Healthy Aging Perspectives

Volume 1 / Issue 1
June 2026

Original Article

Comparative effect of high-intensity atorvastatin and rosuvastatin therapy on the levels of 25-hydroxyvitamin D in patients with acute myocardial infarction: A pilot randomized controlled trial

Seyedeh Samaneh Tabaee [1], Amirhosein Sahebkar [2,3,4], Peyman Habibi [1], Hasan Ghodsi [5], Manizheh Pakdel [6], Seyed Reza Mirhafez [6*]

[1] *Healthy Ageing Research Centre, Neyshabur University of Medical Sciences, Neyshabur, Iran*
[2] *Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*
[3] *Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.*
[4] *School of Medicine, The University of Western Australia, Perth, Australia.*
[5] *Department of nursing and midwifery, Neyshabur University of Medical Sciences, Neyshabur, Iran.*
[6] *Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran*

Corresponding Author

Seyed Reza Mirhafez, Ph.D.

Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran

✉ mirhafezr@nums.ac.ir

✆ +985143353211

0000-0002-4986-0787

Article History

Received: June 9, 2026
Published: June 30, 2026

Keywords

Atorvastatin, Rosuvastatin, Acute myocardial infarction, Vitamin D

Publisher

Neyshabur University of Medical Sciences

ABSTRACT

Background: Despite controlling for other risk factors of coronary artery disease (CAD), the risk of myocardial infarction (MI) due to vitamin D deficiency is increased. In addition to lipid-lowering effects of statins in CAD prevention and heart failure, these drugs exhibit many pleotropic effects. Part of these beneficial results may be due to the effect of statins on vitamin D levels. The current clinical trial aimed to explore the possible effects of high-intensity statin therapy on the levels of vitamin D metabolites in patients with acute myocardial infarction.

Methods: Patients in the Coronary Care Unit (CCU) with a cardiologist's diagnosis of myocardial infarction for the first time (i.e., typical chest pain greater than 20 min and ST-segment elevation greater than 1 mm in two adjacent leads on ECG) were included in the study. Then patients were divided into two equal groups using a block randomization method, who received atorvastatin 80 mg or rosuvastatin 40 mg as a secondary prevention once daily, plus a routine treatment regimen for 8 weeks. Following an overnight fast of 12 h, a venous blood sample (10 ml) was collected from study subjects within the first 24 h and 8 weeks after the patients were admitted to the hospital. The primary endpoint was the between-group difference in the change of serum vitamin D.

Results: In terms of baseline lipid levels, there was no significant difference between the two groups. In both groups, TC, TG, and LDL-C were decreased and HDL-C levels were increased after 8 weeks of treatment, but no significant difference between two groups was detected (p=0.792, p=0.418, p=0.514, p=0.456 respectively). In the rosuvastatin group, the mean values of hemoglobin A1C (HbA1C) and AST were increased significantly (P<0.05). In both groups, initial vitamin D levels were lower than normal and increased after statin consumption, but it was not statistically significant. The variation of ejection fraction after intervention was more increased after rosuvastatin than atorvastatin treatment (P=0.05).

Conclusion: Atorvastatin and rosuvastatin had no significant effects on 25-hydroxyvitamin D levels. Ejection fraction increased in the rosuvastatin group, but it was not statistically significant (p-value of exactly equal to 0.05). This increase could be due to various factors such as medication use and lifestyle changes.

Introduction

Vitamin D as a prohormone needs to be reformed to its active form (i.e., 1 and 25-hydroxyvitamin D) (1) and metabolized in the liver through a common enzyme of the cytochrome P450 system (CYP3A4) (2). LDL-cholesterol is the major carrier of vitamin D in the circulation. Lower levels of circulating vitamin D, despite control for other risk factors

of coronary artery disease (CAD), are related to a higher risk of myocardial infarction (3), and an elevated level of 25-hydroxy vitamin D protects people against cardiovascular diseases (4). Several studies have revealed that sunlight exposure, with the production of 25-hydroxyvitamin D, has a protective role against heart disease (5, 6). Therefore, a diet containing fish oil with large amounts of vitamin D has the potential to protect against heart diseases (7, 8). Lower vitamin D level is associated with the risk of various types of cancers, many chronic disorders, and cardiovascular diseases (9, 10). The association between levels of circulating cholesterol and atherosclerotic diseases has been well documented in the literature (7). Statins are commonly used for hypercholesterolemic patients and as primary and secondary prevention. The term "high-intensity statin" refers to medication doses that are higher than the standard doses recommended (11-13). The activity of these drugs is mainly due to the reduction of cholesterol and triglyceride levels. In addition to lipid-lowering effects of statins in primary and secondary prevention of CAD (14) and heart failure (15, 16), these drugs exhibit advantages in the treatment of infection (15), Alzheimer (17), stroke (18), and rheumatoid arthritis. Part of these beneficial results may be due to the impact of statins on vitamin D levels (19).

Previous studies have shown that treatment with rosuvastatin and atorvastatin increases vitamin D levels during 8 weeks (4, 20-22). This pleiotropic effect may be the mechanism of mortality reduction in ischemic heart disease patients who received rosuvastatin (22). There is conflicting information about the effect of simvastatin on circulating vitamin D (4, 23). A systematic review and meta-analysis of seven studies did not show any significant effect of statins on vitamin D level (24). Also, inconclusive effects of statins on circulating vitamin D was reported in another meta-analysis, due to the contradictory results of interventional and observational studies (25). These discrepancies may be due to variation in doses of statins used, different populations, and methodology were studied.

Therefore, more RCTs need to be designed to determine the possible effects of statin on vitamin D level. Rosuvastatin and atorvastatin are the most commonly used statins in patients with acute myocardial infarction. In previous studies, moderate doses of statin were used, so we designed this study to compare the influence of high-intensity treatment with them on the levels of vitamin D. We also want to assess whether it is a class effect or a pleiotropic effect of certain types of statins.

Methods

This pilot study was an 8-week prospective double blind controlled trial (RCT) study conducted at the department of cardiology of 22 Bahman Hospital in Neyshabur, Iran, a referral center for acute coronary syndrome. The study was approved by the Neyshabur University of Medical Sciences Ethics Committee (Ethics Committee No.: IR.NUMS.REC.1394.19). Also, this study was confirmed in the Iranian Registry of Clinical Trials (IRCT registration Code: IRCT20190902044673N1). Informed written consent was obtained from all participants. Patients admitted to the CCU with a cardiologist's diagnosis of myocardial infarction (i.e., typical chest pain greater than 20 min and ST-segment elevation greater than 1 mm in two adjacent leads on ECG (26)) were included in the study. Given the effect of sunlight and season on vitamin D levels, all patients entered the study at a specific time and season.

The inclusion criteria were 1) typical chest pain greater than 20 min based on clinical symptoms, 2) ST-segment elevation greater than 1 mm in two adjacent leads on electrocardiography (ECG), 3) positive troponin in laboratory tests diagnosed by a cardiovascular specialist, 4) minimum and maximum ages of 35 and 75 years, respectively, (the average age of the patients was over 50 years) and 5) willingness to participate in the study. On the other hand, individuals with 1) pregnancy, 2) alcohol consumption more than 20 grams per day, 3) thyroid and parathyroid disorders, 4) hypocalcemia, 5) hypercalcemia, 6) malignancy (i.e., all types, including basal cell carcinoma, and 7) those who treated with calcium-phosphorus, estrogen, vitamin D, alendronate, risedronate, zoledronate, raloxifene, parathyroid hormone-1-34, strontium ranelate, and cortisone or weight loss drugs three months prior to referral were excluded from this study.

Patients were then divided into two equal groups using a block randomization method, given either atorvastatin or rosuvastatin (80 mg or 40 mg, respectively) as a secondary prevention once daily, plus a routine treatment regimen for 8 weeks. The medications were contained in clear and identical black cans. The contents of the medications could not be identified from the cover of the can. They were also given to the patients in a way that neither the patient nor the researcher had any information about the contents of the medications. After a 12-hour overnight fast, participants' venous blood sample (5 ml) was collected within the first 24 h and 8 weeks after the patients were admitted to the hospital. Using standard protocols, fresh samples were applied to estimate alanine aminotransferase (ALT), fasting blood sugar (FBS), aspartate aminotransferase (AST), and serum creatinine (Cr) (Jaffe method for serum creatinine, Hexokinase method for FBS, and an enzymatic method for ALT AND AST). To estimate lipid parameters (TC, HDL-C, and TG), the enzymatic method was used. LDL-C was calculated using the Friedewald equation (27, 28). The 25OHD was determined using the ELISA method (DLD diagnostics, Germany, intra-assay and inter-assay CV 8%).

The Leicester height meter, Child Growth Foundation, UK, was used to assess height to the nearest 0.1 cm (range 60–207 cm), and weights were measured on an electronic digital scale to the nearest 0.1 kg. Also, body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

The patients were asked to report any symptoms of statin use, including headache, back pain, constipation, fatigue, dizziness, myalgia, muscle weakness, arthralgia, liver failure, rhabdomyolysis, and chondropathy. In case of pregnancy, drug intolerance, serum transaminase elevation, or CK (>3x and >10x the upper limit of normal range, respectively), the statin was stopped, and the subjects were removed from the study.

Continuous variables data is presented as mean as well as standard deviation (SD). Categorical variables data is presented as numbers and/or percentages. The Kolmogorov-Smirnov test was applied to detect the normality of the distribution of continuous variables. Within-variable

differences were assessed using the paired t-test or Wilcoxon Signed Ranks test. To assess between-group differences, the independent t-test or Mann-Whitney was used. A two-sided $p<0.05$ was regarded as significant. SPSS for Windows version 17 was used for statistical analysis (SPSS Inc., Illinois, USA).

Results

In a total of 80 patients aged 35 to 75 years were randomly divided into two groups atorvastatin 80 mg per day or rosuvastatin 40 mg per day, 5 of which were lost to follow-up. Therefore, 75 patients completed the study, 38 from the atorvastatin group (aged 60.50±10.65 years, 17 females) and 37 from the rosuvastatin group (aged 58.61±9.9 years, 12 females). There was no significant difference between the two groups in anthropometric parameters, including age, gender, systolic and diastolic BP, height, and weight at baseline and after 8 weeks (Table 1). Furthermore, the majority of the participants in the atorvastatin (56.4%) and rosuvastatin (69.2%) groups are male. In the atorvastatin group, 36.8%, 21.1%, and only 2.6% of the patients were smokers, addicts, and alcohol users, respectively. On the other hand, 13.5% and 27% of the participants were smokers and addicts in the rosuvastatin group, respectively.

According to Table 2, in both groups after 8 weeks of treatment, the mean value of ejection fraction was increased significantly within groups ($P<0.05$). However, the significance of rosuvastatin was more evident in increasing this fraction ($P<0.001$). Furthermore, there was no significant difference in baseline lipid levels between the two groups. In both groups, cholesterol, TG, and LDL-C were decreased, and circulating HDL-C were increased after 8 weeks of treatment, but the differences were not statistically significant. In terms of anthropometric indices and biochemical markers, no significant changes were detected in both groups after 8 weeks of treatment. However, the level of AST was reduced in both groups, but it was only significant in the atorvastatin group ($P<0.05$). This pattern was reversed for ALP levels, where it was increased in both groups, particularly noticeable in the atorvastatin group ($P<0.05$). In addition, initial vitamin D levels were lower than normal and increased after statin consumption in both groups, but it was not statistically significant.

There was no statistically significant difference between the rosuvastatin and the atorvastatin groups in terms of biochemical markers, as shown in Table 3. However, the results showed some significant mean changes after the therapeutic interventions. With eight weeks of treatment, both groups of atorvastatin 80 mg and rosuvastatin 40 mg showed statistically significant changes in BMI. The group of atorvastatin 80 mg showed lower BMI than the rosuvastatin 40 mg group after eight weeks of therapy (-0.05 vs. 0.16). Likewise, the mean change in ejection fraction has increased after treatment in both the atorvastatin 80 mg group and the rosuvastatin 40 mg group (2.42 vs. 5.42) ($p=0.05$). Another significant change observed after the treatment was related to participants' weight. As seen in Table 3, participants' weight decreased after 8 weeks of treatment with 80 mg of atorvastatin (-0.21), but after a similar period, weight gain was observed in the rosuvastatin 40 mg group (0.38). These weight changes could be due to dietary differences and other environmental and genetic factors that were not controlled for in this study. It is also important to note that the level of vitamin D elevated after the treatment in both groups, but it was not statistically significant ($p=0.472$).

Table 1. Characteristics of patients with acute MI at baseline

Variable	Atorvastatin n=38	Rosuvastatin n=37	P value
Gender, male	22 (56.4%)	27 (69.2%)	0.241
Age, years	60.5±10.6	58.6±9.9	0.435
Ejection fraction,%	60.3±7.0	57.4±10.2	0.140
BMI, kg/m^2	26.3±4.0	25.8 ±5.3	0.615
SBP, mmHg	140.1±23.4	138.3 ±21.1	0.730
DBP, mmHg	83.0±14.2	88.9±14.5	0.082
FBG, mg/dL	133.1±51.4	112.9±43.9	0.066
TC, mg/dL	161.5±52.9	157.1±38.1	0.665
TG, mg/dL	137.6±140.4	149.0±77.1	0.657
HDL-C, mg/dL	44.4±14.2	41.8±8.3	0.311
LDL-C, mg/dL	76.4±27.5	79.5±21.8	0.576
AST, mg/dL	71.5±79.0	59.1±65.9	0.447
ALT, mg/dL	42.9±34.6	33.3±16.4	0.118
ALP, mg/dL	199.5 ±59.4	208.4±59.8	0.517
HbA1C, mg/dL	6.3±1.5	6.0± 1.6	0.383
Vitamin D,ng/mL	19.2±13.2	17.3±14.4	0.707
Height, m	1.6 ±9.4	1.6 ±9.5	0.825
Weight, kg	69.7±12.1	68.3±13.2	0.624
Current smoking,yes	14 (36.8 %)	5 (13.5 %)	0.020
Current addiction,yes	8 (21.1 %)	10 (27.0 %)	0.545
Current Drinking,yes	1 (2.6 %)	0(0%)	0.321
Hypertension Histor,yes	23(60.5%)	15(40.5%)	0.083
Diabetes History, yes	11(28.9%)	9(24.3%)	0.651
MI History, yes	10(26.3%)	7(18.9%)	0.444
Taking medication, yes	24(63.2%)	21(56.8%)	0.572

The continuous and categorical variables were presented as mean±SD and percentage, respectively.
BMI: Body mass index, FBG: Fasting blood glucose, TC: Total Cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, HbA1C: Hemoglobin A1C, MI: myocardial infarction.

Discussion

In this study, atorvastatin and rosuvastatin consumption had no effect on TC, TG, HDL and LDL levels. The relationship between circulating vitamin D levels and serum lipid responses to atorvastatin in 63 patients with acute myocardial infarction was indicated by Pérez-Castrillón et al. No change was indicated in circulating HDL and LDL in vitamin D- deficient individuals; the patients with vitamin D (>30 nmol/L) showed good responses to atorvastatin. In other words, they showed that a good level of vitamin D is necessary for the impact of atorvastatin on lipid profile in patients with myocardial infarction (29). In this study, vitamin D levels were initially low, which may explain why statins have no effect on lipid profiles.

According to a study carried out by Verdoia et al., 70.4 percent of patients who coronary angiography had hypovitaminosis D. Vitamin D deficiency is significantly associated with CAD, particularly in subjects with values of < 10 ng/mL (30). In this study patients had documented CAD and their vitamin D levels were lower than normal. There are conflicts regarding the effectiveness of statins on vitamin D levels. Some studies reported increasing effect (22, 31-33) while no effect (34) was reported by others. Ertugrul et al. conducted a study on 134 patients with hyperlipidemia who had not previously used lipid-lowering drugs. During the

study, the patients were randomly assigned in a 1:1 ratio to either rosuvastatin 10 mg or fluvastatin 80 mg XL. At the baseline and after 8 weeks, the LDL, total cholesterol, and 25 hydroxyvitamin D levels were measured in both groups. According to the results, total cholesterol and LDL cholesterol decreased after 8 weeks in both groups. However, the effect of rosuvastatin was more effective than that of fluvastatin in reducing total cholesterol (P <0.001) and LDL cholesterol (P<0.001). Additionally, in the rosuvastatin group, there was a significant increase in 25hydroxyvitamin D level, whereas in the fluvastatin group there was no significant change in this regard (4). Furthermore, Anagnostis et al. performed a study to compare the effects of atorvastatin (20 mg/day) and rosuvastatin (10 mg/day) on 25-hydroxyvitamin D levels in dyslipidemia patients without diabetes. According to the result of this study, atorvastatin and rosuvastatin had no significant effect on 25-hydroxyvitamin D levels. In the same line, Rejnmark et al. studied 76 hyperlipidemic patients who had not received lipid-lowering medication. The patients were randomly assigned to one of two groups: rosuvastatin 10 mg and atorvastatin 20 mg. After 12 weeks, unlike previous studies, no statistically significant relationship was observed between statins and vitamin D levels. The results of a study performed by Verdoia et al. on patients with CAD showed that high-dose statin therapy significantly increased vitamin D levels in these patients in addition to its lipid-lowering effects (35).

Table 2. Comparison of anthropometric, biochemical and clinical data of patients with acute MI within groups

Characteristics	Atorvastatin (n = 37)			Rosuvastatin (n = 36)		
	Before	After	P-value	Before	After	P value
Ejection fraction, %	60.3±7.3	62.7±5.4	0.018	58.0±10.6	63.4±7.7	< 0.001
Weight, kg	69.7±12.1	69.5±12.1	0.282	68.3±13.2	68.6±12.9	0.046
BMI, kg/m^2	26.3±4.0	26.3±4.1	0.454	25.8±5.3	25.9±5.2	0.043
SBP, mmHg	140.1±23.4	138.0±17.5	0.224	138.3±21.1	138.8±17.7	0.651
DBP, mmHg	83.0±14.2	81.5±10.1	0.179	88.9±14.5	87.6±12.2	0.210
FBG, mg/dL	134.8±52.2	139.1±94.6	0.726	115.3±44.7	119.6±36.1	0.434
TC, mg/dL	161.5±52.9	159.8±63.3	0.838	156.5±38.4	151.1±41.9	0.348
TG, mg/dL	138.4±142.3	135.0±68.8	0.886	149.9±77.8	152.2±106.8	0.876
HDL-C, mg/dL	44.4±14.2	45.9±10.1	0.380	41.8±8.4	43.4±9.6	0.188
LDL-C, mg/dL	77.3±27.4	74.7±26.8	0.492	78.9±21.7	71.6±22.6	0.050
AST, mg/dL	71.5±79.0	43.6±35.8	0.029	59.0±65.9	40.5±41.5	0.073
ALT, mg/dL	42.9±34.6	38.9±36.7	0.558	33.3±16.9	33.8±26.2	0.928
ALP, mg/dL	198.3±60.5	222.2±58.1	0.013	204.8±58.8	223.8±58.8	0.072
HbA1C, mg/dL	6.3±1.5	6.7±1.8	0.104	6.0±1.6	6.5±1.9	0.217
Vitamin D, ng/mL	21.1±13.3	25.1±8.5	0.220	15.1±8.7	16.1±6.8	0.699

Data was expressed as Mean±SD (standard devietion).
BMI: Body mass index, FBG: Fasting blood glucose, TC: Total Cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, HbA1C: Hemoglobin A1C.

The doses selected in this study were based on rosuvastatin (STELLAR) trial, in which 10 mg rosuvastatin had similar effect with 20 mg atorvastatin in reducing lipids (36). On the other hand, newest guidelines recommended high intensity statin therapy in acute coronary syndrome (12, 13). Although we used higher doses of statins, our results were the same as in the Rejnmark study (32). Differences in results may be due to differences in the population of the study, inclusion and exclusion criteria, season, concomitant drug interactions, statin type, statin dose, single centered study, demographic properties (clothing habits), different baseline 25 (OH) D levels and duration of study. Glossmann et al. showed surprising increase in circulating vitamin D after rosuvastatin therapy for 8 weeks (from 14.0 ng per ml to 36.3 ng per ml) (22). In Makariou SE study all patients in rosuvastatin (40 mg), rosuvastatin 10 mg in combination with omega-3 fatty acids 2 g and rosuvastatin 10 mg combined with fenofibrate 200 mg were vitamin D deficient at baseline (mean <15 ng/ml) (37). After 8 weeks of rosuvastatin therapy Ertugrul DT observed mean of 25-hydroxy vitamin D rise from 11.8 ng/ml to 35.2 ng/ml (21).

In the study by Liberopoulos EN, patients receiving simvastatin/ezetimibe 10/10 mg (group 1) had greater increase in vitamin D levels in comparison to simvastatin 40 mg (group 2), mean baseline vitamin D level was (6.7-6.8 ng/ml) in group 1, which was lower than group 2 (28 ng/m) (38). In Panagiotis Anagnostis study mean vitamin D levels in atorvastatin 20 mg/day and rosuvastatin 10 mg/day groups were 21.7±1.9 and 25.3±1.8 at baseline respectively. This study showed atorvastatin and rosuvastatin did not significantly affect 25(OH)D levels (37). In our study baseline vitamin D level were 21.08±13.34 in atorvastatin group and 15.11±8.73 in rosuvastatin group. According to these studies, an increase in vitamin D levels after statin therapy may be seen in low amounts of vitamin D at baseline.

Table 3. Anthropometric, biochemical, and clinical data differences between groups of patients with acute MI

Variables	Atorvastatin (n = 37)	Rosuvastatin (n = 36)	P value
BMI, kg/m^2	-0.05±0.5	0.16±0.5	0.049
SBP, mmHg	-2.023±10.1	0.55±7.2	0.210
DBP, mmHg	-1.47±6.6	-1.25±5.9	0.879
FBG, mg/dL	4.32±71.5	4.35±33.5	0.998
TC, mg/dL	-1.76±52.9	-5.38±35.4	0.724
TG, mg/dL	-3.41±143.3	2.18±86.4	0.837
HDL-C, mg/dL	1.48±10.3	1.59±7.4	0.957
LDL-C, mg/dL	-2.55±22.1	-7.23±22.3	0.365
AST, mg/dL	-27.89±76.9	-18.47±63.4	0.554
ALT, mg/dL	-3.89±40.6	0.43±28.9	0.597
ALP, mg/dL	23.86±54.6	18.48±60.7	0.692
HbA1C, mg/dL	0.43±1.5	0.52±2.4	0.855
Ejection fraction, %	2.42±5.8	5.42±6.9	0.050
Weight, kg	-0.211±1.2	0.38±1.1	0.030
Vitamin D, ng/mL	4.01±10.7	0.96±7.2	0.472

Data was expressed as Mean±SD (standard devietion).
BMI: Body mass index, FBG: Fasting blood glucose, TC: Total Cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, HbA1C: Hemoglobin A1C.

In this study, both drugs increased HbA1C, but only in the rosuvastatin group the increase in HbA1C was significant. Nobuhiro Ooba et al. designed a retrospective cohort study to explore the impact of high-potency statins on HbA1c. They showed that high-potency statins may raise HbA1c levels in diabetic and non-diabetic patients (39). Farnaz Fariba et al. give 80 mg of atorvastatin to patients with acute myocardial infarction for 6 months. In their study, the mean HbA1c increased from 6.19 to 6.43 (P=0.001) and the mean FBS increased from 103.66 to 110.51 (P=0.001). Therefore, along with many benefits, atorvastatin may increase the risk of hyperglycemia. In a study of Simmer et al., two drugs, atorvastatin 80 mg and rosuvastatin 40 mg, were evaluated for their effect on the HbA1c. Both drugs increased HbA1c, but the effect of atorvastatin on HbA1c was higher (40). Sattar et al. in a meta-analysis evaluate the association between statin and HbA1c. They found that according to the potency, statins increased the risk of new-onset diabetes (41). Roshna Roy et al. carried out a 6-month retrospective study on 270 dyslipidemia patients to estimate the prevalence of statin-induced new onset of diabetes. The prevalence was 7.03%. The main risk factors were rosuvastatin therapy, older patients (equal to or more than 60 years), high dose and longer duration therapy (42). However, Sebhat Erqou et al. found Statin therapy in diabetic patients increases HbA1c modestly (43). The results of a study by Anagnostis et al. showed that rosuvastatin and atorvastatin had no significant effect on HbA1C levels (44). Most studies had small sizes and short follow-up periods todelineate the effect of statins on HbA1c (45). Despite the fact that our study found higher HbA1c levels, the effect of high-potency statins on HbA1c in patients without diabetes is unknown. Maybe the effect is related to the beginning HbA1c, follow-up duration, dose, and type of statins.

Furthermore, the results of this study showed that rosuvastatin and atorvastatin increased AST, ALT, and ALP. An increase in AST was significant in the rosuvastatin group. M. Alberton et al. conducted a meta-analysis on adverse events associated with statin therapy. They found that statin therapy significantly elevated AST and ALT levels. Also, atorvastatin significantly elevated AST levels compared to pravastatin, and simvastatin significantly increased CK levels when compared to rosuvastatin. Higher doses of statins had increased risk of AST elevations (46). The results of a study by Anagnostis et al. showed that there was no statistically significant relationship between statins (i.e., rosuvastatin and atorvastatin) and AST (44). However, the small sample sizes, need further study. The current guidelines state that statin prescriptions are allowed unless baseline AST/ALT levels are less than three times the UNL, and in a patient on statin therapy, when the AST/ALT level exceeds three times the UNL, the statin should be discontinued. Although monitoring the changes in AST/ALT levels is recommended, there are no specific guidelines on this point when AST/ALT is less than three times the UNL. (45). Future studies with a larger sample size need to determine the possible risk factors, statin type, dose, baseline AST/ALT levels, and confounding variables that may affect AST/ALT levels. In this study, there ere no statistically significant relationships between the ALT, ALP, Systolic blood pressure, FBS, diastolic blood pressure, cholesterol, and statins (i.e., rosuvastatin and atorvastatin). The results of a study conducted by Anagnostis et al. on these variables were similar to the findings detected in the present study (44). The present study showed that BMI and weight changes in the atorvastatin treatment group were different from those in the rosuvastatin treatment group. Although atorvastatin had a reduction effect in BMI and weight, we

observed a positive relationship between rosuvastatin treatment and BMI and weight gain. Previous studies have shown conflicting results regarding the relationship between statin and BMI and weight. In a longitudinal study conducted in Japan, Takuya Oikawa et al. have indicated that the use of higher-intensity statins has a positive relationship with participants' BMI (47). While Naglaa F et al. showed a significant decrease in BMI in both atorvastatin and rosuvastatin treated group after 6 months of treatment compared with baseline (48). Nevertheless, more dedicated studies need to be done to elucidate the effect of statins on anthropometric indices.

This study also demonstrated that ejection fraction is higher in treated groups compared with non-treated groups. According to the results, this fraction was more increased after rosuvastatin than after atorvastatin treatment. However, this finding should be interpreted with caution as the p-value of this relationship was exactly equal to 0.05. In line with our findings, John Kjekshus et al. have indicated that treatment with rosuvastatin (10 mg) increases the mean value of ejection fraction by 0.31 (49). In a meta-analysis of coenzyme Q10, which is known to be caused by statins, significant improvements in ejection fraction (an increase of 3.7%) were observed in the treated group (50). In a study conducted by Tamara B et al., a comparison of statin-treated patients and non-statin-treated patients did not show a significant difference in ejection fraction (51).

Strenghths and Limitations

A reduction in the number of patients on the second visit (i.e., two months after treatment with statins) was one of the major limitations of the study, which can be partially prevented by a 10% increase in the sample volume. Another limitation of this study was the season in which the participants were included in the study. In sunny seasons, vitamin D levels were different from those in the autumn and winter; therefore, this difference in the two groups might have an effect on the results, which can be resolved by sampling in a specific season and randomized blocking to compare the differences and establish a uniform distribution in the two groups.

Conclusion

The results of this study revealed that the treatment with rosuvastatin and atorvastatin had no effect on 25-hydroxyvitamin D levels. And it is better to have closed glycemic control and AST/ALT levels in patient under high-potency statin therapy. Accordingly, larger, blinded trials are required to elucidate the impact of statins on 25-hydroxyvitamin D levels.

Acknowledgment

We would like to express our sincere gratitude to all those who supported us throughout the course of this research. We are also grateful to Vice President for Research, Neyshabur University of Medical Sciences for providing the resources and facilities necessary for conducting this research. Special thanks go to the 22 Bahman's hospital staff, who assisted with obtaining crucial materials and research tools.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported financially by the Neyshabur University of Medical Sciences.

Ethical Approval

The study was approved by the Neyshabur University of Medical Sciences Ethics Committee (Ethics Committee No.: IR.NUMS.REC.1394.19).

Conflict of Interests

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Brunton L LJ, Parker K. Goodman & Gilman's The Pharmacological Basis of Therapeutics McGraw-Hill New York, NY. 2011:38.
2. Xu Y, Hashizume T, Shuhart MC, Davis CL, Nelson WL, Sakaki T, et al. Intestinal and hepatic CYP3A4 catalyze hydroxylation of 1α, 25-dihydroxyvitamin D3: implications for drug-induced osteomalacia. Molecular pharmacology. 2006;69(1):56-65.
3. Giovannucci E LY, Hollis BW, RimmEB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Archives of internal medicine. 2008;168(11):6.
4. Ertugrul DT YB, 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. Cardiovascular therapeutics. 2011;29(2):7.
5. Grimes DS HE, Dyer T. Sunlight, cholesterol and coronary heart disease. QJM: An International Journal of Medicine. 1996;89(8):11.
6. Mortimer EA J, Monson RR, MacMahon B. Reduction in mortality from coronary heart disease in men residing at high altitude. The New England journal of medicine. 1977;296(11):5.
7. Burr ML FA, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet. 1989;2(8666):5.
8. Kromhout D BE, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. The New England journal of medicine. 1985;312(19):5.
9. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Archives of internal medicine. 2008;168(11):1174-80.
10. Holick M. Vitamin D deficiency N Engl J Med. 2007; 357: 266–81 doi: 10.1056. NEJMra070553.
11. Stone N, Robinson J, Lichtenstein A, Merz CB, Blum C, Eckel R, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1-S45.
12. Blumenthal RS, Buroker AB, Sq E. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary. 2019.
13. Mirhafez SR, Tajfard M, Avan A, Pasdar A, Nedaeinia R, Aghasizade M, et al. Association between serum cytokine concentrations and the presence of hypertriglyceridemia. Clinical biochemistry. 2016;49(10-11):750-5.

14. Thavendiranathan P BA, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. rchives of internal medicine. 2006;166(21):7.
15. Falagas ME MG, Matthaiou DK, Rafailidis PI. Statins for infection and sepsis: a systematic review of the clinical evidence. The Journal of antimicrobial chemotherapy. 2008;61(4):12.
16. van der Harst P VA, van Gilst WH, Bohm M, van Veldhuisen DJ. Statins in the treatment of chronic heart failure: a systematic review. PLoS medicine. 2006;3(8).
17. Sparks DL KR, Sabbagh MN, Connor DJ, Sparks LM, Liebsack C. Reduced risk of incident AD with elective statin use in a clinical trial cohort. Current Alzheimer research. 2008;5(4):6.
18. Goldstein LB AP, LaMonte M, Gilbert S, Messig M, Callahan A, et al. Relative Effects of Statin Therapy on Stroke and Cardiovascular Events in Men and Women Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. stroke. 2008;39(9):5.
19. Abeles AM PM. Statins as antiinflammatory and immunomodulatory agents: a future in rheumatologic therapy? Arthritis & Rheumatism. 2006;54(2):15.
20. Yavuz B ED, 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? ardiovascular drugs and therapy. 2009;23(4):5.
21. 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. Cardiovascular therapeutics. 2011;29(2):146-52.
22. 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? Cardiovascular drugs and therapy. 2009;23(4):295-9.
23. Mazidi M, Rokni H, Sahebkar AH, Mohammadi A, Ghayour-Mobarhan M, Ferns GA. Simvastatin treatment does not affect serum Vitamin D concentrations in patients with dyslipidemia: A randomized double-blind placebo-controlled cross-over trial. International journal of preventive medicine. 2016;7.
24. Sahebkar A, Reiner Ž, E Simental-Mendía L, Ferretti G, Della Corte C, Nobili V. Impact of statin therapy on plasma vitamin D levels: a systematic review and meta-analysis. Current pharmaceutical design. 2017;23(6):861-9.
25. Mazidi M, Rezaie P, Vatanparast H, Kengne AP. Effect of statins on serum vitamin D concentrations: a systematic review and meta-analysis. European journal of clinical investigation. 2017;47(1):93-101.
26. Ibánez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Revista espanola de cardiologia (English ed). 2017;70(12):1082.
27. Chen Y, Zhang X, Pan B, Jin X, Yao H, Chen B, et al. A modified formula for calculating low-density lipoprotein cholesterol values. Lipids in health and disease. 2010;9(1):1-5.
28. Keshavarz P, Nobakht MGBF, Mirhafez SR, Nematy M, Azimi-Nezhad M, Afin SA, et al. Alterations in Lipid Profile, Zinc and Copper Levels and Superoxide Dismutase Activities in Normal Pregnancy and Preeclampsia. The American journal of the medical sciences. 2017;353(6):552-8.
29. Pérez-Castrillón JL AML, Vega G, del Pino Montes J, de Luis D, Dueñas Laita A. Vitamin D levels and lipid response to atorvastatin. International journal of endocrinology. 2009.
30. Verdoia M SA, Sartori C, Barbieri L, Cassetti E, Marino P, et al. Vitamin D deficiency is independently associated with the extent of coronary artery disease. European Journal of Clinical Investigation. 2014;44(7):9.
31. Ott C, Raff U, Schneider MP, Titze SI, Schmieder RE. 25-hydroxyvitamin D insufficiency is associated with impaired renal endothelial function and both are improved with rosuvastatin treatment. Clinical Research in Cardiology. 2013;102(4):299-304.
32. Pérez-Castrillón JL, Vega G, Abad L, Sanz A, Chaves J, Hernandez G, et al. Effects of atorvastatin on vitamin D levels in patients with acute ischemic heart disease. The American journal of cardiology. 2007;99(7):903-5.
33. Sathyapalan T, Shepherd J, Arnett C, Coady A-M, Kilpatrick ES, Atkin SL. Atorvastatin increases 25-hydroxy vitamin D concentrations in patients with polycystic ovary syndrome. Clinical chemistry. 2010;56(11):1696-700.
34. 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. International journal of endocrinology. 2010;2010.
35. Verdoia M PP, Rolla R, Nardin M, Schaffer A, Barbieri L, et al. Impact of high-dose statins on vitamin D levels and platelet function in patients with coronary artery disease. Thrombosis research. 2017;150:6.
36. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). The American journal of cardiology. 2003;92(2):152-60.
37. Makariou SE, Liberopoulos EN, Agouridis AP, Challa A, Elisaf M. Effect of rosuvastatin monotherapy and in combination with fenofibrate or omega-3 fatty acids on serum vitamin D levels. Journal of Cardiovascular Pharmacology and Therapeutics. 2012;17(4):382-6.
38. Liberopoulos EN, Makariou SE, Moutzouri E, Kostapanos MS, Challa A, Elisaf M. Effect of simvastatin/ezetimibe 10/10 mg versus simvastatin 40 mg on serum vitamin D levels. Journal of cardiovascular pharmacology and therapeutics. 2013;18(3):229-33.
39. Ooba N, Tanaka S, Yasukawa Y, Yoshino N, Hayashi H, Hidaka S, et al. Effect of high-potency statins on HbA1c in patients with or without diabetes mellitus. Journal of pharmaceutical health care and sciences. 2016;2(1):8.
40. Simsek S, Schalkwijk C, Wolffenbuttel B. Effects of rosuvastatin and atorvastatin on glycaemic control in type 2 diabetes—the CORALL study. Diabetic Medicine. 2012;29(5):628-31.
41. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. The Lancet. 2010;375(9716):735-42.
42. Roy R, Ajithan A, Joseph A, Mateti UV. Statin-induced new onset of diabetes in dyslipidemic patients: a retrospective study. Postgraduate Medicine. 2019;131(6):383-7.
43. Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. Springer; 2014.
44. Anagnostis P AF, Slavakis A, Polyzos S, Selalmatzidou D, Panagiotou A, et al. Comparative Effect of Atorvastatin and Rosuvastatin on 25-hydroxy-Vitamin D Levels in Non-diabetic Patients with Dyslipidaemia: A Prospective Randomized Open-label Pilot Study. The Open Cardiovascular Medicine Journal. 2014;8:6.
45. Gumprecht J, Gosho M, Budinski D, Hounslow N. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20–40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes, Obesity and Metabolism. 2011;13(11):1047-55.
46. Alberton M, Wu P, Druyts E, Briel M, Mills E. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM: An International Journal of Medicine. 2012;105(2):145-57.
47. Oikawa T, Sakata Y, Nochioka K, Miura M, Tsuji K, Onose T, et al. Prognostic impact of statin intensity in heart failure patients with ischemic heart disease: a report from the CHART-2 (chronic heart failure registry and analysis in the tohoku district 2) study. Journal of the American Heart Association. 2018;7(6):e007524.
48. Werida R, Khairat I, Khedr NF. Effect of atorvastatin versus rosuvastatin on inflammatory biomarkers and LV function in type 2 diabetic patients with dyslipidemia. Biomedicine & Pharmacotherapy. 2021;135:111179.
49. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. New England Journal of Medicine. 2007;357(22):2248-61.
50. Sander S, Coleman CI, Patel AA, Kluger J, White CM. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. Journal of cardiac failure. 2006;12(6):464-72.
51. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. Journal of the American College of Cardiology. 2004;43(4):642-8.