

**ABELARDO C. CRUZ, MD**

Division of Rheumatology, Department of Medicine, State University of New York at Stony Brook

**BARRY L. GRUBER, MD**

Head, Division of Rheumatology, Professor of Medicine and Dermatology, State University of New York at Stony Brook

# Statins and osteoporosis: Can these lipid-lowering drugs also bolster bones?

## ■ ABSTRACT

The statins may not only lower cholesterol, they may stimulate bone formation, as suggested by a number of observational studies and animal research. Whether these drugs will be of benefit in treating osteoporosis awaits further clinical trials.

## ■ KEY POINTS

Several in vitro and animal studies suggest that statin drugs have an anabolic and antiresorptive effect on bone.

A number of observational studies found a decreased incidence of fractures among patients who take statins, but other studies did not. Prospective randomized controlled trials are required to exclude the possibility of unmeasured confounding variables and to define more precisely the impact of statins on fracture risk.

Several observational studies found that people taking statins had higher bone mineral densities than did nonusers.

The current statins, which are designed to lower lipids, may not be ideal for treating osteoporosis; however, they may point the way to similar molecules that would be more effective.

**T**HE CHOLESTEROL-LOWERING “statin” drugs may have the unexpected bonus of stimulating bone formation, according to evidence from animal studies.<sup>1</sup> In contrast, current osteoporosis treatments only slow bone loss.

We review the basic and clinical data about the effects of hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors or statins on bone; however, definitive studies are needed before statins can be considered indicated for preventing or treating osteoporosis.

## ■ OSTEOPOROSIS: SCOPE OF THE PROBLEM

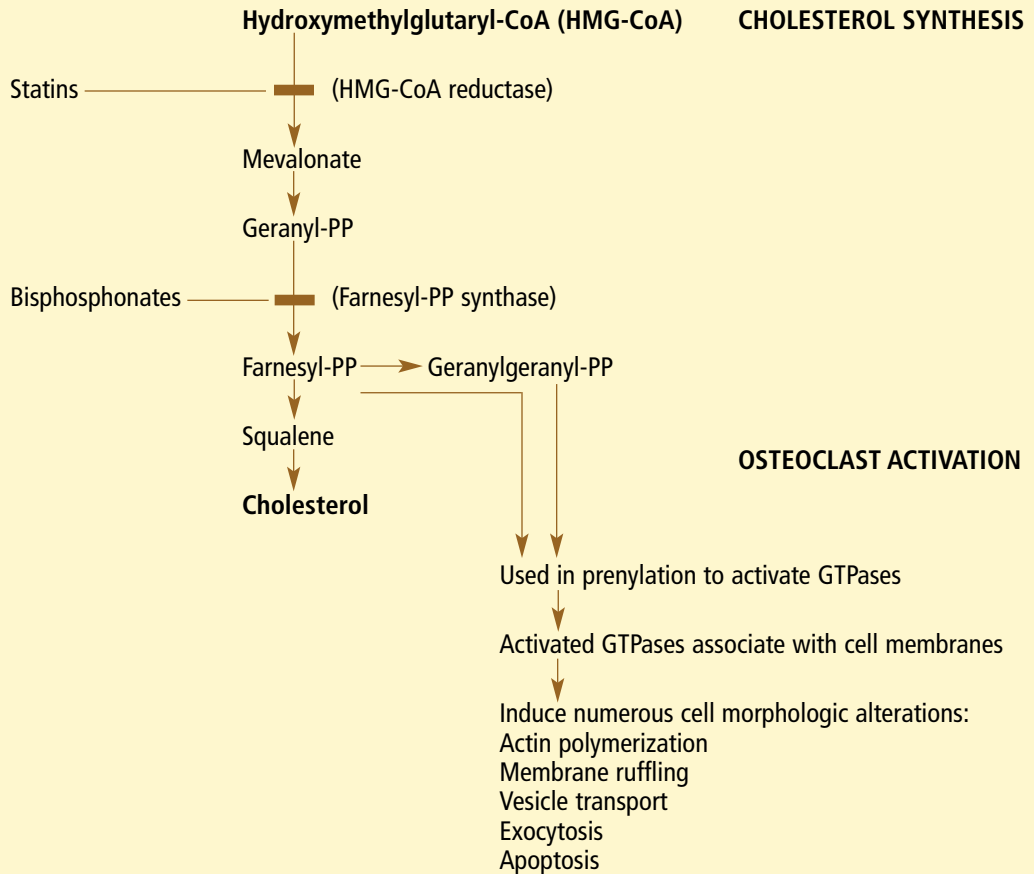
Osteoporosis, the most common disease of bone, affects about 30 million people in the United States<sup>2</sup> and as many as 100 million people worldwide. As the elderly population grows, the prevalence is expected to increase.

Osteoporosis is characterized by reduced bone mass, microarchitectural deterioration, and increased skeletal fragility. Fractures do not usually occur until bone mass falls to 30% to 50% below normal.

Although the precise cause of osteoporosis is unknown, an imbalance between bone formation and resorption presumably causes bone mass to decline in adulthood, and osteoporosis occurs when the amount of bone removed from the skeleton by bone-resorbing osteoclasts exceeds the amount formed by osteoblasts during the coupled process of remodeling. Treatment of osteoporosis is aimed toward restoring this balance.

Drugs such as bisphosphonates, estrogen, and selective estrogen receptor modulators are

## Cholesterol synthesis and osteoclast activation use the same pathway



**FIGURE 1**

widely used to slow bone loss. Although these agents reduce the incidence of fractures, they do not significantly increase bone formation. In theory, a drug that stimulates bone formation and helps restore bone strength would constitute a major breakthrough in osteoporosis treatment.<sup>3</sup> Remarkably, statin drugs may do this.

### ■ IF STATINS BUILD BONE, HOW DO THEY DO IT?

If statins prove to build bone, two recently elucidated pathways may explain the effect.

#### Inhibition of mevalonate production

The first discovery came from investigators at several laboratories who were working inde-

pendently to determine how bisphosphonates inhibit osteoclasts. These workers noted that cholesterol synthesis and osteoclast activation both involve the same biochemical cascade (FIGURE 1).<sup>4-7</sup>

Cholesterol synthesis has several steps. First, HMG-CoA is converted into mevalonate by the enzyme HMG-CoA reductase (which the statin drugs inhibit). Next, mevalonate is converted to geranyl pyrophosphate, which in turn is converted to farnesyl pyrophosphate by the enzyme farnesyl pyrophosphate synthase (which the bisphosphonate drugs inhibit). Next comes squalene and finally cholesterol.

Osteoclasts use the intermediate molecules farnesyl pyrophosphate and geranylgeranyl pyrophosphate (made from farnesyl

## Cholesterol synthesis and osteoclast activation use the same biochemical cascade

TABLE 1

### Do statins decrease fractures? Four studies say yes, four say no

INVESTIGATORS	DESIGN	NO. OF CURRENT STATIN USERS	FRACTURE SITE	FINDINGS*
<b>Studies that found a significantly lower risk</b>				
Meier et al <sup>15</sup>	Case-control	1,030	All	OR 0.55 (0.44–0.69)
Wang et al <sup>16</sup>	Case-control	240	Hip	OR 0.50 (0.33–0.76)
Chan et al <sup>17</sup>	Case-control	333	All	OR 0.48 (0.27–0.83)
Bauer et al <sup>18</sup>	Cohort	598	Hip	OR 0.30 (0.08–1.18)
<b>Studies that found no significantly lower risk</b>				
LaCroix et al <sup>19</sup>	Case-control	7,847	Hip	HR 0.98 (0.60–1.62)
Van Staa et al <sup>20</sup>	Case-control	950	All	OR 1.01 (0.88–1.16)
Reid et al <sup>21</sup>	Randomized	4,512	All	HR 1.05 (0.80–1.37)
Pedersen and Kjekshus <sup>22</sup>	Randomized	2,221	All	Incidence 3.78% vs 3.19%

\*OR odds ratio; HR hazard ratio; numbers in parentheses are 95% confidence intervals

### Statins may help form new bone by activating morphogenetic protein-2 promoter

pyrophosphate) to modify and activate the key intracellular proteins—glutamyl transpeptidases and GTPases—in a process called prenylation.<sup>8</sup> Bisphosphonates, such as alendronate and risedronate, prevent the formation of these lipid products<sup>5</sup> by inhibiting farnesyl synthase<sup>9</sup>; statins (as classic inhibitors of HMG-CoA) are equally effective at preventing osteoclast activation in vitro by preventing mevalonate production.

When exposed to statins or bisphosphonates, osteoclasts die by apoptosis. In turn, bone remodeling is reduced, bone resorption decreases, and the balance of bone resorption and formation is restored. More important, as demonstrated in clinical trials with bisphosphonates, this process reduces the incidence of fragility-related fractures.<sup>10–12</sup>

The structure of bisphosphonates, however, differs significantly from that of statins. Bisphosphonates contain a domain that mimics pyrophosphate and binds tightly to exposed mineralized surfaces under the osteoclast's ruffled border; statins lack this structure. This important difference makes it diffi-

cult to predict with confidence whether statins will retain biologic activity against osteoclasts in vivo.

### Activation of the bone morphogenetic protein-2 promoter

The second mechanism by which statins may affect the skeleton was uncovered by Mundy et al,<sup>13</sup> who screened a library of more than 30,000 natural compounds for osteoinductive substances that activate the promoter for bone morphogenetic protein-2. This protein is a growth factor that causes osteoblasts to proliferate, mature, and create new bone. Only lovastatin, derived from the fungus *Aspergillus terreus*,<sup>14</sup> was found to have this effect.

When lovastatin was injected into organ cultures of calvarial bones from neonate mice three times a day for 5 days, bone volume increased nearly 50% compared with placebo.<sup>13</sup> Histologic examination revealed enhanced bone-forming surfaces and osteoid accumulation.

Similar effects were found with fluvastatin, simvastatin, and mevastatin, which



specifically increased expression of bone morphogenetic protein-2 mRNA and more than doubled production of bone morphogenetic protein-2 by osteoblast-like cell lines *in vitro*.<sup>13</sup>

Further studies demonstrated that ovariectomized female rats (a model of postmenopausal osteoporosis) that were given simvastatin by mouth had an increase in trabecular bone volume of 39% to 94%.<sup>13</sup>

## ■ DO STATINS REDUCE FRACTURES?

Data are mixed on whether statins reduce the incidence of fractures in humans: some studies found a lower risk in statin users than in nonusers, while others did not. However, none of the studies were randomized controlled trials designed to examine this issue.

### Some studies found a lower risk of fractures in statin users

Four observational studies found that the risk of fractures was approximately half as high in people taking statins as in nonusers (TABLE 1). At the same time, people taking non-statin lipid-lowering drugs had approximately the same risk as nonusers.

Together, these findings suggest that the relationship between statin use and decreased fracture risk is causal and related to the biological activity of statins.

**Meier et al**,<sup>15</sup> in a case-control study in the United Kingdom, identified 3,940 patients with fractures and matched them with 23,379 subjects without fractures. After controlling for body mass index, smoking, number of physician visits, and use of corticosteroids and estrogen, the odds ratio for fractures among current statin users was 0.55.

**Wang et al**,<sup>16</sup> in a case-control study in New Jersey Medicaid patients, identified 1,222 patients hospitalized for surgical repair of hip fracture and matched them with 4,888 patients without hip fractures. After controlling for race, health insurance status, ischemic heart disease, cancer, diabetes mellitus, and use of psychoactive medications, estrogen, and thiazides, the odds ratio for hip fractures among current statin users was 0.50.

**Chan et al**,<sup>17</sup> in a case-control study of women older than 60 years in six US health maintenance organizations, identified 928

patients who sustained a fracture of the hip, humerus, distal tibia, wrist, or vertebra and matched them with 2,747 women without fractures. Women who used anti-osteoporosis drugs were excluded.

Compared with women who did not use statins during the previous 2 years, women with 13 or more statin dispensings during this period had an adjusted odds ratio for fracture of 0.48.

**Bauer et al**<sup>18</sup> analyzed data from two large studies of older women: the Study of Osteoporotic Fractures (SOF), with 8,412 women older than 65 years, and the Fracture Intervention Trial (FIT), with 6,459 women ages 55 to 80. At approximately 4 years of follow-up, the adjusted odds ratio for hip fracture in statin users was 0.30, which was not, however, statistically significant.

### Other studies found no difference

**LaCroix et al**,<sup>19</sup> analyzing data from more than 90,000 postmenopausal women, found no link between statin use and risk of hip fractures. However, few women in this study had used statins for more than 3 years. Therefore, the findings do not rule out the possibility that long-term statin use might reduce fracture risk.

**Van Staa et al**,<sup>20</sup> using the same UK database as Meier et al, identified 81,880 patients with fractures and 81,880 matched controls. Statin users had fracture risks comparable to those using non-statin lipid-lowering agents and untreated hyperlipidemic patients.

**Reid et al**<sup>21</sup> analyzed data from the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, in which 9,014 patients (17% women; median age 62) with ischemic heart disease were randomized to receive either pravastatin 40 mg/day or placebo. After a mean follow-up of 6.1 years, the data did not support a significant effect of statins on fracture risk.

**Pedersen and Kjekshus**<sup>22</sup> examined the frequency of fractures in the Scandinavian Simvastatin Survival Study (4S), a randomized, double-blind, placebo-controlled, multicenter trial of simvastatin 20 to 40 mg/day in patients aged 35 to 70 with coronary artery disease. Fractures occurred in 155 patients, with no significant difference between the treatment and placebo groups.

**Four studies found that statins halved the fracture risk; four studies found no such effect**

TABLE 2

### Studies that suggested an increased bone density associated with statins

INVESTIGATORS	DESIGN	NO. OF CURRENT STATIN USERS	SITE	BONE MINERAL DENSITY
Chung et al <sup>23</sup>	Retrospective*	36	Hip	0.88% increase from baseline at 15 months in users; 1.03% decrease at 14 months in nonusers ( $P < .05$ )
Edwards et al <sup>24</sup>	Cohort†	41	Hip	0.76 g/cm <sup>2</sup> in statin users; 0.68 g/cm <sup>2</sup> in nonusers ( $P < .05$ )
			Spine	0.99 g/cm <sup>2</sup> in statin users; 0.91 g/cm <sup>2</sup> in nonusers ( $P < .001$ )
Watanabe et al <sup>25</sup>	Randomized‡	25	Whole body	No change from baseline at 1 year
			Lumbar spine	1% increase from baseline with fluvastatin; 2% decrease with pravastatin ( $P = .04$ )

\*In patients with type 2 diabetes mellitus

†In postmenopausal women

‡Comparing fluvastatin vs pravastatin in postmenopausal women

Data are still mixed on whether statins reduce fracture incidence in humans

#### ■ INCREASED BONE DENSITY

Chung et al,<sup>23</sup> in a retrospective study, found that statin use was associated with increased hip bone density in men with type 2 diabetes (TABLE 2). Of 69 patients, 36 received lovastatin, pravastatin, or simvastatin; the 33 control subjects did not. In patients who received statins, bone density of the femoral neck increased significantly after 15 months. In the control group, bone density of the spine decreased significantly after 14 months.

Diabetes may itself affect bone metabolism. The bone density of patients with type 1 diabetes is lower than in healthy subjects; in contrast, hyperinsulinemia and the relatively high body mass index in patients with type 2 diabetes seem to protect against bone loss.

Bauer et al,<sup>18</sup> in their analysis of data from the SOF and FIT studies, found that women taking statins but not other lipid-lowering drugs had higher bone densities of the hip; however, this association did not reach statistical significance.

Edwards et al,<sup>24</sup> in the United Kingdom, measured the bone density of the hip and spine in 41 postmenopausal women taking statins and in 100 matched controls. The median length of statin use was 48 months; 51% of the statin users took simvastatin, 24% took pravastatin, 15% took atorvastatin, and 10% took fluvastatin.

Bone mineral density was significantly higher in statin users, and the difference remained significant after adjustment for age, height, and weight. In contrast, in another 46 women with total cholesterol levels higher than 290 mg/dL at baseline who did not receive statins, bone density did not differ at the spine or hip compared with controls.

Watanabe et al<sup>25</sup> performed a small randomized trial comparing the effects of fluvastatin and pravastatin in postmenopausal women. At 1 year, neither drug had any effect on the bone mineral density of the whole body, but the bone mineral density of the lumbar spine had increased by 1% in the fluvastatin group, compared with a 2% decrease in the pravastatin group.



## ■ WHY WERE THE FINDINGS INCONSISTENT?

Possible reasons for the divergent findings in the studies of fracture risk include the following:

**The effect of statins on bone may be relatively weak**, apparent in some studies but not in others.

**Statins may have been given preferentially** to patients who were less frail or otherwise at lower risk of fracture. (As with all observational studies, biases or confounders such as this cannot be entirely excluded.)

**The control groups were small.** In most of these studies, the control group of hyperlipidemic patients using non-statin agents was smaller and thus less robust as a comparative group.

**Obesity was not controlled for.** Low body mass is a risk factor for osteoporotic fractures, and high body mass is associated with high blood cholesterol concentrations. Therefore, patients treated with cholesterol-lowering drugs may have a lower intrinsic risk of fracture because of the protective effect of increased adipose tissue. Future studies should include calculations of the body mass index, because obesity may be an important underlying factor that leads to both statin use and a reduced risk of hip fracture.

**The physical activity of subjects was not quantified**, even though physical activity is associated with lower fracture risk.

**Doses may have been too low.** Higher doses of statins may be needed to affect bone than to lower cholesterol. Current statins target the liver, where most cholesterol synthesis occurs, rather than the bones, and less than 5% of a given dose reaches the systemic circulation.<sup>26</sup> Indeed, the efficacy and safety of statins in treating hyperlipidemia is due mainly to their selective localization to the liver. Mundy et al,<sup>13</sup> in their studies in rats, used doses about 10 times higher than those typically given to patients.

**Duration may have been too short.** With their limited bioavailability for osteoclasts, statins may need to be taken long-term to produce a significant biologic response.

## ■ FUTURE STUDY REQUIREMENTS

Prospective randomized controlled trials are needed to better exclude the possibility of unmeasured confounding variables and to delineate precisely the role of statins in skeletal health.


Although the consensus seems to be that statins increase bone density, not all studies demonstrated this association. Furthermore, the primary end points measured in many of these studies did not include bone density or fracture rates. Retrospective analysis of data may be misleading, because not all events and outcomes were comprehensively recorded.<sup>27</sup>

It also is interesting that pravastatin has recently been shown to be ineffective in increasing bone morphogenetic protein-2 or stimulating bone formation, perhaps because of its molecular charge.<sup>28</sup> As might be predicted, the largest clinical trial using pravastatin<sup>21</sup> failed to demonstrate fracture protection. Excluding this pravastatin trial from the analysis may increase the association between statins and decreased risk of fracture.

## ■ TOWARD MORE EFFECTIVE BONE-STRENGTHENING DRUGS

Bisphosphonates reduce bone resorption but do not significantly stimulate bone formation. Conversely, *in vivo* studies and some clinical studies suggest that statins have an anabolic effect on bone.

Statins appear to enhance osteoblastic activity by both increasing expression of bone morphogenetic protein-2, a stimulator of osteoblast differentiation, and diminishing osteoclast activity by preventing prenylation and activation of key intracellular proteins. The mechanism of this effect is unclear because our ability to separate antiresorptive and anabolic effects *in vitro* remains embryonic.

Currently available statins, which are designed for lipid-lowering, may be suboptimal for treating osteoporosis; however, insights from studies such as those reviewed here may lead to development of similar molecules that more effectively promote bone formation and inhibit resorption. 

**Current statins, may be suboptimal for treating osteoporosis**



## REFERENCES

- Vogel G. Cholesterol-lowering drugs may boost bones. *Science* 1999; 286:1825–1826.
- Melton LJ 3rd. How many women have osteoporosis now? *J Bone Miner Res* 1995; 10:175–177.
- Rogers MJ. Statins: lower lipids and better bones? *Nat Med* 2000; 6:21–23.
- Fisher JE, Rogers MJ, Halasy JM, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. *Proc Natl Acad Sci USA* 1999; 96:133–138.
- Luckman SP, Hughes DE, Coxon FP, Russell RG, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 1998; 13:581–589.
- Luckman SP, Coxon FP, Ebetino FH, Russell RG, Rogers MJ. Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: evidence from structure-activity relationships in J774 macrophages. *J Bone Miner Res* 1998; 13:1668–1678.
- Russell RG, Rogers MJ, Frith JC, Luckman SP, Coxon FP, Benford HL. The pharmacology of bisphosphonates and new insights into their mechanisms of action. *J Bone Miner Res* 1999; 14(suppl 2):53–65.
- Zhang FL, Casey PJ. Protein prenylation: molecular mechanisms and functional consequences. *Annu Rev Biochem* 1996; 65:241–269.
- Van Beek E, Pieterman E, Cohen L, Lowik C, Papapoulos S. Farnesyl pyrophosphate synthase is the molecular target of nitrogen-containing bisphosphonates. *Biochem Biophys Res Commun* 1999; 264:108–211.
- McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *Hip Intervention Program Study Group. N Engl J Med* 2001; 344:333–340.
- Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate: a meta-analysis. *Alendronate Osteoporosis Treatment Study Group. JAMA* 1997; 277:1159–1164.
- Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998; 280:2077–2082.
- Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. *Science* 1999; 286:1946–1949.
- Alberts AW, Chen J, Kuron G, et al. Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc Natl Acad Sci USA* 1980; 77:3957–3961.
- Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 2000; 283:3205–3210.
- Wang PS, Solomon DH, Mogun H, Avorn J. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 2000; 283:3211–3216.
- Chan KA, Andrade SE, Boles M, et al. Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 2000; 355:2185–2188.
- Bauer DC, Mundy GR, Jamal SA, et al. Statin use, bone mass and fracture: an analysis of two prospective studies [abstract]. *J Bone Miner Res* 1999; 14:S179.
- LaCroix AZ, Cauley JA, Jackson R, et al. Does statin use reduce risk of fracture in postmenopausal women? Results from the Women's Health Initiative Observational Study (WHI-OS) [abstract]. *J Bone Miner Res* 2000; 15(suppl 1):1066.
- Van Staa TP, Wegman S, de Vries F, Leufkens B, Cooper C. Use of statins and risk of fractures. *JAMA* 2001; 285:1850–1855.
- Reid IR, Hague W, Emberson J, et al. Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. *Lancet* 2001; 357:509–512.
- Pedersen TR, Kjekshus J. Statin drugs and the risk of fracture [letter]. *JAMA* 284:1921–1922.
- Chung YS, Lee MD, Lee SK, Kim HM, Fitzpatrick LA. HMG-CoA reductase inhibitors increase BMD in type 2 diabetes mellitus patients. *J Clin Endocrinol Metab* 2000; 85:1137–1142.
- Edwards CJ, Hart DJ, Spector TD. Oral statins and increased bone-mineral density in postmenopausal women. *Lancet* 2000; 355:2218–2219.
- Watanabe S, Fukumoto S, Takeuchi Y, Fujita H, Nakano T, Fujita T. Effects of 1-year treatment with fluvastatin or pravastatin on bone. *Am J Med* 2001; 110:584–587.
- Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci* 1998; 19:26–37.
- Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. Statins and the risk of fracture. *JAMA* 2000; 284:1921–1922.
- Sugiyama M, Kodama T, Konishi K, Abe K, Asami S, Oikama S. Compactin and simvastatin, but not pravastatin, induce bone morphogenetic protein-2 in human osteosarcoma cells. *Biochem Biophys Res Commun* 2000; 271:688–692.

ADDRESS: Abelardo C. Cruz, MD, State University of New York at Stony Brook, Division of Rheumatology, HSC T-16, Room 040, Stony Brook, NY 11794-8161; e-mail geriatricrheum@yahoo.com.