Boning Up (or Down) on Statins

Linda L. Demer

The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase mediates cholesterol biosynthesis by converting HMG-CoA to mevalonic acid. Although the focus has been on its effects on cholesterol, because mevalonic acid is also required for isoprenoid synthesis, it may also affect other important biological processes. Isoprenoids are converted by transferases to farnesyl and geranylgeranyl pyrophosphate, which are used for protein prenylation, a post-translational modification consisting of covalent addition of the isoprenoid side chains at or near the carboxyl terminus of certain proteins. Prenylation directs proteins to associate with membranes and mediates protein-protein interactions, thus contributing to a wide variety of general cell functions, particularly signal transduction. Not all the proteins that undergo prenylation have been identified.

See article, page 1636

It has been suggested that inhibitors of HMG-CoA reductase (statins), widely used for treatment of hyperlipidemia, may have pleiotropic effects through inhibition of protein prenylation. This may account for effects of statins that are independent of lipid lowering. However, there is also evidence that the mevalonate pathway is so tightly regulated that prenylation could not be significantly affected without toxic doses of statins.

The report by Maritz et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology addresses one of the possible pleiotropic effects of statins: modulation of bone metabolism. This possibility was brought to attention when Mundy et al reported that statins promote bone formation in rats and in calvarial fragments maintained in an organ culture. Although the exact mechanism was not determined, induction of bone morphogenetic protein-2 was observed in a human bone cell line treated with statins.

Triggered by this finding, four clinical studies soon followed. In three of these studies, fracture incidence was reduced by 50% in patients who were taking statins, based on retrospective, observational analysis. The fourth found that bone mineral density was significantly increased in patients receiving statin therapy.

Unfortunately, as with studies of hormone replacement therapy, initial positive findings in the observational studies were not confirmed in a subsequent randomized trial. A re-analysis of the LIPID study, designed to address cardiovascular outcomes in 9000 subjects, found no effect of statins on fracture risk. However, because only 17% of the subjects were women, and because adverse-event reports were used to ascertain fractures, these results may be limited by the low incidence of fractures. Another possibility is that the observational studies were confounded, as were the hormone replacement studies, by lifestyle effects. Patients compliant enough to be included in the statin groups (up to 13 months of consistent statin use) may have been similarly diligent in lifestyle measures, such as exercise, supplements, and medications, that prevent fractures. Nevertheless, the most recent study utilized the same observational approach and an overlapping patient population, but it found no significant effect of statins on fracture incidence.

Studies comparing markers of bone formation and resorption in control and statin-treated subjects have similarly variable results. An observational study of pravastatin in 30 postmenopausal women showed an increase in procollagen I amino-terminal propeptide, a marker for bone formation, in patients receiving statins. However, this effect was not detectable by a more widely used assay for bone formation, bone serum alkaline phosphatase levels. No effect on bone formation or resorption was found in a study of the effect of fluvastatin in 68 elderly women. Moreover, bone serum alkaline phosphatase decreased with statin treatment in a randomized trial of 850 patients, a re-analysis of a previous prospective, randomized trial addressing cardiovascular effects of statins.

In an intriguing development, Maritz and colleagues now find in vivo evidence that statins inhibit bone formation and produce a net reduction in bone density in rats. One possible reason for these apparently disparate results is the effect of serum lipid levels on bone metabolism. Parhami et al found that high lipid levels inhibit bone (osteoblastic) cell differentiation in vitro and ex vivo, and that hyperlipidemia significantly reduces bone mineral density in mice. Clinically, LDL cholesterol levels and atherosclerotic calcification are associated with osteopenia and osteoporosis independently of age.

The possibility that statins act on bone through their lipid-lowering action is supported by the finding that steroid-induced osteoporosis is inhibited equally by statins and by non-statin lipid-lowering agents. Two of the studies showing inhibition of fracture by statins also reported no effect of non-statin lipid-lowering agents. However, by power analysis, the numbers of subjects in this category were far too small to detect such an effect.

The effect of lipids on bone may also explain the disparate clinical and laboratory findings. In the clinical studies of fracture risk, bone density, and bone turnover markers, results may depend on the amount of lipid lowering as well as the degree and duration of preexisting hyperlipidemia. Indeed, in...
the observational studies, patients with hyperlipidemia of greater severity or longer duration may have both a higher fracture risk and a greater likelihood of treatment with statins. Thus, depending on the duration of hyperlipidemia, baseline differences in bone density and fracture risk may outweigh short-term effects of statins. Such an effect may be taken into consideration by using cholesterol-year analysis or by matching subjects for baseline bone density. While neither cholesterol levels nor baseline bone density were determined in the two animal studies, 4,5 the divergent findings in these two studies may be explained if the specific types and doses of statins used in the studies had different effects on lipid levels. Even if the same doses of statins were used in both studies, differences in the fat content of the chow could significantly influence the baseline lipid levels and, thus, the lipid-lowering effect. Rats have relatively low lipid levels, and doses of up to 30 mg/kg can reduce HMG-CoA reductase activity by 50% without affecting serum cholesterol levels. 1 If the fat content in the chow used for the two studies was different, then statin treatment may have resulted in cholesterol reduction in one study but not the other.

Another possible mechanism for statin effects on bone is through inhibition of isoprenoid synthesis and its effects on vitamin K metabolism. Vitamin K subclasses differ in their polyisoprenyl side chains. The form of vitamin K derived from dietary vegetables (phyloquinone) is converted to tissue menaquinone-4 by replacement of its saturated fatty acid side chain by the isoprenoid geranyleranylgeraniol derived from mevalonate. 26 Several proteins that regulate bone mineralization, such as osteocalcin, matrix Gla protein, protein S, and Gas-6 are functionally affected by gamma-carboxylation of glutamate residues by vitamin K–dependent carboxylases. 27 Thus, inhibition of isoprenoid lipid synthesis by statins may influence bone mineralization indirectly not only through lipid-lowering but also through effects on vitamin K metabolism. Overall, additional studies are needed to determine whether HMG-CoA reductase inhibitors influence bone health. If they are found to influence bone mineralization or resorption, it will be important to determine whether they act directly or indirectly through cholesterol lowering or through other mechanisms such as modifications in vitamin K metabolism. Prospective, randomized trials and laboratory studies are needed that take into consideration potential effects of lipids on bone density.

References

Key Words: lipids | bone | statins | osteoporosis
Boning Up (or Down) on Statins
Linda L. Demer

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/10/1565

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/