

Is Vitamin D Level Elevated in Patients on Statin Treatment?

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Abstract

Context: Statins are effective agents on both primary and secondary prevention in patients who are at high risk of cardiovascular disease, and the number of patients taking statins has significantly raised recently. **Aims:** The aim of this study was to evaluate the association between Vitamin D levels and statin usage, statin type, dose, and duration. **Settings and Design:** We enrolled 210 control and 174 patients who were taking statins, and whose Vitamin D levels were checked in the past 3 months. 25-hydroxy Vitamin D levels were analyzed by immunoassay. Subgroup analysis was done firstly according to statin types and other lipid-lowering agents, namely fenofibrate. **Subjects and Methods:** Statin dosage's effect on Vitamin D levels were analyzed in patients taking low-dose (10–20 mg/day) and high-dose (40–80 mg/day) atorvastatin. Patients were divided into three groups according to statin usage duration (short term: >1 month, less than a year, medium-term: 1–5 years, long term: >5 years). **Statistical Analysis Used:** Kolmogorov–Smirnov, Kruskal–Wallis, Bonferroni Dunn's multiple comparisons, Spearman rank tests were used. **Results:** About 71.26% of the patient group was using atorvastatin, 13.21% rosuvastatin, 4.59% pitavastatin, and 10.91% were on fenofibrate treatment. Vitamin D levels were statistically different among statin subtypes ($P < 0.001$); the highest level was observed in patients taking atorvastatin (23.03 ± 9.94). Vitamin D levels were statistically significantly higher in short-term and medium-term statin usage than control group ($P < 0.001$). **Conclusions:** Our study demonstrated that even low-dose statin has a positive effect on Vitamin D. Thereby, it encourages patients to continue with statin therapy more willingly.

Keywords: Cardiovascular disease, statin, Vitamin D

INTRODUCTION

Statins are effective agents on both primary and secondary prevention in patients who are at high risk of cardiovascular disease (CVD).^[1–4] Recently, published articles reveal that statins prevent major cardiovascular events including all-cause mortality, cardiovascular mortality, morbidity, repeating cardiovascular events, and ischemic stroke in patients who have CVD.^[5–8] Hence, the number of patients taking statins has significantly raised recently, and this upward trend will continue upon the rising number of high-risk patients and the aging population.^[9–11]

7-dehydrocholesterol (7-DHC) is the precursor of both Vitamin D and cholesterol in mammal tissues;

therefore, statins are expected to affect their metabolism.^[12] Statins diminish production of cholesterol and Vitamin D by reducing 7-DHC; however, there are some studies demonstrating higher serum Vitamin D levels in statin users.^[13,14] Moreover, there are few researches aligning no correlation between statins and Vitamin D levels in the literature.^[15–17]

Our aim in this retrospective cross-sectional study was to evaluate the association between Vitamin D levels and statin usage, group, dose, and duration.

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SUBJECTS AND METHODS

This study was conducted in cardiology and internal medicine outpatient clinics of the hospital between March 2018 and March 2019. Ethical approval was obtained from Local Ethical Committees of the hospital (2018/427).

We enrolled patients who were taking statins, and whose Vitamin D levels were checked in the past 3 months. The control group was consisted of age- and sex-matched patients who were not using statins.

Patients who had Vitamin D replacement in the past 6 months, under treatment which might effect Vitamin D levels, chronic renal failure, malabsorption syndrome, pregnancy, malignancy, under the age of 18 years, and not capable of giving an informed consent were excluded from the study. Seasonal effects on Vitamin D levels were also taken into account; therefore, the patient and control group was balanced on seasons.

Subgroup analysis was done first according to statin subtypes and other lipid-lowering agents, namely fenofibrate. Statin dosage's effect on Vitamin D levels was analyzed in patients taking low-dose (10–20 mg/day) and high-dose (40–80 mg/day) atorvastatin. Besides, patients were divided into three groups according to statin usage duration (short term: >1 month, less than a year, medium term: 1–5 years, long term: >5 years).

Venous blood samples were collected from patients after 12 h of starvation. Each serum sample was aliquoted into two tubes after centrifuge at 1400 rcf for 10 min, and stored at -80°C until it could be analyzed for 25-hydroxy Vitamin D (25[OH]D). Serum 25(OH)D concentrations were analyzed using Beckman Coulter, UniCel DxI800 Immunoassay analyzer (Beckman Coulter Inc, U.S.A.) device by immunoassay method.

Number Cruncher Statistical System (NCSS) 11 (NCSS, 2017 Statistical Software) program was used for statistical analysis. Categorical variables were defined by frequency and percentage values. Continuous variables were defined by mean, standard deviation, median, minimum, and maximum values. Normal distribution of continuous variables was analyzed by Kolmogorov–Smirnov test. Nonnormally distributed variables were analyzed using Kruskal–Wallis test. Bonferroni Dunn multiple comparison tests was used to determine the source of significance difference among groups with more than two variables. Spearman rank test was employed to analyze correlations among numeric variables. Statistical significance was accepted as $P < 0.05$.

RESULTS

A total of 384 patients (210 control group) were included in the study. Totally, the mean age was 61.01 ± 12.21 , and 57.92% ($n = 223$) were female.

About 71.26% of the patients group was using atorvastatin, 13.21% rosuvastatin, 4.59% pitavastatin, and 10.91% was on fenofibrate treatment [Table 1]. Patients Vitamin D level was statistically higher than control group ($P < 0.001$). Vitamin D levels

were statistically different among statin subtypes ($P < 0.001$), when the pitavastatin data excluded due to the number of patients, the highest level was observed in patients taking atorvastatin (23.03 ± 9.94) [Table 1]. In order to find the source of this difference Bonferroni Dunn's multiple comparison tests was applied for statin subtype dosage, duration, and Vitamin D levels. Overall, Vitamin D levels were statistically significantly higher in short-term and medium-term statin usage than control group ($P = 0.002$, $P < 0.001$) [Table 2]. On the other hand, Vitamin D levels were similar among different atorvastatin and rosuvastatin doses and duration [Table 3]. Vitamin D levels were not different among low-dose (10 mg/d) and high-dose (20 mg/d) rosuvastatin short, medium, and long-term usage ($P > 0.05$) [Table 4]. Pitavastatin dosage and duration was not evaluated due to few numbers of patients on pitavastatin treatment.

DISCUSSION

Our study demonstrated that Vitamin D levels are significantly elevated in patients taking atorvastatin ($P < 0.001$). This finding

Table 1: Vitamin D levels according to cholesterol drugs and control group

	Vitamin D (n) Mean. \pm SD Med. (Min.-Max.)	P
Cholesterol drugs		
Atorvastatin	(n=124)%71.26, 23.03 \pm 9.94, 22- (6-59)	$P < 0.001$
Rosuvastatin	(n=23)%13.21, 21.52 \pm 7.83, 21- (6-42)	
Pitavastatin	(n=8)%4.59, 24.5 \pm 12.82, 23- (5-50)	
Fenofibrate	(n=19)%10.91, 18.74 \pm 8.68, 17- (5-38)	
Control group	(n=210), 18.14 \pm 10.21, 16- (3-65)	

Table 2: Vitamin D levels due to statin usage duration

	Vitamin D (n) Mean \pm SD Med. (Min.-Max.)	P
Statin Duration		
Short term (≤ 1 year)	(n=92), 22.34 \pm 10.3, 21- (5-59)	$P < 0.001$
Medium term (2-5 year)	(n=47), 23.58 \pm 8.03, 23- (8-46)	
Long term (≥ 6 years)	(n=31), 21.19 \pm 11.03, 19- (6-52)	
Control group	(n=210), 18.22 \pm 10.13, 16- (3-65)	

Kruskall Wallis H testi

Table 3: Vitamin D levels in atorvastatin users, due to dosage and duration

Atorvastatin	Vitamin D, (n); mean \pm SD; median (minimum-maximum)	P
Low-dose atorvastatin (years)		
Short term (≤ 1)	(41); 22.46 \pm 8.62; 22 (9-44)	> 0.05
Medium term (2-5)	(31); 24.43 \pm 8; 24 (12-46)	> 0.05
Long term (≥ 6)	(15); 23.93 \pm 10.84; 21 (8-46)	> 0.05
High-dose atorvastatin (years)		
Short term (≤ 1)	(19); 24 \pm 12.95; 22 (8-59)	> 0.05
Medium term (2-5)	(5); 24.2 \pm 9.78; 23 (13-40)	> 0.05
Long term (≥ 6)	(10); 17.8 \pm 13.5; 14.5 (6-52)	> 0.05

Kruskal–Wallis H test. SD: Standard deviation

Table 4: Vitamin D levels in rosuvastatin users, due to dosage and duration

Rosuvastatin	Vitamin D, (n); mean ±SD; median (minimum-maximum)	P
Low-dose rosuvastatin (years)		
Medium term (2-5)	(4); 23±5.42; 25 (15-27)	>0.05
Long term (≥6)	(2); 19.5±9.19; 19.5 (13-26)	
High-dose rosuvastatin (years)		
Short term (≤1)	(5); 20.4±13.39; 19 (6-42)	>0.05
Medium term (2-5)	(4); 23.75±9; 22 (16-35)	>0.05
Long term (≥6)	(4); 23.75±9; 22 (16-35)	>0.05

Kruskal–Wallis H test. SD: Standard deviation

is correlated with the findings of Yavuz *et al.*^[13] They also revealed higher 25(OH) D and 1, 25-dihydroxy Vitamin D3 (1, 25[OH] 2D3) in patients under rosuvastatin and atorvastatin treatment.^[13] Meanwhile, Ertugrul *et al.* showed raised 25(OH) D levels with rosuvastatin, whilst fluvastatin was not associated with 25(OH) D.^[18] On the other hand, although there were few patients in pitavastatin group, Vitamin D was high in all kinds of statin subgroups. Similarly, there are plenty of studies demonstrating an elevation in Vitamin D levels in different statin subtypes.^[19,20] Wilczek *et al.* indicated that serum 25(OH) D levels are rising after 3 months of lovastatin 20–80 mg/day usage.^[21] Likewise, simvastatin escalates levels of plasma Vitamin D metabolites and 1,25(OH)2D3 significantly.^[22]

On the other hand, there are some studies displaying no association between statins and Vitamin D in the literature. Pravastatin was found not to be not affecting Vitamin D production in a research conducted on patients who took daily 10–80 mg pravastatin and was exposed to ultraviolet B light for 3 months.^[16] Furthermore, two other studies could not demonstrate a difference in Vitamin D levels between patients who were taking pravastatin 20 mg/day and 40–80 mg/day for 24 and 8 weeks, respectively.^[17,23]

Meanwhile, analysis about the effect of statin usage duration on Vitamin D levels revealed that Vitamin D levels were significantly lower in the control group than short- and medium-term statin users in our study. Pérez-Castrillón *et al.* also demonstrated similar findings in their study conducted in 2007.^[14] Patients who had coronary artery disease and Vitamin D deficiency were given 10–80 mg/day atorvastatin for 12 months, and at the end, mean Vitamin D levels were raised to 18.8 ± 7.6 ng/mL from 16.4 ± 7.6 ($P = 0.003$).^[24] The ratio of patients with Vitamin D deficiency was diminished to 57% after 12 months of statin treatment.^[14] The mechanism of the ability of statins to raise Vitamin D levels is not completely understood yet. While statins decrease both 7-DHC and cholesterol production, Vitamin D levels are expected to deescalate; however, no study has shown a drop in Vitamin D levels in statin users.^[24] According to the hypothesis of Grimes, there is a striking similarity between benefit of Vitamin D and statins which may be related with the activation

of Vitamin D receptors by statins.^[24] Other researchers have also suggested plenty of potential mechanisms about this unexpected rise in Vitamin D with statins.^[12,25,26] First, Vitamin D is metabolized in liver and intestines by CYP3A4, and statins are also metabolized by CYP3A4.^[25] The competition in this common pathway might be associated with increased Vitamin D levels in patients on statin treatment.^[25] Second, 3-hydroxy-3-methylglutaryl-CoA (HmG-CoA) reductase inhibition by statins may be increasing 7-DHC levels in skin which is essential for 25(OH) D synthesis.^[12] This increment can explain bone mineral density increase and bone fracture decrease in statin users.^[12] A research related with this view was done by Aloia *et al.*^[26] They demonstrated higher Vitamin D levels in patients taking statins than who were not on statin treatment (20.51 ± 8.05 vs. 17.31 ± 7.21 ng/mL, respectively) ($P < 0.008$) in a study aimed to show the benefits of Vitamin D3 on bone calcium levels conducted on postmenopausal African American women.^[26]

The main limitations of our study are its single-centered basis and relatively low number of patients. Besides, as this was a cross-sectional study, we did not know initial Vitamin D levels before statin usage; hence, we could not evaluate the rise in Vitamin D levels with statins.

Conclusion

Advances in therapeutic methods led to longer life span, so increased number of patients with CVD and on statins is inevitable. Hence, the effects of statins besides cardiovascular ones will continue to interest researchers. Although our study aligned higher Vitamin D levels in statin users, large scale comprehensive studies are needed to validate these results.

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Conflicts of interest

There are no conflicts of interest.

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