A Systematic Review on the Relation between use of Statins and Osteoporosis

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Abstract: The association between cardiovascular diseases and senile chronic diseases has been thought from many years ago. Osteoporosis is one of the major senile and chronic disease which accounts for high morbidity and mortality as well as high cost among elderly patients. Concerning the importance of prevention and treatment of cardiovascular disease as well as osteoporosis, and the pleiotropic effects of statins, the theory of the beneficial effects of statins on bone was proposed from different aspects such as the effect of statins on bone formation, bone resorption, bone mineral density and fracture risk. The probable link between cholesterol synthesis and bone metabolism has been also suggested. Regarding the link between cardiovascular disease and osteoporosis, in vitro studies show beneficial effects of statins on bone formation, however, most of clinical trials do not completely confirm the issue. Meanwhile, some investigators believe in the impact of statins on bone turnover. However, there is no conclusive data and agreement yet to recommend use of statins neither as a treatment nor prevention of osteoporosis. More longitudinal studies in different ethnicities with large sample sizes are suggested.

Key words: Statin, osteoporosis, bone formation, bone mineral density

INTRODUCTION

Skeleton composed of bone tissue which faces with multiple mechanical and metabolic activities. Bone consists of an organic and mineralized matrix. The main deposited mineral components of bone are calcium and phosphate which are under cellular control. The cellular component contains two distinct cell types specifically osteoblasts and osteoclasts. Bone health depends on the balance between the bone formation activity of osteoblasts and bone resorption activity of osteoclasts.

The process is named remodeling. Several bone diseases cause imbalance between bone formation and bone resorption such as osteoporosis, hyperparathyroidism, metastatic bone disease, hypercalcemia of malignancies, hyperhomocysteinemia (Salari et al., 2008a) or use of drugs (Salari-Sharif and Abdollahi, 2010; Salari and Abdollahi, 2009). Reduction in bone mass results in bone fragility and susceptibility to fracture. The important thing which has to be noticed principally is that in most bone disorders, increased bone resorption is the main reason for osteoporosis. Therefore inhibition of bone resorption can be considered as the mainstay of osteoporosis prevention and treatment and this is possible by reducing either osteoclast generation or its activity (Woo et al., 2008). Bone resorption by osteoclasts mediates via several stages as follows: changes of progenitor cells to precursor cells, differentiation of preosteoclasts from hematopoietic cells, maturation of osteoclasts, conjunction of osteoclasts to mineralized bone surface, excretion of acids and lysosomal enzymes. Several compounds have known to affect osteoclastic bone resorption via this process such as genistein, vitamin K2, tyrosine kinase inhibitors and some other compounds which are under investigation such as statins, cyclosporine A, FK506, etc. (Woo et al., 2008). Nowadays strong evidences put special attention on oxidative stress as the major causative agent (Abdollahi et al., 2005; Yousefzadeh et al., 2006). Many inflammatory mediators are related to the formation of osteoclasts including tumor necrosis factor-a (TNF-a), receptor activator of nuclear factor xB ligand (RANKL), interleukin-1 (IL-1), interleukin-6 (IL-6) and macrophage-colony stimulating factor (M-CSF) (Ahn et al., 2008; Cao et al., 2003; Kong et al., 1999). In the recent statins are considered as the main stay in treating cardiovascular diseases which are in the center of
Fig. 1: The pleiotropic effects of statins. May the triangle be true? While the beneficial effects of statins on lipids, inflammation, angiogenesis, and platelet aggregation have been demonstrated; the benefits of statins on bone are under question. In this triangle (the relationship between statins, CVD, and osteoporosis) two sides are well known, while the third one (the link between statin use and osteoporosis) is not truly clear. Plt: Platelet, T cells: T lymphocytes; Aβ: β-amyloid peptide; CVD: Cardiovascular disease.

attention. In addition to some of their pleiotropic effects (decreasing platelet aggregation, promoting angiogenesis, decreasing β-amyloid peptide and suppressing T-lymphocyte activation) (Horiuchi and Maeda, 2006), recently statins are considered as bone anabolic agents which motivated a great deal of interests into basic and clinical investigations (Fig. 1). On the other hand, several investigators have theorized the association between brittle bone and cardiovascular diseases as two common chronic diseases affecting elderly population (McFarlane et al., 2004).

Theoretically numerous activities of statins enable them to inhibit production of inflammatory mediators such as TNF-α, IL-6, C-Reactive Protein (CRP), etc. (Rosenson et al., 1999, Ikeda and Shimada, 1999, Strandberg et al., 1999). Based on these theories and their high usage and the concerns about their safety, several investigations were performed in order to find their net effect and mechanisms of action. Therefore the goal of this review is to evaluate the most relevant studies in this issue and make a conclusion if possible.

MATERIALS AND METHODS

Concerning this area of investigation, all published papers from 2000-2009 were searched by different search engines such as Web of Sciences, Pubmed, Scopus, and Google Scholar. The selected search terms were as osteoporosis, bone, bone markers, statins, and HMG CoA inhibitors. Only articles with accessible abstract were reviewed. Due to the controversies between the results of human and animal studies, animal studies, and letter to editor articles were excluded.

RESULTS

Relevant studies have been summarized in Table 1.

The link between lipids and osteoporosis: It has been claimed that the inverse correlation between low BMD and cardiovascular mortality is stronger than blood pressure and serum cholesterol (McFarlane et al., 2004, Tanko et al., 2003). Also the link between low triglycerides and vertebral fractures strengthens the possibility of interrelation between lipids and bone mass (Yamaguchi et al., 2002). The association between cardiovascular diseases and osteoporosis was considered from many points of views such as matrix proteins and factors shared by bone and arterial wall which were known to be the 12-15 lipoxigenase system and peroxisome proliferator-activated receptor (PPARγ), osteopontin, osteocalcin, osteoprotegerin, the low-density Lipoprotein Receptor-related Protein (LRP), NF-κB, leptin and adiponectin (Hamerman, 2005).

Some other scientists proposed the byproducts of cholesterol biosynthetic pathway substantial for differentiation of marrow stromal cells into functional osteoblastic cells (Parhami et al., 2002), while
Table 1: The summarized results of the relevant studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study</th>
<th>Target</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Bone formation</td>
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<tr>
<td>Mundy et al. (1999)</td>
<td>CT</td>
<td>Rodents</td>
<td>Lovastatin and simvastatin</td>
<td>-</td>
<td>Lovastatin and simvastatin increased BMP-2</td>
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<tr>
<td>Sugiyama et al. (2000)</td>
<td><em>In vitro</em> study</td>
<td>HOS</td>
<td>Simvastatin</td>
<td>-</td>
<td>Simvastatin activated BMP-2 promoter</td>
</tr>
<tr>
<td>Ohnaka et al. (2001)</td>
<td><em>In vitro</em> study</td>
<td>HOS</td>
<td>Pitavastatin</td>
<td>-</td>
<td>Pitavastatin augments BMP-2 and OC</td>
</tr>
<tr>
<td>Maeda et al. (2001)</td>
<td><em>In vitro</em> study</td>
<td>MC3T3-E1 cells</td>
<td>Simvastatin</td>
<td>-</td>
<td>Simvastatin promotes osteoblastic differentiation and mineralization</td>
</tr>
<tr>
<td>Chan et al. (2001)</td>
<td>PS</td>
<td>17 HP</td>
<td>Simvastatin 20 mg day⁻¹</td>
<td>4 weeks</td>
<td>Simvastatin increased OC level, but not BALP, NTx, Dpyd</td>
</tr>
<tr>
<td>Bjarnason et al. (2001)</td>
<td>RCT</td>
<td>68 PMOW</td>
<td>Fluvastatin 40 mg day⁻¹</td>
<td>12 weeks</td>
<td>Fluvastatin had no influence on bone markers</td>
</tr>
<tr>
<td>Rejmark et al. (2002)</td>
<td>CSS</td>
<td>140 PMW</td>
<td>Statin</td>
<td>&gt;2 years</td>
<td>Statin users had lower OC, BALP, CTX levels, no change in BMD</td>
</tr>
<tr>
<td>Tikiz et al. (2004)</td>
<td>PS</td>
<td>38 PMHW</td>
<td>Simvastatin 20 mg day⁻¹</td>
<td>3 months</td>
<td>Simvastatin increased OC, BALP, no significant change in CTX, IL-6 decreased TNF-α</td>
</tr>
<tr>
<td>Majima et al. (2007a)</td>
<td>CT</td>
<td>101 HP</td>
<td>Pitavastatin 1 mg day⁻¹</td>
<td>3 months</td>
<td>Pitavastatin decreased NTX</td>
</tr>
<tr>
<td>Majima et al. (2007b)</td>
<td>CT</td>
<td>22 HM</td>
<td>Atorvastatin 10 mg day⁻¹</td>
<td>3 months</td>
<td>Atorvastatin decreased NTX</td>
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<tr>
<td>Bone resorption</td>
<td></td>
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<tr>
<td>Ahn et al. (2008)</td>
<td><em>In vitro</em> study</td>
<td>-</td>
<td>Simvastatin</td>
<td>-</td>
<td>Simvastatin suppressed osteoclastogenesis via NF-κB pathway</td>
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<tr>
<td>BMD</td>
<td></td>
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<tr>
<td>Sirota et al. (2002)</td>
<td>PCS620 PMW</td>
<td>-</td>
<td>Simvastatin 40 mg day⁻¹</td>
<td>2 years</td>
<td>Lack of protective effects of statin use in early PMW</td>
</tr>
<tr>
<td>Lupattelli et al. (2004)</td>
<td>RCT</td>
<td>60 PMHW</td>
<td>Simvastatin 40 mg day⁻¹</td>
<td>2 years</td>
<td>BMD increased significantly in the treatment group after 8 and 24 months</td>
</tr>
<tr>
<td>de Leo et al. (2003)</td>
<td>RS</td>
<td>174 PMW</td>
<td>Simvastatin/pravastatin 20 mg+HRT</td>
<td>1 year</td>
<td>Higher BMD in the statin group</td>
</tr>
<tr>
<td>Montagnani et al. (2003)</td>
<td>CT</td>
<td>30 PMHW</td>
<td>Simvastatin 40 mg day⁻¹</td>
<td>1 year</td>
<td>BMD and BALP increased significantly in treatment group at 12 months</td>
</tr>
<tr>
<td>Rejmark et al. (2004a)</td>
<td>RCT</td>
<td>82 PMOW</td>
<td>Simvastatin 40 mg day⁻¹</td>
<td>1 year</td>
<td>No significant changes were seen in bone markers or BMD, except for forearm BMD</td>
</tr>
<tr>
<td>Nakashima et al. (2004)</td>
<td>CT</td>
<td>122 Diabetic Patients</td>
<td>Simvastatin/Pravastatin 10 mg day⁻¹</td>
<td>2 years</td>
<td>Smaller annual decrease in radial BMD</td>
</tr>
<tr>
<td>Solomon et al. (2005a)</td>
<td>Cohort analysis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No significant relationship between cholesterol level and BMD</td>
</tr>
<tr>
<td>Taniyama et al. (2005)</td>
<td>RCT</td>
<td>120 PMHW + Osteopenia/ Osteoporosis</td>
<td>BP-atorvastatin 20 mg day⁻¹</td>
<td>6 months</td>
<td>Modest additive effect of statins to BP in improving BMD</td>
</tr>
<tr>
<td>Bone et al. (2007)</td>
<td>RCT</td>
<td>626 PMHW</td>
<td>Atorvastatin 10, 20, 40, +Osteopenia</td>
<td>52 weeks</td>
<td>No effect of atorvastatin at relevant doses on BMD</td>
</tr>
<tr>
<td>Fracture risk</td>
<td></td>
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<tr>
<td>Chan et al. (2000)</td>
<td>CC</td>
<td>3675 Women</td>
<td>-</td>
<td>-</td>
<td>Decreased risk of non-pathological fractures in statin users</td>
</tr>
<tr>
<td>Reid et al. (2001)</td>
<td>RCT</td>
<td>9014 Women +HD</td>
<td>Pravastatin 40 mg</td>
<td>6 years</td>
<td>No support for the meaning full impact of statins on fracture risk</td>
</tr>
<tr>
<td>Park et al. (2002)</td>
<td>CSS</td>
<td>1375 Women</td>
<td>-</td>
<td>-</td>
<td>60% reduction in fracture risk with statin use</td>
</tr>
<tr>
<td>Ray et al. (2002)</td>
<td>RCS</td>
<td>-</td>
<td>12506 = 50 years</td>
<td>10 years</td>
<td>Observed protective effects of statin may be justified by unmeasured confounding factors</td>
</tr>
<tr>
<td>Bauer et al. (2004)</td>
<td>Post hoc analysis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Post hoc analysis of CV studies do not support reduction of fracture risk in statin users</td>
</tr>
<tr>
<td>Nguyen et al. (2007)</td>
<td>Bayesian approach</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Statin use reduces hip fracture</td>
</tr>
</tbody>
</table>

CC: Case control; RCT: Randomized clinical trial; IHD: Ischemic heart disease; CSS: Cross-sectional study; RCT: Retrospective cohort study; CV: Cardiovascular; CT: Clinical trial; BMP-2: Bone matrix protein-2; HOS: Human osteoblasts; OC: Osteocalcin; PS: Prospective study; HP: Hypercholesterolemic patients; BALP: Bone alkaline phosphatase; NTx: Cross-linked N-telopeptides of type I collagen; Dpyd: Des oxy pyridinoline; PMOW: Postmenopausal osteoporotic women; PMW: Postmenopausal women; PMHW: Postmenopausal hypercholesterolemic women; HM: Hypercholesterolemic men; CTX: C-telopeptide; IL-6:Interleukin-6; TNF-α: Tumor necrosis-α; NF-κB: Nuclear factor-κB; PCS: Prospective cohort study; RS: Retrospective study; BMD: Bone mineral density; HRT: Hormone replacement therapy; BP: Bisphosphonate.
Solomon et al. (2005a) could not find any relationship between lipid levels and bone mineral density. Omoigui (2005) stated that the trigger and the common causative factor and therapeutic target for atherosclerotic vascular disease and osteoporosis are cholesterol synthesis and isoprenoid dependent interleukin-6 (IL-6) mediated inflammation, while IL-6 promotes bone remodeling by activating osteoclastogenesis and osteoclasts (Manolagas and Jilka, 1995).

Aminobophonlates, as the potent anti-resorptive agents, affect cholesterol pathway and similar to statins influence mevalonate pathway (Jadhav and Jain, 2006). It has been known that prostaglandin (PG) synthesis has a substantial role in bone healing. As essential fatty acids influence PG synthesis, each affecting agent in this pathway may have an important impact such as non-steroidal anti-inflammatory drugs (NSAIDs), and statins as well (Salari and Abdollahi, 2009). Das (2001) considered the essential fatty acids (EFAs) and their metabolites as the second messengers of the actions of statins, while there is no conclusive data about the anabolic effects of EFAs on bone (Salari-Sharif et al., 2010; Salari et al., 2008b).

STATINS AND BONE METABOLISM

Statins and bone formation: Bone formation is the result of various functional factors such as growth factors [fibroblast growth factor-1 (FGF-1)] (Fromilne et al., 2004), transcription factors [core binding factor (cbfa 1)] (Komori, 2000) which have a substantial role in the development of osteoblasts (Manolagas, 2000). Among these, bone morphogenic proteins (BMPs) by enhancing osteoblast differentiation play critical role (Mathews, 2005) and can be considered as a target for treating osteoporosis (Kugimiyaa et al., 2005). Previously it was hypothesized that statin use may influence bone formation. The hypothesis was supported by in vivo and in vitro animal studies as well as experimental investigations on cell lines. Mundy et al. (1999) found that lovastatin and simvastatin intensify bone formation by increasing expression of BMP-2. Sugiyama et al. (2000) showed the impact of simvastatin but not pravastatin on bone morphogenic protein-2 (BMP-2). Ohnaka et al. (2001) found that pitavastatin not only enhances BMP-2 but also augments osteocalcin expression in human osteoblasts. The anabolic effects of simvastatin on bone as a result of advancement of osteoblastic differentiation led to the recommendation of it as a treatment of common metabolic bone diseases by Maeda et al. (2001) who observed increasing bone formation by statins via acting on osteoblasts.

The positive impact of statins on bone formation was also shown by studying on bone biomarkers. Chan et al. (2001) observed increased osteocalcin (OC) levels in non-osteoporotic subjects treated with simvastatin for 4 weeks in a prospective study, whereas no change was detected in the other bone markers such as bone-specific alkaline phosphatase activity (BALP), deoxypyridinoline (DPD) and cross-linked N-telopeptides of type I collagen (NTx). Bjarnason et al. (2001) could not show significant effect of fluvastatin on bone remodeling markers. In another study, more than 2 years treatment with a statin could not affect bone mineral density while could lower bone turnover markers in postmenopausal women (Rejmark et al., 2002). Tikiz et al. (2004) observed significant increase in OC and BALP as markers of bone formation after 6 months treatment with simvastatin in addition to significant decrease in serum level of TNF-α, although the negative correlation between TNF-α and anabolic bone markers was found in hypercholesterolemic postmenopausal women.

Mediating the effect of statins on bone by affecting vitamin D synthesis is the other theoretical action of statins on bone. In the study of Perez-Castrillon et al. (2007), atorvastatin increased vitamin D levels in 12 months; this effect was formerly reported by simvastatin and lovastatin in two small studies (Wilczek et al., 1989; Wilczek et al., 1994). In contrast, Aliai et al. (2007) could not find a significant relationship between total cholesterol and vitamin D levels.

Significant decrease in NTx was found in hypercholesterolemic patients on pitavastatin after 3 months by Majjina et al. (2007b) while no significant changes were found in BALP. They also observed similar results in men on atorvastatin (Majjina et al., 2007a).

Statins and bone resorption: Aminobophonlates and statins share their capability in inhibiting geranylgeranyl diposphate (GGPP) formation which results in suppressing osteoclast function and reducing their number (Horiiuch and Maeda, 2006). Also other investigations demonstrated the effect of statins via affecting osteoclasts (Grasser et al., 2003). Ahm et al. (2008) found that the process of nuclear factor-κB (NF-κB) activation by RANKL can be suppressed by simvastatin. In addition, simvastatin inhibited RANKL-induced NF-κB degradation, and phosphorylation. Furthermore it blocked osteoclastogenesis induced by RANKL or tumor cells.

Staal et al. (2003) assumed that the inhibitory effect of statins on osteoclast activity is related directly to their potency in inhibiting HMG-CoA reductase activity.

Statins and BMD: Regardless of the mechanism of action of statins on bone, the net effect of an anabolic agent on
bone can be increasing BMD. A 4.5 year cohort study showed lack of protective effect of statin use in early postmenopausal bone loss (Sirola et al., 2002). Lupattelli et al. (2004) compared BMD in two groups of patients in a longitudinal study. In contrast to control group, a significant increase was seen in the patients treated with simvastatin. De Leo et al. (2003) observed higher bone mineral density in postmenopausal women on statins and HRT comparing with HRT alone. In a 1-year longitudinal study, Montagnani et al. (2003) found significant changes in BMD of patients treated with simvastatin in comparison with control group as well as in BALP level. In a one year double-blind controlled trial no substantial change was found in BMD or bone markers in healthy postmenopausal women (Rejmark et al., 2004a). Nakashima et al. (2004) showed a significant smaller annual decrease of BMD in statin users comparing to non-users in diabetic patients. Some other cross-sectional surveys in postmenopausal women using statins for hypercholesterolemia support the association between statin use and higher BMD, however it is unknown whether the link is by chance (Solomon et al., 2005b). The modest additive effects of statins to bisphosphonates in recovering BMD in hypercholesterolemic postmenopausal women with confirmed osteoporosis-osteopenia was demonstrated by Tarriverdi et al. (2005). In a double-blind placebo-controlled trial in hypercholesterolemic postmenopausal women, Bone et al. (2007) found no significant differences between atorvastatin and placebo groups in BMD.

**Statins and fracture risk:** The inverse association between risk of fracture and statin use was uncovered many years ago in some observational studies (Mundy et al., 1999; Chan et al., 2000; Meier et al., 2000; Wang et al., 2000; Rejmark et al., 2004b). Chan et al. (2000) reported decreased risk of non-pathological fractures (odds ratio 0.48 [95% CI, 0.27-0.83]) in a population-based case-control study in statin users. While Reid et al. (2001) could not find support for the meaningful impact of statins on risk of fracture, Pasco et al. (2002) stated that the reduction of fracture risk with statin use is more than presumed from increases in BMD alone. Also there are some other researches which suggest that the observed protective effect of statins on fracture risk may be justified by unmeasured confounding factors (Ray et al., 2002). Results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials and post hoc analysis of cardiovascular trials could not add any further proof to this theory (Bauer et al., 2004; Reid et al., 2005; Scranton et al., 2005). Of these, Bauer et al. (2004) determined odds ratio of 0.87 (95%CI, 0.48-1.58) for hip fracture and odds ratio of 1.02 (95% CI, 0.83-1.26) for nonspine fracture, however Nguyen et al. (2007) supported the link between hip fracture and statin use according to Bayesian model.

**DISCUSSION**

While nearly most of *In vitro* studies disclosed promising effects of statins on bone, several in-vivo studies presented controversial results. In fact by suggesting the link between cardiovascular diseases and osteoporosis as two chronic senile diseases, there is no unique treatment modalities affecting both. Not only there are controversial results from several studies investigated the association between statin usage and bone formation or resorption but also the surveys on their impact on BMD or fracture risk is misleading. The probable reasons for these inconsistencies are as below:

- Unmeasured confounders such as hyperlipidemia may explain the discrepancies while to date no conclusive data is available about the relationship between hyperlipidemia and low bone mineral density
- In many studies, the patients status from functional, drug history, alcohol intake, and smoking points were not assessed. Omission of these variables may help more accurate findings
- Most of the studies are cross-sectional, while longitudinal studies would give us information about the changes over time and can be more applicable
- Genetic heritage is the other factor which has to be considered seriously
- Osteoclastic overcoming the inhibition of HMG-CoA reductase must be considered and evaluated
- Obvious differences in the sites of action of statins and aminoacidophosphonates is the other issue (Horiuchi and Maeda, 2006)
- The optimum concentration of statins in bone context is questionable, while their liver specificity and low oral bioavailability is a major problem and may be solved by special drug delivery systems which were investigated in an in-vivo study by Gutierrez et al. (2001). They compared transdermal administration of statins with oral administration and showed a larger effect on bone metabolism
- Lack of radiologic evaluation could not provide information about subclinical vertebral fractures
- Small number of patients and short duration of study can be modified as a matter
- Measuring bone specific biomarkers for bone formation and bone resorption is more sensitive in
exposing slight changes in bone metabolism, while case-control epidemiological studies consider BMD or calculate fracture risk as odds ratio. However the sensitivity and specificity of each bone marker has to be investigated

- In most of the retrospective studies, the subjects were on statin treatment, therefore this type of data analysis do not give us obvious conclusion about the usefulness of statins in osteoporosis
- Furthermore the effect of statin use on bone markers in osteoprotic patients with normal lipid levels has to be surveyed
- In addition, difference in body weight has been proposed to be another possible confounder (Ray et al., 2002; Van Staa et al., 2001)
- Randomization technique is of great significance especially in preventive medicine. Thus it has to be noticed more precisely in the future investigations
- In different studies different statins were used, while the effects of reductase inhibitors on bone may vary with each statin. Also their effective concentration is different. Although lovastatin and simvastatin contribute in in-vitro osteoblastic differentiation and BMP-2 induction in human cells at micromolar concentrations (Mundy et al., 1999), simvastatin showed its influence in osteoblastic differentiation in mouse calvarial cells at nanomolar concentrations (Maeda et al., 2001)
- Additionally it has to be noted that culture conditions and cell types may change in vitro findings
- Most of the hyperlipidemic patients are taking more cardiovascular drugs which may affect bone turnover

CONCLUSION

Considering conflicting results, although use of statins seem hopeful but at present they cannot be recommended for osteoporosis. This is because of publication bias, heterogeneity among observational studies, and lack of association in randomized trial. Prospective large placebo-controlled trials are needed. Further investigations warrants powerful results about the relationship between statin use and bone mineral density and the possible mechanism of action of statins on bone.

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