

Review

Statins and Bone: Myth or Reality?

C. J. Edwards,¹ R. G. G. Russell,² T. D. Spector³

¹The Kennedy Institute of Rheumatology, Imperial College School of Medicine, 1 Aspenlea Road, London, W6 8LH, UK

²Nuffield Department of Orthopaedic Surgery, Nuffield Orthopaedic Centre, University of Oxford, Oxford, OX3 7LD, UK

³Twin Research and Genetic Epidemiology Unit, St Thomas' Hospital, London, SE1 7EH, UK

Received: 1 February 2001 / Accepted: 26 February 2001 / Online publication: 27 July 2001

Abstract. In the space of a few weeks, four articles appeared in the *The Lancet* and *JAMA* suggesting that using 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) is associated with increased bone mineral density (BMD) [1] and a reduced fracture risk [2–4]. The stimulus for these case-control studies came from reports that the statins have unexpected effects on bone, increasing bone formation in rodents [5]. These observations offered a new insight into the potential importance of the cholesterol synthesis pathway in bone turnover and future therapeutic opportunities.

Statins are well established as lipid-lowering drugs that reduce the likelihood of cardiovascular events including myocardial infarction [6]. They act by inhibiting HMG CoA reductase, the rate-limiting step in cholesterol synthesis. This reduces cholesterol formation and leads to increased expression of LDL receptors on the cell surface of hepatocytes. The four recently published case-control studies have shown effects on BMD and fracture risk in a large number of patients. In the smallest of the studies, *with the most* clinical information, an association was seen between BMD and statin use in a well-described population-based cohort of postmenopausal women (mean age 66.2 years) [1]. BMD at the spine and hip were approximately 7–8% higher in 41 women taking statins compared with a control group from the same population similar in terms of age, height, weight, years since menopause, and hormone therapy (HRT) use. Adjustment for these variables, plus smoking, did not alter the results. A group of women with significant hypercholesterolemia, on no lipid-lowering treatment, were also analyzed and did not differ at the hip or spine for BMD when compared with controls. No dose or duration subanalyses were performed because of small numbers of women.

In the same edition of *The Lancet* Chan et al. [2] reported a population-based case-controlled study using the health maintenance records from 928 women aged 60 or over with fracture of the hip, humerus, distal tibia, wrist, or vertebrae and compared them with 2747 controls with no fracture. All individuals taking osteoporosis treatments were excluded from the analysis. Women who had taken statins for at least 1 year had a reduced risk of fracture [odds ratio 0.48 (95% CI 0.27–0.83)] after adjusting for age, number of hospital admissions, chronic disease score, and the use of nonstatin lipid-lowering drugs. There was no clear dose-dependent relationship between length of statin use and fracture risk. Then, Meier et al. [4] published a population-based, nested case-control study in *JAMA*, using a UK-based general practice research database. They identified 28,340 men and women aged at least 50 years taking lipid-lowering drugs, 13,271 with hyperlipidemia not taking lipid-lowering drugs, 50,000 randomly selected individuals without hyperlipidemia, and 3,940 individuals with a previous bone fracture. After controlling for body mass index, smoking, number of physician visits, and corticosteroid and estrogen use, current use of statins was associated with a reduced fracture risk [odds ratio 0.55 (95% CI 0.44–0.69)]; other lipid-lowering drugs had no such effect. Once again there was no clear relationship between the number of statin prescriptions and fracture risk.

Also in *JAMA*, Wang et al. [3] reported a case-control study of 6110 individuals aged 65 and over who were registered with Medicare and Medicaid or the Pharmacy Assistance for the Aged and Disabled program. Of these patients, 1222 had undergone surgical repair of a hip fracture. Use of statins in the previous 180 days [odds ratio 0.5 (95% CI 0.33–0.76)] or previous 3 years [odds ratio 0.57 (95% CI 0.40–0.82)] was associated with a reduction in hip fracture. This held true even after adjusting for race, insurance status, psychoactive medications, estrogen use, ischemic heart disease, cancer, and diabetes mellitus. Once again, no reduc-

tion in fracture risk was seen with the nonstatin lipid-lowering drugs. Adjusting for number of medications, the Charlson comorbidity index score and hospital or nursing home admissions to identify the presence of chronic disease had no effect on the results. Interestingly, this study did show a significant dose-response effect when the patients were divided into quartiles on the basis of the length of statin use. Those individuals who had used the most statins also had the lowest fracture risk.

Overall, these studies have surveyed a large number of individuals and attempted to control for the major confounding variables. In particular, the possibility that hypercholesterolemia may itself be associated with raised BMD or protection from fracture risk has been partly addressed. All the studies examined controls that were hypercholesterolemic and not taking any lipid-lowering treatment; the studies found no evidence of raised BMD or a reduced fracture risk. Similarly, the use of other nonstatin lipid-lowering drugs such as fibrates did not appear to produce a decreased fracture risk. Other studies are in progress and a preliminary report from a prospective study has suggested that statin use was associated with a nonsignificant decrease in fractures of the hip [7]. A retrospective cohort study of 36 diabetic patients has also shown a significant increase in BMD at the hip after 15 months of statin use [8]. In contrast, a retrospective study of Japanese diabetic patients found a decrease in lumbar spine BMD of 131 statin users when compared with controls [0.884 (0.15) vs 0.965 (0.11) g/cm², $P < 0.001$] [9]. However, no information was included on other variables important to BMD and the majority of individuals were taking pravastatin, a statin that may have no effect on bone [10]

In addition, at the recent 22nd meeting of the ASBMR, several abstracts were presented with new information on the effect of statin use on bone. Overall, these showed mixed results, with positive effects on BMD and bone markers but no clear effect on fracture risk in statin users. A small study by Watanabe et al. [11] looked at the effects of fluvastatin in 10 male and 10 female patients being treated for hypercholesterolemia over a period of 1 year. Urinary N-terminal telopeptide of type I collagen was decreased to a small but significant extent in the female patients ($69.2 \pm 8.5\%$ of baseline) after 1 month, but bone-specific alkaline phosphatase and osteocalcin did not change in either group even after a year. BMD of the lumbar spine was significantly increased in women taking fluvastatin ($102.2 \pm 0.7\%$ of baseline) at 6 months and was maintained at 1 year. However, 10 female patients treated with pravastatin had no such changes. In a much larger study, Cauley et al. [12] looked at statin use in 6,442 women enrolled in the women's health initiative observational study (WHI-OS). Statin use of greater than 3 years duration ($n = 79$) was associated with an increased body mass index adjusted BMD at the hip in users compared with nonusers (0.87 g/cm² vs 0.84 g/cm², $P = 0.03$) and lumbar spine (100 g/cm² vs 0.98 g/cm², $P =$

0.05). It also suggested that users of atorvastatin and simvastatin had higher BMDs than users of pravastatin, lovastatin, and fluvastatin. In addition, Bjarnason et al. [13] showed no effect of fluvastatin in combination with vitamin C on bone formation (serum osteocalcin and total alkaline phosphatase), but a weak inhibition of bone resorption (measured as urinary CrossLaps) in 68 postmenopausal women with hip or spine T-score less than -2 SD.

However, the fracture prevention data reported at the ASBMR meeting does not support the already published data, even on the same populations. Using data again from the WHI-OS, La Croix et al. [14] compared fracture rates in 7847 postmenopausal women using statins to fracture rates in 85,876 nonusers over 2–3 years. They found no significant difference in hip, wrist, or other fractures after adjustment, although many women were taking HRT, and fracture rates were lower in non-HRT statin users. Van Staa et al. [15], using the same dataset as Meier et al. [4], failed to confirm a decreased risk of forearm, hip, and vertebral fractures using different analytic techniques even after many of the potential confounding variables were taken into account [15]. Reid et al. [16] looked retrospectively at 9014 patients randomized to pravastatin 40 mg/day with ischemic heart disease in the previously published LIPID study. There was no significant effect of statin use on fracture risk when analyzed after follow-up of 6.1 years. Analysis of fracture data from the LIPID study has recently been published in full [17].

Despite the encouraging consistencies of the reports in *The Lancet* and *JAMA*, the more recent abstracts, although not subject to full peer review, remind us to be cautious in interpreting observational data. Drugs and diseases that are associated with diet, weight, and lifestyle changes can be very difficult to separate. An interesting parallel is with the case control studies of the use of estrogen replacement therapy (ERT), which appear to have exaggerated the health benefits compared with randomized trials, possibly due to healthy lifestyle selection biases. Many US statin studies have high rates of ERT users. Another concern is the speed of action. There is a marked lack of data on a dose-response effect, e.g. does 10 years treatment provide more benefit than 1–3 years? Or is current use more or less important than past use? Although one study [3] suggested a dose-response relationship, other studies failed to show a similar effect. However, it would be surprising if the perfect dose and timing for lowering cholesterol was also the perfect bone dose.

A biological explanation for these observations would certainly help in establishing causality. Possible mechanisms are emerging as to how statins might work to decrease fracture risk and increase BMD. There are two series of recent observations that point to the key role of the mevalonate pathway in bone metabolism, which encouraged the clinical studies described here. Firstly, during studies of the mechanism of action of bisphosphonates [18], it was shown

The Mevalonate Pathway

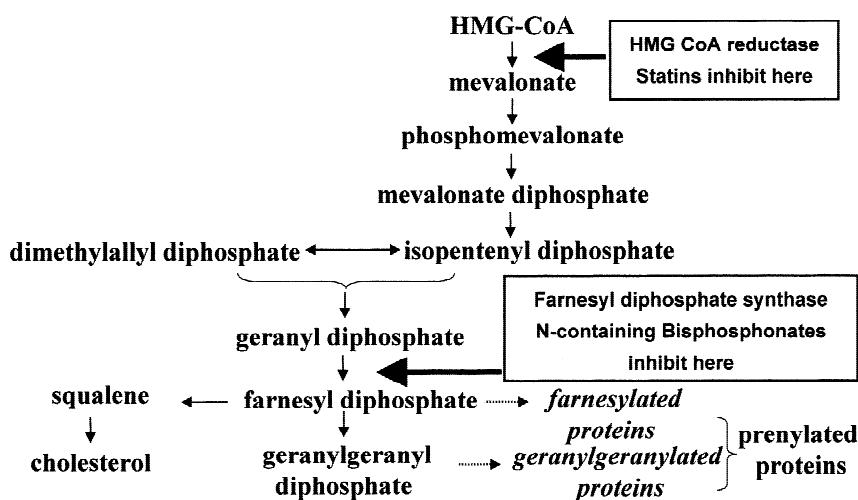


Fig. 1. Sites of action of statins and bisphosphonates on the cholesterol synthetic pathway. Statins antagonize the conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonate by HMG-CoA reductase which is the rate limiting step of the cholesterol synthetic pathway. Nitrogen containing bisphosphonates antagonize protein prenylation by inhibiting formation of farnesyl pyrophosphate and geranylgeranyl pyrophosphate.

that the nitrogen-containing bisphosphonates inhibit the mevalonate pathway in osteoclasts and prevent the synthesis of isoprenoids [19–21]. This leads to a decrease in the prenylation of key regulatory GTP-binding proteins, which block bone resorption by inhibiting osteoclast activity and eventually inducing osteoclast apoptosis [22]. As expected, inhibition of bone resorption, also perhaps involving osteoclast apoptosis, was then shown to be induced by statins themselves [19].

Secondly, statins are potential stimulators of bone formation. Using a bone morphogenetic protein-2 (BMP-2) promoter linked to a luciferase reporter gene transfected into an immortalized murine osteoblast cell line, Mundy et al. [5] screened more than 30,000 compounds and identified lovastatin, and subsequently simvastatin, mevastatin, and fluvastatin as having bone-forming effects. BMP-2 is a powerful inducer of new bone formation and anything that increases the activity of the BMP-2 promoter is likely to increase bone formation. The statins increased BMP-2 mRNA and the production of BMP-2 protein by osteoblast cell lines, increased bone formation in explant bone cultures, and oral administration of statins to rats increased bone formation even after ovariectomy. However, the doses of statins used in the rats were higher than the equivalent dose for lipid-lowering in humans, as rats are relatively resistant to the effects of statins. Statins inhibit the rate-limiting step in cholesterol synthesis, the formation of mevalonate from 3-hydroxy-3-methyl-glutaryl CoA (Fig. 1). The effect of statins on luciferase activity was completely inhibited by adding mevalonate in this study and in similar experiments with a BMP-2 promoter-luciferase reporter in an osteosarcoma cell line [5, 23]. This suggested that the activation of the BMP-2 promoter was due to the inhibition of HMG-CoA reductase. Taken together these studies indicate that products of mevalonate metabolism in the cholesterol synthesis pathway have important effects on

both bone formation and resorption. They provide a compelling case for evaluating the effects of statins on bone, and also offer novel opportunities for therapeutic manipulation.

However, how likely is it that statins used for controlling cholesterol metabolism might also affect the skeleton? The statins currently used for treating hyperlipidemia have largely been selected for actions on the liver and reach bone in only low concentrations. As little as 5% of ingested statins may reach the peripheral circulation after first pass metabolism [24]; this is important in reducing their adverse effects on other tissues. The circulating concentrations in man, unlike rats, are very low, in the submicromolar range, and are probably below those needed to produce effects in experimental studies. However, little seems to be known about their uptake into bone, for example, into the adipose tissue of bone marrow. In order to optimize these potential effects of existing statins, alternative modes of administration may be needed. Thus, lovastatin, given by topical application to skin in rats, resulted in blood concentrations two-fold greater than when the drug was given orally [25]. Lovastatin administered in this way was 50 times more active on bone formation in rats than after oral administration. In the future, statin-like drugs may be designed that are selectively targeted to bone rather than the liver.

These observations, although leaving unanswered questions, provide an exciting new direction for the treatment of osteoporosis and a greater understanding of the key pathways involved in bone formation and resorption. In addition, a recent meta-analysis of eight observational studies on the effect of statins on fracture risk suggested a protective effect on non-spine [RR 0.66 (95% CI 0.55–0.88)] and hip fractures [RR 0.43 (95% CI 0.25–0.75)] (DC Bauer, DM Black, M van der Klift, personal communication). The analysis included published studies, one unpublished study, and abstracts from major meetings, with a total of 151,500 individuals with 2814 fractures of whom 9946 were statin

users. However, before we rush into prescribing statins for bone, the most encouraging epidemiological observations must first be validated by randomized controlled studies, assessing effects of different compounds, and their duration and doses on bone turnover, BMD, and if possible, the ultimate endpoint, fracture.

References

1. Edwards CJ, Hart DJ, Spector TD (2000) Oral statins and increased bone-mineral density in postmenopausal women. *Lancet* 355:2218–2219
2. Chan KA, Andrade SE, Boles M, Buist DS, Chase GA, Donahue JG, Goodman MJ, Gurwitz JH, LaCroix AZ, Platt R (2000) Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 355:2185–2188
3. Wang PS, Solomon DH, Mogun H, Avorn J (2000) HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 283:3211–3216
4. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H (2000) HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 283:3205–3210
5. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutteriez G (1999) Stimulation of bone formation in vitro and in rodents by statins. *Science* 286:1946–1949
6. LaRosa JC, He J, Vupputuri S (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 282:2340–2346
7. Bauer DM, Mundy GR, Jamel SA, Black DM, Cauley JA, Duong T, Cummings SR (1999) Statin use, bone mass and fracture: an analysis of two prospective studies (abstract). *J Bone Miner Res* 14 (suppl):S179
8. Chung YS, Lee MD, Lee SK, Kim HM, Fitzpatrick LA (2000) HMG-CoA reductase inhibitors increase BMD in type 2 diabetes mellitus patients. *J Clin Endocrinol Metab* 85:1137–1142
9. Wada Y, Nakamura Y, Koshiyama H (2000) Lack of positive correlation between statin use and bone mineral density in Japanese subjects with type 2 diabetes. *Arch Intern Med* 160:2865
10. Garrett IR, Escobedo A, Esparza J, Mundy GR (1999) Cerivastatin increases BMP-2 expression in vivo and bone formation in concentrations of two orders of magnitude lower than other statins. *J Bone Miner Res* 14 (suppl 1):1189
11. Watanabe S, Fukumoto S, Takeuchi Y, Nakapo T, Fujita T (2000) Effects of one year treatment with statins on bone mass and metabolism (abstract). *J Bone Miner Res* 15 (suppl 1):S194
12. Cauley JA, Jackson R, Pettinger M, LaCroix A, Bauer D, Chen Z, Daugherty S, Hsia J, Lewis CE, McGowan J, McNeeley SG, Passero M (2000) Statin use and bone mineral density (BMD) in older women: the Women's Health Initiative Study (WHI-OS) (abstract). *J Bone Miner Res* 152 (suppl 1):S155
13. Bjarnason NH, Shalmi M, Riis BJ, Christiansen C (2000) No clinically relevant effect of fluvastatin on postmenopausal bone remodeling (abstract). *J Bone Miner Res* 15 (suppl 1):S427
14. LaCroix AZ, Cauley JA, Jackson R, McGowan J, Pettinger M, Hsia J, Chen Z, Lewis CE, Bauer D, Daugherty S, McNeeley SG, Passero M (2000) Does statin use reduce risk of fracture in postmenopausal women? Results from the women's health initiative study (WHI-OS) (abstract). *J Bone Miner Res* 15 (suppl 1):S155
15. Van Staa TP, Wegman SL, de Vries F, Leufkens HG, Cooper C (2000) Use of statins and risk of fractures (abstract). *J Bone Miner Res* 15 (suppl 1):S155
16. Reid IR, Hague W (2000) Effect of pravastatin on fracture incidence in the lipid study: a randomised controlled trial (abstract). *J Bone Miner Res* 15 (suppl 1):S225
17. Reid IR, Hague W, Emberson J, Baker J, Tonk A, Hunt D, MacMahon S, Sharpe N (2001) Effect of pravastatin on fracture incidence in the lipid study: secondary analysis of a randomised controlled trial. *Lancet* 357:509–512
18. Russell RGG, Rogers MJ (1999) Bisphosphonates. From the laboratory to the clinic and back again. *Bone* 25:97–106
19. Luckman SP, Hughes DE, Coxon FP, Russell RG, Rogers MJ (1998) Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 13:581–589
20. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA (1999) 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 U S A* 96:133–138
21. van Beek E, Pieterman E, Cohen L, Lowik C, Papapoulos S (1999) Farnesyl pyrophosphate synthase is the molecular target of nitrogen-containing bisphosphonates. *Biochem Biophys Res Commun* 264:108–111
22. Coxon FP, Helfrich MH, Van't Hof R, Sebt S, Ralston SH, Hamilton A, Rogers MJ (2000) Protein geranylgeranylation is required for osteoclast formation, function, and survival: inhibition by bisphosphonates and GGTI-298. *J Bone Miner Res* 15:1467–1476
23. Sugiyama M, Kodama T, Konishi K, Abe K, Asami S, Oikawa S (2000) Compactin and simvastatin, but not pravastatin, induce bone morphogenetic protein-2 in human osteosarcoma cells. *Biochem Biophys Res Commun* 271:688–692
24. Hamelin BA, Turgeon J (1998) Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci* 19:26–37
25. Gutierrez G, Garrett LR, Rossini G, Castano M, Chapa G, Escobedo A, Esparza J, Horn D, Oino M, Taylor S, Lalka D, Mundy GR (2000) Dermal application of lovastatin to rats causes greater increases in bone formation and plasma concentrations than when administered by oral lavage (abstract). *J Bone Miner Res* 15 (suppl 1):S427