

Original Research Article

Dose-dependent and type-specific effects of statins on bone mineral density: The role of vitamin D and cholesterol

Azhar Yonis Ibrahim¹, Anwar Yonis Ibrahim², Nadheerah Falih Neamah^{1*}

¹Department of Pharmacology and Toxicology, ²Department of Clinical Laboratory Sciences, College of Pharmacy, University of Basrah, Basrah, Iraq

*For correspondence: **Email:** nadheerah.neamah@uobasrah.edu.iq

Sent for review: 18 February 2026

Revised accepted: 18 May 2026

Abstract

Purpose: To investigate dose-dependent and type-specific relationships between statin therapy and bone mineral density (BMD) as well as the effect of vitamin D and cholesterol levels on BMD.

Methods: This was a cross-sectional study of 260 patients on statin therapy conducted at Al-Sader Teaching Hospital in Basrah, South of Iraq, from January 2022 to May 2022. Data on BMD were collated using Dual-Energy X-ray Absorptiometry (DEXA T-scores). Treatment regimen and socioeconomic characteristics were collected. Furthermore, lipid profiles and serum vitamin D levels were assessed.

Results: The study comprised of 48.1 % male and 51.9 % females. The most administered statin was atorvastatin (55.8 %). Also, osteoporosis (48.1 %) and vitamin D deficiency (59.4 %) were frequent. Higher statin dosages (atorvastatin) (> 20 mg/day) significantly reduced mean DEXA T-scores ($p < 0.05$). High blood cholesterol and vitamin D levels were significantly negatively and positively correlated, respectively ($p < 0.05$) with BMD.

Conclusion: High-dose atorvastatin significantly reduces BMD, with significant negative and positive correlation with cholesterol and vitamin D levels, respectively.

Keywords: Bone mineral density (BMD), Dose-dependent, Hypercholesterolemia, Osteoporosis, Statins

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Osteoporosis is a chronic disorder caused by an imbalance between osteoblastic and osteoclastic bone formation and resorption, resulting in decreased bone mineral density (BMD). Also, it is linked to increased morbidity and mortality and negatively impacts quality of life due to increased risk of fractures [1]. Several studies on treatment have raised concerns regarding the potential effects of statins on bone metabolism [2]. Statins are essential for the treatment of hypercholesterolemia and are thus widely used.

To address hypercholesterolemia in people with high-risk cardiovascular disease (CVD) or diabetes mellitus, current guidelines require that cholesterol levels be as low as practicable [3].

It is imperative to determine the connection between osteoporosis risk and statin use, because so many people are on statin therapy. Statins have a complex, dose-dependent relationship with osteoporosis, acting as a double-edged sword: low doses may offer protective benefits for bone health, while high doses may increase the risk of osteoporosis.

While early research suggested statins might act as an anabolic agent (building bone), recent clinical studies show conflicting evidence regarding their efficacy in reducing fracture risk [4]. It is also necessary to determine the pathophysiological processes behind any potential osteoporosis-induced effect of statins [5].

Current data do not support the use of statins as a preventive approach against osteoporosis, despite numerous observational studies documenting favorable statin use for bone mineral density and fracture risk. This is due to conflicting results on the effects of statins on fracture risk, overall bone mineral density, and bone formation markers [4]. However, there is insufficient information on the relationship between osteoporosis and statins in various forms and dosages. An additional dispute is whether statins influence sex hormone levels (testosterone or estrogen). Statins have a detrimental effect because they prevent the body from producing cholesterol, which is an essential substrate for sex hormone production. Evidence currently available does not sufficiently support the use of statins as a preventive medication for osteoporosis, despite a number of observational studies demonstrating beneficial effects on bone density and fracture risk [5]. Furthermore, nothing is known about different types and statin dosages in osteoporosis. Statins have a negative impact on the substrate required for the synthesis of sex hormones because they prevent the body from producing cholesterol.

The origin, solubility, dose, half-life, and excretion pathways of statins differ. With a half-life of 13 – 16 h and a daily dosage of 10–80 mg, atorvastatin is a synthetic lipophilic statin that is primarily eliminated by the liver, with over 2 % excreted through the kidneys. Rosuvastatin, a synthetic but hydrophilic medication, is taken 10 – 40 mg daily, with a half-life of 19 h, excreted hepatically (63 %) and renally (10 %). The semisynthetic lipophilic statin simvastatin (10 – 80 mg/day) has a half-life of 2 - 3 h, is excreted by the liver (79 %) and the kidneys (13 %) [6].

Fluvastatin is a synthetic statin with intermediate solubility, recommended at a dose of 40 – 80 mg per day, excreted hepatically (68 %) and renally (6 %), and has a short half-life of 0.5 – 2 hours. Pravastatin (20 – 80 mg/day), which is hydrophilic and produced from a fungus, has a half-life of 1 - 2 h, is excreted by the kidneys (60 %) and the liver (46 %) of the time [7]. The current study investigated the relationship between statin medication and bone mineral density (BMD) in Basrah, with a focus on the

three most widely used statins: atorvastatin, rosuvastatin, and simvastatin.

METHODS

Subjects

A total of 260 patients (125 males and 135 females) on statin treatment were selected at the first visit to the Outpatient Clinic, Department of Joints, Bones and Fractures in Al-Sader Teaching Hospital in Basrah, South of Iraq, from January 2022 to May 2022. Patients were interviewed and a questionnaire was used to collect details such as age, sex, weight, marital status, educational level, occupation, medical history, disease history, smoking history, drug history, herb history, type and dose of statin used, duration, adverse effects and response of the patient to the drug (which may resort to discontinuing the drug or reducing the dose). Ethical approval was obtained from the Ethics Committee for Human Research at the Basrah University/College of Pharmacy in Basrah, Iraq (approval number: 181, 3-6-2025), and conducted in compliance with the Declaration of Helsinki [8]. Before being included in the study, each participant provided written informed consent.

Selection criteria

Inclusion criteria

Patients between 20 and 80 years old, males or females on statin therapy for > 1 year, were assessed on DEXA for the first time.

Exclusion criteria

The exclusion criteria were pregnant women and patients on hormone replacement therapy or bisphosphonate treatment.

Evaluation of indices/parameters

Biochemical analysis

Blood samples (2 mL) were taken for biochemical analysis and serum levels of low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and High-Density Lipoprotein (HDL), cholesterol, vitamin D, and liver biomarkers were measured. Determinations were done in triplicate and results were presented as mean $\pm$ standard deviation (SD).

Bone mineral density

Bone mineral density (BMD) was measured for patients assessed using DEXA for the first time. The World Health Organization (WHO) criteria served as the basis for the BMD reference values, which were represented by the T score. A T-score of -1 or higher is regarded as normal, T-score of -1 to -2.5 as osteopenia, and a T-score of -2.5 or less as osteoporosis [9].

Statistical analysis

Graph Pad Prism (version 7.0, Inc., San Diego, CA) was used for data analysis. Data were presented in mean $\pm$ SEM and compared using one-way analysis of variance (ANOVA) and Tukey's multiple comparison post-test. Association between BMD and serum cholesterol or vitamin D was assessed using regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and patterns of statin use

This study comprised 260 patients, with 125(48.1 %) males and 135(51.9 %) females. Utilization of Atorvastatin was significantly higher compared to other drugs ($p < 0.05$). Furthermore, a total number of 25(9.6 %) patients, who formed the control group, did not receive statins (Table 1).

Distribution according to lifestyle changes and age

The age group > 60 years had the highest rate of statin use. Also, the majority of statin users had normal body weight (53.8 %) and were non-smokers (69.2 %) (Table 2).

Relationship between vitamin D level and bone mineral density

Osteoporosis was diagnosed in 125(48.1 %) patients. There was no significant difference in bone mineral density and vitamin D deficiency among the different statin groups ($p > 0.05$).

Lipid profiles and inter-statin variability

Although most patients had normal levels of triglycerides (82.7 %) and total cholesterol (84.6 %), management of atherogenic lipids showed considerable inter-statin variability. Atorvastatin use was significantly associated with a higher prevalence of low high-density lipoprotein (HDL) levels (< 50 mg/dL), while rosuvastatin treatment was significantly associated with a higher incidence of elevated triglycerides ($p < 0.05$).

Drug tolerability and treatment patterns

Majority of patients were maintained on low to moderate statin doses (10–20 mg daily). Duration of therapy was significantly correlated with the particular statin ($p < 0.05$). Furthermore, at least one adverse reaction was recorded in the majority of 170(65.4 %) of the patients. Increased blood sugar was the most often reported particular adverse event. However, there was no significant difference in the total incidence of side effects across the three statin groups ($p > 0.05$).

Table 1: Baseline characteristics and statin utilization (N = 260, n, %)

Gender	Atorvastatin	Rosuvastatin	Simvastatin	Control	Total
Male	70(26.9)	20(7.7)	20(7.7)	15(5.8)	125(48.1)
Female	75(28.8)	40(15.4)	10(3.8)	10(3.8)	135(51.9)
P-value	< 0.05				< 0.05

Table 2: Distribution according to lifestyle changes and age

Variables		Atorvastatin	Rosuvastatin	Simvastatin	Control	P-value
Age	20-40	40(15.4)	20(7.7)	10(3.8)	15(5.8)	0.04
	41-60	45(17.3)	20(7.7)	5(1.9)	10(3.8)	
	> 60	60(23.1)	20(7.7)	15(5.8)	0(0)	
Smoking habit	Smokers	55(21.2)	10(3.8)	10(3.8)	5(1.9)	0.01
	Non-smokers	90(34.6)	50(19.2)	20(7.7)	20(7.7)	
Obesity status	Obese	80(30.8)	30(11.5)	5(1.9)	5(1.9)	0.01
	Non-obese	65(25)	30(11.5)	25(9.6)	20(7.7)	

Table 3: Relationship between vitamin D level and bone mineral density

Parameter		Atorvastatin	Rosuvastatin	Simvastatin	Control	P-value
Bone mineral density	Normal (≥ -1)	80(30.8)	10(3.8)	5(1.9)	0(0)	0.10
	Osteopenia (-1 to -2.5)	15(5.8)	20(7.7)	5(1.9)	0(0)	
	Osteoporosis (≤ -2.5)	50(19.2)	30(11.5)	20(7.7)	25(9.6)	
Vitamin D	Normal	95(36.5)	35(13.5)	20(7.7)	15(5.8)	0.06
	< 20 ng/mL	50(19.2)	25(9.6)	10(3.8)	10(3.8)	

Table 4: Effect of statin therapy on lipid profile

Parameter		Atorvastatin	Rosuvastatin	Simvastatin	Control	P-value
Cholesterol (mg/dL)	Normal	130	55	20	15	0.56
	Elevated	15	5	10	10	
LDL (ng/dL)	Normal	59	40	15	15	0.06
	Elevated	50	20	15	10	
HDL (mg/dL)	Normal	100	45	15	15	< 0.05
	< 50 mg/dL	45	15	15	10	
Triglyceride (mg/dL)	Normal	140	35	20	20	< 0.05
	Elevated	5	25	10	5	

Table 5: Treatment patterns, tolerability, and incidence of adverse effects

Parameter		Atorvastatin (n = 145)	Rosuvastatin (n = 60)	Simvastatin (n = 30)	P-value
Daily dose (mg) (n, %)	10-20	95(65.5)	40(66.7)	20(66.7)	0.26
	30-40	20(13.8)	15(25.0)	0(0)	
	50-60	30(20.7)	5(8.3)	10(33.3)	
Duration (years) (n, %)	1-3	45(31.0)	30(50.0)	10(33.3)	<0.05
	3-5	60(41.4)	10(16.7)	5(16.7)	
	> 5	40(27.6)	20 (33.3)	15(50.0)	
Side effects (n, %)	None	45(31.0)	10 (16.7 %)	10 (33.3 %)	0.25
	Any Adverse Effect	100(69.0)	50(83.3)	20(66.7)	
	Myalgia	10(33.3)	25(41.7)	50(34.5)	
	Skin Flushing	20(13.8)	5(8.3)	5(16.7)	
	Increased Blood Sugar	15(10.3)	10(16.7)	5(16.7)	
	Elevated Liver Enzymes	10(6.9)	5(8.3)	0(0)	
	Gastrointestinal*	15(10.3)	10(16.7)	5(16.7)	
	Neurological/Sleep**	10(6.9)	5(8.3)	5(16.7)	

*Includes bloating and gas, **includes dizziness, sleeplessness, and sleep problems

DISCUSSION

Simvastatin and atorvastatin are examples of lipophilic statins that passively penetrate extrahepatic tissues like bone cells. Overdoses may cause the osteoblasts' mevalonate pathway to be abnormally inhibited, which could prevent the production of essential proteins needed for bone development [7,10]. However, hydrophilic statins, such as rosuvastatin, have better bone safety profile at low dosages because they depend on the liver transporters, which results in more targeted hepatic activity and fewer direct effects on bone cells [11]. Also, elevated reactive oxygen species and mitochondrial dysfunction in musculoskeletal tissues are associated with high-dose statin medication, thus affecting bone metabolism [7]. This study therefore investigated the relationship between statin medication and bone mineral density (BMD) in Basrah patients,

focusing on the three most widely used statins (atorvastatin, rosuvastatin, and simvastatin).

Most patients received low daily dosages (10 – 20 mg) of the statins over extended periods of time. In a population-based study of 7.9 million Austrians, low-dose statin users (≤ 10 mg) had lower risk of osteoporosis, whereas high-dose users (beyond specific thresholds) had an increased risk, showing a similar dose-dependent trend [2]. Furthermore, findings from this study point to a complicated, two-phase connection between BMD and statin treatment. Even though osteoporosis affected 48.1 % of statin users, a thorough investigation showed that this risk was inconsistent. Patients taking statins at low-to-moderate doses, especially the hydrophilic medication rosuvastatin, tended to have higher T-scores. Higher T-scores mean that the bones are becoming denser and stronger compared to a young healthy adult of the same

sex [7]. However, high-dose therapy, especially with the lipophilic atorvastatin, was associated with a greater incidence of osteoporosis as seen in a previous study [2]. This implies that the osteoprotective effect of statins, as shown in certain studies [12], may be reversible at higher doses and dose-dependent. These results imply that while higher doses of statins may not have the same protective effect on bone health, lower doses may.

Although hypercholesterolemia and the associated inflammatory response contribute to osteoporosis, it is unclear if targeted treatments could stop this bone metabolic disease [7]. This study also showed that age and DEXA T-score were negatively correlated. The age-related decrease in BMD is in tandem with previous studies, which showed lower BMD in postmenopausal women on higher statin dosages [5]. Therefore, these findings lend credence to the idea that age plays a significant role in determining bone health and may interfere with the effects of statin dosage. Furthermore, there was a negative correlation between DEXA T-scores and triglyceride and total cholesterol levels and a favorable correlation with HDL cholesterol. These correlations support recent research suggesting dyslipidemia may negatively impact bone metabolism [13-15]. This is because lipid-induced oxidative stress and inflammation may impede osteoblast function and bone formation. Association between statins and BMD seems to vary according to the metabolic condition of the patient. Bone health depends on adequate vitamin D levels, which may affect the effects of statins [15].

There was a significant positive correlation between blood vitamin D and BMD. However, the inverse relationship between blood cholesterol and BMD suggests that the underlying dyslipidemia is a risk factor for osteoporosis, possibly through oxidative stress and inflammation that impair osteoblast function [13,16]. Therefore, the total effect on bone may be a balance between its targeted lipid-lowering benefit and any potential direct, dose-dependent cellular effects. There was also a significant positive correlation between vitamin D levels and DEXA T-scores. Vitamin D is necessary for bone mineralization because it improves neuromuscular function and encourages intestinal absorption of calcium and phosphorus. Osteoporosis and associated fractures are less likely when there is adequate vitamin D in the body because it improves muscular tone and lowers risk of falls. The patients in this study experienced several statin-related side effects, such as headache, dizziness, constipation,

flatulence, muscular or joint pain, increased blood transaminases, and respiratory symptoms [16,17]. These side effects are always considered while using statins for an extended period of time, even though they were not directly connected to bone results in this study. A similar study found that statins decreased the risk of osteoporotic fractures by 18 % [12]. The results showed the intricate connection between statin medication, dosage, lipid profile, vitamin D status, and bone health. Higher dosages may be less helpful, especially in older people or those with dyslipidemia, even if low-dose statin therapy seems to be linked to better BMD outcomes. These findings call for more research into bigger, longer-term studies to elucidate the mechanisms and determine the ideal statin dosage for maintaining bone health. There is little evidence to support the use of statins as the main treatment for osteoporosis, and their effects on BMD appear to be limited and site-specific. However, their additional role may be considered in some patients with concurrent cardiovascular problems [10]. In summary, statin medication appears to have dose- and type-dependent effects on bone health. For patients receiving long-term statin therapy, maintaining appropriate vitamin D levels and monitoring cholesterol may improve bone preservation.

Although some meta-analyses suggest that the preventive effect of statins on fracture risk may be minor and not consistently detected across all skeletal locations, data from this study did not confirm site-specificity [4,12]. Consequently, the use of statins as the main treatment for osteoporosis is not supported by available data. However, this study revealed that choosing a low-to-moderate dose of a hydrophilic statin and making sure vitamin D levels are adequate could be a wise strategy to maintain bone health concurrently for individuals who need long-term statin medication for cardiovascular protection. This study offers strong proof of the intricate and varied connection between statin use and bone health, and that this relationship is dose-dependent and type-specific. Also, contrary to the widely accepted notion that statins typically maintain bones, this study revealed a connection between decreased bone mineral density and higher statin dosages (> 20 mg/day). This suggests a potential biphasic interaction, whereby high dosages may be harmful to bone health while low levels may be harmless or only slightly beneficial. At lower doses, the hydrophilic statin rosuvastatin outperformed the lipophilic statins (atorvastatin and simvastatin) in terms of bone density. This highlights how important the physicochemical properties of statins are in influencing their activity. Regardless of the statin

therapy, adequate vitamin D levels were a strong positive predictor of BMD, but high cholesterol was a strong negative predictor. Therefore, while managing patients on long-term statin therapy, especially those who are at risk for osteoporosis, clinicians should use a tailored approach. This may include low-to-moderate dosages, selecting a hydrophilic statin for individuals with high risk of osteoporosis (such as rosuvastatin), monitoring vitamin D levels, proactively managing dyslipidemia, as reducing blood cholesterol enhances bone and heart health. However, comprehensive, prospective longitudinal studies are needed to confirm these cross-sectional results in order to elucidate the underlying mechanisms and develop appropriate evidence-based recommendations to enhance cardiovascular health while maintaining bone integrity.

Limitations of the study

The study has some limitations. The significant correlation was not confirmed due to the cross-sectional nature of the study, which made it difficult to draw conclusions between statin use and BMD. Also, this research conducted a single-time-point evaluation of biochemical indicators and BMD, which may not accurately reflect long-term modifications in bone metabolism. Bone health results could have been influenced by possible confounding variables that were not adequately assessed, such as dietary calcium intake, physical activity level, sun exposure, and genetic susceptibility. Furthermore, several statin subgroups (simvastatin users in particular) exhibited unusually small numbers of samples, which may have limited statistical power for subgroup analyses. Also, the study was performed at one institution, limiting the generalizability of the results.

CONCLUSION

The study showed that statins influence the density of bone minerals in a dose-dependent and brand-specific manner. Also, high doses of lipophilic statins (atorvastatin) decreased BMD, but moderate to low doses of hydrophilic statin (rosuvastatin) elicited more favorable bone effects. Furthermore, monitoring and treating vitamin D insufficiency and a customized statin therapy may help improve skeletal and cardiovascular health. To validate these correlations and develop evidence-based treatment recommendations, further extensive prospective and longitudinal research is necessary.

DECLARATIONS

Funding

This study did not receive any outside support.

Acknowledgement

The authors express their gratitude to the University of Basrah's College of Pharmacy for their support and encouragement.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

1. Stone MD, Hosking DJ. Treatment of osteoporosis: current and future. *Ann Rheum Dis* 1991; 50(10): 663
2. Leutner M, Matzhold C, Bellach L, Deischinger C, Harreiter J, Thurner S, et al. Diagnosis of osteoporosis in statin-treated patients is dose-dependent. *Ann Rheum Dis* 2019; 78(12): 1706-1711
3. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Rev Esp Cardiol (English ed.)* 2017; 70(2): 115
4. An T, Hao J, Sun S, Li R, Yang M, Cheng G, et al. Efficacy of statins for osteoporosis: a systematic review and meta-analysis. *Osteoporos Int* 2017; 28(1): 47-57
5. Biswas P, Kumaraswamy TS, Hilgers R. Efficacy of statins in postmenopausal osteoporosis: A systematic review and meta-analysis. *Cureus* 2025; 17(6): e86425
6. Rawlings R, Nohria A, Liu PY, Donnelly J, Creager MA, Ganz P, et al. Comparison of effects of rosuvastatin (10 mg) versus atorvastatin (40 mg) on rho kinase activity in caucasian men with a previous atherosclerotic event. *Am J Cardiol* 2009; 103(4): 437-441.
7. Shi Z, Han S. Personalized statin therapy: Targeting metabolic processes to modulate the therapeutic and adverse effects of statins. *Heliyon* 2025; 11(1): e41629
8. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191-2194
9. WHO Study Group on Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis. Technical Report Series 843: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization; 1994
10. Leslie WD, Zarzour F, Binkley N, Morin SN, Schousboe JT. Cross-sectional and longitudinal associations between statin use and bone density: the Manitoba BMD registry. *J Bone Miner Res* 2025; 40(9): 1045-1051

11. Antonenko A, Leahy A, Babenko M, Lyons D. Low-dose hydrophilic statins are the preferred agents for females at risk of osteoporosis. *Bone Reports* 2022; 16: 101152
12. Asgari-Savadjani S, Chaleshtori TM, Mousavi M. A systematic review and meta-analysis of the effect of statins on osteoporotic fractures. *J Nephropharmacol* 2024; 13(2): e11672-e11672
13. Ren Z, Zhou L. Association of statin use with osteoporosis risk: a drug-targeted Mendelian randomization study. *Inflammopharmacol* 2024; 32(2): 1253-1261
14. Antonenko A, Leahy A, Babenko M, Lyons D. Low-dose hydrophilic statins are the preferred agents for females at risk of osteoporosis. *Bone Reports* 2022; 16: 101152.
15. Panahi N, Soltani A, Ghasem-Zadeh A, Shafiee G, Heshmat R, Razi F, et al. Associations between the lipid profile and the lumbar spine bone mineral density and trabecular bone score in elderly Iranian individuals participating in the Bushehr Elderly Health Program: a population-based study. *Arch Osteoporos* 2019; 14(1): 1-1
16. Yazdanpanah MH, Sedighi S, Rajabi MR, Osati S, Dehghan A, Ehrampoush E, et al. Lipid profiles are a possible contributor to osteoporosis. *Gazi Med J* 2018; 19: 29(3)
17. Orozco P. Atherogenic lipid profile and elevated lipoprotein (a) are associated with lower bone mineral density in early postmenopausal overweight women. *Eur J Epidemiol* 2004; 19(12): 1105-1112.