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

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Abstract: *Aims:* Low 25-hydroxy-vitamin D [25(OH)D] levels have been associated with increased risk for cardiovascular disease. Conflicting data exist regarding the effect of statins on 25(OH)D levels. The aim of this study was to compare the effect of atorvastatin and rosuvastatin on 25(OH)D levels in non-diabetic patients with dyslipidaemia.

Methods: This was a prospective randomized open-label study. Patients were assigned to atorvastatin 20 mg/day (n=28, age: 56.1±2.2 years, 22 females) or rosuvastatin 10 mg/day (n=24, age: 57.4±1.9 years, 20 females). Total cholesterol (TC), low- (LDL-C) and high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting plasma glucose, insulin, glycosylated haemoglobin A_{1c} (HbA_{1c}) and high sensitivity C-reactive protein (hsCRP) levels were measured, and homeostatic model of assessment insulin resistance (HOMA-IR) was calculated at baseline and 12 weeks post-treatment.

Results: There were no within or between group significant differences in 25(OH)D levels (atorvastatin: 21.7±1.9 ng/ml at baseline and 23.5±2.3 ng/ml at week 12; rosuvastatin: 25.3±1.8 and 27.0±2.4 ng/ml, respectively; p=0.172 and p=0.306 for between groups, respectively). Both statins significantly reduced TC, TG and LDL-C levels, with a greater LDL-C reduction being observed by rosuvastatin.

Conclusion: Atorvastatin and rosuvastatin did not significantly affect 25(OH)D levels in this study.

Keywords: 25(OH)D, atorvastatin, glucose homeostasis, rosuvastatin, systemic inflammation, vitamin D.

INTRODUCTION

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first-line agents for the treatment of hypercholesterolaemia and have been associated with a substantial reduction in cardiovascular disease (CVD) events [1, 2]. Apart from their lipid-lowering action, these agents exert some cholesterol-independent effects, also known as "pleiotropic effects", such as improve-ment in endothelial function, stabilization of atherosclerotic plaque and inhibition of vascular inflammation and oxidative stress [3]. It has been proposed that some of these actions may be partly mediated through their effect on vitamin D metabolism [4, 5]. In this regard, some studies have shown a beneficial effect of statins on 25-hydroxy-vitamin D [25(OH)D] levels, the main indicator of vitamin D status [4-7]. However, other studies have not shown any effect [8-10], although various doses of statins and different populations were studied. The effect of statins on vitamin D status may be relevant because there is some evidence that suggests that low 25(OH)D levels are associated with increased CVD morbidity and mortality [11, 12].

The aim of the present study was to evaluate the comparative effect of atorvastatin and rosuvastatin at equivalent doses on 25(OH)D levels in non-diabetic patients with dyslipidaemia, who have not met the goals for low-density lipoprotein cholesterol (LDL-C).

MATERIALS AND METHODS

Study Design and Subjects

This was a 12-week prospective randomized open-label pilot study conducted at the Department of Endocrinology in Hippokration General Hospital (Thessaloniki, Greece), a tertiary referral center for endocrinology and diabetes. The study was conducted from September 2011 to April 2012. It

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was approved by the local ethics committee and all the participants provided their informed consent.

We included patients ≥18 years of age with dyslipidaemia not meeting the goal for LDL-C, according to the European Society of Cardiology (ESC) and the European Atherosclerosis Society guidelines for the management of dyslipidaemias [13]. Exclusion criteria were: 1) diabetes mellitus (DM) or treatment with any anti-diabetic medication; 2) malignancy; 3) thyroid or parathyroid dysfunction; 4) hypercalcemia or hypocalcemia; 5) pregnancy or breast feeding; 6) a history of adverse reaction to statins; 7) transaminase level >2x and creatine kinase (CK) >3x the upper limit of normal range; 8) use of the following medications within a 3-month period before screening: cholecalciferol or other vitamin D supplementation, calcium supplementation, lipid-lowering or anti-obesity agents and corticosteroids.

At screening, physical examination and laboratory assessment were performed, including lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG)], fasting plasma glucose, haemoglobin A_{1c} (HbA_{1c}), urea, creatinine, uric acid, CK, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Anthropometric parameters, such as body mass index (BMI), systolic and diastolic blood pressure (BP) and waist circumference (WC) were recorded at the screening visit. LDL-C was calculated according to the Friedewald equation.

Patients were randomly assigned to receive either atorvastatin 20 mg (group A) or rosuvastatin 10 mg (group B) once daily for 12 weeks. Randomization was performed by Microsoft Excel software before baseline assessment. The statin was discontinued and the subjects were withdrawn from the study in case of drug intolerance, pregnancy, AST and/or ALT elevation >3x or CK >10x the upper limit of normal range. We used some serum samples from patients from our previously published study [14], kept at -27^0C, if they fulfilled the present study's criteria. We further extended the study by enrolling 19 patients (during the same seasonal period).

Assessments

All blood samples were obtained between 8:00 and 9:00 am after an overnight fast. Basal laboratory parameters, as mentioned at the screening visit, 25(OH)D, serum insulin and hsCRP levels were measured at baseline and 12 weeks. Insulin resistance (IR) was calculated using the homeostatic model of assessment IR (HOMA-IR), calculated by the following formula: [fasting serum insulin (μIU/L) x fasting plasma glucose (mmol/L)]/22.5 [15].

Biochemical parameters were measured with standard methods using an automated analyzer (Olympus AU2700; Olympus, Hamburg, Germany). Insulin and 25(OH)D were measured with immuno-chemiluminescence (ICMA) on an Immulite 2500 automated immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL); intra-assay and total coefficient of variation (CV) was 3.3-5.5%, and 4.1-7.3% for insulin, and 2.9-5.5% and 6.3-12.9% for 25(OH)D, respectively. hsCRP was measured with latex-enhanced immunonephelometric assay on a BNII analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA; total CV 4.0-5.0%).

Statistical Analysis

Data for continuous variables are presented as mean ± standard error of the mean (SEM). Data for categorical variables are presented as numbers and/or percentages. The normality of distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. The paired t- or Wilcoxon Signed Ranks test was used to assess within variables differences. The independent t- or Mann-Whitney test was used to evaluate between group differences. Pearson's or Spearman's coefficients were used to assess correlations. A two-sided $p < 0.05$ was considered significant. A power calculation could not be performed because of the heterogeneity of previous studies with regard to the population included and baseline 25(OH)D levels. Statistical analysis was performed using SPSS for Windows version 17 (SPSS Inc., Illinois, USA).

RESULTS

Patient Characteristics

In total, 63 patients were randomly assigned to atorvastatin 20 mg⁄day (group A) or rosuvastatin 10 mg⁄day (group B), 4 of which were lost to follow-up and 7 withdrew the drug due to adverse events. Therefore, 52 patients completed the study, 28 from group A (aged 56.1±2.2 years, 22 females) and 24 from group B (aged 57.4±1.9 years, 20 females).

The two groups were comparable at baseline in terms of anthropometric parameters including age, gender, weight, systolic and diastolic BP, BMI and WC. The clinical characteristics of the patients at baseline and at 12 weeks are presented in Table **1**. No significant differences were noted regarding these parameters after treatment.

Effect of Statins on 25(OH)D Levels

There were no statistically significant differences between the two groups at baseline and week 12 in serum 25(OH)D levels. No significant difference was also observed in 25(OH)D levels after treatment within either group (Table **2**).

Effects of Statins on Lipid Levels

There was no significant difference between the two groups in terms of baseline lipid levels (Table **2**). In both groups, TC, TG and LDL-C were significantly decreased after 12 weeks of treatment ($p < 0.001$, for either group), whereas there was a significant reduction in HDL-C levels only in group A ($p=0.007$). The reduction in LDL-C was greater with rosuvastatin (49.4 vs. 41.7%, $p=0.015$) while the reductions in TC and TG levels were similar between the 2 groups (37 vs. 32.9%, respectively; $p=0.05$ and 27.4 vs. 22.5%, respectively; $p=0.168$) (Table **2**).

Table 1. Baseline and 12-week anthropometric and clinical comparative data of both groups.

Variable	Time	Group A (n=28)	Group B (n=24)	*p-value (between groups)*
Female/Male	-	22/6	20/4	0.736
Age (years)	Baseline	56.1±2.2	57.4±1.9	0.673
Body Mass Index (kg/m^2)	Baseline	30.9±0.8	29.7±0.7	0.322
	12 weeks	30.8±0.9	29.9±0.9	
	p-value (within group)	0.697	0.660	
Waist circumference (cm)	Baseline	101.2±2.6	98.5±2.2	0.448
	12 weeks	100.9±2.5	96.7±2.4	0.233
	p-value (within group)	0.788	0.096	
Systolic blood pressure (mmHg)	Baseline	145±4	141±5	0.598
	12 weeks	138±4	133±5	0.406
	p-value (within group)	0.079	0.038	
Diastolic blood pressure (mmHg)	Baseline	86±4	82±2	0.471
	12 weeks	78±2	77±3	0.835
	p-value (within group)	0.093	0.026	

Table 2. Baseline and 12-week serum comparative data of both groups.

Variable	Time	Group A (n=28)	Group B (n=24)	*p-value (between groups)*
Total cholesterol (mg/dl)	Baseline	284±8	275±7	0.388
	Month 3	188±6	172±6	0.050
	p-value (within group)	<0.001	<0.001	
Triglycerides (mg/dl)	Baseline	166±14	150±14	0.434
	Month 3	117±10	100±7	0.168
	p-value (within group)	<0.001	<0.001	
HDL-C (mg/dl)	Baseline	60±2	60±3	0.965
	Month 3	55±2	59±3	0.264
	p-value (within group)	0.007	0.711	
LDL-C (mg/dl)	Baseline	192±6	185±5	0.464
	Month 3	110±5	94±5	0.015
	p-value (within group)	<0.001	<0.001	
25(OH)D (ng/ml)	Baseline	21.7±1.9	25.3±1.8	0.172
	Month 3	23.5±2.3	27.0±2.4	0.306
	p-value (within group)	0.205	0.306	
Serum calcium (mg/dl)	Baseline	9.4±0.1	9.5±0.1	0.442
	Month 3	9.2±0.1	9.5±0.1	0.133
	p-value (within group)	0.069	0.443	
Serum phosphate (mg/dl)	Baseline	3.6±0.2	3.5±0.1	0.615

Table 2. Contd…..

Variable	Time	Group A (n=28)	Group B (n=24)	*p-value (between groups)*
	Month 3	3.6±0.1	3.5±0.1	0.436
	p-value (within group)	0.698	0.696	
Serum glucose (mg/dl)	Baseline	94.3±2.1	91.0±2.4	0.319
	Month 3	95.0±2.2	90.0±2.3	0.146
	p-value (within group)	0.738	0.703	
Insulin (μIU/ml)	Baseline	6.7±1.0	6.7±0.8	0.992
	Month 3	7.6±1.2	5.2±0.7	0.091
	p-value (within group)	0.722	0.048	
HOMA-IR	Baseline	1.75±0.28	1.52±0.19	0.497
	Month 3	1.59±0.23	1.16±0.16	0.191
	p-value (within group)	0.318	0.061	
HbA1c (%)	Baseline	5.6±0.1	5.5±0.1	0.577
	Month 3	5.7±0.1	5.5±0.1	0.363
	p-value (within group)	0.072	0.168	
hsCRP (mg/l)	Baseline	4.1±1.4	2.8±0.5	0.571
	Month 3	3.0±0.7	2.1±0.4	0.407
	p-value (within group)	0.025	0.130	
AST (IU/l)	Baseline	22±1	23±2	0.581
	Month 3	23±1	25±1	0.376
	p-value (within group)	0.320	0.328	
ALT (IU/l)	Baseline	24±2	24±3	0.953
	Month 3	25±2	24±2	0.875
	p-value (within group)	0.490	0.926	
CK (IU/l)	Baseline	103 ±12	111±13	0.648
	Month 3	112±12	123±16	0.557
	p-value (within group)	0.470	0.394	

Abbreviations: LDL-C: low density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment-insulin resistance, HbA1c: haemoglobulin A1c, hsCRP: high sensitivity C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatine kinase.

Effect of Statins on hsCRP Levels and Glucose Metabolism

There were no significant differences between the two groups regarding baseline hsCRP, fasting plasma glucose, HbA_{1c}, insulin and HOMA-IR levels. Regarding systemic inflammation, only atorvastatin significantly reduced hsCRP levels (-13.5%, p=0.025). In terms of glucose homeostasis, only rosuvastatin caused a significant reduction in insulin compared with baseline levels (-8.5%, p=0.048), with a tendency for reduction in HOMA-IR (p=0.061). The effect of both statins on fasting plasma glucose and HbA_{1c} levels was not significant.

CORRELATIONS

Baseline 25(OH)D levels were positively associated with insulin (r_s=0.309, p=0.033) levels and HOMA-IR (r_s=0.335, p=0.019), while no associations with hsCRP, TC, TG, LDL-C, HDL-C, glucose, HbA_{1c} levels or anthropometric parameters was found. Baseline hsCRP was positively associated with BMI (r_s=0.436, p=0.001), WC (r_s=0.426, p=0.002), diastolic BP (r_s=0.289, p=0.04) and HbA_{1c} (r_s=0.358, p=0.011).

Adverse Events

One patient from group A and four from group B reported myalgia, without CK elevation, which resolved after drug discontinuation. One patient reported epigastric pain and another one dizziness in group A, which also resolved after drug withdrawal. No significant difference within or between group was found in serum transaminases, CK, urea, creatinine or uric acid levels (Table **2**).

DISCUSSION

The main finding of this study was that both these potent and widely-prescribed statins did not exert any significant effect on serum 25(OH)D levels. It should be emphasized that the doses of statins used in our study were broadly equivalent, based on the results of the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, in which 10 mg rosuvastatin treatment was equivalent to 20 mg atorvastatin in reducing TC, LDL-C, non-HDL-C and TG [16].

Few studies have been published regarding the effect of statins on vitamin D levels. A beneficial effect of rosuvastatin [4, 5] or atorvastatin [6, 7] has been reported by some authors, while no effect of simvastatin [8], pravastatin [9, 10] or fluvastatin [17] was reported by others. Existing data permit no general conclusions (i.e. whether there is a statin-class effect and to what extent), since different populations have been studied, with various statin doses, different baseline 25(OH)D levels and follow-up intervals. These reasons may partly account for the differences observed compared with our study. A distinct population-related difference in our study compared with the previous ones performed with atorvastatin or rosuvastatin is that the previous studies had enrolled patients with impaired renal or endothelial function [4], diabetes [5], acute ischemic heart disease [6] and polycystic ovary syndrome [7], whereas apparently healthy non-diabetic individuals were enrolled in our study.

Furthermore, limited comparative studies exist dealing with this issue. In a study of hyperlipidaemic patients, 10 mg rosuvastatin increased 25(OH)D levels significantly more compared with 80 mg fluvastatin after 8 weeks of treatment [17]. In a second study of patients with type 2 DM, 10 mg atorvastatin increased 25(OH)D levels more significantly compared with 40 mg simvastatin, after 3 months of treatment [18]. In a third study involving hypercholesterolaemic Greek patients, simvastatin/ezetimibe 10/10 mg was associated with a greater increase in 25(OH)D levels compared with simvastatin 40 mg (36.7 vs. 76.1%) [19]. It should be noted that mean baseline 25(OH)D concentrations in this study (6.7-6.8 ng/ml) were in the severe deficiency range (<10 ng/ml) compared with those in the aforementioned study of simvastatin treatment [8], that showed no effect on vitamin D status [mean baseline 25(OH)D levels 28 ng/ml]. In a fourth study in patients with mixed dyslipidaemia, high daily dose of rosuvastatin (40 mg), was compared with rosuvastatin 10 mg plus fenofibrate 200 mg or rosuvastatin 10 mg plus omega-3 fatty acids 2 g. The increase in 25(OH)D after 3 months of treatment was significant compared with baseline, but comparable among the 3 groups. Again, the patients were vitamin D deficient at baseline [mean 25(OH)D concentrations were <15 ng/ml] [20]. All the above considering, a possible explanation for the null effect of atorvastatin and rosuvastatin on 25(OH)D levels in our study may be that baseline 25(OH)D levels were >20 ng/ml and, thus, any increment would be difficult to achieve by statin administration. The relationship of the magnitude of 25(OH)D increment with baseline 25(OH)D levels has also been supported by others [21].

Regarding the effect of statins on hsCRP levels, only atorvastatin reduced hsCRP levels. Few comparative studies exist, evaluating equivalent statin doses, with rosuvastatin causing similar [22] or greater reduction in hsCRP levels [23]. A recent meta-analysis of randomized trials showed no significant difference between these two statins regarding their effect on hsCRP [24]. The superiority of atorvastatin vs. rosuvastatin found in this study regarding hsCRP is reported for the first time in the literature. Regarding glucose homeostasis, as shown in our previous study [14], the effect of both statins on HbA_{1c} and glucose levels was null, whereas rosuvastatin significantly reduced insulin levels, with a tendency towards reduction in HOMA-IR. The effect of statins on glucose metabolism still remains a matter of debate [25] and it should be emphasized that data from large interventional studies have shown that the CVD risk reduction by statins is greater in patients with type 2 DM than in non-diabetics, thus counteracting a potential increase in CVD risk related to new-onset diabetes mellitus [26].

The strengths of the present study are its prospective randomized design, the stringent inclusion and exclusion criteria and the fact that the two groups were well-matched at baseline. However, we acknowledge certain limitations: the study was open-label rather than blinded, its duration was relatively short and the sample size was small. The differential effect of season and sunlight exposure on 25(OH)D levels in previous studies should also been taken into account when interpreting these data.

In conclusion, atorvastatin and rosuvastatin did not exert a significant effect on serum 25(OH)D levels in this study. Larger, blinded trials are needed to elucidate the impact of statins on 25(OH)D levels.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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