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Commentary

Statins as modulators of bone formation

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Abstract

The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to reduce serum cholesterol is well described. However, the recent finding that statins have direct effects on bone was unexpected. A number of epidemiological studies have recently been published that explore the effects of statins on bone mineral density and risk of fracture in humans. Statins may act by directly stimulating the expression of bone morphogenetic protein-2 and increasing osteoblast differentiation or, like nitrogen-containing bisphosphonates, may have effects on the mevalonate pathway that leads to inhibition of osteoclast activity and osteoblast apoptosis. In addition, the demonstration that statins can inhibit inflammation and encourage angiogenesis offers other possibilities for action.

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The actions of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) on serum cholesterol concentrations are well documented and are associated with a decrease in cardiovascular events and death [1]. However, statins also appear to modulate bone formation, inflammation, and angiogenesis. As well as providing an increased understanding of the biological importance of cholesterol synthetic pathways, the suggestion that statins can increase bone formation has provided an exciting new direction for research.

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In late 1999, experimental work produced the unexpected finding that statins may have direct effects on bone [2]. This work was carried out to look for new stimulators of bone formation that might be useful therapeutically. More than 30,000 compounds were screened for their ability to stimulate the bone morphogenetic protein-2 (BMP-2) promoter in an osteoblast cell line. It was thought that because bone morphogenetic proteins are the most potent stimulators of bone formation known, any compound stimulating the BMP-2 promoter would have a strong positive effect on bone formation. Only two compounds, lovastatin and simvastatin, had a positive effect. Further work to confirm these findings showed that statins could stimulate bone formation when administered locally to bony sites or when given systemically in rats.

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Since those findings, a number of epidemiological studies have been published that explore the effects of statin use on bone mineral density and risk of fracture in humans. These studies have produced mixed results: one showed an increased bone mineral density associated with statin use, three showed an association with a reduced risk of fracture, and two showed no effect.

In a cross-sectional population study, our group demonstrated an association between bone mineral density and statin use in post-

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menopausal women [3]. Bone mineral density at the spine and hip were approximately 7–8% higher in women taking statins than in controls of similar age, height, weight, years since menopause, and use of hormone replacement therapy. A case-control study using the health-maintenance records from 928 women aged 60 years or over with a fracture of the hip, humerus, distal tibia, wrist, or vertebrae showed a lower risk of fracture (odds ratio [OR] 0.48 [95% confidence interval [CI] 0.27–0.83]) in those who had taken statins for at least one year than in 2747 controls with no fracture [4]. This was maintained after excluding individuals taking osteoporosis treatments and after adjusting for age and number of hospital admissions and score for chronic disease. A nested case-control study using a UK-based general practice research database has also shown that current use of statins was associated with a reduced risk of fracture (OR 0.55 [95% CI 0.44–0.69]) [5]. The study included 28,340 men and women aged at least 50 years taking lipid-lowering drugs, 13,271 with hyperlipidaemia not taking lipid-lowering drugs, 50,000 randomly selected individuals without hyperlipidaemia, and 3940 individuals with a previous bone fracture. Results were controlled for body mass index, smoking, number of visits to physician, and use of corticosteroids or oestrogen. In a case-control study of 6110 individuals aged 65 years and over who were registered with Medicare and Medicaid or the programme Pharmacy Assistance for the Aged and Disabled, 1222 individuals had had surgical repair of a hip fracture. Use of statins in the previous 180 days (OR 0.5 [95% CI 0.33–0.76]) or previous 3 years (OR 0.57 [95% CI 0.40–0.82]) was associated with a reduction in hip fracture [6]. This reduction persisted even after adjustment for race, psychoactive medications, oestrogen use, and a number of chronic diseases. This study is the only one that has shown a dose relationship between the amount of statin used and protection against risk of fracture. The possibility that these effects were via reducing cholesterol levels seems unlikely, because all the above studies showed no effect from non-statin cholesterol-lowering drugs.

More recently, two large studies have failed to demonstrate an association between statin use and risk of fracture. The first of these had the benefit of being a randomised trial and looked retrospectively at the frequency of fractures occurring in a large group of patients with ischaemic heart disease treated with pravastatin in the LIPID study [7]. There was no difference in fractures occurring in the pravastatin group ($n = 107$) as compared with the placebo group ($n = 101$) (OR 1.05 [95% CI 0.80–1.37]). The second study used the same General Practice

database as Meier *et al.* [6] but different analytic methods and time periods and a slightly different subsample [8]. They found no association between use of statin and risk of fracture in 81,880 individuals sustaining a fracture of the vertebrae, clavicle, humerus, radius/ulna, carpus, hip, ankle, or foot after adjusted for smoking, medications, and illnesses associated with risk of fracture. However, the results suggested a modest protection for hip fracture.

Where do these results leave us? It is perhaps surprising that statins designed for their effects on hepatic synthesis of cholesterol seem to have biological effects on bone. Only 5% of ingested statins may finally reach the peripheral circulation after first-pass metabolism [9]. In addition, the doses of statins given to laboratory rats to get an effect on bone were many times higher than the equivalent doses normally given for hypercholesterolaemia in humans [2]. However, a meta-analysis of eight observational studies has also shown support for the protective effect of statins on risk of fracture [10]. This analysis showed a greater protective effect fracture of the hip than of other sites and suggests the possibility that statins have site-specific effects on risk of fracture. In addition, increasing evidence for an effect of statins on bone is coming from experimental work that shows direct effects of statins on osteoblastic cells. Statins may also have indirect effects on bone formation through effects on inflammation or angiogenesis. The laboratory work has also shown differential effects between statins that may explain some of the differences seen in the epidemiological studies.

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Simvastatin, mavastatin, fluvastatin, and lovastatin have all been shown to stimulate bone formation [2]. In addition, both simvastatin [11] and pitavastatin [12] increased human osteoblast differentiation as measured by, respectively, alkaline phosphatase expression and mineralisation or expression of BMP-2 and osteocalcin. However, pravastatin, in contrast to simvastatin, did not induce BMP-2 expression of human osteosarcoma cells [13]. Pravastatin also has different pharmacokinetics from other statins, with a large uptake to the liver via an active transport system [14] that might limit its availability at other sites. This may explain the lack of effect seen in the analysis of the LIPID study, in which all the patients were taking pravastatin. All the other epidemiological studies included a minority of patients taking

pravastatin.

In addition to stimulating bone formation, statins may also inhibit resorption, in a similar way to that described for some bisphosphonates. Nitrogen-containing bisphosphonates act on the mevalonate pathway to reduce the prenylation of GTP-binding proteins (key regulators of receptor-mediated signaling pathways), which blocks osteoclast activity [15] and inhibits osteoblast apoptosis [16].

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In addition to direct effects on bone, statins may increase bone formation by other, indirect, actions. It now appears that statins have effects on endothelial cell function and the numbers of circulating endothelial precursor cells. Vascular invasion is a prerequisite for calcification during endochondral bone formation [17]. Thus, a proangiogenic effect of statins may conceivably increase bone formation. Statins produce increased proliferation and differentiation of progenitors of endothelial cells [18]. In addition, atorvastatin increased the numbers of circulating endothelial progenitor cells [19].

Statins may also affect bone formation indirectly by inhibiting inflammation. It is now believed that the effect of statins on cardiovascular events occurs partly via effects on inflammation. Recently, pravastatin has been shown to reduce C-reactive protein in cardiology patients [20]. The negative effect of inflammation on bone is well described and statins could increase bone formation by inhibiting this. However, it seems unlikely that effects on inflammation have an important effect on bone formation in normal subjects, especially because pravastatin appears to have no effect on bone formation despite well described effects on inflammation.

Outline **Conclusion**

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Introduction

Unexpected effects on bone

Future work needs to demonstrate that statins have effects on bone turnover, density, and risk of fracture in prospective trials. However, this may be missing the point. The unfolding story of

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the effects of statins on bone, inflammation, and the cholesterol synthetic pathway is intriguing and points the way to future work. This is not the time to start prescribing statins to patients. The evidence for a clinical effect is strong but not overwhelming. However, the effects on bone seem real, and further work will demonstrate if manipulating the cholesterol and mevalonate synthetic pathways can be used to increase bone formation and reduce the risk of fracture.

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BMD = bone mineral density; BMP-2 = bone morphogenetic protein-2; CI = confidence interval; HRT = hormone replacement therapy; OR = odds ratio; statins = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

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