

Statins and Bone Morphogenetic Proteins: New Pathways in Bone Formation

C J Edwards,*^{BSc, MD, MRCP}

Abstract

Introduction: Osteoporosis is a major public health problem leading to morbidity and mortality in many individuals. Treatment for osteoporosis has generally relied on mechanisms that decrease osteoclastic bone resorption. This review outlines new evidence that the cholesterol synthetic pathway may be important in bone metabolism and that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins may increase bone formation. **Results:** An experimental observation reported that statins increase bone formation in rodents and that statins have an important role for the cholesterol synthetic pathway in bone formation. This may be via potent bone-forming growth factors, the bone morphogenetic proteins (BMPs). Subsequent epidemiological studies (including a meta-analysis of 8 studies) have suggested that statin use may be associated with increased bone mineral density (BMD) and decreased fracture risk in humans. However, more recently published studies have challenged the effect on fracture risk. **Conclusion:** The effect of statins on bone mineral density and fracture risk in retrospective studies suggests an exciting new direction for research in bone formation that may lead to advances in the therapy of osteoporosis.

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Key words: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, Bone mineral density, Cholesterol, Fracture, Osteoporosis

Introduction

Osteoporosis is a major public health problem causing considerable morbidity and mortality in Asian women. It is estimated that half of the world's hip fractures will occur in Asia in 50 years' time.¹ Fracture risk for the hip and spine is related to bone mineral density (BMD) at these sites. BMD is a result of a balance between bone formation by osteoblasts and bone resorption by osteoclasts. Recent years have seen the development of several therapies that increase BMD and decrease osteoporotic fractures. These include bisphosphonates, hormone replacement therapy (HRT), selective oestrogen receptor modulators (SERMs) and calcitonin. However, currently available therapies rely on inhibiting osteoclastic bone resorption and there is as yet no widely available therapy to increase bone formation.

Statins Increase BMD and Reduce Fracture Risk?

An exciting breakthrough was made in late 1999 when an article published in *Science* showed that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) increased bone formation in rodents.² Statins are well established as lipid-lowering drugs that reduce the incidence of cardiovascular events including myocardial infarction.³ They act by inhibiting the rate-

limiting step in cholesterol synthesis, the formation of mevalonate from 3-hydroxy-3-methylglutaryl coenzyme A (Fig. 1). Since the publication of this work, a number of observational studies have been completed that looked for an association between statin use and BMD/fracture risk in humans. The first study showed an association between statin use and increased BMD in postmenopausal women, with statin users having a 7% to 8% increased BMD after using it for a median of 48 months.⁴ Three further studies have shown an association between statin use and decreased fracture risk with odds ratios of 0.48 to 0.55.⁵⁻⁷ Although a recent study has shown no effect of statin use on fracture risk,⁸ a meta-analysis of 8 epidemiological studies has shown a protective effect of statins on hip and non-spine fractures.⁹

The Mevalonate Pathway and Bone

There are two series of observations that suggest possible mechanisms for how statins might decrease fracture risk and increase BMD. They point to the key role of the mevalonate pathway in bone metabolism, which lead to the clinical studies described here. The first observations came from studies of the mechanism of action of bisphosphonates. These showed that nitrogen-containing bisphosphonates,

* Consultant Rheumatologist

Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital

Address for Reprints: Dr Christopher Edwards, Department of Rheumatology, Southampton General Hospital, Tremona Road, Hampshire, Southampton SO16 6YD, United Kingdom.

E-mail: cedwards@soton.ac.uk

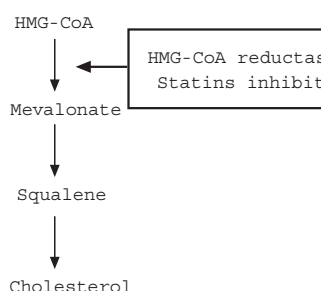


Fig. 1. The site of action of statins in the cholesterol synthetic pathway. Statins inhibit the conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonate by HMG-CoA reductase, the rate limiting step of the cholesterol synthetic pathway.

including alendronate and risedronate, inhibit the mevalonate pathway in osteoclasts and prevent the synthesis of isoprenoids.¹⁰⁻¹³ 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.¹⁴ As expected, inhibition of bone resorption, also perhaps involving osteoclast apoptosis, was then shown to be induced by statins themselves.¹¹

Statins Increase BMP-2 Expression

More importantly, however, statins are potential stimulators of bone formation. They may act by inducing the expression of potent bone growth factors, the bone morphogenetic proteins (BMPs). Using a BMP-2 promoter linked to a luciferase reporter gene transfected into an immortalised murine osteoblast cell line, Mundy et al² 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 factors that increase the activity of the BMP-2 promoter are likely to increase bone formation. Statins increase BMP-2 mRNA and the production of BMP-2 protein by osteoblast cell lines, and increase bone formation in explant bone cultures; oral administration of statins to rats showed increased bone formation even after ovariectomy. However, the doses of statins used in these rats were higher than the equivalent dose for lipid lowering in humans, as rats are relatively resistant to the effects of statins. 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.^{2,15} This suggests that the activation of the BMP-2 promoter is due to the inhibition of HMG-CoA reductase.

These studies suggest that products of mevalonate metabolism in the cholesterol synthesis pathway have important effects on both bone formation and resorption. They provide a strong case to evaluate the effects of statins on bone and offer new opportunities for therapeutic manipulation.

Statins May Act on Bone by Inhibiting Inflammation

However, statins may also have other indirect effects on bone. It is a well known fact that inflammation decreases bone formation and increases its resorption, and it would be expected that inhibition of inflammation would lead to an increased bone density. It has been suggested that statins are anti-inflammatory and reduce markers of inflammation including highly sensitive C reactive protein (hs-CRP).^{16,17} Thus, the effects of statins on bone could also be indirectly through the effects of inflammation. This possible mechanism is currently being studied in our Department.

Conclusion

Despite the encouraging start, the actions of statins on bone have not been established in controlled prospective studies. Thus, we should remain cautious as retrospective studies often exaggerate the effects of therapeutic interventions. However, these studies give an exciting insight into the importance of the cholesterol synthetic pathway in bone formation and suggest a new direction for osteoporosis treatment. In addition, it suggests that the activity of bone growth factors such as BMPs can be manipulated by the addition of oral pharmacological agents.

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