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Review

Statins, bone metabolism and treatment of bone catabolic diseases

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ABSTRACT

The discovery that statins had bone anabolic properties initiated many investigations into their use for treatment of bone catabolic diseases, such as osteoporosis. This paper reviews the molecular basis of statin's role in bone metabolism, and animal and human studies on the impact of systemic statins on osteoporosis-induced bone fracture incidence and healing, and on bone density. Limitations of systemic statins are described along with alternative dosing strategies, including local applications and bone-targeting systemic preparations. The principal findings of this review are: (1) traditional oral dosing with statins results in minimal efficacy in the treatment of osteoporosis; (2) local applications of statins show promise in the treatment of accessible bony defects, such as periodontitis; and (3) systemically administered statins which can target bone or inflammation near bone may be the safest and most effective strategy in the treatment of osseous deficiencies.

Contents

Abbreviations: BMD, bone mineral density; BMP, bone morphogenetic protein; DBBM, demineralized bovine bone matrix; ERα, estrogen receptor-alpha; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; GGPPs, GGPP synthase; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; mPEG, methoxy polyethylene glycol; OBs, osteoblasts; OCs, osteoclasts; OPG, osteoprotegerin; OVX, ovariectomized; PI3-K, phosphatidylinositol 3 kinase; RANKL, receptor activator of nuclear factor kappa-B ligand; RCT, randomized controlled trials; rh, recombinant human; SIM, simvastatin; Smad3, mothers against decapentaplegic homolog 3; SRP, scaling and root planing; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

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1. Introduction

Since Mundy et al. [1] first described the bone anabolic properties of statins almost 15 years ago, the search for possible applications to bone catabolic diseases, such as osteoporosis, has been robust. In vitro investigations have explored the mechanisms of statin effects on the mevalonate pathway, as well as osteoblast and osteoclast function. In vivo animal studies confirmed that systemic statins could reduce ovariectomy- and inflammation-induced bone loss, and early, mostly cross-sectional or observational human clinical studies showed promise that systemic statins could reduce osteoporotic fracture risk and increase bone mineral density. Results in randomized controlled trials were mixed. Local application of statins showed enhanced bone apposition in animal bone fracture, implant and bone defect models. Also, early human clinical trials demonstrated that locally applied statins may be useful in the treatment of periodontal bone loss.

The purpose of this review is to summarize findings in the studies categorized above, and to define where statins may or may not be useful in the treatment of bone catabolic diseases. Finally, we will suggest where deficiencies in conventional statin-dosing approaches may be improved.

2. Molecular basis for statins' impact on bone metabolism

In addition to the cholesterol-lowering effect, statins have a series of pleiotropic effects, including bone anabolic, vasodilative, antithrombotic, antioxidant, anti-inflammatory, and immunosuppressive actions [2]. Among these diverse effects, bone anabolism has been the focus of researchers for more than a decade, due to the potential clinical applications of statins to treat osteoporosis and other bone deficiencies.

Despite the fact that some aspects of the mechanism involved in the statin-induced bone anabolism still remain unclear, the review of recent literature suggests it may be summarized into three major mechanisms: promotion of osteogenesis, suppression of osteoblast apoptosis and inhibition of osteoclastogenesis.

2.1. Statin-induced osteogenesis

As we know, statins inhibit the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol metabolism pathway. An immediate consequence of this inhibition is the diminished synthesis of mevalonate and downstream isoprenoid precursors (farnesyl pyrophosphate, FPP and geranylgeranyl pyrophosphate, GGPP) in the pathway [3] (Fig. 1).

Both FPP and GGPP are involved in stain-induced osteogenesis. It was reported that FPP and GGPP decreased during statin-induced osteoblast differentiation [4] and the osteoblast differentiation was inhibited by the expression of exogenous FPP [5]. Another study found that GGPP and GGPP synthase (GGPPs) decreased during mineralization in MC3T3-E1 cells [6], a mouse osteoblastic cell line. These studies indicate that statins induce osteogenesis, at least in part, by reducing FPP and GGPP levels [7].

On the other hand, FPP and GGPP are of vital importance for post-translational lipid modification (prenylation) of certain GTP binding proteins (e.g. Rho), which will be activated after prenylation and take part in various signal transduction events [3]. Thus, statin-induced suppression of FPP or GGPP might impair protein prenylation of such GTP binding proteins and then further affect the relevant pathways. This was proven by a study using pitavastatin to stimulate the expression of BMP-2 and osteocalcin by suppressing the activation of Rho and Rho kinase [8].

Another consequence of the inhibition of protein prenylation is the increased expression of vascular endothelial growth factor (VEGF), an anabolic factor for osteoblasts via the increased production of phosphatidylinositol 3 kinase (PI3-K) [9].

2.2. Statin-inhibited osteoblast apoptosis

Statins may also increase bone formation by inhibiting osteoblast apoptosis through the transforming growth factor-beta (TGF-β)/mothers against decapentaplegic homolog 3 (Smad3) signaling pathway. TGF-β plays a critical role in bone formation and Smad proteins are key components of the TGF-β signaling pathway [10]. Smad3 is regulated by the TGF-β receptor. TGF-β activates type II receptors resulting in the activation of type I receptors, and the phosphorylation of TGF-β type I receptor-like kinase activates Smad3, which is essential for bone mass maintenance. The deletion of Smad3 results in a decrease of bone formation by stimulating the apoptosis of osteoblasts [11].

Recently, it was found that pitavastatin, mevastatin and simvastatin induced the expression of Smad3 in MC3T3-E1 cells and UM-106 cells, and this study further demonstrated that these statins may antagonize dexamethasone-induced osteoblastic apoptosis in a dose-dependent manner [12].

2.3. Statin-suppressed osteoclastogenesis

The osteoprotegerin (OPG)/receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK system is the final mediator in the regulation of osteoclastogenesis and it plays an essential role in the proliferation and differentiation of osteoclasts [13]. Statins' anti-osteoclastic effect seems to be due to their effect on the OPG/RANKL/RANK signaling pathway. An in vitro study found that mevastatin and simvastatin increased OPG mRNA expression and decreased RANKL mRNA expression in mouse bone cell culture, demonstrating a clear inhibition action on the principal mechanism of osteoclast formation [14].

On the other hand, estrogen and estrogen receptor (ER) also play an important role in the inhibition of osteoclastogenesis, especially in postmenopausal osteoporosis. Estrogen can reduce RANKL and further lead to the inhibition of osteoclastogenesis [15]. It was reported that simvastatin induces estrogen receptor-alpha (ERα) in murine bone marrow stromal cells in vitro [16] and also induces ERα expression in the bone tissue of ovariectomized rats, which leads to restoration of lost bone [17].

Last but not least, statins may inhibit osteoclastogenesis by impairing the maturation and the integrity of the osteoclast cytoskeleton. An ex vivo study indicated that compactin inhibited the fusion of preosteoclasts and disrupted the actin ring of osteoclasts. These effects are a consequence of the inhibition of prenylation of target proteins by prenyl protein transferases through a decrease in their substrates, including FPP and GGPP [18].

2.4. Statin-vitamin D interactions

Since vitamin D is important in regulating calcium homeostasis and maintaining of bone density, its interaction with statins may be metabolically and clinically relevant. Two clinical studies showed that 25-hydroxyvitamin D levels increased significantly with rosuvastatin treatment [19,20]. This might provide another explanation that the improvement in bone mineral density with the treatment of statins in some clinical studies may be caused by the increase in vitamin D levels. However, fluvastatin [20] and simvastatin [21] treatment resulted in no increase in the levels of 25-hydroxyvitamin D. The mechanism underlying the effect of statins on vitamin D has not been clarified, but the common catabolic pathway (cytochrome P-450, CYP enzyme system) for