RESEARCH

Cardiovascular Therapeutics

STATIN-D Study: Comparison of the Influences of Rosuvastatin and Fluvastatin Treatment on the Levels of 25 Hydroxyvitamin D

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Several studies have shown that low 25-hydroxyvitamin D levels are associated with higher risk of cardiovascular disease and an increase in 25-hydroxyvitamin D levels protects against cardiovascular disease. In this study, we aimed to compare the effects of rosuvastatin and fluvastatin on vitamin D metabolism. The study population consisted of 134 hyperlipidemic patients who had not previously been treated with lipid lowering medications. Patients were randomized in a 1:1 ratio to rosuvastatin 10 mg or fluvastatin 80 mg XL during the study. Lipid parameters, 25 hydroxyvitamin-D, and bone alkaline phosphatase (BALP) were obtained at baseline and after 8 weeks of rosuvastatin and fluvastatin treatment. Sixty-nine patients were administered rosuvastatin, and 65 patients fluvastatin. Total Cholesterol and LDL cholesterol decreased after 8 weeks of both rosuvastatin and fluvastatin treatments. Rosuvastatin was significantly more effective than fluvastatin on lowering total ($P < 0.001$) and LDL cholesterol ($P < 0.001$). There was a significant increase in 25-hydroxyvitamin D with rosuvastatin treatment ($P < 0.001$), whereas no significant change in 25-hydroxyvitamin D was observed with fluvastatin treatment. Mean BALP fell from 18.5 to 9.6 u/I ($P < 0.001$) with rosuvastatin and from 17.0 to 12.8 with fluvastatin ($P = 0.004$). There was no significant difference in BALP levels between rosuvastatin and fluvastatin treatment ($P = 0.368$). The present study demonstrated that 25-hydroxyvitamin D levels increased with rosuvastatin treatment; whereas fluvastatin treatment had no effect on 25-hydroxyvitamin D. This disparity could be related to the potency or the bioavailability of these two statins. Further studies are needed to clarify the relationship between statins and the vitamin D physiology.

Introduction

Statins are widely used drugs in hypercholesterolemic patients in both primary and secondary prevention [1,2]. These drugs have not only cholesterol lowering effect, but also many pleiotropic effects [3]. One of these pleiotropic effects may be mediated in part by an effect on vitamin D metabolism.

Several studies have shown that low 25-hydroxyvitamin D levels were associated with higher risk of cardiovascular disease and an increase in 25-hydroxyvitamin D levels protects against cardiovascular disease [4–8]. In our previous study, we demonstrated the effect of rosuvastatin on vitamin D metabolism, an increase in 25-hydroxyvitamin D levels after 8 weeks of treatment [9]. There is no study comparing the effects of two statins on the levels of 25-hydroxyvitamin D. In this study, we aimed to assess whether increase in 25-hydroxyvitamin D levels is a class effect of statins, or a pleiotropic effect specific to rosuvastatin. Therefore, we

conducted this randomized study to compare the influences of rosuvastatin and fluvastatin on the levels of 25-hydroxyvitamin D.

Methods

Design and Participants

The study was performed in a prospective, randomized design. In order to minimize the effect of seasonal changes on 25-hydroxyvitamin D levels, the study was conducted between October 2008 and March 2009. All of the patients enrolled in the study were living in Ankara, where these months are considered to be winter, with little exposure to ultraviolet light.

The study population consisted of 134 hyperlipidemic patients who had not previously been treated with lipid lowering medications. Patients with a fasting low-density lipoprotein-cholesterol (LDL-C) > 100 mg/dL after 6 weeks of National Cholesterol Education Program (NCEP) diet were considered hyperlipidemic and enrolled in the study [10]. Patients were randomized in a 1:1 ratio to rosuvastatin 10 mg (Crestor) or fluvastatin 80 mg XL (Lescol XL) during the trial. Eligible subjects underwent a comprehensive medical assessment including documentation of the detailed history, physical examination, and measurement of the essential laboratory variables. Exclusion criteria were alcoholism (>20 g/day alcohol), malignancy (all types of malignancy including basal cell carcinoma), hypercalcemia, hypocalcemia, and hyperparathyroidism. Patients who were on phosphorus-calcium modifying drugs before and after treatment were excluded. Patients who were already receiving fibrate or other statins were also excluded.

According to NCEP ATP III guideline, rosuvastatin (10 mg) (Crestor) or fluvastatin 80 mg XL (Lescol XL) were given to the subjects as primary or secondary prevention. Lipid parameters, 25-hydroxyvitamin D, renal and liver function tests, electrolytes, bone alkaline phosphatase (B-ALP) were obtained at the baseline and after 8 weeks of treatment. The Local Ethics Committee approved the study, and all patients gave informed consent.

Laboratory Analyses

Fasting blood samples were obtained by the venipuncture of the large antecubital veins of the studied patients without stasis, after a 12-h fast. The samples were then centrifuged immediately; the serum and plasma (EDTA) were separated and stored at −80°C. In order to avoid variation, all samples were studied on the same day and the same kit.

The measurements of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) employing the routine procedures were performed at 37°C on a Konelab analyzer (Konelab 60İ, Thermo Scientific, Vantaa, Finland) with commercial test kits from Thermo Scientific following the IFCC reference methods. The serum creatinine was measured with the alkaline picrate (Jaffe) method (Lot No: C092, Konelab).

Serum cholesterol (Lot No: B540, Konelab) levels were measured by cholesterol oxidase without triglyceride blank. The measurement range is 0.2–15.0 mmol/L and extended measuring range after secondary dilution is 0.2–45.0 mmol/L. The within run and betweenday CV (Coefficient of variation) are 1.1–2.0%, respectively, at 3.9 mmol/L and 0.9–0.9% at 6.3 mmol/L.

Triglyceride (Lot No: C186, Konelab) levels were measured with enzymatic (glycerol phosphate oxidase and peroxidase) colorimetric method. The measurement range is 0.05–11.0 mmol/L and extended measuring range after secondary dilution is 0.05–55.0 mmol/L. The within run and betweenday CV are 1.0–2.5%, respectively, at 1.10 mmol/L and 1.0–2.5% at 2.84 mmol/L.

Low-density lipoprotein-cholesterol (Lot No: C435, Konelab) were measured with the homogeneous enzymatic colorimetric test, where in the presence of magnesium ions, a sugar compound markedly reduced the enzymatic reaction for the cholesterol measurement in VLDL and chylomicrons. The combination of a sugar compound with detergent enables the selective determination of LDL-cholesterol in serum. The measurement range is 0.09–11.0 mmol/L and extended measuring range after secondary dilution is 0.09–33.0 mmol/L. The within run and betweenday CV are 1.1–1.1%, respectively, at 2.64 mmol/L and 0.9–1.3% at 4.86 mmol/L.

HDL-C (Lot No: C136, Konelab) were measured with the homogeneous enzymatic colorimetric test, where in the presence of magnesium, dextran sulfate selectively forms water-soluble complexes with LDL, VLDL, and chylomicrons, which are resistant to PEG (Polyethylene glycol) modified enzymes. The concentration of HDL-cholesterol is determined enzymatically by cholesterol oxidase coupled with PEG. The measurement range is 0.16–2.80 mmol/L and extended measuring range after secondary dilution is 0.16–8.40 mmol/L. The within run and betweenday CV are 0.5–1.6%, respectively, at 1.26 mmol/L and 0.6–1.7% at 2.40 mmol/L.

Osteocalcin was measured with Immulite 1000 (Siemens Healthcare Diagnostics IL, USA) by using osteocalcin kit (Catalog No: LKON1). Serum 25-hydroxyvitamin D and B-ALP levels were measured by RIA. 25OH-VIT.D3-RIA-CT kit (Catolog No: KIP1961) (Biosource, Neville, Belgium) was used. Bone alkaline phosphatase level was measured by Ostease IRMA kit

Table 1 Demographic characteristics and medications of patients

	Rosuvastatin 10 mg (n = 69)			Fluvastatin 80 mg XL (n = 65)			*P
Age (mean ± SD)	59.7 ± 12.2			57.7 ± 11.3			0.331
Female/male (no., %)	41/28 (59/41%)			44/21 (68/32%)			0.320
Hypertension (no., %)	36 (52%)			26 (40%)			0.158
Diabetes Mellitus (no., %)	19 (28%)			22 (34%)			0.428
β-blocker (no., %)	12 (17%)			14 (22%)			0.544
ACE inhibitor/ARB (no., %)	19 (28%)			18 (28/)			0.984
CCB (no., %)	6 (9%)			15 (23%)			**0.022**
	Baseline	**After treatment**	****P**	**Baseline**	**After treatment**	****P**	
SBP (mmHg)	126.4 ± 9.9	124.3 ± 4.9	**0.029**	125.5 ± 8.4	126.9 ± 4.8	0.118	0.322
DBP (mmHg)	80.2 ± 7.5	80.7 ± 6.5	0.602	79.9 ± 7.0	79.9 ± 6.9	1	0.556

*P: *P* value between rosuvastatin and fluvastatin.

**P: *P* value between baseline and after treatment.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Continuous variables with normal distribution were expressed as mean ± SD. Variables with skew distribution are expressed as median (minimum–maximum), and categorical variables are expressed as percentage.

(Immunotech, Beckman Coulter, Inc. Fullerton, CA, USA).

Statistical Analyses

Distribution of the continuous variables was determined by the Kolmogorov–Smirnov test. Continuous variables with normal distribution were expressed as mean ± SD. Variables with skew distribution are expressed as median (minimum–maximum), and categorical variables are expressed as percentage. Pearson chi-square test or Fischer test were performed for the comparison of categorical variables. The paired sample *t*-test was used to compare normally distributed variables, and the Wilcoxon rank-sum test for skew distributed variables. Pearson or Spearman analysis, where appropriate, was used to identify correlations between study parameters. For all statistics, a two-sided *P* value < 0.05 was considered to be statistically significant. All analyses were performed with SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

None of the 134 patients with hyperlipidemia recruited into the study withdrew as a result of adverse effects. The majority of the patients were female (63.4%). Forty-six (34%) patients were diabetic, and 60 (45%) patients had systemic hypertension. Sixty-nine patients were administered rosuvastatin, and 65 patients fluvastatin. Demographic data, clinical characteristics, and medications are shown in Table 1.

The effects of rosuvastatin and fluvastatin on biochemical and lipid parameters are listed in Table 2. Total cholesterol and LDL-C decreased after 8 weeks of both rosuvastatin and fluvastatin treatment. Rosuvastatin was significantly more effective than fluvastatin on lowering total ($P < 0.001$) and LDL cholesterol ($P < 0.001$). There was no significant change in HDL-C with rosuvastatin and fluvastatin.

There was a significant increase in 25-hydroxyvitamin D from 11.8 to 35.2 ng/mL ($P < 0.001$) with rosuvastatin treatment, whereas no significant change in 25-hydroxyvitamin D was observed with fluvastatin treatment. Rosuvastatin significantly increased 25-hydroxyvitamin D levels compared to fluvastatin ($P < 0.001$). The box plot graphic of 25-hydroxyvitamin D levels with rosuvastatin and fluvastatin treatment was shown in Figure 1. The levels of 1,25-hydroxyvitamin D significantly increased after rosuvastatin treatment. However, no significant difference was found with fluvastatin (Table 3). There was no significant difference in increment of 1,25-hydroxyvitamin D levels between rosuvastatin and fluvastatin ($P = 0.144$). Mean bone alkaline phosphatase fell from 18.5 to 9.6 u/I ($P < 0.001$) with rosuvastatin and from 17.0 to 12.8 with fluvastatin ($P = 0.004$). There was no significant difference in BALP levels between rosuvastatin and fluvastatin treatment ($P = 0.368$). There was no significant change in the levels of osteocalcin, calcium, and phosphate with rosuvastatin and fluvastatin treatment (Table 3).

There was no statistically significant difference between rosuvastatin and fluvastatin receiving subjects

Table 2 Biochemical parameters before and after rosuvastatin and fluvastatin treatment

	Rosuvastatin 10 mg (n = 69)			Fluvastatin 80 mg XL (n = 65)			*P
	Baseline	After treatment	**P	Baseline	After treatment	**P	
FPG (mmol/L)	5.4 (4.3–14.8)	5.3 (4.2–14.7)	0.922	5.8 (3.8–15.8)	5.8 (3.8–19.9)	0.532	0.313
TG(mmol/L)	2.1 (1.2–5.2)	1.4 (0.2–5.0)	<0.001	2.1 (0.9–5.6)	1.9 (0.3–5.4)	0.016	0.006
TC (mmol/L)	6.5 (4.5 -7.7)	4.1 (2.8–6.5)	<0.001	6.3 (4.1–8.6)	4.8 (3.1–7.5)	<0.001	<0.001
LDL-C (mmol/L)	4.4 ± 0.5	2.3 ± 0.7	<0.001	4.4 ± 0.9	3.1 ± 0.9	<0.001	<0.001
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.2	0.281	1.2 ± 0.3	1,2 ± 0.4	0.227	0.103
ALT (U/L)	19.8 ± 11.7	21.2 ± 11.2	0.473	25.4 ± 13.5	26.0 ± 11.4	0.839	0.779
AST (U/L)	19.5 ± 7.3	20.1 ± 5.6	0.190	22.9 ± 11.6	21.7 ± 7.7	0.355	0.239
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.5	0.652	0.9 ± 0.2	0.9 ± 0.1	0.551	0.819
CK (U/L)	42.3 ± 12.1	43.1 ± 18.2	0.337	40.8 ± 12.1	41.3 ± 12.5	0665	0.334

FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, Triglyceride; TC, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotranferease; CK, creatine kinase.

**P*: *P* value between rosuvastatin and fluvastatin.

***P*: *P* value between baseline and after treatment.

Continuous variables with normal distribution were expressed as mean ± SD. Variables with skew distribution are expressed as median (minimum–maximum), and categorical variables are expressed as percentage.

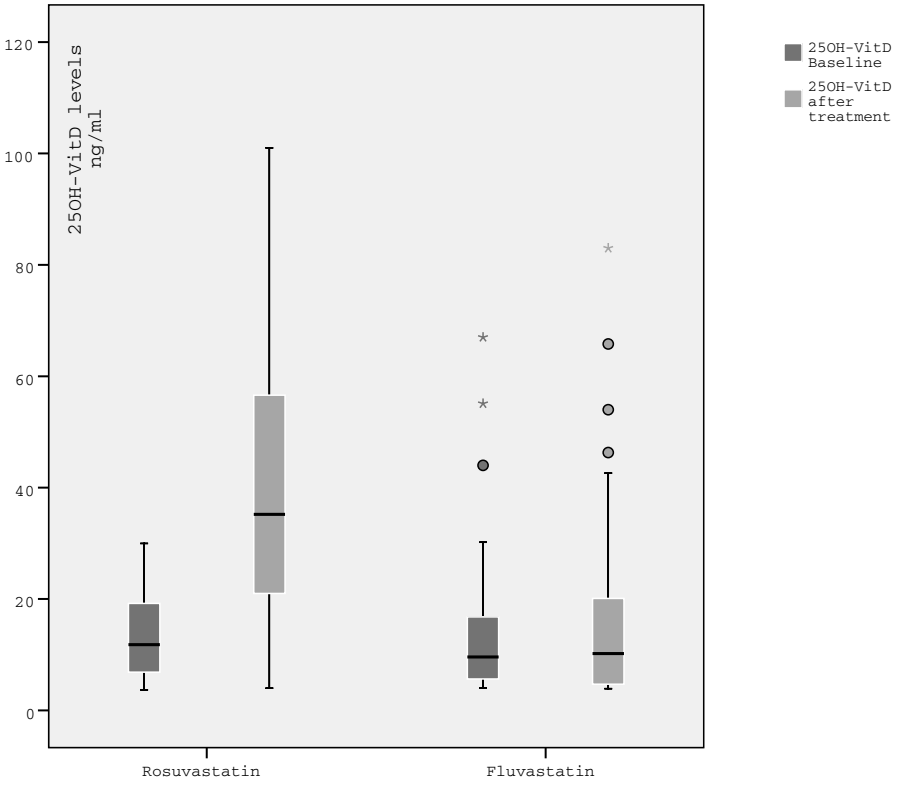

Figure 1 The box plot graphic of 25-hydroxyvitamin D with rosuvastatin and fluvastatin treatment.

with regard to risk factors and medications except calcium channel blockers (CCB) in univariate analyses. Multivariate analyses showed no significant effect of CCB usage on 25 OH vitamin D levels.

Discussion

This randomized study showed that 25-hydroxyvitamin D levels increased significantly with rosuvastatin

Table 3 Bone parameters before and after rosuvastatin and fluvastatin treatment

	Rosuvastatin 10 mg (n = 69)			Fluvastatin 80 mg XL (n = 65)			*P
	Baseline	After treatment	**P	Baseline	After treatment	**P	
25-OHvitD (ng/mL)	11.8 (3.7–30.0)	35.2 (4.0–101.0)	**<0.001**	9.6 (4.0–67.0)	10.2 (3.9–83.0)	0.557	**<0.001**
1,25 OHvitD (pg/mL)	18.3 (5.6–145.0)	24.0(10.5–51.0)	**0.008**	19.4 (2.8–43.0)	20.7 (6.4–56.4)	0.241	0.144
BALP (U/L)	18.4 (2.6–214.0)	9.6 (0.9–21.6)	**<0.001**	17.0 (2.99–258.0)	12.8 (0.7–167.0)	**0.004**	0.368
OCL (ng/mL)	4.3 (1.0–35.0)	4.5 (1.0–24.7)	0.927	4.8 (1.0–32.0)	4.0 (1.2–35)	0.178	0.123
Ca (mg/dL)	9.4 ± 0.6	9.4 ± 0.5	0.774	9.6 ± 0.5	9.4 ± 1.0	**0.041**	0.056
P (mg/dL)	3.1 ± 0.7	3.1 ± 0.5	0.768	3.1 ± 0.7	3.2 ± 0.6	0.181	0.222

25-OHvitD: 25 Hydroxyvitamin D; 1,25 OHvitD: 1,25-hydroxyvitamin D.

BALP, bone alkaline phosphatase; OCL, osteocalcin; P, phosphorus; Ca, calcium.

**P*: *P* value between rosuvastatin and fluvastatin.

***P*: *P* value between baseline and after treatment.

Continuous variables with normal distribution were expressed as mean ± SD. Variables with skew distribution are expressed as median (minimum–maximum), and categorical variables are expressed as percentage.

treatment; however, there was no increase in the levels of 25-hydroxyvitamin D with fluvastatin treatment. This is the first study comparing the effect of two different statins on the levels of 25-hydroxyvitamin D. In our previous study, we demonstrated that 25-hydroxyvitamin D levels increased significantly after 8 weeks of rosuvastatin treatment [9]. There are very few studies in the literature investigating the role of statins on the vitamin D metabolism.

Currently, several studies demonstrated that 25-hydroxyvitamin D may be a novel marker for cardiovascular disease. Melamed et al. have recently shown that a 25-hydroxyvitamin D level lower than 17.8 ng/mL was independently associated with all-cause mortality compared to the general population [11]. Giovannucci et al. reported that men with 25-hydroxyvitamin D levels of 30 ng/mL or greater had approximately half the population risk of myocardial infarction, independent from other cardiovascular risk factors [4].

Statins have unexpected beneficial effects other than lowering LDL-C levels. These pleiotropic effects such as reduction in the rate of transplant rejection, decrease in disease activity score in rheumatoid arthritis, and decrease in number of lesions in multiple sclerosis were achieved with different statin regimens [12]. One of these unexpected beneficial effects is the influences on vitamin D metabolism. Pérez-Castrillón et al. have previously shown that vitamin D levels significantly increased in patients with acute ischemic heart disease after the treatment of atorvastatin [13]. Studies with lovastatin and simvastatin showed similar results in patients with familial hypercholesterolemia [14,15].

There are several studies evaluating the relationship between statin and bone metabolism [16,17]. A *meta*-analysis found fewer hip fractures, improved hip bone mineral density and a decrease in bone alkaline phosphatase levels with statin treatment [16]. The improvement in bone mineral density with the treatment of statins may be caused by the increase in vitamin D levels. However, different statins may not have the same effect on bone. In cell culture experiments, it was demonstrated that inhibition of osteoclastic activity was inversely correlated with the magnitude of a HMG-CoA reductase activity [17].

At equal doses rosuvastatin decreases LDL-C much more efficiently than fluvastatin [18]. We chose fluvastatin as a control group to find out whether efficiency in HMG-CoA reductase inhibition is related to increase in levels of 25-hydroxyvitamin D. Rosenson et al. randomized 55 adults to placebo, pravastatin 40 mg/day, simvastatin 20 mg/day or simvastatin 80 mg/day groups. Only high-dose simvastatin (80 mg/day) produced a significant reduction in bone-specific alkaline phosphatase after 8 week treatment. Their findings suggest that reduced bone turnover may be related to the intensity of HMG-CoA reductase inhibition [19]. In our study, there was no significant difference in BALP levels between rosuvastatin and fluvastatin treatment.

There are very few studies investigating the effect of fluvastatin and rosuvastatin on bone physiology. Bjarnason et al. investigated the effect of fluvastatin on parameters of bone remodeling. Sixty-eight elderly postmenopausal women with osteoporosis and mild hypercholesterolemia were randomly assigned to 12-week open treatment with fluvastatin plus vitamin C or vitamin C only. They found that fluvastatin had no effect on the markers of bone formation (serum total alkaline phosphatase and osteocalcin) [20]. In this study, bone alkaline phosphatase levels were not measured. Galus et al. investigated the role of fluvastatin in early phase of

periosteal osteogenesis model and found no significant proosteogenic potential in mice [21]. Hughes et al. compared the effects of hydrophobic statins (cerivastatin and simvastatin) and hydrophilic statins (rosuvastatin and pravastatin) on osteoclasts *in vitro* and on bone turnover in ovariectomized mice. All of these four statins tested were able to inhibit osteoclast function *in vitro* by preventing the prenylation of small GTPases. The order of potency for inhibiting prenylation *in vitro* was cerivastatin > simvastatin > rosuvastatin > pravastatin [22]. In our study, there was a significant decrease in BALP levels with both rosuvastatin and fluvastatin treatment. However, no increase in 25-hydroxyvitamin D levels with fluvastatin treatment was determined. On the other hand, rosuvastatin treatment resulted in a significant increase in 25-hydroxyvitamin D levels.

The mechanism by which 25-hydroxyvitamin D levels increase during statin treatment is not clarified. CYP3A4 catabolizes vitamin D in liver and intestine [23]. Statins are extensively metabolized by CYP3A4 and CYP3A5. This common catabolic pathway may be responsible for the increased 25-hydroxyvitamin D levels with the statin treatment. Statins can cause drug interactions by inhibiting CYP enzyme system. For example administration of rosuvastatin and simvastatin to patients receiving Warfarin can cause a moderate increase in prothrombin time, requiring a reduction in Warfarin dosage. Fluvastatin is a lipophylic compound whereas rosuvastatin is a hydrophilic statin and has a relatively higher bioavailability. The hydrophilic rosuvastatin has a slow rate of diffusion across cell membranes, but is taken up rapidly by hepatocytes via active transporter proteins such as organic anion transporting polypeptide [24]. Therefore differences in the bioavailability and pattern of liver uptake between fluvastatin and rosuvastatin may explain their different actions on vitamin D metabolism. Further *in vitro* studies are necessary to find out the mechanism underlying the effect of rosuvastatin on vitamin D.

Conclusion

This study shows that 25-hydroxyvitamin D levels increased with rosuvastatin treatment, whereas fluvastatin treatment had no effect on 25 hydroxyvitamin D levels. This disparity could be related to the potency or the bioavailability of these two statins. Further studies are needed to clarify the relationship between statins and the vitamin D physiology.

Conflict of Interest

The authors declare no conflict of interests.

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