, decreased gastrointestinal absorption of dietary vitamin D
Obesity ^a	Sequestration of vitamin D in adipose tissue
Dark skin ^a	Impaired activation of vitamin D due to the pigment melanin in skin
Certain chronic conditions (e.g., inflammatory bowel disease, celiac disease, chronic pancreatitis) ^a	Fat malabsorption
Use of certain medications (e.g., rifampin, phenytoin) ^a	Hepatic enzyme induction and accelerated vitamin D clearance

^aThere is evidence that larger-than-recommended daily doses of vitamin D are needed in this patient population to achieve and maintain vitamin D levels in the sufficient range.

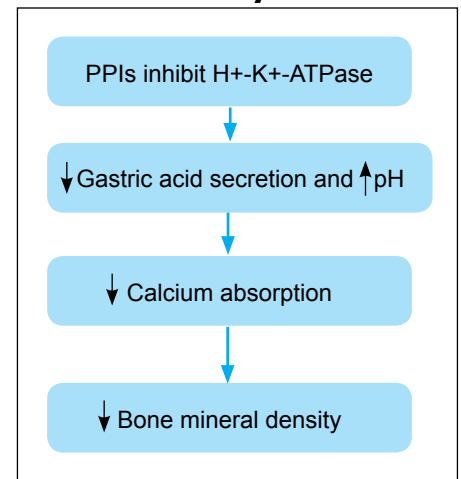
Caucasian men and women 18-65 years of age.¹² This threshold was achieved in approximately two thirds of African Americans and Caucasians using a mean daily vitamin D dose of 3840 units and 2840 units, respectively. Considerable variability in the dose-response relationship between vitamin D dose and vitamin D level was observed.

Vitamin D has a wide margin of safety with rare toxicity. No evidence of toxicity has been observed with daily doses up to 10,000 units for 6 months.¹³ Dr. Vondracek recommends a daily vitamin D intake of at least 800-1000 units to maintain sufficient levels in the majority of patients with or at risk for osteoporosis. Larger doses should be used for patients with vitamin D deficiency to achieve and maintain a level in the sufficient range.

Question: What commonly-used medications have the potential to increase the risk of fractures?

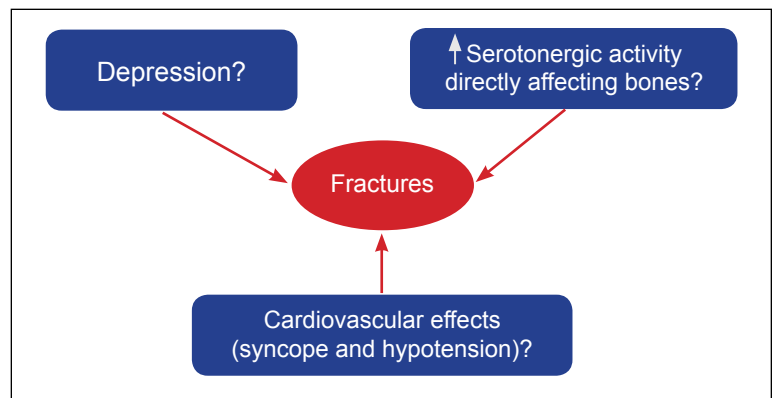
An increased risk of fractures may be associated with the use of proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), and thiazolidinediones.¹⁴⁻¹⁷ Proton pump inhibitors may reduce bone mineral density (BMD) by reducing gastric acid secretion, increasing gastric pH, and reducing GI calcium absorption (Figure 1).¹⁴ The data linking PPIs with fractures are conflicting. Prospective studies are needed to assess causality. Dr. MacLaughlin recommended using PPIs in patients with or at risk for osteoporosis only in situations where the drug is clearly indicated (e.g., patients with gastroesophageal reflux disease, peptic ulcer disease, or receiving long-term nonsteroidal anti-inflammatory drug therapy) and ensuring that calcium and vitamin D intake are adequate. If acid-suppressive therapy (i.e., histamine H₂-receptor antagonists or proton pump inhibitors) is needed in a patient with or at risk for osteoporosis, calcium citrate is preferred over calcium carbonate because calcium citrate is more readily absorbed than calcium carbonate in these patients.¹⁸

Figure 1. Effects of Proton Pump Inhibitors on Bone Mineral Density¹⁴



Case-controlled studies have found an increased risk of fractures in patients receiving SSRIs.¹⁵ The mechanism for fractures in these patients is unclear (Figure 2) and may involve a direct effect from increased serotonergic activity on bones or indirect cardiovascular effects (i.e., hypotension, syncope, and falls). Confounding variables may be involved.¹⁶ For example, in patients who take SSRIs for depression, a direct effect of the illness on bone may contribute to fractures.¹⁶ Prospective randomized studies are needed to clarify the relationship between SSRI use and bone health. Bone health strategies, including ensuring an adequate calcium and vitamin D intake and performing weight-bearing exercise, should be encouraged for patients with or at risk for osteoporosis who take SSRIs. Exercise may be beneficial for patients with depression.¹⁹

Figure 2. Selective Serotonin Reuptake Inhibitors and Fractures^{15,16}



The thiazolidinediones rosiglitazone and

pioglitazone are agonists of the peroxisome proliferator-activated receptor (PPAR)- γ nuclear transcription factor. These agents have been linked with an increased risk of fractures in observational and randomized, controlled studies.^{17,20-22} Fractures of the upper and distal lower limbs were most common, especially in women.²⁰ Activation of PPAR- γ appears to inhibit osteoblast differentiation and function and bone formation, and it may increase bone resorption by stimulating osteoclasts.¹⁷ Decreased bone turnover, increased bone loss, and reduced BMD have been demonstrated during thiazolidinedione treatment in healthy persons and patients with type 2 diabetes.¹⁷

Type 2 diabetes mellitus itself is a risk factor for fracture.¹⁰ Thiazolidinediones typically are reserved for third-line treatment of type 2 diabetes.^{23,24} These drugs might be avoided in patients with or at high risk for osteoporosis who have type 2 diabetes because of the link to fractures. Bone health strategies should be emphasized to decrease the risk for fractures in these patients.

Emerging News

Online Update to Clinician's Guide

In January 2010, the National Osteoporosis Foundation (NOF) updated the online version of the *Clinician's Guide to Prevention and Treatment of Osteoporosis*, and it can be downloaded from the NOF Web site at www.nof.org.¹⁰ Published in 2008, the *Clinician's Guide* offers concise recommendations regarding the prevention, risk assessment, diagnosis, and treatment of osteoporosis in postmenopausal women and men age 50 and older.

The January 2010 update is not substantially different from the 2008 version. The chapter on diagnosis and management now lists specific biochemical markers of bone remodeling. In that same chapter, rather than stating that the FRAX[®] tool applies only to previously untreated patients, the updated version specifies that clinical judgment must be used in interpreting FRAX[®] scores in patients currently or previously treated with pharmacotherapy for osteoporosis because the tool has not been validated in these patients. The update also clearly advises clinicians to use clinical judgment and consider individual patient factors not captured in the FRAX[®] model, such as frailty and recent decline in bone density, when making treatment decisions. In addition, the chapter on pharmacologic therapy provides updated indications from the U.S. Food and Drug Administration (FDA) for both zoledronic acid and parathyroid hormone.

NOF advises practitioners to visit its Web site regularly to see if an updated online version of the *Clinician's Guide* is available.

FDA Safety Announcement Related to Oral Bisphosphonate Use and Atypical Femur Fractures

FDA distributed a drug safety communication on March 10, 2010, related to its ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures.²⁵ The communication indicated that, although news reports have raised the question of an increased risk of this type of fracture in patients with osteoporosis taking bisphosphonates, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of these atypical femur fractures. FDA is working with outside experts to gather more information related to this issue. In the meantime, FDA recommends that patients currently taking an oral bisphosphonate should not stop

taking the medication unless told to do so by their health care professional. FDA's recommendations for health care professionals are as follows:

- Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates,
- Continue to follow recommendations in the drug label when prescribing oral bisphosphonates,
- Discuss with patients the known benefits and potential risks with using oral bisphosphonates, and
- Report any adverse events to FDA's MedWatch program.

AJHP Posts Ahead-of-Print Article on Long-Term Bisphosphonate Therapy

A Clinical Consultation review article on "Risks and Benefits of Long-Term Bisphosphonate Therapy" was made available online (PDF) ahead of its print publication in the June 15, 2010, issue of the *American Journal of Health-System Pharmacy*.²⁶ In the article, pharmacists Ginelle A. Schmidt and colleagues review the available evidence and conclude that it is reasonable for patients with the highest risk for fracture to continue bisphosphonate therapy beyond 10 years. But in patients with a lower risk of fracture and no history of fracture and who have consistently adhered to bisphosphonate therapy for two to five years, consideration could be given to stopping therapy for 2-5 years to avoid the risk of fragility fractures.

The issue of bisphosphonate drug holidays was covered in the Winter 2010 issue of this e-Newsletter if you would like more information on this topic.

Practice Changes Related to Bone Health and New Educational Opportunities

When pharmacists participate in educational activities, what do they do with their new knowledge? Here are some of the changes in practice that participants in the 2009 Midyear Symposium, "Looking Beyond the 'Obvious' to Promote Bone Health," reported in a survey about two months later:

- Counseling patients about a bone-healthy lifestyle,
- Counseling patients about calcium and vitamin supplementation,
- Getting more involved in assessing patients for risk of osteoporosis,
- Assessing the fall risk of patients,
- Educating colleagues about osteoporosis prevention and treatment,
- Recommending bisphosphonates as first-line therapy in most cases, and
- Considering cost and frequency of administration when evaluating therapies.

In addition, several individuals indicated that they were developing an osteoporosis initiative or clinic and developing osteoporosis screening recommendations for patients with breast or prostate cancer.

If these practice changes pique your interest and you want to learn more about bone health, a web-based activity based on the symposium is available. In addition, a supplement entitled, "Promoting Bone Health: Focus on Postmenopausal Women and Patients Receiving Systemic Therapy for Breast or Prostate Cancer," was published in the April 1, 2010, issue of the *American Journal of Health-System Pharmacy*. Both the web-based activity and the *Journal* supplement are approved for 2 hours (0.2 CEUs) of continuing pharmacy education, and they can be accessed from the web portal for the bone health educational initiative (www.ashpadvantage.com/bonehealth).

References

1. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007; 357:266-81.
2. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and recommendations for supplementation. *Am J Med*. 2009; 122:793-802.
3. Heaney RP, Dowll MS, Hale CA et al. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr*. 2003; 22:142-6.
4. Cauley JA, Lacroix AZ, Wu L et al. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. *Ann Intern Med*. 2008; 149:242-50.
5. Bischoff-Ferrari HA, Willett WC, Wong JB et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005; 293:2257-64.
6. Bischoff-Ferrari HA, Giovannucci E, Willett WC et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr*. 2006; 84:18-28.
7. Broe KE, Chen TC, Weinberg J et al. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc*. 2007; 55:234-9.
8. National Osteoporosis Foundation. Prevention: vitamin D. www.nof.org/prevention/vitaminD.htm (accessed 2010 Apr 9).
9. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for calcium, phosphorous, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
10. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2010. www.nof.org/professionals/Clinicians_Guide.htm (accessed 2010 Apr 9).
11. Thomas MK, Demay MB. Vitamin D deficiency and disorders of vitamin D metabolism. *Endocrinol Metab Clin North Am*. 2000; 29:611-27.
12. Aloia JF, Patel M, DiMaano R et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr*. 2008; 87:1952-8.
13. Holick MF. Optimal vitamin D status for the prevention and treatment of osteoporosis. *Drugs Aging*. 2007; 24:1017-29.
14. Fournier MR, Targownik LE, Leslie WD. Proton pump inhibitors, osteoporosis, and osteoporosis-related fractures. *Maturitas*. 2009; 64:9-13.
15. Ginzburg R, Rosero E. Risk of fractures with selective serotonin-reuptake inhibitors or tricyclic antidepressants. *Ann Pharmacother*. 2009; 43:98-103.

16. Zieme G, Dieleman JP, van der Cammen TJ et al. Association between SSRI use and fractures and the effect of confounding by indication. *Arch Intern Med*. 2007; 167:2369-70; author reply 2370-1.
17. Bodmer M, Meier C, Kraenzlin ME et al. Risk of fractures with glitazones: a critical review of the evidence to date. *Drug Saf*. 2009; 32:539-47.
18. National Institutes of Health, Office of Dietary Supplements. Dietary supplement fact sheet: calcium. <http://ods.od.nih.gov/factsheets/calcium.asp> (accessed 2010 Apr 9).
19. Blumenthal JA, Babyak MA, Doraiswamy PM et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007; 69:587-96.
20. Home PD, Pocock SJ, Beck-Nielsen H et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009; 373:2125-35.
21. Nissen SE, Nicholls SJ, Wolski K et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008; 299:1561-73.
22. Kahn SE, Haffner SM, Heise MA et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006; 355:2427-43.
23. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009; 32:193-203.
24. Rodbard HW, Jellinger PS, Davidson JA et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract*. 2009; 15:540-59.
25. U.S. Food and Drug Administration. FDA drug safety communication: ongoing safety review of oral bisphosphonates and atypical subtrochanteric femur fractures [03-10-2010]. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm (accessed 2010 Apr 9).
26. Schmidt GA, Horner KE, McDanel DL et al. Risks and benefits of long-term bisphosphonate therapy. *Am J Health-Syst Pharm*. 2010;67:e12-19. www.ajhp.org/misc/ClinConsult_Schmidt.pdf (accessed 2010 Apr 12).

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