International Journal of Preventive Medicine

Original Article Open Access

Simvastatin Treatment Does Not Affect Serum Vitamin D Concentrations in Patients with Dyslipidemia: A Randomized Double-blind Placebo-controlled Cross-over Trial

Mohsen Mazidi[1,2], Haleh Rokni[3], Amir Hossein Sahebkar[4], Akram Mohammadi[2], Majid Ghayour-Mobarhan[3,5], Gordon A. Ferns[6]

[1]Key State Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Chaoyang, Beijing, China, [2]University of Chinese Academy of Sciences, Beijing, China, [3]Cardiovascular Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [4]Biotechnology Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [5]Biochemistry of Nutrition Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [6]Division of Medical Education, Brighton and Sussex Medical School, University of Brighton, BN1 9PH, UK

Correspondence to:
Dr. Majid Ghayour-Mobarhan, Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: ghayourm@mums.ac.ir

How to cite this article: 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. Int J Prev Med 2016;7:80.

ABSTRACT

Background: Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are antihyperlipidemic drugs with an established efficacy in stabilizing atherosclerotic plaques and preventing atherogenesis and reducing cardiovascular events. The purpose of this study was to determine the effect of simvastatin on serum Vitamin D status in dyslipidemic patients as Vitamin D status has an impact on monocyte/macrophage function and may also contribute to cardiovascular risk.

Methods: Selected individuals ($n = 102$) were treated with simvastatin (40 mg/day), or matching placebo in a randomized, double-blind, placebo-controlled, crossover trial. Each treatment period (with simvastatin or placebo) lasted for 30 days and was separated by a 2-week washout phase. Serum Vitamin D concentration was assessed pre- and post-treatment.

Results: Seventy-seven completed the trial, noncompliance with the study protocol and drug intolerance or relocation were the causes for drop-out. No significant carry-over effect was observed for the assessed parameters. There was a reduction in the serum levels of low-density lipoprotein cholesterol ($P < 0.001$), total cholesterol ($P < 0.001$), and triglycerides ($P < 0.05$). Nevertheless, simvastatin therapy did not significantly affect serum level of high-density lipoprotein cholesterol and Vitamin D level ($P > 0.05$).

Conclusions: Short-term treatment with simvastatin (40 mg/day) does not have a significant affect on serum levels of Vitamin D.

Keywords: Randomized controlled trial, simvastatin, Vitamin D

INTRODUCTION

Atherosclerosis is the major cause of cardiovascular disease (CVD) and mortality globally.[1] Very recent studies in Iran displayed the prevalence of the obesity,[2]

Access this article online

Quick Response Code:

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/2008-7802.183652

hypertension,[3] and hypercholesterolemia[4] are 30.9%, 23%, and 41.6%, respectively.

The statin group of drugs is widely used to treat hypercholesterolemia in patients at CVD risk.[5] Statins inhibit the rate-limiting enzyme in cholesterol biosynthesis, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, and reduce serum low-density lipoprotein cholesterol (LDL-C) levels substantially.[5] Further to their conventional lipid-modulating effects, statins possess so-called "pleiotropic" properties, which comprise improvement of endothelial function, antioxidant properties, anti-inflammatory properties, plaque stabilization, and inhibition platelet aggregation and thrombus formation.[6] It has been reported that statins treatment may be associated with an improved Vitamin D status,[7-10] but this is not a consistent finding.[11-13] There is emerging evidence suggesting that a decreased Vitamin D concentration might rise the possibility of several conditions including cancers and CVD.[14,15] If statins do have an impact on Vitamin D concentration this could be a reasonable elucidation of the described results of diminished risk of fracture; moreover, reduced risk of malignant illnesses in patients on this class of drugs.[16] Thus, the present randomized controlled study set out to investigate the effects of treatment with simvastatin on serum Vitamin D in a group of dyslipidemic patients who were suitable for statin therapy.

METHODS

Study design and participants

A total of 102 male and female patients, age (20–88 old), who were not formerly receiving lipid-lowering drugs, registered from the Clinics of Ghaem Hospital, a teaching hospital located in Mashhad, Iran, between June 2010 and August 2012. The study was a randomized placebo-controlled cross-over trial; in this study, each patient took simvastatin or a placebo and next crossed over to the substitute. Inclusion criteria were based on the National Cholesterol Education Program-ATP III guidelines.[17] Cardiovascular risk factors were defined as age more than 65 years old, receiving antihypertensive medication or systolic blood pressure of more than 140 mmHg or diastolic blood pressure of more than 90 mmHg, fasting blood glucose (FBG) greater than or equal to 126 mg/dL, positive family history of CVD, smoking, male sex, body mass index (BMI) more than or equal to 30 kg/m^2. History of malignancy, recent history of infections, connective tissue disorders, treatment with immunomodulatory drugs (e.g., corticosteroids), liver or renal disease, leukocytosis (white blood cell count >10,000/L), thrombocytosis (platelet count >450,000 × 10^9/L), and anemia (hematocrit <40%) were the exclusion criteria. Each subject gave informed written consent to participate in the study, which had previously been approved by the Ethics Committee of Mashhad University of Medical Sciences (code: 88585). Each treatment period takes 1 month and there was a 14-day washout between the treatment periods. We asked the people to do not change the lifestyles during the trial also medications. At the first visit, patients were randomly assigned (random number tables) to one of the two treatment regimens. More details of the study have been published elsewhere.[5] Fifty-one patients received 40 mg/day simvastatin for 1 month, and another group (51) received a placebo (same size and color with treatment capsules and filled with starch) for 30 days. After a further 2-week washout period, the patients crossed over to the other form of treatment. The sample size was based on the between-group mean comparison formula, according to the study conducted by Hu *et al*. with confidence interval of 95%, and power of 80% was calculated as for at least 45 subjects for each arm.[18]

Vitamin D measurement

Serum Vitamin D levels were measured using a competitive electroluminescence protein binding assay with the Roche Diagnostics Vitamin D total assay kit (Roche Diagnostics, Mannheim, Germany). The interday precision of this assay has been reported to be 4.9% and 1.9% at mean concentrations of 43.3 and 105 nmol/L, respectively, using the manufacturer's original control material.[19]

Anthropometric and biochemical evaluation

As previously described for each subject, weight, height, and BMI were measured two times (before randomization and at the end of each period observation) according to standard methods previously described.[20] Blood sampling and biochemical analyses were done as previously fully described.[20]

Statistical analysis

SAS software (version 8) (SAS Institute Inc., Cary, NC) was used for statistical analysis. Data were expressed as means ± standard deviation or median and interquartile range. Value assessed for normality using the Kolmogorov–Smirnov test. *T*-test was used for a comparison between before and after treatments. For the analysis, the mixed-model analysis of variance for cross-over studies was used. The differences of these cross-over analyses were compared; they were normally distributed. Bivariate correlations between changes in Vitamin D and biochemical parameters were assessed. $P \leq 0.05$ was reflected significant. The primary end-point was the change in serum fasting lipid profile and Vitamin D after treatment for 4 weeks. The secondary endpoints were changes in fasting blood glucose and high sensitive C-reactive protein (hsCRP).

RESULTS

From 102 patients, who came into the trial, 25 (24.5%) dropped out; hence, the final sample size was 77 (78.2%). Noncompliance with the study protocol ($n = 21$), drug intolerance ($n = 2$), and relocation ($n = 2$) were the

reasons for the drop-out. We failed to find any significant difference ($P > 0.05$) when we compared the baseline data of biochemical and anthropometric factors before the first treatment period with those before the second treatment period. Moreover, no significant difference was found for age, sex, presence of hyperlipidemia, BMI, presence of hypertension, presence of diabetes, and smoking status between the two groups [Table 1].

Effects of simvastatin versus placebo on Vitamin D

Statin therapy did not have a significant effect on serum levels of Vitamin D in either the statin-placebo or the placebo-statin group [$P = 0.90$, Table 2]. Bivariate correlations were assessed between baseline values of Vitamin D and other evaluated biochemical parameters (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides [TGs], FBG, and hs-CRP), as well as between changes in Vitamin D and other parameters during each study period. No significant correlation was found between baseline values of Vitamin D and evaluated biochemical parameters ($P > 0.05$) [Table 3]. Furthermore, significant correlations were observed between serum Vitamin D and the following parameters: FBG (statin-placebo group, second period; $P < 0.01$), TGs (placebo-statin group, second period; $P < 0.05$ and statin-placebo first period; $P < 0.01$), LDL-C (placebo-statin group, first period; $P < 0.05$), and HDL-C (statin-placebo group, first period; $P < 0.05$) [Table 4].

DISCUSSION

The aim of this study was to investigate the impact of simvastatin therapy on serum Vitamin D levels in dyslipidemic patients. Our results showed that simvastatin therapy for 4 weeks (40 mg/day) does not alter serum Vitamin D levels. Previous investigations on the impact of statin therapy on circulating Vitamin D levels have been inconsistent. While atorvastatin[21] and rosuvastatin[22,23] have been shown to raise 25(OH) Vitamin D levels, there are reports with opposite findings showing that HMG-CoA reductase inhibitors do not affect serum Vitamin D concentrations.[23] It is not well known how statins might affect Vitamin D concentration, and numerous potential mechanisms have been put forward.[24] The first and by far the most plausible mechanism regards to the common metabolic fate of statins and Vitamin D. Both 25(OH) Vitamin D, and statins are metabolized in the liver by CYP3A4.[24] Therefore, the occupation of the active site of this enzyme by statins may account for the elevated 25(OH) Vitamin D levels reported in some trials. Ertugrul *et al.* indicated that rosuvastatin (40 mg/day) as monotherapy and rosuvastatin (10 mg/day) plus fenofibrate (200 mg/day) or omega-3 fatty acids (2 g/day) cause substantial elevations in the 25(OH) Vitamin D levels (53%, 64%, and 61%, respectively).[25] Moreover, in study by Thabit *et al.*, they found that simvastatin and atorvastatin, at any dose for duration of more than 1 year, have no additive effect on 25(OH)D level.[26] Unlike rosuvastatin and atorvastatin, no considerable change in Vitamin D concentration has been reported in patients that used fluvastatin.[23] A new randomized controlled trial could not prove an effect of 12 months simvastatin therapy (40 mg/day) on Vitamin D concentration.[27]

The physicochemical characteristics of different statins may also play a role in their differential effects on Vitamin D metabolism.[22,23] The present study had several limitations. First, the study design did not allow adequate time for a new steady-state level of Vitamin D, did not control or report Vitamin D intake, did not analyze for seasonal effects, and the 25(OH) Vitamin D assay was not the MS/MS gold standard. The main strength of the present study was being based on a robust placebo-controlled and cross-over design as well as being conducted in a target population, not under concomitant lipid-lowering therapy. Therefore, many of the confounding factors that may generally affect lipid alterations were eliminated from the present trial.

Table 1: Comparison of baseline characteristics of subjects

Parameter	Statin-placebo	Placebo-statin	*P*
Age (years)	46.00±14.83	44.18±12.07	0.231
Female (%)	36	26	0.124
BMI (kg/m^2)	31.12±6.43	28.83±6.18	0.219
SBP (mmHg)	111±16	109±15	0.423
DBP (mmHg)	66±12	64±13	0.342
Smoker (%)	2	4	0.264
Diabetic (%)	9	3	0.129
Hyperlipidemic (%)	26	27	0.865
Hypertensive (%)	2	6	0.111

Between-group comparisons were assessed using independent-samples *t*-test for normally distributed data, Mann-Whitney U-test for nonparametric data, and Chi-square test for categorical data. Data are presented as mean±SD. BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, SD=Standard deviation

CONCLUSIONS

We found that statin had no significant effect on serum Vitamin D status in dyslipidemic patients. Further

Table 2: Effect of simvastatin versus placebo on Vitamin D status

Parameter	Group	First period		Second period		Treatment effect
		Pretreatment	Posttreatment	Pretreatment	Posttreatment	
Vitamin D (nmol/L)	Stain-placebo	20.27±8.58	20.09±10.35	19.00±10.69	19.72±10.13	*P*=0.90
	Placebo-statin	17.36±8.63	17.05±6.72	16.89±6.83	14.47±5.34	

Values expressed as mean±SD, Statin-placebo group took statin at first, while placebo-statin group received statin following placebo. SD=Standard deviation

Table 3: Correlation between baseline biochemical parameters and Vitamin D in placebo-statin group and statin-placebo group

	Vitamin D			
	Statin-placebo		Placebo-satin	
	R	*P*	*R*	*P*
Total cholesterol	−0.091	0.776	−0.04	0.854
LDL-C	−0.311	0.351	0.039	0.873
HDL-C	0.089	0.780	−0.063	0.796
TGs	0.078	0.808	−0.170	0.485
FBG	−0.073	0.820	−0.126	0.606
hs-CRP	0.459	0.133	−0.018	0.940

Correlations were assessed using Pearson's correlation coefficients. FBG=Fasting blood glucose, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, TGs=Triglycerides, hs-CRP=High sensitive C-reactive protein

Table 4: Correlation between changes in biochemical parameters in two periods of placebo-statin group and statin-placebo

	Vitamin D							
	Statin-placebo				Placebo-statin			
	First period		Second period		First period		Second period	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Total cholesterol	−0.40	0.18	0.05	0.87	0.07	0.76	0.34	0.14
LDL-C	−0.21	0.53	−0.24	0.50	−0.01	0.04	0.26	0.26
HDL-C	−0.70	0.01	0.50	0.11	0.06	0.78	0.29	0.21
TGs	−0.59	0.04	0.48	0.13	0.10	0.67	0.43	0.06
FBS	0.16	0.59	0.84	0.001	0.18	0.43	0.20	0.39
hs-CRP	0.09	0.76	0.39	0.23	−0.10	0.65	0.15	0.52

Correlations were assessed using Pearson's correlation coefficients. FBS=Fasting blood sugar, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, hs-CRP=High sensitive C-reactive protein, TGs=Triglycerides

research might explore the effects of long-term statin therapy on Vitamin D status.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Received: 08 Sep 15 **Accepted:** 17 Apr 16
Published: 08 Jun 16

REFERENCES

1. Glass CK, Witztum JL. Atherosclerosis. The road ahead. Cell 2001;104:503-16.
2. Heidari-Bakavoli AR, Esmaeili H, Hosseini Z, Moohebati M, Azarpazhooh MR, Mazidi M, *et al.* Prevalence of obesity in Iran and its related socio-economic factors. Med J Nutr Metab 2015;8:109-18. DOI:10.3233/MNM-150033.
3. Ebrahimi M, Heidari-Bakavoli AR, Mazidi M, Moohebatia M, Azarpazhooh MR, Nematy M, *et al.* Prevalence of hypertension, pre-hypertension and undetected hypertension in Mashhad, Iran. Mediterr J Nutr Metab 2016:9:1-10.
4. Tabatabaei-Malazy O, Qorbani M, Samavat T, Sharifi F, Larijani B, Fakhrzadeh H. Prevalence of dyslipidemia in iran: A systematic review and meta-analysis study. Int J Prev Med 2014;5:373-93.
5. Moezzi A, Parizadeh SM, Tavallaie S, Mazidi M, Afzali F, Adab A, *et al.* Effects of simvastatin treatment on serum adiponectin concentrations in patients with dislipidemia. Iran Red Crescent Med J 2014;16:e6915.
6. Walter DH, Dimmeler S, Zeiher AM. Effects of statins on endothelium and endothelial progenitor cell recruitment. Semin Vasc Med 2004;4:385-93.
7. Pérez-Castrillón JL, Abad L, Vega G, Sanz-Cantalapiedra A, García-Porrero M, Pinacho F, *et al.* Effect of atorvastatin on bone mineral density in patients with acute coronary syndrome. Eur Rev Med Pharmacol Sci 2008;12:83-8.
8. Aloia JF, Li-Ng M, Pollack S. Statins and Vitamin D. Am J Cardiol 2007;100:1329.
9. Wilczek H, Sobra J, Justová V, Ceska R, Juzová Z, Procházková R, *et al.* Iatropathogenic effect of Mevacor on Vitamin D metabolism. Cas Lek Cesk 1989;128:1254-6.
10. Wilczek H, Sobra J, Ceska R, Justová V, Juzová Z, Procházková R, *et al.* Monitoring plasma levels of vitamin D metabolites in simvastatin (Zocor) therapy in patients with familial hypercholesterolemia. Cas Lek Cesk 1994;133:727-9.
11. Montagnani M, Loré F, Di Cairano G, Gonnelli S, Ciuoli C, Montagnani A, *et al.* Effects of pravastatin treatment on Vitamin D metabolites. Clin Ther 1994;16:824-9.
12. Ismail F, Corder CN, Epstein S, Barbi G, Thomas S. Effects of pravastatin and cholestyramine on circulating levels of parathyroid hormone and Vitamin D metabolites. Clin Ther 1990;12:427-30.
13. Dobs AS, Levine MA, Margolis S. Effects of pravastatin, a new HMG-CoA reductase inhibitor, on Vitamin D synthesis in man. Metabolism 1991;40:524-8.
14. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
15. Giovannucci E, Liu Y, Hollis BW, Rimm EB 25-hydroxyvitamin D and risk of myocardial infarction in men: A prospective study. Arch Intern Med 2008;168:1174-80.
16. Farwell WR, Scranton RE, Lawler EV, Lew RA, Brophy MT, Fiore LD, *et al.* The association between statins and cancer incidence in a veterans population. J Natl Cancer Inst 2008;100:134-9.
17. LaRosa JH. National Cholesterol Education Program: Report of the expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults. J Occup Med 1988;30:826-9.
18. Hu Y, Tong G, Xu W, Pan J, Ryan K, Yang R, *et al.* Anti-inflammatory effects of simvastatin on adipokines in type 2 diabetic patients with carotid atherosclerosis. Diab Vasc Dis Res 2009;6:262-8.
19. Abdel-Wareth L, Haq A, Turner A, Khan S, Salem A, Mustafa F, *et al.* Total Vitamin D assay comparison of the Roche Diagnostics "Vitamin D total" electrochemiluminescence protein binding assay with the chromsystems HPLC method in a population with both D2 and D3 forms of Vitamin D. Nutrients 2013;5:971-80.
20. Kermani T, Mousavi SH, Shemshian M, Norouzy A, Mazidi M, Moezzi A, *et al.* Saffron supplements modulate serum pro-oxidant-antioxidant balance in patients with metabolic syndrome: A randomized, placebo-controlled clinical trial. Avicenna J Phytomed 2015;5:427-33.
21. 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. Am J Cardiol 2007;99:903-5.
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? Cardiovasc Drugs Ther 2009;23:295-9.
23. 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.
24. Xu Y, Hashizume T, Shuhart MC, Davis CL, Nelson WL, Sakaki T, *et al.* Intestinal and hepatic CYP3A4 catalyze hydroxylation of 1alpha, 25-dihydroxyvitamin D(3): Implications for drug-induced osteomalacia. Mol Pharmacol 2006;69:56-65.
25. Ertugrul DT, Yavuz B, Cil H, Ata N, Akin KO, Kucukazman M, *et al.* STATIN-D study: Comparison of the infl uences of rosuvastatin and fl uvastatin treatment on the levels of 25 hydroxyvitamin D. Cardiovasc Ther 2011;29:146-52.

26. Thabit A, Alhifany A, Alsheikh R, Namnqani S, Al-Mohammadi A, Elmorsy S, *et al.* Effect of simvastatin and atorvastatin on serum Vitamin D and bone mineral density in hypercholesterolemic patients: A cross-sectional study. J Osteoporos 2014;2014:468397.

27. 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;2010:957174.