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STATINS AND BONE HEALTH: A MINI REVIEW

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Abstract

Statins are a widely prescribed class of medications that inhibit similar pathways as the anti-resorptive bisphosphonate drugs. Statins target the mevalonate pathway by blocking HMG-CoA reductase. Several recent meta-analyses concluded statins are osteoprotective in the general population. Here we present current literature exploring the mechanisms underlying the putative osteoprotective effects of statins. We also review recent clinical studies, ranging from observational cohort studies to randomized clinical trials, testing the effect of statins on bone health in various populations.

Key words: statins; bone loss, fracture healing.

Resumen

ESTATINAS Y SALUD ÓSEA: UNA MINIREVISIÓN

Las estatinas son un grupo de drogas prescriptas en forma habitual, con la capacidad de bloquear vías de señalización similares a las inhibidas por los amino-bisfosfonatos. Las estatinas inhiben la vía del mevalonato, a través del bloqueo de diferentes enzimas. Varios metaanálisis recientes llevaron a la conclusión de que las estatinas tienen capacidad osteoprotectora en la población general. En esta revisión presentamos la literatura actual describiendo los mecanismos que subyacen en el potencial efecto osteoprotector de las estatinas, como así también estudios observacionales y clínicos aleatorizados sobre el efecto de estatinas en la salud ósea en diversas poblaciones.

Palabras clave: *estatinas, pérdida de masa ósea, reparación de fracturas.*

Statins and bone metabolism

Bisphosphonates are commonly used to treat osteoporosis and reduce fracture risk in the general population. They inhibit osteoclast activity by blocking the farnesyldiphosphate synthase in the mevalonate pathway. Statins are another widely prescribed class of medications that also inhibit the mevalonate pathway by blocking HMG-CoA reductase. Substantial clinical trials data demonstrate statin safety and efficacy in both men and women. The statin effect on bone metabolism was originally discovered by screening for agents that activate the promotor of the bone morphogentetic protein-2 (BMP-2) in mice.[1] An elegant series of experiments confirmed that statins increase expression of BMP-2, a protein critical for bone formation, in rodent and *in vitro* studies.[1]

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The osteogenic activity of statins has been attributed to both activation and inhibition of Ras/Rho family small G proteins. Inhibition of downstream products of mevalonic acid, including farnesylpyrophosphate and geranylgeranylpyrophosphate, indirectly blocks farnesylation and/or geranylgeranylation of small G proteins. Small G proteins regulate gene expression, cytokine production, and vesicular trafficking. While FDA-approved to treat dyslipidemia, there is *in vitro* evidence that statins simultaneously inhibit osteoclast activity, inhibit osteoblast apoptosis, and stimulate osteoblast activity.[1-5] The resulting osteogenic stimulus is one of many pleiotropic effects that have been reported with statin use.[6,7] This combined antiresorptive/osteoanabolic action is attributed to statins but not bisphosphonates. Different statin doses may preferentially affect specific small G proteins with different effects on bone cell activities. Statins have low bioavailability in bone, but lipophilic statins may have greater capacity to enter bone cells than hydrophilic statins.[4] Table 1 lists commonly prescribed hydrophilic and lipophilic statins.

Table 1. Commonly Prescribed Statins

Lipophilic Statins	Hydrophilic Statins
Atorvastatin (Lipitor)	Rosuvastatin (Crestor)
Lovastatin (Mevacor)	Pravastatin (Pravachol)
Simvastatin (Zocor)	Pitavastatin(Livalo)
	Fluvastatin (Lescol)

Statins, bone density, and bone loss

To date, translation of the statin/bone *in vitro* and rodent findings has been mostly conducted in observational and cohort studies. A positive association between lipophilic statin use and bone density has been reported in cross-sectional studies of post-menopausal women[8] and older men.[9] Oral statin use was associated with greater bone density in 1003 postmenopausal women living in the UK assessed in the population-based cohort Chingford study.[8] The Concord Health and Aging in Men Project (CHAMP) reported statin use was associated with higher bone mineral density at the hip in 1,705 men age 70-97 from Sydney Australia. This effect was associated with use of lipophilic statins as opposed to hydrophilic statins, possibly due to the greater bioavailability of lipophilic statins in the bone microenvironment.[10]

However, there is controversy in the literature regarding statin use and longitudinal change in bone density. A one-year randomized controlled trial (RCT) of 40 mg simvastatin failed to demonstrate significant increases in bone density in post-menopausal women with no known hypercholesterolemia at study entry.[11] Similarly, an 8-week course of 20 mg daily atorvastatin did not cause significant changes in markers of bone turnover in post-menopausal women compared to placebo.[12] However, the remodeling index (ratio of C-telopeptide to osteocalcin) was reduced suggesting reduced bone resorption compared to formation. This effect was seen only in participants age 62 or older in the atorvastatin group, suggesting an age-dependent effect of statins on bone turnover. An anabolic bone effect was reported in hypercholesterolemic post-menopausal women taking 40 mg of simvastatin for one year[13] or two years.[14] Similarly, lipophilic statin use for one year or more mitigated bone loss over a mean period of 21 months in 152 men and women with spinal cord injury (SCI) enrolled in the Fracture Risk after SCI (FRASCI) longitudinal cohort study.[15] A retrospective chart review of 69 Korean men and women with diabetes mellitus and 33 healthy controls suggested that statin treatment for 15 months increased bone density at the femoral neck.[16]

Statin use has also been associated with decreased risk of hip fracture[17] and vertebral fracture[18] in a dose-dependent fashion. Long-term statin use was associated with 50% lower vertebral fracture risk in 3,105 men and 4,878 women age 55 or older enrolled in the Rotterdam study.[18] Statin use was associated with reduced risk of hip fracture in 6,660 participants with hip

fracture and 33,274 gender- and age-matched population controls enrolled in a Danish population-based case-control study.[17] Similarly, the Geelong osteoporosis study reported a 60% reduction in fracture risk associated with statin use in 1,375 Australian women age 50-95. These findings are consistent with recent meta-analyses that conclude that statins maintain and improve bone density in the general population and recommend prospective RCTs to confirm this in different populations.[19,20]

Statins and fracture healing

In addition to the putative osteogenic effects, statins may also promote fracture healing. In a mouse femur fracture model, simvastatin (120 mg/kg oral dose) treatment increased callous size by 53% and the force required to break bone by 63% in 41 male mice compared to untreated controls.[21,22] Consistent with these findings, a 5-day course of transdermal lovastatin dosed at 10-fold the oral dose accelerated fracture healing in a mouse fracture model by enhancing generation of nitric oxide by bone cells.[23] These findings have been confirmed in multiple studies with more recent focus on novel drug formulations to improve targeting of system statins to the site of fracture, including simvastatin nanoparticles and pro-drug micelles.[25,26]

Conclusions

Bisphosphonates are commonly prescribed to treat osteoporosis and inhibit osteoclast activity by blocking the farnesyl-diphosphate synthase in the mevalonate pathway. Statins are another widely prescribed class of medications that also inhibit the mevalonate pathway by blocking HMG-CoA reductase. Several recent meta-analyses concluded statins are osteoprotective in the general population and recommend RCTs to determine the efficacy of statins to prevent bone loss or promote bone regeneration in various populations. Preclinical evidence also supports future clinical trials testing statins to promote fracture healing.

Disclosures

All authors have no conflicts of interest.

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