Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Original Article Open Access

From Lipids to Ligaments: The Surprising Link Between Statins and Bone Health

Rufaida Wasim[1], Sumaiya Azmi[2], Aamir Anwar[1]

ARTICLE INFO

Article history:
Received 26 October 2025
Received in revised form
4 December 2025
Accepted 5 December 2025
Available online 7 December 2025

Keywords:
Statins,
HMG-CoA reductase inhibitors,
osteoporosis,
fracture prevention,
bone health

ABSTRACT

The main purposes of statins, commonly referred to as HMG-CoA reductase inhibitors, are to decrease cholesterol and lower the risk of cardiovascular disease (CVD). According to recent studies, statins can additionally enhance bone health by influencing the processes involved in bone remodeling.

Objective: The purpose of the article is to assess the preclinical and clinical data currently available on how statin medication affects bone mineral density (BMD), osteoporosis risk, and fracture reduction.

To evaluate the impact of statins on bone metabolism, a thorough assessment of preclinical data, observational studies, and randomized controlled trials (RCTs) was carried out. To explain discrepancies in results, variables including patient characteristics, statin class, dosage, and length of therapy were considered.

According to preclinical research, statins promote bone formation by increasing osteoblast development and preventing osteoclast-mediated bone resorption. A number of observational studies and meta-analyses show that statin use is positively correlated with both higher BMD and a lower risk of osteoporotic fractures. Randomized trials, however, provide conflicting results; many do not demonstrate statistically significant advantages, most likely as a result of differences in research design, population size, and treatment settings.

Existing clinical data is unclear, despite preliminary findings suggesting a positive function of statins to safeguard bone health. Large-scale, carefully planned RCTs are necessary to elucidate their safety and effectiveness in conditions pertaining to the bones. Statins may be a promising adjuvant treatment for osteoporosis, particularly for those who already have CVD.

INTRODUCTION

Originally developed from mold fungi, statins are a class of lipid-lowering drugs widely prescribed for the management of dyslipidemia, a major risk factor for atherosclerosis and cardiovascular diseases such as coronary artery disease and peripheral vascular disease [1–3].

These agents act through competitive and reversible inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis. Inhibition of this enzyme reduces intracellular cholesterol levels and upregulates low-density lipoprotein (LDL) receptor expression, thereby enhancing the clearance of circulating LDL cholesterol [4,5].

Correspondence: rufaidaw@iul.ac.in (Rufaida Wasim)
[1]Department of Pharmacology, Faculty of Pharmacy, Integral University, Lucknow, India
[2]Departmentof Periodontics, Career Post Graduate Institute of Dental Sciences and Hospital Lucknow, India

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

]. In addition to lowering LDL, statins modestly increase high-density lipoprotein (HDL) levels and reduce triglycerides (TG), further contributing to their cardiovascular benefits [6]. Beyond lipid regulation, statins exhibit several pleiotropic effects, including improvement of endothelial function through enhanced nitric oxide (NO) bioavailability, stabilization of atherosclerotic plaques, reduction of oxidative stress, and suppression of inflammatory mediators [7–13]. These properties have expanded scientific interest in their potential actions beyond the cardiovascular system. Statins used in clinical practice include semi-synthetic agents such as simvastatin, naturally occurring compounds such as lovastatin, and fully synthetic drugs such as rosuvastatin [14,15]. Differences in molecular structure influence their lipophilicity, tissue distribution, and biological behavior [14,16].

More recently, increasing attention has been directed toward the potential role of statins in bone metabolism. Experimental studies suggest that statins may influence osteoblast differentiation, osteoclast activity, angiogenesis, and bone remodeling through several cellular signaling pathways. One of the most widely investigated mechanisms is stimulation of bone morphogenetic protein-2 (BMP-2), a key regulator of osteogenesis, although the consistency of this effect in human bone cells remains controversial. Statins have also been shown to modulate vascular endothelial growth factor (VEGF), potentially enhancing angiogenesis, a process closely linked to bone formation and fracture healing.

Although statins are primarily prescribed for lipid-related cardiovascular diseases, their potential actions on bone metabolism, osteoporosis, fracture risk, angiogenesis, and vitamin D regulation have generated significant research interest.

Moreover, statins have also been explored for effects on muscle repair, liver regeneration, and anti-inflammatory or anti-fibrotic pathways, indicating their broad biological activity [19,20]. However, clinical findings regarding their skeletal and vitamin D-related benefits remain inconsistent, necessitating a balanced and critical synthesis of available evidence.

This review therefore aims to comprehensively evaluate the current experimental and clinical evidence regarding the effects of statins on bone health and vitamin D metabolism, with particular emphasis on mechanistic pathways, human clinical outcomes, and areas of ongoing controversy.

The molecular basis of statins: Impact on bone metabolism

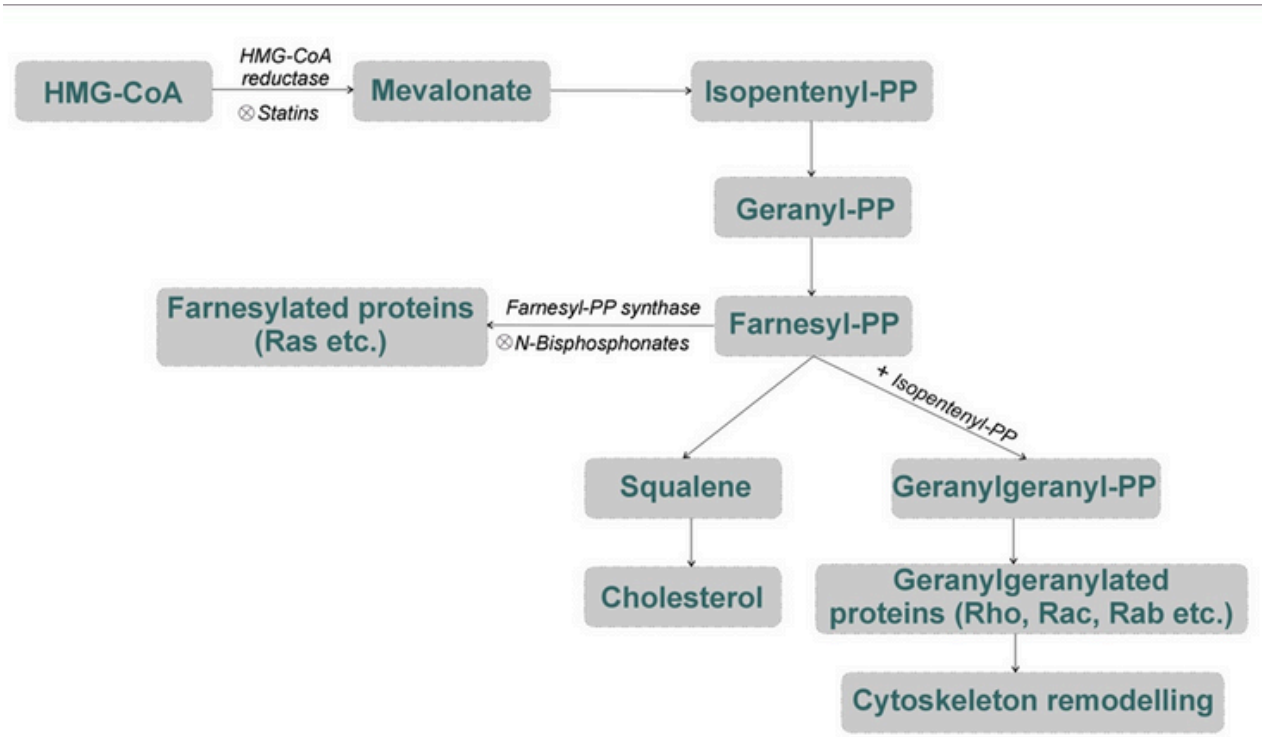
Statins have a variety of pleiotropic effects, such as vasodilatory, antioxidant, antithrombotic, and bone-anabolic activity, in addition to their ability to decrease cholesterol [21]. Over the last ten years, their capacity to stimulate bone production has garnered a lot of attention, especially for potential benefits in diseases like osteoporosis. An increasing amount of data indicates that three main mechanisms—stimulating osteoblast differentiation, preventing osteoblast death, and suppressing osteoclast development—are responsible for the bone-anabolic actions of statins. The whole molecular underpinnings of these impacts are still being investigated.

Osteogenesis Induced by Statins

The rate-limiting enzyme in the pathway leading to the generation of cholesterol, HMG-CoA reductase, is inhibited by statins. Mevalonate and the subsequent isoprenoid intermediates, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), are reduced as an outcome of this process [22] (Figure 1).

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Figure 1: Pathway of statin in bone health



Studies show that both GGPP and FPP contribute to osteoblast activity. Statins are known to boost osteoblast differentiation by lowering FPP and GGPP concentrations [24, 25], whereas the inclusion of exogenous FPP has been demonstrated to have a deleterious effect on osteoblast differentiation [23]. Furthermore, GGPP and GGPP synthase levels decreased during the mineralization process, according to research employing the MC3T3-E1 mouse osteoblastic cell line [26]. These results lend credence to the notion that increased osteogenesis is a result of decreased FPP and GGPP concentrations brought on by statin therapy [27].

The prenylation of other guanosine triphosphate (GTP)-binding proteins, including Rho, which are implicated in several signaling processes, depends on FPP and GGPP as well [23]. Consequently, statins may prevent the prenylation of FPP and GGPP by reducing their levels, changing signal transduction pathways that are important for bone formation.

. For example, it has been demonstrated that lipophilic statins, including pitavastatin and simvastatin, increase the expression of osteocalcin and bone morphogenetic protein-2 (BMP-2) through suppression of the Rho/Rho-kinase signaling pathway. However, this effect is not universal to all statins, as hydrophilic statins such as pravastatin fail to effectively inhibit Rho-kinase due to limited cellular membrane permeability and reduced intracellular availability. Consequently, Rho-kinase inhibition and the downstream osteogenic signaling appear to be statin class–specific rather than a class-wide pharmacological property [28]. Moreover, increased levels of vascular endothelial growth factor (VEGF) and phosphatidylinositol 3 kinase (PI3-K), each of which promote osteoblast function and bone anabolism, have been connected to the suppression of protein prenylation [29].

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Inhibition of Osteoclastogenesis Mediated by Statin

One of the primary regulators of osteoclast development and activity is the osteoprotegerin (OPG)/receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK signaling system [33]. Statins may have anti-resorptive effects by altering this route, according to evidence. Mevastatin in particular, have been shown in vitro to limit osteoclastogenesis by raising OPG mRNA levels and decreasing RANKL mRNA production in cultured mouse bone cells [34]. Statins may have an effect on osteoclast formation via processes associated with estrogen alongside their effects on the OPG/RANKL/RANK axis. Osteoclast production is suppressed by estrogen and its receptor (ER), especially in postmenopausal osteoporosis. It is well known that estrogen inhibits osteoclast development by downregulating RANKL expression [35]. Simvastatin was shown to promote bone regeneration by increasing the expression of estrogen receptor-alpha (ERα) in the bone tissue of rats that have had their ovaries removed [36].

Simvastatin treatment of murine bone marrow stromal cells in vitro has also been shown to boost ER expression [37]. Furthermore, by interfering with cytoskeletal architecture, statins may impair osteoclast function. An ex vivo investigation showed that compactin disrupted the actin ring and prevented preosteoclast union, hence impairing osteoclast cytoskeletal integrity. Restricted supply of prenylation substrates such as GGPP and FPP, which are essential for the correct operation of prenylated proteins associated with osteoclast maturation, was cited as the cause of this consequence [38].

Interactions between vitamin D and statin

The combination of vitamin D with statins may have metabolic and clinical implications, as it is essential for preserving bone mineral density (BMD) and controlling calcium homeostasis. Two clinical trials' results have demonstrated that rosuvastatin treatment significantly raises the levels of 25-hydroxyvitamin D in the blood [39, 40]. Improved BMD in certain statin-treated patients may be explained by this increase in vitamin D. For example, fluvastatin [40] and simvastatin [41] did not raise 25-hydroxyvitamin D levels, indicating that not all statins have this impact.

It is unclear exactly how statins affect the metabolism of vitamin D, although it has been proposed that they may both use the cytochrome P-450 (CYP) enzyme system as a metabolic pathway [20]. In addition this system also contributes to the stimulation and breakdown of vitamin D. Vitamin D is known to regulate cytochrome P450 enzymes (notably CYP3A4) via the vitamin D receptor in intestinal and hepatic tissues, and it has been hypothesized that vitamin D status could modify statin metabolism. However, randomized clinical evidence does not support the assertion that vitamin D supplementation prevents statin-associated muscle symptoms (SAMS) or reduces statin discontinuation. In a large randomized, placebo-controlled substudy of the VITAL trial, new statin users assigned to vitamin D or placebo reported SAMS at identical rates (31% vs 31%) and discontinued statins at identical rates (13% vs 13%). A separate randomized controlled trial of patients with prior SAMS also found no benefit of vitamin D supplementation on objective muscle function or patient-reported SAMS

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Thus, while vitamin D can modulate CYP expression mechanistically, current RCT data indicate no clinically meaningful protection from statin-induced myopathy attributable to routine vitamin D supplementation; the relationship between vitamin D status and SAMS therefore remains uncertain and likely multifactorial [42]. Elevated vitamin D levels may influence statin metabolism indirectly through modulation of cytochrome P450 (CYP) enzyme expression, particularly CYP3A4; however, direct human pharmacokinetic evidence demonstrating enhanced statin clearance due to vitamin D supplementation remains limited. A clinical pharmacokinetic study by Schwartz et al. demonstrated that vitamin D supplementation significantly reduced atorvastatin plasma concentrations while enhancing its lipid-lowering efficacy, suggesting a pharmacokinetic–pharmacodynamic dissociation rather than simple accelerated clearance. Therefore, while vitamin D may modify statin disposition in humans, its effect on systemic exposure and toxicity requires further controlled pharmacokinetic validation [43]. Atorvastatin's effective CYP-mediated metabolites may also be a factor in its therapeutic advantages. The lipid-lowering properties of atorvastatin, especially in lowering LDL cholesterol levels, were enhanced by co-supplementing with 800 IU of vitamin D daily, according to one clinical research [44].

In vivo animal studies

According to research, statins like lovastatin whether injected to the mice calvarial bone or taken orally might increase the generation of BMP-2 and encourage the development of new bone (Mundy et al., 21).

Thus, while vitamin D can modulate CYP expression mechanistically, current RCT data indicate no clinically meaningful protection from statin-induced myopathy attributable to routine vitamin D supplementation; the relationship between vitamin D status and SAMS therefore remains uncertain and likely multifactorial [42]. Elevated vitamin D levels may influence statin metabolism indirectly through modulation of cytochrome P450 (CYP) enzyme expression, particularly CYP3A4; however, direct human pharmacokinetic evidence demonstrating enhanced statin clearance due to vitamin D supplementation remains limited. A clinical pharmacokinetic study by Schwartz et al. demonstrated that vitamin D supplementation significantly reduced atorvastatin plasma concentrations while enhancing its lipid-lowering efficacy, suggesting a pharmacokinetic–pharmacodynamic dissociation rather than simple accelerated clearance. Therefore, while vitamin D may modify statin disposition in humans, its effect on systemic exposure and toxicity requires further controlled pharmacokinetic validation [43]. Atorvastatin's effective CYP-mediated metabolites may also be a factor in its therapeutic advantages. The lipid-lowering properties of atorvastatin, especially in lowering LDL cholesterol levels, were enhanced by co-supplementing with 800 IU of vitamin D daily, according to one clinical research [44].

According to research, statins like lovastatin whether injected to the mice calvarial bone or taken orally might increase the generation of BMP-2 and encourage the development of new bone (Mundy et al., 21).

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Oral statins have been shown to have a beneficial effect on bone growth in a number of animal models. For instance, simvastatin enhanced bone volume and osteoblast numbers in the femur, and vertebrae of ovariectomized (OVX) rats [46], and it did the same for mice following early recovery from fractures [45]. In OVX rats, atorvastatin was also shown to improve femur mechanical strength and BMD [47], and in an animal model of periodontitis, it restored the loss of alveolar bone [48]. Furthermore, in fructose-fed OVX rats, fluvastatin prevented BMD loss, compared to pravastatin [49]. By reducing oxidative stress (OS) and reviving NO production, simvastatin seems to prevent osteoporosis in OVX in elderly rat models [50]. Simvastatin also reduced bone resorption associated with inflammation in periodontitis, perhaps because of its anti-inflammatory and antioxidant qualities [51], and it assisted rats with Freund's adjuvant-induced arthritis regain their BMD [52].

Not all models produced favorable results. Male rats' age-related decline in bone mass was not prevented by cerivastatin [53], and ovariectomy (OVX) rats' alveolar bone density was not appreciably changed by simvastatin when contrasted with controls [54]. Simvastatin taken orally also had no impact on BMD or spinal fusion rates in a rabbit model of posterolateral lumbar intertransverse process fusion [55]. Additionally, statins have been demonstrated to affect biochemical indicators of bone turnover. Simvastatin stopped the rise in blood pyridinoline in arthritis models [56], while atorvastatin decreased the amount of carboxy-terminal cross-linking telopeptide of type 1 collagen (CTX-1), a crucial indicator of bone resorption, in male rats [57].

Recent studies have looked into taking statins along with other medications. Simvastatin, while antagonistic to estradiol in uterine tissue, worked in concert with it to support bone health, according to one study, which also indicated that six weeks of therapy increased lumbar vertebral BMD and strength [58]. Lovastatin and delta-tocotrienol, a substance that promotes the breakdown of HMG-CoA reductase, together raised osteocalcin levels and decreased CTX levels in OVX mice, indicating improved bone production and decreased resorption [59]. But in rabbits, atorvastatin did not stop the decrease of cortical bone strength brought on by corticosteroids [60]. Conversely, simvastatin plus exercise were more effective than statin treatment alone at increasing femoral bone strength and bone mineral density. All of these results point to the potential benefits of statins for improving bone characteristics, such as volume, strength, and mineral density, while also lowering bone resorption indicators in animal models of osteoporosis and fracture.

Clinical studies

According to a number of observational cohort studies and meta-analyses, statin users typically have greater BMDs and a lower risk of fractures than non-users. However, there have occasionally been conflicting findings from randomized clinical trials (RCTs), particularly those carried out in Asian communities [61].

Using Taiwan's National Health Insurance Research Database, a sizable retrospective population-based cohort study tracked 45,343 statin users between the ages of 51 and 91 who had started taking the medication on January 1, 2002, until December 31, 2013. 115,595 statin non-users served as controls in the study.

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

The relationship between statin use and osteoporosis risk was evaluated using multivariable Cox proportional hazards models. Statin use was linked to a 49% lower risk of incident osteoporosis (adjusted hazard ratio [HR] 0.52; 95% CI 0.50–0.54), according to Lin et al. Additionally, a dose-dependent relationship was found, with decreasing adjusted HRs for new-onset osteoporosis going hand in hand with increasing cumulative defined daily doses (cDDDs): 0.84 (95% CI 0.78–0.90) for 28–90 cDDDs, 0.56 (95% CI 0.52–0.60) for 91–365 cDDDs, and 0.23 (95% CI 0.21–0.25) for more than 365 cDDDs. Moderate-potency statins like simvastatin and high-potency statins like atorvastatin and rosuvastatin seemed to provide a protective advantage against osteoporosis [61].

Thabit et al. found that statin use was associated with a lower incidence of osteoporosis in both men and women in a different population-based cohort analysis. Both the cumulative dosage and the statin's efficacy were necessary for the beneficial effect. Serum 25-hydroxyvitamin D (25OHD) levels did not significantly differ among statin users and controls (P = 0.47), according to this study, which involved 115 patients (57 in each group). Nonetheless, lumbar spine and femoral neck BMD gains were statistically significant (P = 0.05 and 0.03, respectively). After almost a year of use, both atorvastatin and simvastatin increased BMD, but they did not seem to have an impact on 25-hydroxyvitamin D (25OHD) levels [62].

Statin use with osteoporotic fractures was evaluated in a systematic review and meta-analysis that followed PRISMA guidelines. Statins generally decreased the risk of osteoporotic fractures, according to this analysis, which included roughly 12 studies (odds ratio [OR]: 0.82; 95% CI: 0.72–0.94). Case-control studies (OR: 0.92; 95% CI: 0.76–1.11), randomized controlled trials (OR: 1.67; 95% CI: 0.86–3.26), and cohort studies (OR: 0.70; 95% CI: 0.59–0.83) were the study designs used to analyze the connection. Statins such as atorvastatin (OR: 0.92; 95% CI: 0.76–1.10), rosuvastatin (OR: 0.85; 95% CI: 0.66–1.08), fluvastatin (OR: 0.88; 95% CI: 0.75–1.03), pravastatin (OR: 0.96; 95% CI: 0.87–1.07), and simvastatin (OR: 0.98; 95% CI: 0.92–1.03) did not significantly increase fracture risk. Interestingly, statin use did not significantly affect hip fractures (OR: 0.78; 95% CI: 0.60–1.01) but was linked to a lower incidence of vertebral fractures (OR: 0.74; 95% CI: 0.65–0.86). Moreover, statin use did not significantly correlate with osteoporotic fractures in the 30–364 cDDD (OR: 0.84; 95% CI: 0.65–1.08) or ≥365 cDDD (OR: 0.50; 95% CI: 0.25–1) categories. [63].

Randomized controlled trials have had conflicting results, despite observational evidence that statins protect bone health. The effects of statins on adult BMD and fracture risk were assessed in a meta-analysis that included seven qualified RCTs with a total of 27,900 individuals. Five studies examined changes in BMD, and two evaluated fracture outcomes. Statin use was linked to a slight but statistically significant increase in BMD of 0.03 g/cm^2 (95% CI: 0.006–0.053; I^2 = 99.2%; P < 0.001) when contrasted with controls, according to the meta-analysis. However, a pooled hazard ratio (HR) of 1.00 (95% CI: 0.87–1.15; I2 = 0; P = 0.396) showed no significant correlation between statin use and fracture risk. The robustness of these findings was validated by sensitivity analysis [64].

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Contradictory Evidence on Statin-Induced BMP-2 and VEGF Expression

1.

While several experimental studies suggest that statins stimulate osteogenesis through upregulation of BMP-2 and VEGF, a number of well-controlled investigations in human osteoblast models have reported no significant effect, highlighting important biological and methodological discrepancies. Maeda et al. demonstrated that simvastatin failed to induce BMP-2 expression in primary human osteoblast cultures, despite positive effects observed in murine models [65]. Similarly, Kupcsik et al. reported that neither simvastatin nor atorvastatin significantly enhanced BMP-2 or VEGF secretion in human mesenchymal stem cell–derived osteoblasts under physiological conditions [66].

Furthermore, clinical translational studies by Montecucco et al. showed that circulating VEGF levels remained unchanged in patients receiving statin therapy, questioning the systemic angiogenic role of statins in humans [67]. A randomized in vitro–clinical correlation study by Tresguerres et al. demonstrated that pravastatin did not significantly alter osteogenic gene expression, including BMP-2, in human bone-derived cells [68]. In addition, Moshiri et al. found that rosuvastatin failed to induce VEGF-mediated angiogenesis in human osteoblast-like cells under normoxic conditions [69]. Another human cell-based study by Ruiz-Gaspa et al. confirmed that statin-induced osteogenic signaling observed in rodents is not consistently reproducible in human osteoblasts [70].

These inconsistencies may be explained by species-specific differences, variations in statin lipophilicity, drug concentration, duration of exposure, and dependence on local versus systemic delivery.

Notably, many positive BMP-2 and VEGF findings are derived from high-dose local statin delivery in animal models, conditions that are not achievable with routine oral statin therapy in humans. Therefore, although statins exhibit clear osteoanabolic effects in experimental systems, their direct ability to stimulate BMP-2 and VEGF in human osteoblasts remains controversial.

Conflicting Clinical Evidence on the Effect of Statins on Vitamin D Levels

Despite several small interventional studies reporting an increase in serum 25-hydroxyvitamin D (25OHD) levels following rosuvastatin therapy, larger randomized and population-based studies have failed to consistently reproduce this effect. Notably, the large JUPITER trial, which evaluated rosuvastatin in more than 17,000 participants, demonstrated no significant change in circulating 25OHD levels, challenging earlier smaller reports. Similar neutral findings have been observed in multiple large observational cohorts and randomized studies involving atorvastatin, simvastatin, and pravastatin. This discrepancy between small controlled trials and large-scale clinical studies suggests that the apparent vitamin D elevation may be influenced by baseline vitamin D deficiency, ethnic variation, seasonal sun exposure, statin lipophilicity, treatment duration, and assay variability. Therefore, while statin-induced elevation of vitamin D remains biologically plausible, current evidence does not support a uniform or class-wide effect of statins on 25OHD levels, necessitating cautious interpretation [71-80] .

Conclusion:

Statins, widely prescribed for the management of dyslipidemia and prevention of cardiovascular diseases, have gained considerable attention for their potential pleiotropic effects on bone metabolism

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Preclinical evidence strongly supports the osteoanabolic and anti-resorptive properties of statins through multiple molecular mechanisms, including stimulation of osteoblast differentiation, inhibition of osteoblast apoptosis via the TGF-β/Smad3 pathway, suppression of osteoclastogenesis through modulation of the OPG/RANKL/RANK axis, enhancement of estrogen receptor signaling, and interference with cytoskeletal organization in osteoclasts. These mechanisms collectively contribute to increased bone formation and reduced bone resorption in experimental models.

Animal studies consistently demonstrate that statins improve bone mineral density, enhance bone strength, increase osteoblast numbers, stimulate BMP-2 and VEGF expression, and reduce biochemical markers of bone resorption. However, not all experimental models show favorable outcomes, emphasizing that the skeletal effects of statins may vary depending on statin type, dosage, route of administration, disease model, and duration of therapy.

In contrast, clinical evidence remains inconsistent. While several observational studies and large population-based cohorts suggest that statin use is associated with higher bone mineral density and a reduced risk of osteoporosis and vertebral fractures, randomized controlled trials and meta-analyses have generally failed to demonstrate a significant reduction in fracture risk. These discrepancies are likely attributable to heterogeneity in study design, population characteristics, statin potency, treatment duration, baseline vitamin D status, and outcome measures.

The interaction between statins and vitamin D metabolism remains particularly controversial. Although small interventional studies—especially with rosuvastatin—have reported increases in serum 25-hydroxyvitamin D levels, larger randomized trials, population cohorts, and systematic reviews do not support a consistent or class-wide effect of statins on vitamin D status. Furthermore, high-quality randomized data indicate that vitamin D supplementation does not prevent statin-associated muscle symptoms, underscoring the complexity of statin–vitamin D interactions.

Importantly, translational human studies have challenged the reproducibility of statin-induced BMP-2 and VEGF expression observed in animal models, suggesting that the osteogenic actions of statins may be species-specific or dependent on supraphysiological local drug concentrations not achievable with routine oral therapy.

In summary, while statins demonstrate strong bone-protective potential at the molecular and experimental levels, current clinical evidence does not yet justify their routine use solely for the prevention or treatment of osteoporosis. Their skeletal benefits appear to be modest, context-dependent, and secondary to their cardiovascular indications. Well-designed, large-scale, long-term randomized controlled trials with standardized bone endpoints are essential to definitively establish the therapeutic role, optimal statin type, dosage, and target population for statin-based bone protection.

Future Perspective:

Future studies should focus on large, well-designed randomized controlled trials with bone-specific endpoints to clearly define the role of statins in osteoporosis prevention and treatment. Stratification by age, sex, menopausal status, vitamin D levels, and metabolic profile will help identify patient populations most likely to benefit.

Wasim et al. Current Trends in Medicine and Clinical Research
Curr. Trends Med. Clin. Res. 2025; Vol.1 Sep-Nov 2025-: 18-30

Translational human studies are needed to confirm whether key osteogenic pathways demonstrated in experimental models operate at clinically relevant statin doses. The complex interaction between statins and vitamin D metabolism also requires further pharmacokinetic, pharmacogenomic, and mechanistic evaluation.

Innovative strategies such as localized statin delivery, nanoparticle-based systems, and combination therapy with established anti-osteoporotic agents may enhance bone-specific benefits while minimizing systemic risks. Overall, while statins show promise as bone-modulating agents, rigorous clinical validation is essential before they can be integrated into routine osteoporosis management.

List of abbreviations
HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A
BMD: Bone mineral density
CVD: Cardiovascular disease
LDL: Low density lipoprotein
HDL: High Density Lipoprotein
TG: Triglycerides
NO: Nitric oxide
CYP: Cytochrome
OATP-2: organic anion transporting polypeptide-2
FPP: Farnesyl pyrophosphate
GGPP: Geranylgeranyl pyrophosphate
GTP: Guanosine triphosphate
BMP-2: Bone morphogenetic protein-2
VEGF: Vascular endothelial growth factor
PI3-K: Phosphatidylinositol 3 kinase
TGF-β: Transforming growth factor-beta
OPG: Osteoprotegerin
RANKL: Receptor activator of nuclear factor kappa-B ligand
RANK: Receptor activator of nuclear factor kappa-B
ERα: Estrogen receptor-alpha
OVX: Ovariectomy
CTX-1: Carboxy-terminal cross-linking telopeptide of type 1 collagen
cDDDs: Cumulative defined daily doses
25OHD: 25-hydroxyvitamin D
Wnt/β-catenin: Wingless/Integrated pathway that involves beta-catenin

Acknowledgement:
Authors express their gratitude toward Hon. Chancellor, Prof. Syed Waseem Akhtar, Integral University and Career Post Graduate Institute of Dental.

Conflicts of Interest
TNo conflict of interest to declare

Financial Support
This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. It was conducted as part of academic research under institutional support from RDT Hospital, Andhra Pradesh.

Data Availability
None

Protection of humans and animals.
The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval
None

Declaration on the use of artificial intelligence.
The authors declare that no generative artificial intelligence was used in the writing of this manuscript

Authors contribution:
R.W. drafted the manuscript, S.A. formal analysis, A.A. investigation

REFERENCES

- Wasim R, Mahmood T, Siddiqui MH, Singh A, Ahsan F. Cardioprotective potential of Rosuvastatin against isoproterenol induced cardiac dysfunction and hypertrophy in the experimental model of rodents. Intelligent Pharmacy. 2024 Oct 1;2(5):651-61.
- Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation. 2000 Jan 18;101(2):207-13.
- Wasim R, Mahmood T, Shamim A, Ahsan F, Singh A. Metaphorical investigation of aqueous distillate of Cichorium intybus, Foeniculum vulgare and Solanum nigrum along with atorvastatin and orlistat in experimental rodent models of dyslipidaemia and obesity. Intelligent Pharmacy. 2024 Feb 1;2(1):1-1.
- Wasim R, Mahmood T, Siddiqui MH, Wani TA, Zargar S, Singh A, Mohammed S, Ahsan F, Wahajuddin M. Entanglement of AGE-RAGE axis in cardiac pathosis. bioRxiv. 2023 Jul 25:2023-07.
- Wasim R, Ansari TM, Ahsan F, Siddiqui MH, Singh A, Shariq M, Parveen S. Pleiotropic benefits of statins in cardiovascular diseases. Drug Research. 2022 Nov;72(09):477-86.
- Wasim R, Ansari TM, Ahsan F, Siddiqui MH, Singh A, Ahmad A. Exploring the effect of Rosuvastatin on AGE-RAGE pathway concerning its cardioprotective potential. Annals of Phytomedicine.2024 June 3(1):1-8
- Mohammadkhani N, Gharbi S, Rajani HF, Farzaneh A, Mahjoob G, Hoseinsalari A, Korsching E. Statins: Complex outcomes but increasingly helpful treatment options for patients. European Journal of Pharmacology. 2019 Nov 15;863:172704.
- Lahera V, Goicoechea M, Garcia de Vinuesa S, Miana M, Heras ND, Cachofeiro V, Luno J. Endothelial dysfunction, oxidative stress and inflammation in atherosclerosis: beneficial effects of statins. Current medicinal chemistry. 2007 Jan 1;14(2):243-8.
- Vaughan CJ, Gotto AM, Basson CT. The evolving role of statins in the management of atherosclerosis. Journal of the American College of Cardiology. 2000 Jan;35(1):1-0.
- Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundamental & clinical pharmacology. 2005 Feb;19(1):117-25.
- Bellosta S, Fed N, Bernini F, Paoletti R, Corsini A. Non-lipid-related effects of statins. Annals of medicine. 2000 Jan 1;32(3):164-76.
- Athyros VG, Kakafika AI, Tziomalos K, Karagiannis A, Mikhailidis DP. Pleiotropic effects of statins-clinical evidence. Current pharmaceutical design. 2009 Feb 1;15(5):479-89.
- Rossini E, Biscetti F, Rando MM, Nardella E, Cecchini AL, Nicolazzi MA, Covino M, Gasbarrini A, Massetti M, Flex A. Statins in high cardiovascular risk patients: do comorbidities and characteristics matter?. International Journal of Molecular Sciences. 2022 Aug 18;23(16):9326.
- Sirtori CR. The pharmacology of statins. Pharmacological research. 2014 Oct 1;88:3-11.
- Koch CG. Statin therapy. Current Pharmaceutical Design. 2012 18:6284–6290.
- Climent Biescas E, Benaiges Foix D, Pedro-Botet JC. Hydrophilic or lipophilic statins?. Front Cardiovasc Med. 2021 May 20; 8: 687585. 2021.
- Waters DD. What the statin trials have taught us. The American journal of cardiology. 2006 Jul 1;98(1):129-34.
- McKenney JM. Pharmacologic characteristics of statins. Clinical Cardiology: An International Indexed and Peer‐Reviewed Journal for Advances in the Treatment of Cardiovascular Disease. 2003 Apr;26(S3):32-8.
- Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacology & therapeutics. 1999 Dec 1;84(3):413-28.
- Dagli-Hernandez C, Zhou Y, Lauschke VM, Genvigir FD, Hirata TD, Hirata MH, Hirata RD. Pharmacogenomics of statins: lipid response and other outcomes in Brazilian cohorts. Pharmacological Reports. 2022 Feb;74(1):47-66.
- Wasim R, Ansari TM, Ahsan F, Siddiqui MH, Singh A, Shariq M, Parveen S. Pleiotropic benefits of statins in cardiovascular diseases. Drug Research. 2022 Nov;72(09):477-86.
- Baneu P, Prelipcean A, Buda VO, Jianu N, Tudor A, Andor M, Merlan C, Romanescu M, Suciu M, Buda S, Mateoc T. Under-Prescription of Drugs in the Elderly Population of Western Romania: An Analysis Based on STOPP/START Version 2 Criteria. Journal of Clinical Medicine. 2024 Oct 8;13(19):5970.
- Weivodaand MM, Hohl RJ. Effects of farnesyl pyrophosphate accumulation on calvarial osteoblast differentiation. Endocrinology 2011;152:3113–22.
- Weivodaand MM, Hohl RJ. The effects of direct inhibition of geranylgeranyl pyrophosphate synthase on osteoblast differentiation. J Cell Biochem 2011;112:1506–13.
- Yoshida T, Asanuma M, Grossmann L, Fuse M, Shibata T, Yonekawa T, et al. Geranylgeranyl-pyrophosphate (GGPP) synthase is down-regulated during differentiation of osteoblastic cell line MC3T3-E1. FEBS Lett 2006;580:5203–7.
- Ruan F, Zheng Q, Wang J. Mechanisms of bone anabolism regulated by statins. Biosci Rep 2012;32:511–9.
- Ohnaka K, Shimoda S, Nawata H, Shimokawa H, Kaibuchi K, Iwamoto Y, et al. Pitavastatin enhanced BMP-2 and osteocalcin expression by inhibition of Rho-associated kinase in human osteoblasts. Biochem Biophys Res Commun 2001;287:337–42.
- Luisetto G, CamozziV. Statins,fracture risk, and bone remodeling.J Endocrinol Invest 2009;32:32–7.
- Heldin CH, Miyazono K, ten Dijke P. TGF-beta signaling from cell membrane to nucleus through SMAD proteins. Nature 1997;390:465–71.
- Borton AJ, Frederick JP, Datto MB, Wang XF, Weinstein RS. The loss of Smad3 results in a lower rate of bone formation and osteopenia through dysregulation of osteoblast differentiation and apoptosis. J Bone Miner Res 2001;16:1754–64.

- Kaji H, Naito J, Inoue Y, Sowa H, Sugimoto T, Chihara K. Statin suppresses apoptosis in osteoblastic cells: role oftransforming growth factor-beta Smad3 pathway. Horm Metab Res 2008;40:746–51.
- Khosla S. Minireview: the OPG/RANKL/RANK system. Endocrinology 2001;142:5050–5.
- Kaji H, Kanatani M, Sugimoto T, Chihara K. Statins modulate the levels of osteoprotegerin/receptor activator of NFkappaB ligand mRNAin mouse bonecell cultures. Horm Metab Res 2005;37:589–92.
- Syedand F, Khosla S. Mechanisms of sex steroid effects on bone. Biochem Biophys Res Commun 2005;328:688–96.
- Song C, Wang J, Song Q, Li X, Chen Z, Ma Q, et al. Simvastatin induces estrogen receptor-alpha (ER-alpha)in murine bone marrow stromal cells. J Bone Miner Metab 2008;26:213–7.
- Li X, Song QS, Wang JY, Leng HJ, Chen ZQ, Liu ZJ, et al. Simvastatin induces estrogen receptor-alpha expression in bone, restores bone loss, and decreases ER alpha expression and uterine wet weight in ovariectomized rats. J Bone Miner Metab 2011;29:396–403.
- Woo JT, Kasai S, Stern PH, Nagai K. Compactin suppresses bone resorption by inhibiting the fusion of prefusion osteoclasts and disrupting the actin ring in osteoclasts. J Bone Miner Res 2000;15:650–62.
- Yavuz B, Ertugrul DT, Cil H, Ata N, Akin KO, Yalcin AA, et al. Increased levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D after rosuvastatin treatment: a novel pleiotropic effect of statins. Cardiovasc Drugs Ther 2009;23:295–9.
- Ertugrul DT, Yavuz B, Cil H, Ata N, Akin KO, Kucukazman M, et al. STATIN-D study: comparison of the influences of rosuvastatin and fluvastatin treatment on the levels of 25-hydroxyvitamin D. Cardiovasc Ther 2011;29: 146–52.
- Rejnmark L, Vestergaard P, Heickendorff L, Mosekilde L. Simvastatin does not affect vitamin D status, but low vitamin D levels are associated with dyslipidemia: results from a randomised, controlled trial. Int J Endocrinol 2010.
- Thummel KE, Brimer C, Yasuda K, Thottassery J, Senn T, Lin Y, et al. Transcriptional control of intestinal cytochrome P-4503A by 1alpha,25- dihydroxyvitamin D3. Mol Pharmacol 2001;60:1399–406.
- Drocourt L, OurlinJC, PascussiJM,Maurel P,VilaremMJ. ExpressionofCYP3A4, CYP2B6, and CYP2C9 is regulated by the vitamin D receptor pathway in primary human hepatocytes. J Biol Chem 2002;277:25125–32.
- Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. Clin Pharmacol Ther. 2009;85(2):198–203.
- Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. Clin Pharmacol Ther 2009;85:198–203.
- Skoglund B, Forslund C, Aspenberg P. Simvastatin improves fracture healing in mice. J Bone Miner Res 2002;17:2004–8.
- Ho M-L, Chen Y-H, Liao H-J, Chen CH, Hung S-H, Lec M-J, et al. Simvastatin increases osteoblasts and osteogenic proteins in ovariectomized rats. Eur J Clin Invest 2009;39:296–303.
- Uyar Y, Baytur Y, Inceboz U, Demir BC, Gumuser G, Ozbilgin K. Comparative effects of risedronate, atorvastatin, estrogen and SERMs on bone mass and strength in ovariectomized rats. Maturitas 2009;63:261–7.
- Goes P, Lima APS, Melo IM, Rego ROCC, Lima V. Effect of atorvastatin in radiographic density on alveolar bone loss in Wistar rats. Braz Dent J 2010;21:193–8.
- Hanayama R, Shimizu H, Nakagami H, Osako MK, Makino H, Kunugiza Y, et al. Fluvastatin improves osteoporosis in fructose-fed insulin resistant model rats through blockade ofthe classical mevalonate pathway and antioxidant action. Int J Mol Med 2009;23:581–8.
- Yin H, Shi ZG, Yu YS, Hu J, Wang R, Luan ZP, et al. Protection against osteoporosis by statins is linked to a reduction of oxidative stress and restoration of nitric oxide formation in aged and ovariectomized rats. Eur J Pharmacol 2012;674:200–6.
- Seferos N, Pantopoulou A, Kotsiou A, Rallis G, Tesseromatis C. The influence of simvastatin in rats mandible and femur bone mass under Freund's adjuvant arthritis. Stomatologija 2012;14:46–52.
- Dalcico R, de Menezes AM, Deocleciano B, Oriá RB, Vale ML, Ribeiro RA, et al. Protective mechanisms of simvastatin in experimental periodontal disease. J Periodontol 2013;84:1145–57.
- Banu J, Kalu DN. Site-specific effects of cerivastatin on bone in male SpragueDawley rats. Bone 2004;34:432–42.
- Anbinder AL, Prado Fde A, Prado Mde A, Balducci I, Rocha RF. The influence of ovariectomy, simvastatin and sodium alendronate on alveolar bone in rats. Braz Oral Res 2007;21:247–52.
- Yee AJ, Bae HW, Friess D, Roth SM, Whyne C, Robbin M, et al. The use of simvastatin in rabbit posterolateral lumbar intertransverse process spine fusion. Spine J 2006;6:391–6.
- Funk JL, Chen J, Downey KJ, Clark RA. Bone protective effect of simvastatin in experimental arthritis. J Rheumatol 2008;35:1083–91.
- Gradosova I, Zivna H, Palicka V, Hubena S, Svejkovska K, Zivny P. Protective effect of atorvastatin on bone tissue in orchidectomised male albino Wistar rats. Eur J Pharmacol 2012;15:144–50.
- Abdul-Majeed S, Mohamed N, Soelaiman IN. Effects of tocotrienol and lovastatin combination on osteoblast and osteoclast activity in estrogendeficient osteoporosis. Evid Based Complement Alternat Med 2012.
- Handal JA, John TK, Goldstein DT, Khurana JS, Saing M, Braitman LE, et al. Effects of atorvastatin on the cortical bones of corticosteroid treated rabbits. J Orthop Res 2012;30:872–6.
- Starnes JW, Neidre DB, Nyman JS, Roy A, Nelson MJ, Gutierrez G, et al. Synergistic effect of exercise and statins on femoral strength in rats. Exp Gerontol 2013;48:751–5.
- Lin TK, Chou P, Lin CH, Hung YJ, Jong GP. Long-term effect of statins on the risk of new-onset osteoporosis: a nationwide population-based cohort study. PLoS One. 2018 May 3;13(5):e0196713.
- Thabit A, Alhifany A, Alsheikh R, Namnqani S, Al-Mohammadi A, Elmorsy S, Qari M, Ardawi M. Effect of simvastatin and atorvastatin on serum vitamin d and bone mineral density in hypercholesterolemic patients: a cross-sectional study. Journal of Osteoporosis. 2014;2014(1):468397.
- Asgari-Savadjani S, Chaleshtori MT, Mousavi M. A systematic review and meta-analysis of the effect of statins on osteoporotic fractures. Journal of Nephropharmacology. 2024 Jun 29;13(2):e11672.
- Wang Z, Li Y, Zhou F, Piao Z, Hao J. Effects of statins on bone mineral density and fracture risk: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2016 May;95(22):e3042.
- Maeda T, Matsunuma A, Kawane T, Horiuchi N. Simvastatin promotes osteoblast differentiation and mineralization in MC3T3-E1 cells, but fails to induce BMP-2 expression in human osteoblasts. Journal of Bone and Mineral Research.2004 Aug;19(8):1290–1297.
- Kupcsik L, Meury T, Flury M, Stoddart MJ, Alini M. Statin-induced calcification in human mesenchymal stem cells is cell death related. Journal of Cellular and Molecular Medicine. 2009 Nov-Dec;13(11–12):4465–4473.
- Montecucco F, Mach F, Stergiopulos N, Pende A, Mantovani A, Viviani GL. Statins and angiogenesis: role of vascular endothelial growth factor in patients receiving statin therapy. Atherosclerosis. 2009 Aug;205(2):255–260.
- Tresguerres IF, Torres J, López-Quiles J, Hernández G, Vega JA, Tresguerres JAF. Statins inhibit osteogenic differentiation of human bone-derived cells in vitro. Histology and Histopathology. 2006 May;21(5):497–506.

- Moshiri A, Oryan A, Meimandi-Parizi A, Maffulli N. Rosuvastatin fails to induce VEGF-mediated angiogenesis in human osteoblast-like cells under normoxic conditions. Acta Biomaterialia. 2013 Aug;9(8):7827–7835.
- Ruiz-Gaspa S, Guañabens N, Peris P, Enjuanes A, Alvarez L, De Osaba MJ, et al. Simvastatin and atorvastatin do not stimulate osteoblast differentiation in human primary cultures. Journal of Bone and Mineral Metabolism. 2010 Nov;28(6):653–661.
- Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. The New England Journal of Medicine. 2008 Nov;359(21):2195–2207.
- Rejnmark L, Vestergaard P, Heickendorff L, Mosekilde L. Simvastatin does not affect vitamin D status, but low vitamin D levels are associated with dyslipidemia: results from a randomized controlled trial. Atherosclerosis. 2010 Jun;210(2):540–545.
- Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. The New England Journal of Medicine. 2012 Nov;367(19):1792–1802.
- Skaaby T, Husemoen LLN, Thuesen BH, Pisinger C, Jørgensen T, Linneberg A. Prospective association between vitamin D status and incident cardiovascular disease: a cohort study. British Journal of Nutrition. 2014 Jul;112(1):71–80.
- Schwartz JB, Kane L, Bikle D, Ginsberg HN. Pharmacokinetics and pharmacodynamics of atorvastatin in hypercholesterolemic patients with low vitamin D levels. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2009 Jun;29(6):694–703.
- Verdoia M, Schaffer A, Barbieri L, Di Giovine G, Marino P, Suryapranata H, et al. Impact of statins on vitamin D status in patients undergoing coronary angiography. Journal of Cardiovascular Medicine (Hagerstown). 2013 Jul;14(7):491–496.
- van der Mheen A, van der Veen Y, Lips P, Simsek S. Effect of simvastatin on vitamin D metabolism in patients with hypercholesterolemia. Clinical Endocrinology. 2013 Apr;78(4):563–568.
- Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Effect of vitamin D on falls: a meta-analysis. Journal of the American Medical Association. 2012 Feb;307(6):599–609.
- Challoumas D, Stavrou A, Georgiopoulos G, Prodromidi E, Apostolopoulos D. Effects of statins on vitamin D levels: a systematic review of clinical data. Journal of Cardiovascular Medicine (Hagerstown). 2016 Sep;17(9):644–652.
- Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. The New England Journal of Medicine. 2019 Jan;380(1):33–44.