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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 κB 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

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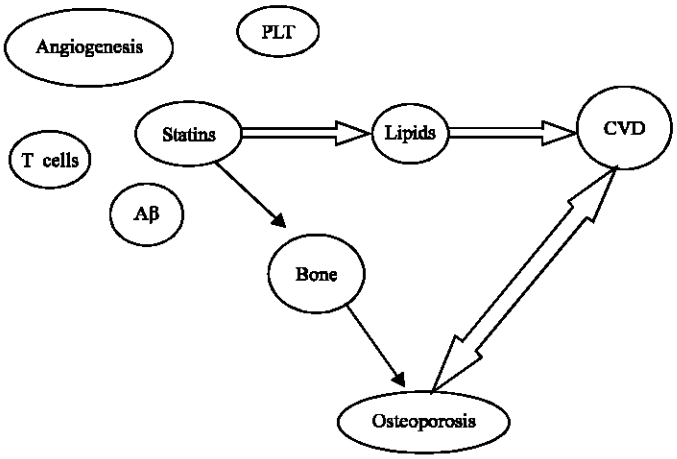

Fig. 1: The pleiotropic effects of statins. May the triangle be true? While the beneficial effects of statins on lipids, inflammation, angiogenesis, and platelet aggregation have been demonstrated; the benefits of statins on bone are under question. In this triangle (the relationship between statins, 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 lipoxygenase 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

Author (year)	Study	Target	Intervention	Duration	Outcome
Bone formation					
Mundy *et al.* (1999)	CT	Rodents	Lovastatin and simvastatin	-	Lovastatin and simvastatin increased BMP-2
Sugiyama *et al.* (2000)	*In vitro* study	HOS	Simvastatin	-	Simvastatin activated BMP-2 promoter
Ohnaka *et al.*(2001)	*In vitro* study	HOS	Pitavastatin	-	Pitavastatin augments BMP-2 and OC
Maeda *et al.* (2001)	*In vitro* study	MC3T3-E1 cells	Simvastatin	-	Simvastatinpromotes osteoblastic differentiation and mineralization
Chan *et al.* (2001)	PS	17 HP	Simvastatin 20 mg day^{-1}	4 weeks	Simvastatin increased OC level, but not BALP, NTx, Dpyd
Bjarnason *et al.* (2001)	RCT	68 PMOW	Fluvastatin 40 mg day^{-1}	12 weeks	Fluvastatin had no influence on bone markers
Rejnmark *et al.* (2002)	CSS	140 PMW	Statin	>2 years	Statin users had lower OC, BALP, CTX levels, no change in BMD
Tikiz *et al.* (2004)	PS	38 PMHW	Simvastatin 20 mg day^{-1}	3 months	Simvastatin increased OC, BALP, no significant change in CTX, IL-6 decreased TNF-α
Majima *et al.* (2007a)	CT	101 HP	Pitavastatin 1 mg day^{-1}	3 months	Pitavastatin decreased NTX
Majima *et al.* (2007b)	CT	22 HM	Atorvastatin 10 mg day^{-1}	3 months	Atorvastatin decreased NTX
Bone resorption					
Ahn *et al.* (2008)	*In vitro*	-	Simvastatin	-	Simvastatin suppressed osteoclastogenesis via NF- κB pathway
BMD					
Sirola *et al.* (2002)	PCS620 PMW	-	-		Lack of protective effects of statin use in early PMW
Lupattelli *et al.* (2004)	RCT	60 PMHW	Simvastatn40 mg day^{-1}	2 years	BMD increased significantly in the treatment group after 8 and 24 months
de Leo *et al.* (2003)	RS	174 PMW	Simvastatin/pravastatin 20 mg/d+HRT	1year	Higher BMD in the statin group
Montagnani *et al.* (2003)	CT	30 PMHW	Simvastatin 40 mg day^{-1}	1 year	BMD and BALP increased significantly in treatment group at 12 months
Rejnmark *et al.* (2004a)	RCT	82 PMOW	Simvastatin 40 mg day^{-1}	1 year	No significant changes were seen in bone markers or BMD, except for forearm BMD
Nakashima *et al.* (2004)	CT	122 Diabetic Patients	Simvastatin/ Pravastatin 10 mg day^{-1}	2years	Smaller annual decrease in radial BMD
Solomon *et al.* (2005a)	Cohort analysis	-	-	-	No significant relationship between cholesterol level and BMD
Tanriverdi *et al.* (2005)	RCT	120 PMHW +Osteopenia/ Osteoporosis	BP ±atorvastatin 20 mg day^{-1}	6months	Modest additive effect of statins to BP in improving BMD
Bone *et al.* (2007)	RCT	626 PMHW	Atorvastatin 10, 20, 40, +Osteopenia	52 weeks 80 mg day^{-1}	No effect of atorvastatin at relevant doses on BMD
Fracture risk					
Chan *et al.* 2000	CC	3675 Women	-	-	Decreased risk of non-pathological fractures in statin users
Reid *et al.* (2001)	RCT	9014 Women +IHD	Pravastatin 40 mg	6 years	No support for the meaning full impact of statins on fracture risk
Pasco *et al.* (2002)	CSS	1375 Women	-	-	60% reduction in fracture risk with statin use
Ray *et al.* (2002)	RCS	12506 = 50 years	-	10 years	Observed protective effects of statin may be justified by unmeasured confounding factors
Bauer *et al.* (2004)	Post hoc analysis	-	-	-	post hoc analysis of CV studies do not support reduction of fracture risk in statin users
Nguyen *et al.* (2007)	Byesian approach	-	-	-	Statin use reduces hip fracture

CC: Case control; RCT: Randomized clinical trial; IHD: Ischemic heart disease; CSS: Cross-sectional study; RCS: 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: Desoxypyridinoline; PMOW: Postmenopausal osteoporotic women; PMW: Postmenopausal women; PMHW: Postmenopausal hypercholesterolemic women; HM: Hypercholesterolemic men; CTX: C-telopeptide; IL-6:Interlenkine-6; TNF-α: Tnmor necrosis- α; NF-κB: Nuclear factor- κB; PCS: Prospective cohort study; RS: Retrospective study; BMD: Bone mineral density; HRT: Hormone replacement therapy; BP: Biphosphonate.

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).

Aminobyphosphonates, 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)] (Fromihue *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 (Kugimiya *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 osteoclacin 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 (Dpyd) 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 (Rejnmark *et al.*, 2002). Tikiz *et al.* (2004) observed significant increase in OC and BALP as markers of bone formation after 3 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 hypercholestrolemic 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, Aloia *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 Majima *et al.* (2007b) while no significant changes were found in BALP. They also observed similar results in men on atorvastatin (Majima *et al.*, 2007a).

Statins and bone resorption: Aminobyphosphonates and statins share their capability in inhibiting geranylgeranyl diphosphate (GGPP) formation which results in suppressing osteoclasts function and reducing their number (Horiuchi and Maeda, 2006). Also other investigations demonstrated the effect of statins via affecting osteoclasts (Grasser *et al.*, 2003). Ahn *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 (Rejnmark *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 biphosphonates in recovering BMD in hypercholestrolemic postmenopausal women with confirmed osteoporosis-osteopenia was demonstrated by Tanriverdi *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; Rejnmark *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 aminobiphosphonates 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 osteoporotic 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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