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Review

Statins and osteoporosis: new role for old drugs

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Abstract

Osteoporosis is the most common bone disease, affecting millions of people worldwide and leading to significant morbidity and high expenditure. Most of the current therapies available for its treatment are limited to the prevention or slowing down of bone loss rather than enhancing bone formation. Recent discovery of statins (HMG-CoA reductase inhibitors) as bone anabolic agents has spurred a great deal of interest among both basic and clinical bone researchers. In-vitro and some animal studies suggest that statins increase the bone mass by enhancing bone morphogenetic protein-2 (BMP-2)-mediated osteoblast expression. Although a limited number of case–control studies suggest that statins may have the potential to reduce the risk of fractures by increasing bone formation, other studies have failed to show a benefit in fracture reduction. Randomized, controlled clinical trials are needed to resolve this conflict. One possible reason for the discrepancy in the results of preclinical, as well as clinical, studies is the liver-specific nature of statins. Considering their high liver specificity and low oral bioavailability, distribution of statins to the bone microenvironment in optimum concentration is questionable. To unravel their exact mechanism and confirm beneficial action on bone, statins should reach the bone microenvironment in optimum concentration. Dose optimization and use of novel controlled drug delivery systems may help in increasing the bioavailability and distribution of statins to the bone microenvironment. Discovery of bone-specific statins or their bone-targeted delivery offers great potential in the treatment of osteoporosis. In this review, we have summarized various preclinical and clinical studies of statins and their action on bone. We have also discussed the possible mechanism of action of statins on bone. Finally, the role of drug delivery systems in confirming and assessing the actual potential of statins as anti-osteoporotic agents is highlighted.

Introduction

Osteoporosis (literally meaning the porous bone) is the most common debilitating skeletal disorder, characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and increased susceptibility to fractures, especially of hip, spine and wrist (National Osteoporosis Foundation 2005). Osteoporosis is characterized by a decline in the quality and quantity of both the cancellous and cortical bone. It has been called a silent disease because it usually does not cause any pain or symptoms until a bone actually breaks. Osteoporosis has become one of the main concerns for the medical field. Patients with established osteoporosis lose more than 50% of bone mass at critical sites in the skeleton and, moreover, have marked disruption of trabecular bone micro-architecture. Therefore, anabolic therapies are desperately needed to replenish the lost bone mass and cure the prevailing disease conditions.

Currently marketed drugs to treat osteoporosis include anti-resorptive agents, like bisphosphonates, calcitonin, oestrogen, selective oestrogen receptor modulators, vitamin D analogues, calcium supplementation and ipriflavone. These drugs decrease bone turnover mainly by inhibiting the activity of osteoclasts, the bone resorbing cells. Although they reduce the fracture risk and bone turnover, they exhibit a very weak, or moderate, effect on bone mineral density (BMD) ascribable to an increase in mean bone tissue mineralization. By inhibiting the osteoclastic phase of basic multicellular units (BMUs) that ensure bone remodelling, anti-resorptive agents reduce the frequency of activation of new modelling units, thereby increasing the time during which the basic structural units can undergo secondary mineralization. Thus, these drugs act mainly to stabilize bone mass and do not have substantial effects on bone formation (Baylink et al 1999; Rosen & Bilezikian 2001; Meunier 2001). Therefore, there is an urgent need for effective and clinically acceptable

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drugs that are able to stimulate new bone formation and improve the trabecular micro-architecture with subsequent enhancement in bone mineral density.

Two anabolic agents currently under investigation are parathyroid hormone (PTH) and sodium fluoride. Both of these agents cause substantial increase in bone formation. Sodium fluoride was the first anabolic agent to be discovered and used in the treatment of postmenopausal osteoporosis. Although it showed initial promise, the results of controlled clinical trials were discouraging (Riggs et al 1990; Meunier et al 1998). Fluoride is also associated with some gastrointestinal side effects. Despite attempts to reduce these side effects using lower doses or modified formulations, its clinical utility is still not confirmed (Pak et al 1995; Reginster et al 1998). PTH is another promising anabolic agent associated with reduction in fractures in postmenopausal osteoporosis. When used intermittently and in a low dose, it exhibits a bone anabolic action that is mediated by growth factors, such as insulin-like growth factor I (IGF-I) and transforming growth factor β (TGF-β) (Canalis et al 1989). Various clinical studies have also endorsed its anabolic activity (Reeve et al 1980; Kurland et al 2000; Neer et al 2001). The bone anabolic efficacy of PTH was also assessed when used in combination with anti-resorptive agents (Lindsay et al 1997; Rittermaster et al 2000). Although its bone anabolic efficacy is proven, there are some unanswered questions about PTH therapy. These include its long-term effects on bone and dosage schedule. Due to its peptide nature, its stability, need for parenteral administration and cost involved are also issues of concern. Another bone anabolic agent currently under investigation is strontium ranelate (Meunier et al 2004; Fogelman & Blake 2005; Reginster et al 2005).

Statins are specific inhibitors of 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme of the cholesterol synthesis pathway, which provides substrates for prenylation of small glutamyl transpeptide (GTP) binding proteins, like Rho, Rac and Rab, and for the building blocks for cholesterol synthesis (Takai et al 2001). They are among the most widely used drugs in the treatment of atherosclerosis and other cardiovascular events (Pedersen et al 1996). The structures of the most commonly used statins are shown in Figure 1.

Both lovastatin and simvastatin possess a lactone ring and are pro-drugs. In-vivo, they are reversibly converted into an active β-hydroxyacid form primarily in the gut and liver by the action of carboxyesterase enzymes. Except for lovastatin and simvastatin, all statins are in the form of an open β-hydroxyacid and are hydrophilic in nature. Cerivastatin, the most lipophilic statin, was withdrawn from the market in 1987 owing to potential side effects in man (Furberg & Pitt 2002).

Statins are rapidly absorbed after oral administration. Their bioavailability is low due to an extensive first-pass metabolism. Their principal target organ is the liver, irrespective of animal species, dosing schedule and the statin used (Corsino et al 1999; Reinoso et al 2002).

Recent findings indicating their anabolic action on bone have generated large interest among researchers and clinicians and their combined efforts may lead to an exciting option for the treatment of osteoporosis. The aim of this review is to present different preclinical and clinical studies carried out to evaluate the action of statins on bone and to address their plausible mechanisms of action. The most important aim of this review is to address the need for achieving bone-specific pharmacokinetics of statins so as to explore their potential as anti-osteoporotic agents. Different routes of drug administration and drug delivery systems being tried in this direction are summarized in this review.

Preclinical paradox

In-vitro studies

New bone formation is an event involving production of new bone matrix by osteoblasts, the bone forming cells, and its subsequent mineralization. In the process of bone formation, various growth factors, like fibroblast growth factor-1 (FGF-1) (Fromigue et al 2004), and transcription factors, like core binding factor (cbfa1) (Karsenty 2000; Komori et al 2000), play a critical role in the proliferation and differentiation of osteoblasts (Manolagas 2000). Bone morphogenetic proteins (BMPs) deserve special place among these growth factors. Although they are members of the TGF-β superfamily, their effects on osteoblasts are very different from those of TGF-β. Unlike TGF-β, BMPs enhance osteoblast differentiation (Mathews 2005). BMP-2, the most common among the BMP family, is an autocrine factor that controls osteoblast differentiation, as well as enhancing the expression of the structural proteins of the bone matrix, such as type-1 collagen, osteopontin, osteocalcin and bone sialoprotein (Rickard et al 1994; Xiao et al 2002). It also enhances the expression of transcription factor cbfa1 and stimulates osteoblast proliferation (Cao & Chen 2005). Thus, BMP-2 serves as an ideal target for enhancing bone formation (Harris et al 1994; Hoffmann & Gross 2001; Kugimiya et al 2005).

In search of small molecules that stimulate BMP-2 expression and thus promote bone formation, Mundy et al (1999) developed a cell-based screening assay in which murine BMP-2 gene was transfected into osteoblasts linked to the firefly luciferase reporter gene and screened an extensive library of chemical compounds, including natural products. Out of 30 000 compounds from natural products collection, only statins (HMG-CoA reductase inhibitors) specifically increased luciferase activity. The increase in luciferase activity was blocked by mevalonate, the immediate downstream metabolite of HMG-CoA reductase, suggesting that their action on bone is due to inhibition of HMG-CoA reductase enzyme. Cultured murine (2T3) and human (MG-63) bone cells exposed to statins also showed enhanced expression of BMP-2 mRNA specifically (Mundy et al 1999). Experiments using human osteosarcoma cells confirmed that compactin and simvastatin stimulated the BMP-2 promoter (Sugiyama et al 2000) but pravastatin was not effective in these assays.

To investigate the biological effects of statins on bone, an in-vitro model of bone formation was developed utilizing cultures of neonatal murine calvaria. Lovastatin, simvastatin, fluvastatin and atorvastatin were found to increase osteoblast cell numbers and new bone formation by approximately 2–3 fold in this assay. This increase was of similar magnitude to that seen after treatment with BMP-2 and FGF-1, a known

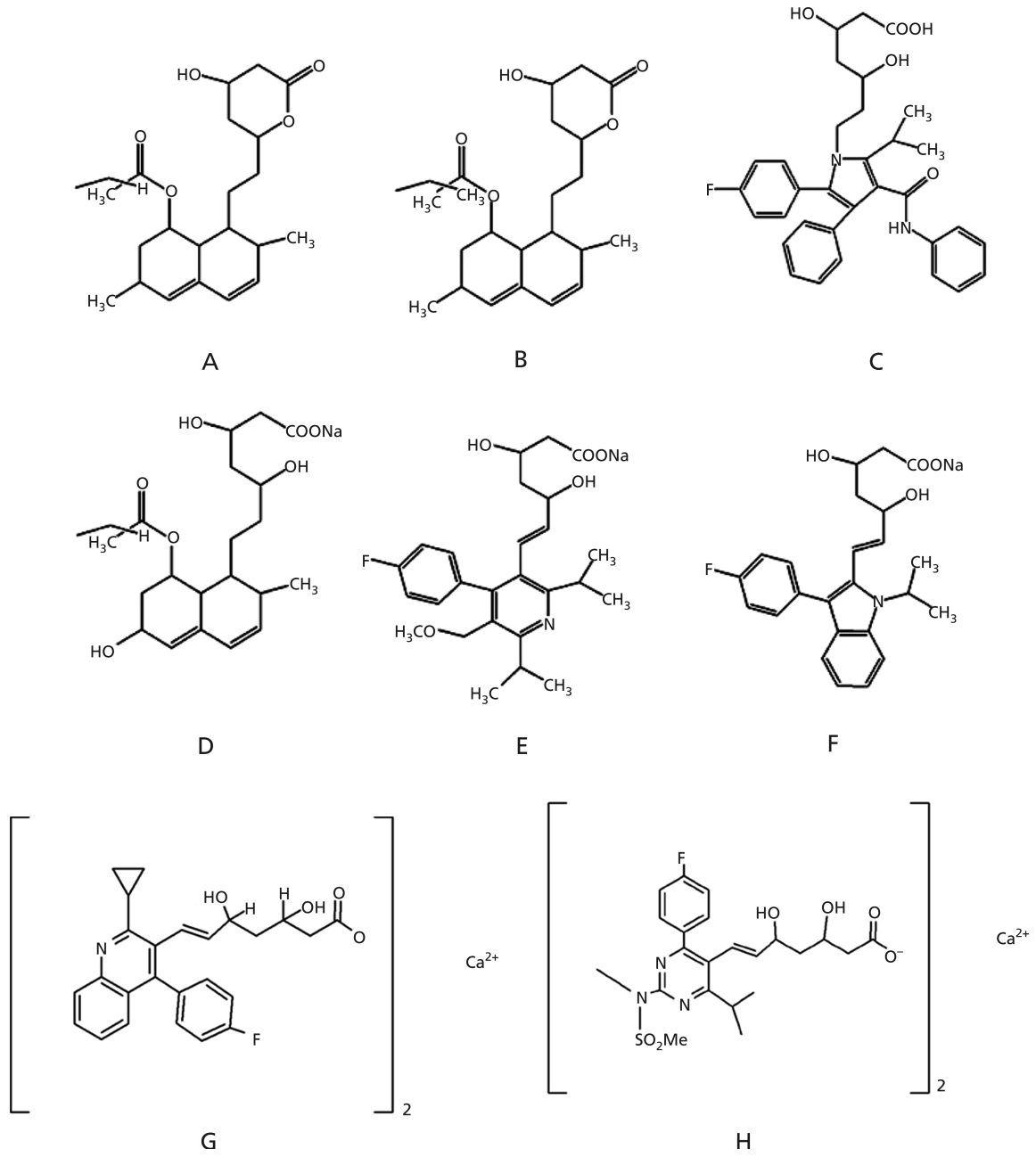

Figure 1 Structures of lovastatin (A), simvastatin (B), atorvastatin (C), pravastatin (D), cerivastatin (E), fluvastatin (F), pitavastatin (G) and rosuvastatin (H).

bone anabolic agent. Cerivastatin was the most potent agent, while pravastatin was unable to stimulate BMP-2 promoter activity and new bone formation in neonatal murine calvaria (Garrett et al 2001b). Investigation of the effects of simvastatin on cell proliferation and osteoblastic differentiation in human periodontal ligament (PDL) cells showed that simvastatin enhanced cell proliferation and alkaline phosphatase activity in a dose-dependent fashion (Yazawa et al 2005).

Maeda et al (2001) studied the effect of simvastatin on osteoblast differentiation and function using a non-transformed osteoblast (MC3T3-E1) cell line and rat bone marrow cells. Simvastatin was found to enhance bone formation through induction of BMP-2 and alkaline phosphatase and by the accumulation of bone matrix proteins, such as type 1 collagen. Statins also stimulated MC3T3-E1 mouse osteoblastic cells to express BMP-2 and enhanced alkaline phosphatase activity, vascular endothelial growth factor (VEGF) type I collagen, bone sialoprotein, osteocalcin and mineralization of extracellular matrix. Pretreating cells with mevalonate or geranylgeranyl pyrophosphate abolished these statin-induced effects (Maeda et al 2004). The effect of pitavastatin was studied on primary cultures of human osteoblasts and it

was found that it increases the expression of BMP-2 and osteocalcin mRNA through inhibition of the Rho-kinase pathway. Pitavastatin induced enhanced expression of BMP-2 and osteocalcin mRNA was also abolished by down-stream metabolites of HMG-CoA, suggesting that these effects result from the inhibition of HMG-CoA reductase (Ohnaka et al 2001).

Simvastatin and lovastatin are lactone pro-drugs and in-vivo are converted into the active β-hydroxyacid form. The bone anabolic activity of both the lactone and the β-hydroxyacid form of simvastatin and lovastatin was evaluated using cultures of murine neonatal calvaria. Only the β-hydroxyacid form and not the lactone form inhibited HMG-CoA reductase, but both forms contributed to the bone anabolic activity. These findings indicate that enzymes such as the esterases present in the local bone environment are responsible for the conversion of the lactone form to the β-hydroxyacid form. The role of esterases was further investigated by using an esterase inhibitor. In the presence of esterase inhibitor, statins did not stimulate new bone formation. Also, the esterase inhibitor did not inhibit bone formation stimulated by other factors, such as acidic fibroblast growth factor or bone morphogenetic proteins. This data indicates that the β-hydroxyacid, not the lactone form, of simvastatin and lovastatin stimulates bone formation. Except for pravastatin, other statins such as fluvastatin, atorvastatin and cerivastatin, all with free β-hydroxyacid functionality, stimulated bone formation in the neonatal murine calvaria assay (Garrett et al 2001b).

Although most of the in-vitro studies were designed to assess the anabolic potential of statins and involved a variety of osteoblast culture experiments, there are few examples in which the anti-resorptive potential of statins was assessed utilizing osteoclast cell culture assays. Inhibition of osteoclast formation by lovastatin was observed in bone marrow culture (Baumann et al 2001). In fetal rat long bone culture, simvastatin and cerivastatin were able to inhibit PTH-induced bone resorption at nanomolar concentrations and this inhibitory activity of statins was dependent on their potency to inhibit HMG-CoA reductase (Staal et al 2003).

Thus, in-vitro experiments utilizing osteoblastic cell cultures confirm the anabolic action, which is mediated by enhanced BMP-2 expression. Statins also inhibited osteoclastic activity and can act as anti-resorptive agents. Thus both anabolic and anti-resorptive actions exhibited by statins are attributed to their HMG-CoA reductase inhibitory property.

In-vivo studies

In contrast to all in-vitro studies, which asserted the beneficial effects of statins (anabolic/anti-resorptive), results of various in-vivo studies made it a point of controversy.

On local subcutaneous injection of lovastatin and simvastatin over the calvarial bone in mice for 5 days, Mundy et al (1999) observed a 50% increase in new bone formation. Upon oral administration of simvastatin, there was a significant increase in the trabecular bone volume and bone formation rate with a concomitant decrease in osteoclast numbers in ovariectomized rats, as well as in rats with intact ovaries. This finding is of particular importance in view of local stimulation of bone formation.

Evidence of the in-vivo anabolic action of statins further came in a series of experiments that studied the effects of statins on bone. Cerivastatin increased cortical bone strength in ovariectomized rats when used in doses as low as $0.1\,mg\,kg^{-1}$ daily and, in addition, significantly increased bone mineral density, bone formation rate, osteocalcin mRNA levels and resistance to fracture (Wilkie et al 2000). In the ovariectomized rat model, simvastatin improved bone formation parameters at cortical bone in accordance with the increase in serum osteocalcin concentration. It also minimized the ovariectomy-induced reduction in cancellous bone volume in agreement with decreased activity of serum-tartrate-resistant acid phosphatase 5b (TRAP-5b), indicating decreased osteoclast activity in simvastatin-treated rats (Oxlund et al 2001; Oxlund & Andreassen 2004).

The ability of statins to inhibit protein prenylation in osteoclasts and osteoblasts was studied in-vivo. Cerivastatin, but not pravastatin, was found to inhibit protein prenylation in osteoclasts but not in osteoblasts in-vivo, suggesting an anti-resorptive rather than an anabolic action (Frith et al 2001). A study by Jiang et al (2001) evaluated the effect of orally administered simvastatin on three-dimensional bone architecture using micro-computed tomography (μCT), a non-destructive advanced imaging technique, and confirmed that simvastatin prevents ovariectomy-induced bone loss. In an attempt to compare the skeletal effects of statins with those of alendronate and PTH in adult ovariectomized rats, Masarachia et al (2001) observed that simvastatin, but not atorvastatin, partially prevented ovariectomy-induced bone loss. Simvastatin's modest prevention of bone loss was likely due to inhibition of bone resorption.

Most of the publications have considered statins as potential agents for the prophylactic treatment of osteoporotic fractures and dealt with undisturbed bone. Skoglund et al (2002) investigated the effect of statins in a murine femur fracture model and found that simvastatin improved fracture healing. Transplanted bones treated with high-dose cerivastatin induced bone union as effectively as ciclosporin, indicating the ability of statins to heal osteoporotic fractures of transplant recipients (Ohno et al 2003).

Another school of thought disagrees with the bone anabolic activity of statins; Maritz et al (2001) investigated the effects of different doses of simvastatin, atorvastatin and pravastatin on intact and ovariectomized rats and found very contradictory results in that statins decreased bone formation and BMD and increased bone turnover and bone resorption. Cerivastatin did not have any effect on calcium normalization in thyro-parathyroidectomy (TPTX) acute model of bone resorption (Staal et al 2003). In an ovariectomized mouse model, simvastatin failed to stimulate bone formation (von Stechow et al 2003). In one study, fluvastatin was locally administered over mice calvaria and cerivastatin was given orally to intact and ovariectomized rats. No anabolic effect was observed at the administered dose. The authors concluded that disruption of capillary integrity and local bleeding might be a reason for previously reported bone responses in the mouse calvarial model (Gasser 2001). Sato et al (2001) compared the efficacy of statins with that of PTH only to find that they do not have any significant action on bone. Simvastatin did not prevent cancellous bone loss and did not stimulate cancellous and cortical bone formation following ovariectomy (Yao et al 2001). Different skeletal sites in male

rats were studied using peripheral computed tomography (pQCT) after administration of cerivastatin and it was found to be ineffective when compared with PTH in preventing age-related bone loss (Banu & Kalu 2002).

Mechanism of action

Statins inhibit the rate-limiting enzyme HMG-CoA reductase in the cholesterol metabolism pathway (Figure 2). An immediate consequence of this inhibition is the diminished synthesis of mevalonate and downstream isoprenoid precursors in the pathway. The isoprenoid precursors, such as geranyl pyrophosphate, are of vital importance for post-translational lipid modification (prenylation) of certain GTP binding proteins (glutamyl transpeptidases) viz. Rho, Rac and Rab. These proteins are activated after prenylation and take part in various signal transduction events like cytoskeleton modelling. Prenylation adds a lipid chain that anchors the GTP binding proteins into the membrane of the osteoclasts. This step is required for the osteoclast to form ruffled borders to seal off a section of bone, and allow release of vesicles of proteolytic enzymes and acid that physicochemically dissolve underlying bone (Coxon & Rogers 2003).

Nitrogen-containing bisphosphonates, one of the potent anti-resorptive agents, also act on the cholesterol pathway downstream to the HMG-CoA reductase enzyme (Figure 2). They inhibit farnesyl pyrophosphate synthase enzyme and thus inhibit prenylation of GTP binding proteins, inducing osteoclast apoptosis. As for statins, nitrogen-containing bisphosphonates also interfere with the mevalonate pathway and may have a beneficial effect in-vivo on plasma lipid levels and the atherosclerotic process (Luckman et al 1998; Dunford et al 2001). Similarly by inhibiting HMG-CoA reductase, statins not only inhibit cholesterol synthesis but also exhibit various other beneficial effects independent of their cholesterol-lowering activity. These additional effects are collectively called as their pleiotropic effects, one of them being on bone. Statins inhibit osteoclast generation as do nitrogen-containing bisphosphonates (Benford et al 1999; Fisher et al 1999; van Beek et al 1999). Further, there is growing evidence establishing a link between the mechanisms of action of statins and bisphosphonates vis-a-vis the biological association between cardiovascular and bone diseases (Burnett & Vasikaran 2000; McFarlane et al 2004; Hamerman 2005).

In a classic set of experiments by Mundy et al (1999), statins have been shown to possess anabolic action due to enhanced BMP-2 expression. Although observations by Mundy et al emphasize the role of the mevalonate pathway in the regulation of bone formation, the exact molecular mechanism by which statins increase bone formation remains to be identified. One possibility is that small GTPase prenylated byproducts of the mevalonate pathway negatively regulate expression of BMP-2. By inhibiting the mevalonate pathway and preventing the prenylation and function of small GTPase, BMP-2 expression may be stimulated, causing increased osteoblast expression and differentiation and subsequent enhancement of bone formation. This hypothesis is supported by a preliminary report from the same group, which showed that the anabolic effect of statins can be overcome by addition of isoprenoid substrates required for protein prenylation (Garrett et al 2000). In agreement with these results, compactin and simvastatin stimulated BMP-2 activity in human osteosarcoma cells. Pravastatin, due to its hydrophilic nature, was unable to enter human osteosarcoma cells and could not affect BMP-2 expression (Sugiyama et al 2000). Similarly, pitavastatin increased the expression level of BMP-2 and osteocalcin in human osteoblastic cells and this stimulatory effect was abolished by addition of geranylgeranyl pyrophosphate, required for prenylation of Rho GTPase. Also, the direct inhibition of Rho-kinase using hydroxyfasudil, a specific Rho-kinase inhibitor, increased the expression of BMP-2 and osteocalcin similarly to pitavastatin (Ohnaka et al 2001). This enhanced bone formation activity of statins due to increased BMP-2 expression is attributed to an increase in endothelial nitric oxide synthase (eNOS) and increased nitric oxide (NO) production in bone cells (Garrett et al 2001a).

The decrease in bone volume associated with osteoporosis is accompanied by an increase in marrow adipose tissue. Osteogenic and adipogenic cells arise from a common multi-

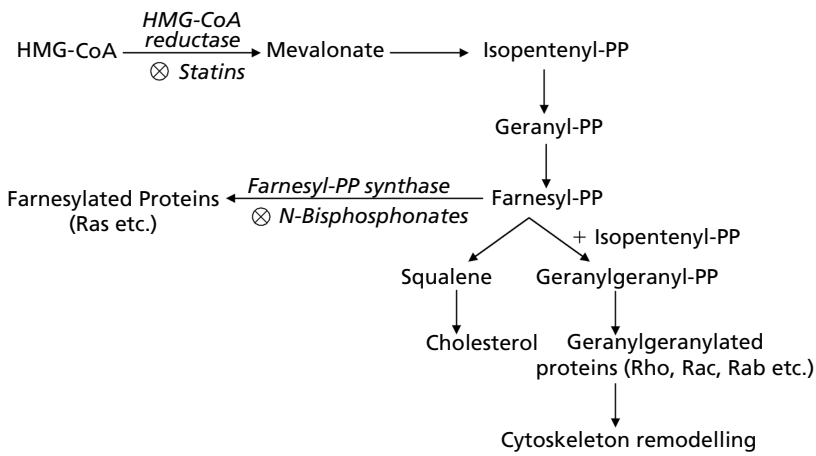

Figure 2 Cholesterol synthesis pathway and sites of action of statins and nitrogen-containing bisphosphonates (N-bisphosphonates).

potential precursor, bone marrow stromal cells (BMSCs), and a reciprocal relationship exists between adipogenesis and osteogenesis. Inhibition of marrow adipocyte differentiation and a concomitant enhancement of osteogenesis may provide a novel strategy for osteoporosis treatment (Nuttal & Gimble 2000). There is experimental evidence to show that BMP-2 stimulates osteogenesis and suppresses adipogenesis in BMSCs. This was further confirmed in a study where simvastatin inhibited adipogenesis and enhanced osteoblast differentiation by inducing BMP-2 expression (Song et al 2003). Li et al (2003) observed a very significant increase in the expression levels of transcription factor Cbfa1/Runx2 and osteocalcin promoter activity and, at the same time, a 60% reduction in PPAR γ expression levels after lovastatin treatment. Thus, shunting of uncommitted osteoprogenitor cells in marrow from the adipocytic to the osteoblastic differentiation pathway may open up a new modality for the treatment of osteoporosis.

Although BMP-2 certainly plays a role in osteoblast maturation and bone formation induced by statins, several other factors, like TGF-β, fibroblast growth factor-2 (FGF-2), insulin like growth factor-1 (IGF-I) and vascular endothelial growth factor (VEGF) are involved in promoting osteoblast differentiation and stimulating bone formation. Maeda et al (2003) investigated statin-induced enhancement in VEGF expression in three different osteoblast cell lines – MC3T3-E1, ST2 and UMR-106. This effect was mediated by reduced protein prenylation and phosphatidylinositide-3 kinase (PI3K) pathway.

In search of mediators of the anabolic effects of simvastatin on osteoblasts, Hwang et al (2004) tried to identify and characterize simvastatin-induced proteins by using proteomic analysis and found that calcyclin and annexin-I was upregulated in MC3T3-E1 cells. Wang et al (2003) studied the effect of simvastatin on heat shock proteins (HSP) induction and observed that simvastatin stimulated the induction of HSP27 in osteoblasts mediated by phosphorylation of p38 mitogen-activated protein (MAP) kinase. Lipophilic statins can be osteogenic by promoting Cbfa1- and BMP-2-independent calcification (Izumo et al 2001). Although compactin did not influence expression of osteogenic markers, it greatly enhanced the formation of bone nodules in embryonic stem cells (Phillips et al 2001).

Clinical conflict

The preclinical discovery of statins as bone anabolic agents led to the development of a great interest in the clinical community and subsequently many studies appeared to evaluate the clinical utility of statins with respect to bone health. Most of them were observational and have recently been excellently reviewed (Bauer 2003; Gonyeau 2005). These clinical studies can broadly be categorized in the following three groups, depending on the parameters of diagnosis of the osteoporosis assessed.

Statins and fracture risk

In a pioneering observational study by Wang et al (2000), an association between reduction in hip fracture and statin use was studied by analysing a database containing information on all filled prescriptions, hospital care, surgical procedures and physician visits for patients ≥65 years old. The study reported a 50% reduction in hip fracture among statin users. The results were not influenced, even after controlling for potential confounding variables. There was a clear use–response relationship for both short-term and long-term exposure to statins. Further, the lowest risk of hip fracture was observed with current statin users. In another large study by Meier et al (2000), a nested case–control analysis was performed using the UK-based General Practitioners Record Database (GPRD). This analysis also reported a statistically significant reduction in the risk of overall fractures and hip fractures among statin users as compared with control subjects. This association was predominant in current statin users. But unlike the previous study, this study showed a clear use–response relationship only for short-term (1–4 months) treatment and there was no further improvement with longer exposure. Adjustment for a variety of potential confounding factors, such as age, sex, race, insurance status, medication and disease status did not influence the results. Both studies further revealed that the use of non-statin cholesterol-lowering drugs such as fibrates was not associated with a reduction in fracture risk. These results are also consistent with preliminary findings from two other observational studies (Bauer et al 1999) and a case–control study (Chan et al 2000) showing that women who take statins, but not other cholesterol-lowering drugs, have a lower risk of hip fractures. In a population-based case–control study, a substantial reduction in the risk of hip fracture with number of statin prescriptions was reported in the Danish population (Rejnmark et al 2004a). Recently in a study, long-term statin use was significantly associated with a reduction in symptomatic and non-symptomatic fracture risk in elderly patients. But the use of pravastatin and non-statin lipid-lowering drugs did not have any association with fracture risk (Schoofs et al 2004).

In contrast to the aforementioned studies, another case–control study based on the same database used by Meier et al (2000) found that statin use was not associated with a reduction in the risk of fractures (van Staa et al 2001). In one historical cohort study, Ray et al (2002) found a 38% reduced risk of hip fractures in statin users compared with control population. Surprisingly, in the same study, the risk of hip fracture was reduced in users of non-statin lipid-lowering drugs compared with the control population. Based on these findings, the authors argued that the reduced fracture risk observed by other investigators was due to factors associated with lipid-lowering treatment in general rather than a specific effect of statin treatment (i.e., that unmeasured confounding factors may have influenced the results of previous studies). According to Ray et al (2002), a healthy drug user effect could be an unmeasured confounding factor (i.e. a tendency for patients who are compliant with preventive medicine to have fewer illnesses than non-users of preventive medicine, even after controlling for known risk factors). However, as other studies have been unable to show effects of non-statin lipid-lowering drugs on fracture risk, further research is needed to resolve this issue.

In addition to a potential healthy drug user effect, a difference in body weight has been suggested as a potential confounder, not controlled for in studies using databases to assess statin use and fracture occurrence (van Staa et al 2001; Ray et al 2002). A high body weight increases bone mineral density and protects against fractures. Therefore, it has been

suggested that hyperlipidaemic patients using statins may have a higher body weight than non-hyperlipidaemic subjects, and that the reduced fracture risk found in statin users may be due to an increased body weight.

There are no placebo-controlled trials specifically designed to assess the relationship between statin use and fracture risk, but two previous trials, namely Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) and the Scandinavian Simvastatin Survival Study (4S), with cardiovascular endpoints, have been analysed to examine the fracture risk in statin-treated and placebo groups (Table 1). In the 6-year LIPID trial, researchers evaluated the effects of pravastatin on the frequency of fractures only to find that there was no difference in fracture rates in the pravastatin versus placebo groups in the entire cohort (Reid et al 2001). Pravastatin, being a hydrophilic molecule, may not reach the bone micro-environment and indeed it was found to be ineffective in stimulating bone formation in rats (Mundy et al 1999). However, simvastatin, a lipophilic statin, also had no beneficial effect on the risk of fractures as found in a report from the 4S trial (Pedersen & Kjekshus 2000). Similarly, the Women's Health Initiative (WHI) Observational Study, a very large prospective cohort study of postmenopausal women, found no statistically significant improvement in fracture risk or bone density with statin use, even after adjustment for potential confounders (LaCroix et al 2003).

In a recent cumulative meta-analysis of selected observational and controlled trials, statins were associated with a trend in lowering hip and non-spine fractures in the four prospective trials conducted (Bauer et al 2004). The four cohorts included were: the Study of Osteoporotic Fractures (SOF); the Fracture Intervention Trial (FIT); the Heart and Estrogen/Progestin Replacement Study (HERS); and the Rotterdam Study. After adjustment for age, body mass index, physical activity, smoking status and use of bisphosphonates and oestrogen, analysis of the observational studies revealed a 57% reduction in hip fracture and a 31% reduction in non-spine fractures. Two clinical trials mentioned previously (Pedersen & Kjekshus 2000; Reid 2001) were also pooled and analysed, but results showed no statistically significant differences in hip fracture. Because these trials were designed to detect differences in the rates of cardiovascular events, the studies, taken individually, may not have enough statistical power to detect clinically meaningful reduction in risk of fractures.

In summary, as evident from all these studies, the association between statin use and risk of fracture is a contentious issue. The studies positively asserting the beneficial effects are paralleled by studies arguing against it (Table 2). Uncontrolled confounding variables could also have caused the protective effect of statins on the risk of fracture. A definitive answer will require evidence from large randomized trials.

Statins and bone mineral density

Bone mineral density (BMD), along with bone turnover, is one of the most important determinants of fracture risk and is considered essential in studies assessing the effect of any drug on bone (Kanis et al 2000). The studies listed in Table 3 have evaluated the effect of statins on BMD.

Edwards et al (2000) conducted an observational case–control study to evaluate the effect of statins on BMD in participants of the Chingford study and observed that BMD at the spine and femoral neck was significantly higher in statin users. In an even larger study from the Women's Health Initiative observational cohort, Cauley et al (2000) reported higher spine and hip BMD among statin users. In a retrospective case–control study of 69 patients with type-2 diabetes mellitus, statin-treated patients experienced an increase in BMD in the femoral neck and total hip, but a non-significant decrease in BMD in the lumbar spine as compared with the control group (Chung et al 2000). No significant differences in BMD scores were noted in groups prescribed different statins. As compared with the female population, a significant increase in BMD was noted in statin-treated male patients. A possible explanation for the sex difference was that osteoporosis in men is usually the result of decreased osteoblast function, whereas women's primary defect occurs with increased bone resorption due to oestrogen loss during menopause. Although this study observed that the benefit with statins is not likely to be due to chance, the small and very specific population, the retrospective design and the disparity of results in the female population limits the ability to extrapolate these data to a larger patient base. In Japanese type-2 diabetic patients, BMD was significantly lower in subjects receiving statins than in those not receiving statins (Wada et al 2000). Further, there was negative correlation between BMD and total serum cholesterol level in these subjects. Apart from the type of statin used, insulin resistance or hyperinsulinaemia (or both) might have caused these surprising results (Wada et al 2000). A longitudinal study performed by Lupattelli et al (2004) indicated that simvastatin treatment exerts a beneficial effect on BMD. In the Geelong osteoporosis study (Pasco et al

Table 1 Clinical trials of statins and fracture outcome

Study	Population	Duration	Statin	Fracture type	Outcome	Reference
LIPID	9014 men & women 17% with heart disease average age 62 years	6 years	Placebo (n = 4502) Pravastatin 40 mg (n = 4512)	358 any fracture 208 hospitalized fractures 23 hip fractures	OR 0.94 95% CI 0.77–1.16 OR 1.05 95% CI 0.80–1.37 OR 0.77 95% CI 0.34–1.75	Reid et al (2001)
4S study	4444 men & women 19% with heart disease	5.5 yrs	Placebo (n = 2223) Simvastatin 20–40 mg (n = 2221)	155 any fracture 20 hip fractures	OR 1.11 95% CI 0.81–1.51 OR 1.00 95% CI 0.42–2.42	Pedersen et al (2004)

OR, odds ratio; CI, confidence interval.

Table 2 Observational studies of statin use and fracture risk

Study/design	Population	Statin use	Fracture type	Adjustments	Outcomes	Reference
Studies that support reduction in fracture risk						
Geelong Case–control	1384 women 50–95 years	69	Any (573)	Unadjusted, no change after adjustment for age, weight, medication & lifestyle factors	Whole body: OR 0.43, 95% CI 0.24–0.78 Spine: OR 0.42, 95% CI 0.24–0.75 Femoral neck: OR 0.45, 95% CI 0.25–0.8	Pasco et al (2002)
SOF Prospective cohort	8422 women over 65 years	324	Hip (180) Non-spine (897)	Age, BMI, exercise, smoking, health status, ERT	Hip: OR 0.19, 95% CI 0.03–1.38 Non-spine: OR 0.76, 95% CI 0.50–1.16	Bauer et al (2004)
HMO Case–control	3675 women over 65 years	109	Hip (262) Hip, spine, arm (928)	Unadjusted, age, no. of hospitalizations, chronic disease, other lipid-lowering drugs	Hip: OR 0.22, 95% CI 0.03–1.66 Hip, spine, arm: OR 0.48, 95% CI 0.27–0.83	Chan et al (2000)
Rotterdam Prospective cohort	8529 men & women	145	Hip (180) Non-spine (546)	Unadjusted, age, BMI, disability, smoking, ERT	Hip: OR 0.31, 95% CI 0.04–2.25 Non-spine: OR 0.37, 95% CI 0.12–1.17	Bauer et al (2004)
HERS Prospective cohort	3763 women 44–79 years	1001	Hip (23) Non-spine (248)	Age, BMI, exercise, smoking, health status, ERT	Hip: OR 0.62, 95% CI 0.16–2.35 Non-spine: OR 0.92, 95% CI 0.64–1.32	Bauer et al (2004)
FIT Prospective cohort	6459 women 55–80years	284	Hip (76) Non-spine (825) Vertebra (340)	Age, BMI, exercise, smoking, alendronate health status	Hip: OR 0.53, 95% CI 0.07–3.82 Non-spine: OR 0.95, 95% CI 0.59–1.52 Vertebral: OR 0.60, 95% CI 0.26–1.39	Bauer et al (2004)
NJ Medicaid Case–control	6110 men & women	230	Hip (1222)	Age & sex matched adjusted for ERT, other medications, other disease	Hip: OR 0.5 , 95% CI 0.33–0.76	Wang et al (2000)
GPRD 1 Case–control	27 319 men and women 50–79 years	1030	Hip (678) Non-spine (3940)	Age, sex, and matched. Adjusted for BMI, smoking, physician visits, ERT/ steroid use	Hip: OR 0.12, 95% CI 0.04–0.41 Non-spine: OR 0.55, 95% CI 0.44–0.66	Meier et al (2000)
Studies that do not support reduction in fracture risk						
GPRD 2 Case–control	27319 men & women, 50–89 years	1030	Hip (687) Non-spine (3940)	Age, sex, practice matched, Adjusted for BMI, smoking, physician visits, ERT use	Hip: OR 0.59, 95% CI 0.31–1.13 Non-spine: OR 1.01, 95% CI 0.88–1.16	van Staa et al (2001)
WHI Case–control	81 896 women 50–79 years	6782	Hip (321) Wrist/arm (1582) Others (5864)	Age, race, ethnicity, BMI, fracture history, smoking, steroid use, walking, physical function, years of HRT use, Ca intake, alcohol and coffee consumption	Hip: OR 0.98, 95% CI 0.73–1.62 Wrist/arm: OR 0.85, 95% CI 0.68–1.08 Other non-spine: OR 1.00, 95% CI 0.90–1.12	LaCroix et al (2003)

OR, odds ratio; CI, confidence interval.

Table 3 Statins and BMD outcome

Study/design	Population	Duration of statin use	BMD site	Outcomes	Reference
Studies that support increase in BMD					
Case–control	41 postmenopausal women statin users	48 months	Lumbar spine	Lumbar spine: 8.9% change*	Edwards et al (2000)
WHI, cohort	422 women statin users	—	Total hip	Total hip: 2.4% change*	Cauley et al (2000)
Prospective cohort	40 statin users	24 months	Lumbar spine, hip	Lumbar spine 3.3% change* Hip: 2.7% change	Lupattelli et al (2004)
Prospective cohort	30 postmenopausal hypercholesterolaemic women statin users	12 months	Lumbar spine, femur, femoral neck	Lumbar spine: 2.8% change* Femoral neck: 1.0% change* Femur: 0.8% change*	Montagnani et al (2003)
Retrospective, case–control	36 type 2 diabetic statin users	14 months	Spine, total hip, femoral neck	Total hip: 0.88% change* Femoral neck: 2.32% change*	Chung et al (2000)
Studies that don't support increase in BMD					
OSTPRE Prospective case–control	55 continuous statin users	4.5 years	Spine, femur	Spine: –0.2% change ($P = 0.134$) Femur: –0.47% change ($P = 0.628$)	Sirola et al (2002)
Double blind randomized	82 postmenopausal statin users	1 year	Lumbar spine, hip, forearm and whole body	Lumbar spine: 0.5% change ($P = 0.46$) Total hip: 0.2% change ($P = 0.52$) Forearm: 1.1% change ($P = 0.01$)	Rejnmark et al (2004b)

*$P < 0.05$.

2002), the association between statin use, fracture risk and BMD in Australian postmenopausal women was evaluated. BMD measurements were obtained for both fracture and non-fracture cases. Though there was no statistically significant increase in BMD, the fracture risk was significantly reduced in statin users (Pasco et al 2002). Even adjustments for confounding factors, like age, weight, medication and lifestyle, had no substantial effect on the odds ratio for fractures.

Hormone replacement therapy (HRT) is the front-line and most commonly used treatment in osteoporosis. To study the effect on BMD of statins when administered along with HRT, retrospective evaluation was performed on women who used HRT and statins for three years. Eighty-seven postmenopausal women on combination therapy were compared with subjects taking only HRT (De Leo et al 2003). BMD was significantly higher in the HRT plus statin groups as compared with subjects taking only HRT. This study showed that statins could enhance the effect of oestrogen on BMD. Similarly, atorvastatin, when administered along with risedronate, was shown to have an additive effect in improving lumbar spine BMD in hypercholesterolaemic postmenopausal women with established osteoporosis (Tanriverdi et al 2005).

Funkhouser et al (2002) reported an increase in BMD and a lower risk of osteoporosis in patients taking statins. No statistically significant differences were noted in BMD at the femoral neck or lumbar spine between users and non-users of statins in a prospective case–control study of 620 patients from the Kupio Osteoporosis Risk Factor and Prevention trial (Sirola et al 2002). An interesting finding noted by these researchers is the potential for hyperlipidaemia itself to be protective against osteoporosis and fractures, as the smallest annual bone loss and greatest gain of lumbar bone were seen in hyperlipidaemic control subjects. This finding confirmed the previously examined relationship between lipid profile and BMD among healthy men aged 40–70 years (Adami et al 2001). The subjects with the most favourable lipid profile consistently had the lowest bone mass values expressed in terms of Z score even after adjustment for various confounders. Yataru et al (2001) did not observe any significant difference between the changes in BMD of patients who were on statins alone or other anti-resorptive agents in addition to statins. No significant association between statin use and spinal and femoral BMD was observed in another study (Solomon et al 2001). Watanabe et al (2000) found a 2.2% increase in lumbar BMD in women treated with fluvastatin for 6 months, whereas it decreased by 0.4% in a similar group treated with pravastatin.

Statins and biochemical markers of bone metabolism

Most of the above epidemiological case–control studies are based on either measurement of BMD or fracture risk. Also, they differ in recruitment criteria, period of statin exposure and outcome assessment. Biochemical markers of bone metabolism comprise both markers for bone formation (e.g. osteocalcin, bone specific alkaline phosphatase) and for bone resorption (e.g. urinary crosslinks). These markers serve as a tool for the diagnosis of osteoporosis and have been studied to assess the potential of statins in the treatment of osteoporosis (Table 4).

Table 4 Statins and biochemical markers of bone metabolism

Study/design	Population	Statin daily dose	Effect on markers	Reference
Cohort	n = 17, men & women 40–70 years	Simvastatin 20 mg for 4 weeks	Increase in serum osteocalcin ($\mu g\ L^{-1}$) 15.6 vs 28.9 ($P < 0.05$)	Chan et al (2001)
Cohort	n = 36, women >50 years	Pravastatin 20 mg for 16 weeks	Increase in procollagen I N-terminal propeptide (PINP) ($\mu g\ L^{-1}$) 33.6 vs 37.4 ($P < 0.05$)	Mostaza et al (2001)
Randomized, open label controlled trial	n = 85 per group, women 21–70 years	Simvastatin 20, 40 mg, Atorvastatin 20, 40 mg and for 12 weeks	Decrease in bone specific serum alkaline phosphatase (BSAP) 4.1% ($P < 0.05$)	Stein et al (2001)
Randomized controlled trial	n = 68 women above 65 years	Fluvastatin 40 mg/ vitamin C for 12 weeks	Weak decrease in bone resorption markers (14% decrease in urinary NTx ($P > 0.05$)	Bjarnason et al (2001)
Randomized, double blind controlled trial	n = 49 women 55–65 years	Atorvastatin 20 mg for 8 weeks	Age dependent increase in osteocalcin ($P < 0.05$) in older individuals above 63 years	Berthold et al (2004)
Prospective cohort	30 postmenopausal hypercholesterolaemic women users 61 ± 4.9 years	Simvastatin 40 mg/day for 12 months	Increase in bone specific serum alkaline phosphatase (BSAP) ($\mu g\ L^{-1}$) 10. 6 vs 12.2 ($P < 0.05$)	Montagnani et al (2003)

In the first prospective study, in which concentrations of various markers of bone metabolism in hypercholesterolaemic patients treated with simvastatin were measured, the authors found a significant increase in serum osteocalcin concentration after 4 weeks of therapy (Chan et al 2001). Other bone markers, including serum bone-specific alkaline phosphatase activity, urine deoxypyridinoline and cross-linked N-telopeptide of type I collagen (NTx), did not show any significant changes. These observations suggest the possible bone anabolic action of simvastatin observed by Mundy et al (1999). A small short-term trial was carried out on 14 postmenopausal women to find out the effect of two-week treatment with 0.4 mg of cerivastatin per day on bone instead of serum cholesterol levels (Cosman et al 2001). Bone formation markers (type-I procollagen propeptide and osteocalcin) remained unchanged but the resorption markers (urinary N- and C- terminal telopeptides) reduced slightly (<20%) within 6 weeks in the cerivastatin-treated group. The authors concluded that cerivastatin did not detectably stimulate bone formation, but it might have had a modest bisphosphonate-like anti-resorptive action.

In the first ever longitudinal study where the actual potential of statins in osteoporosis could be found, the effect of a one-year treatment with simvastatin on BMD and bone turnover changes was evaluated in hypercholesterolaemic postmenopausal women (Montagnani et al 2003). The authors found a moderate increase in spinal BMD and a significant increase in bone alkaline phosphatase, whereas serum C-telopeptide of type I collagen (CTx) showed a non-significant increase in the treatment group. The main limitation of this study was the short study duration and small population of statin users, limiting the extrapolation of the data to larger populations. In a randomized controlled trial of simvastatin in postmenopausal osteopenic women, plasma levels of PTH and biochemical markers of bone formation didn't differ in the subjects treated with simvastatin as compared with placebo. Also simvastatin caused no change in BMD in lumbar spine, total hip, femoral neck or whole body, but there was a significant increase in BMD in the forearm (Rejnmark et al 2004b). The same group had previously studied the effects of statins on calcium homoeostasis, bone turnover and bone mineral density, in a cross-sectional design. Plasma levels of bone turnover markers were lower in the statin-treated subjects than in the controls. On the other hand, plasma PTH levels were 16% higher in the statin-treated subjects than in the controls. However, body composition and BMD in the lumbar spine, hip, forearm and whole body did not differ between the two groups (Rejnmark et al 2002). Fluvastatin has also been shown to have no effect on biochemical markers of bone formation although it resulted in a slight reduction in markers of bone resorption in elderly, postmenopausal women with osteoporosis and mild hypercholesterolaemia (Bjarnason et al 2001).

In a randomized controlled trial of short-term atorvastatin treatment in hypercholestrolaemic patients, urinary CTx excretion decreased significantly although bone-specific alkaline phosphatase and osteocalcin did not change significantly (Salbach et al 2001). Berthold et al (2004) analysed age-dependent effects of atorvastatin on biochemical markers of bone turnover in a randomized controlled trial in postmenopausal women and suggested beneficial effects of statins on bone turnover exclusively in older individuals. The biochemical markers of bone formation in stored serum samples from a previously completed randomized clinical trial conducted to compare the effects of simvastatin and atorvastatin on the lipid profile of patients with hypercholesterolaemia were determined (Stein et al 2001). Bone-specific alkaline phosphatase and CTx were reduced on treatment with simvastatin in a dose-dependent fashion, while treatment with atorvastatin exhibited no significant effect on either marker (Stein et al 2001). Pravastatin treatment increased procollagen I N-terminal propeptide (PINP) levels, a marker of bone formation, in hypercholesterolaemic, postmenopausal women, without affecting bone resorption (Mostaza et al 2001). A randomized, double-blind, placebo-controlled, dose-ranging trial in osteopenic women identified no effect of simvastatin on markers of bone formation (bone-specific serum alkaline phosphatase) or bone resorption (N-telopeptides and C-terminal propeptide of type-I collagen) at doses that significantly inhibited HMG-CoA reductase activity (Hsia et al 2002).

Finally, a systematic analysis was performed in one study to assess the potential impact of statins on fractures, bone mineral density and bone markers. All observational and randomized controlled trials to date investigating the effect of statins on bone were considered for the meta-analysis. They found a strong association between reduction in hip fracture and improved hip BMD and statin use in case–control studies and not in either prospective or randomized controlled trials. Again this association was absent in the case of vertebrae. There was only small effect of statins on bone markers (Hatzigeorgiou & Jackson 2005).

In summary, there are several retrospective observational studies suggesting that statin use is associated with higher bone mineral density in the hip and spine, and with fewer fractures. These data are also supported by short-term prospective studies showing favourable effects of some statins on biomarkers of bone metabolism. However, these initial reports suggesting a favourable effect on fractures have not been confirmed in preliminary reports of several other large observational studies and, more importantly, no evidence of benefit has been found in secondary analysis of randomized clinical trials of statin therapy for prevention of cardiovascular diseases. This indicates that observational data may be biased by a healthy user effect that can only be fully removed with placebo-controlled randomization. Again, the issue of relative efficacy of individual statins for the indication of osteoporosis remains unsolved. Lipophilic statins may be more effective than hydrophilic statins, as evident from the inactivity of pravastatin both in preclinical and clinical studies. Thus, until randomized clinical trials designed to study the effects of specific statins on BMD and fracture risk are performed, recommendation of statin use for prevention of osteoporosis can not be made. Even though statins seems to be quite safe, it is important to remember that drugs that seem effective in observational studies may not prove to be effective in randomized trial. For example, sodium fluoride increases bone mass and observational studies initially demonstrated a substantial reduction in risk of vertebral fracture (Riggs et al 1990). However, a randomized trial showed that daily administration of 75 mg of sodium fluoride increased spine bone density but failed to reduce the risk of vertebral fractures (Riggs et al 1982). So a randomized controlled trial with a larger sample size and or a longer duration of treatment is needed to understand the exact effect of statins on bone and unravel the association of statin use and risk of fracture.

Delivering statins for bone

Although relatively abundant information about statins, available both in the preclinical and clinical field, indicates their possible beneficial effect on bone, a few studies have some reservations about it. The method of administration, duration of exposure and experimental animal model seem to cause disagreement. Further, osteoclasts and osteoblasts might have different sensitivity to statins, leading to stimulation of one or the other at different doses, thus creating confusion about anti-osteoclastic or pro-osteoblastic activity of statins. Different baseline lipid levels in animals could be another explanation for the divergent results (Demer 2001). Products of the cholesterol biosynthetic pathway are important for proper development of mesenchymal stem cells (MSCs) into functional osteoblastic cells capable of forming a mineralized matrix (Parhami et al 2002). It is also known that lipid levels can affect bone metabolism (Parhami et al 1997, 2000, 2001) and lipid-lowering drugs can affect steroid-induced osteoporosis and hence a difference in lipid-lowering effect between various studies might explain the difference in results.

Statins are widely used lipid-lowering drugs. By inhibiting HMG-CoA reductase, they reduce cholesterol production in the liver. Both hydrophilic and lipophilic statins are selectively targeted to liver. Lipophilic and hydrophilic statins are taken up in liver by passive diffusion and by active transport, respectively. An important consideration in evaluating the potential for a skeletal effect of statins is the extent of their uptake into bone. Due to their high lipophilicity and first-pass effect, the bioavailability of lipophilic statins is very low, at less than 5% (Corsino et al 1999; Reinoso et al 2002; William & Feely 2002). Oral administration of these statins as anti-osteoporotic drugs is not an ideal method of delivery because of their low oral bioavailability. The statins are designed to act selectively in the liver, where they undergo conversion to the active β-hydroxyacid moiety, which in turn reduces cholesterol synthesis. Due to their liver specificity and very poor distribution to the periphery, the probability of statins reaching the bone micro-environment is very low. Even the active transport system present in liver for the uptake of hydrophilic statins is absent in bone (Mundy 2001). Thus, their plausible low bone specificity due to poor peripheral distribution seems to be the major factor responsible for the discrepancies in the results obtained by various researchers. The minimum concentration of statins required to have beneficial action on bone is a critical need in exploring statins as anti-osteoporotic agents. Then they have to be delivered specifically to bone so as to achieve the optimum required concentration in the local bone micro-environment.

Indeed, Mundy et al (1999) had observed an almost 50% increase in new bone formation after only five days of treatment when lovastatin and simvastatin was injected into the subcutaneous tissue overlying the calvaria of mice. In an attempt to deliver statins to bone in optimum amount, lovastatin was applied topically to rats. Dermal application of lovastatin to rats caused a greater increase in bone formation and plasma concentration than when administered by oral gavage (Gutierrez et al 2000, 2001). Crawford et al (2001) compared the effect of lovastatin on bone after local (bone marrow injection) and systemic (subcutaneous injection) administration. Lovastatin increased cortical bone in young male rats by single local administration to the bone marrow cavity but failed to restore bone mass in ovariectomized rats by subcutaneous injection. The mechanism of action of lovastatin in this case was not clear.

With the increasing development of polymer science, various biocompatible polymers are being widely used in novel drug delivery systems. This polymeric delivery has the advantage of controlling the release of embedded drug from a matrix, thereby reducing the dose and dosage frequency. The controlled delivery of simvastatin manifested a significant effect on bone formation (Thylin et al 2002). Subcutaneous

injection of simvastatin formulated in methylcellulose gel stimulated a 53% increase at the thickest point of calvarial bone. Implanted polylactide (PLA) membrane containing gel and simvastatin also caused a highly significant increase in bone thickness and bone area compared with controls (Thylin et al 2002). In another study, Whang et al (2000) administered lovastatin from a poly(lactide-co-glycolide) (PLG) scaffold fabricated by an emulsion-freeze drying process and implanted into the skin over the mouse skull. The continuous zero-order release of lovastatin from the scaffold induced new bone area formation and the effect was found to be significantly higher than that induced by local injection of lovastatin. Simvastatin grafted onto PLG was shown to significantly enhance in-vitro bone cell mineralization through degradation-controlled release kinetics (Whang et al 2005). Another advantage with this type of delivery system is the requirement of a low amount of drug for the desired effect. To maximize their efficacy as anti-osteoporotic agents, the route of administration and dosage form of statins have to be optimized.

Site-specific targeted delivery is another exciting option for achieving maximum concentration of drug in the bone micro-environment. Site-specific drug delivery via a pro-drug approach has generated considerable interest for enhancing the potency or diminishing the side effects of a drug. Recently, there have been many reports of targeting drugs to osseous tissue by conjugating them with osteotropic moieties, like bisphopshonates (Fujisaki et al 1995, 1996, 1997, 1998; Hirabayashi et al 2001). The drug is linked to a bisphosphonic moiety via bioreversible bonds. After systemic administration, a bisphosphonic conjugate is rapidly delivered to the bone owing to its affinity for hydroxyapatite, and then subjected to enzymatic or chemical hydrolysis (or both) to provide a parent drug, depending on its cleavage rate. Furthermore, the bone tissue acts as a reservoir and finally the regenerated parent drug is released to the systemic circulation. This osteotropic drug delivery as a controlled-release system might also be useful for maintaining the plasma drug concentration for a long period of time. By targeting statins specifically to bone one can achieve the desired effect at a reduced dose. Also, it can unravel the exact action of statins on bone.

Conclusion

While the majority of marketed drugs for the treatment of osteoporosis are anti-resorptive, bone anabolic agents are in great demand to replenish the lost bone. Statins are already on the counter for the treatment of atherosclerosis and offer a great potential for osteoporosis treatment with unique anabolic, as well as anti-resorptive, properties. They enjoy the advantage of patient compliance and cost effectiveness as compared with PTH. The disparity in the results observed by various preclinical and clinical researchers may be due to liver-specific pharmacokinetics and poor distribution of statins to bone. Optimization of the route of administration, dosage form and use of controlled drug delivery systems can help to achieve their bone-specific pharmacokinetics and reposition them for the treatment of osteoporosis.

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