Reumatología Clínica

Editorial

Statins and osteoporosis: A latent promise☆

Estatinas y osteoporosis: una promesa latente

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The clinical use of statins as therapeutic tools for osteoporosis has not yet reached the status of solid scientific dogma, even though it has been almost 15 years since the emergence of the first experimental evidence on the effect of this class of drugs on bone metabolism, specifically stimulating the formation of "new bone". Statins are a group of competitive inhibitors consisting of the hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase and therefore have been widely used for the treatment of hypercholesterolemia.

The first experimental evidence in an animal model of the osteo-modulador effect of statins was reported by Mundy et al.,[1] who demonstrated that treatment with lovastatin, simvastatin, fluvastatin and mevastatin resulted in a significant increase (up to 2–3 times compared with controls) in the rates and bone formation markers, and that the effect of statins were comparable to that induced by treatment with bone morphogenetic protein-2 (BMP-2) and fibroblast growth factor, which are known stimulants of bone metabolism.[2] Other studies conducted in animal models, replicated the effects of statins as stimulating bone formation. However, the application of this knowledge to the treatment of metabolic bone diseases in humans has not been able to find solid support, as studies in humans have shown conflicting results.

The potential positive effect of statins on bone formation can be explained from three mechanisms: (a) the promotion of osteogenesis (b) suppression of apoptosis of osteoblasts and (c) inhibition of osteoclastogenesis.[3]

The promotion of osteogenesis appears to be linked to mechanisms of prenylation as a posttranslational modification and necessary for certain key proteins in some signaling cascades. The HMG-CoA reductase enzyme catalyzes the synthesis of mevalonate, which is a limiting step for the formation reactions of farnesyl pyrophosphate and geranyl isoprenoids, which are the initial actions for the synthesis of cholesterol. The major effect of the statins is a decrease of the catalytic activity of HMG-CoA reductase, for the transformation of HMG-CoA to mevalonate, and finally the formation of farnesyl and geranyl pyrophosphate. These compounds are essential for small protein prenylation of guanosine triphosphate-binding proteins (G proteins monomeric),[4] required for activation and attachment to cell membranes, thereby terminating a series of signal transduction events. An example of these monomeric proteins is prenylated Rho G, which has shown to have an anti-osteogenic role. There is evidence that Rho and its target protein, Rho kinase, have a negative effect on bone formation[5] and its inhibition promotes osteoblast differentiation.[6] Additionally, it has been shown that pitavastatin increases bone formation by inhibiting the prenylation and, therefore, the action of Rho and Rho kinase in addition to increasing the expression of BMP-2 mRNA and osteocalcin.[5] Some studies demonstrated that lovastatin at high serum concentrations (10–50 μM) inhibits the prenylation of Ras, Rho and Rap. Although the effect of these proteins is not observed with the therapeutic concentrations achieved using lipid-lowering doses (0.05–0.5 μM)[7] there is evidence to suggest that these concentrations would have some positive effect on a downstream signaling cascade composed of Akt and ERK molecules that are involved in the stimulation of osteogenesis.[8]

As for the second proposed mechanism, suppression of osteoblast apoptosis mediated by statins, a certain degree of apoptotic inhibition modulated by pitavastatin, mevastatin and simvastatin has been described, which is explained by the increased expression of the Smad3 protein ("mothers against decapentaplegic homolog 3").[9] The Smad3 proteins are signal transducers and transcriptional modulators activated by transforming growth factor beta, which has a critical role in bone formation.[10] Additionally, inhibition of osteoblast apoptosis mediated by simvastatin in the cultured murine osteoblastic cell line MC3T3-E1 in a dose dependent manner has been demonstrated.[11]

Finally, suppression of osteoclastogenesis promoted by statins appears to have a connection with the signaling pathway of osteoprotegerin (OPG), which is a ligand of receptor activator of nuclear factor κ B (RANK-L) and the activating nuclear factor receptor κ B (RANK). An in vitro study demonstrated that simvastatin and mevastatin increased the expression of OPG mRNA and caused reduced corresponding transcript expression of RANKL in primary cell cultures from explants of mouse bone.[12] In addition to this, it has been shown that inhibition of osteoclast function by statins could be explained by the effect exhibited by simvastatin on induction of the expression of estrogen receptor alpha in bone tissue of ovariectomized rats and their effect on the restoration of bone loss,[13]

because this receiver has an important role in inhibiting osteo-clastogenesis. Another plausible explanation for the inhibition of osteoclastogenesis is mediated by statins, in terms of interference with cytoskeletal osteoclast formation due to poor protein preny-lation required for cell function.[14]

The mismatch on the osteomodulador results of statins in humans can be explained by the extreme heterogeneity and methodological deficiencies in the design, and outcome measures of studies and the type of identifiable clinical reports devoted to topic analysis. Most studies have been cross-sectional and/or obser-vational, or have relied on post hoc analysis of the data. Studies motivated by the publication of Mundy et al.,[1] have mostly studied patients with hypercholesterolemic in whom the outcome mea-sure was bone mineral density (BMD),[15–19] biochemical markers of bone remodeling, such as alkaline phosphatase, the amino-terminal propeptide of collagen type 1, the carboxy-terminal telopeptide of collagen[20–24]; or combinations of BMD and bio-chemical indicators.[25–27] The few clinical studies using the reduced risk of fractures as an outcome measure show conflicting results, ranging from no effect to[28–31] significant reduction in fracture risk.[32–34]

Besides methodological issues, there are specific aspects that could explain, additionally, the discrepancy in the results on the osteomodulator clinical effect of statins in humans.

Statin doses used in clinical practice for the control of hyper-cholesterolemia exhibit no effect on the stimulation of bone formation, and that the doses used and the concentration ratios were much higher in the experimental models, studies reporting beneficial effects on bone formation compared to those used in human clinical studies.[1,35,36]

Additionally, the type of statin used is a confounding factor to consider as the level of lipophilicity, polarity and bone avidity of the various compounds of class can result in a differential effect osteo-modulador. The lipophilic statins appear more effective for bone formation than those of a hydrophilic nature, because apparently the first stimulate transcription of BMP-2, while the latter have not exhibited this action.[27]

Another confounding factor in this respect lie in the hep-atospecificity of statins. Taking into account the first step effect, the distribution of statins to the bone microenvironment could be much lower than expected. This explains the need of larger doses and concentrations for bone modulation compared with those required for the treatment of hypercholesterolemia, as only 5% of the ingested drug reaches the systemic circulation after the[37] hypolipidemic action in the liver.

In conclusion, there is evidence from a number of from basic science and clinical research studies indicating that statins may be effective treatments for osteoporosis. However, this question needs to be answered by studies with appropriate experimental designs, sample sizes suitable for relevant results and analy-sis, as well as controlling the currently identified technical and methodological confounding factors. These research activities will surely discard the hypothesis of potential effectiveness or, on the contrary, redeemed a promise that remained latent for three decades.

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