ORIGINAL ARTICLE

No effect of switching to high-dose rosuvastatin, add-on nicotinic acid, or add-on fenofibrate on serum vitamin D levels in patients with mixed dyslipidemia

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Abstract

Background: Low 25-hydroxy-vitamin D [25(OH)VitD] levels may represent a novel cardiovascular disease risk factor. Several statins may increase 25(OH)VitD concentration. The effect of other lipid-lowering drugs is unknown.

Aim: To investigate whether switching to high-dose rosuvastatin, add-on-statin nicotinic acid or add-on-statin fenofibrate would alter 25(OH)VitD levels in patients with mixed dyslipidemia who are already on a conventional statin dose.

Methods: This is a prespecified analysis of a previously published study. Forty-four patients with mixed dyslipidemia not at treatment goal despite treatment with simvastatin 10-40 mg or atorvastatin 10-20 mg or rosuvastatin 5-10 mg were randomly allocated to switch to rosuvastatin 40 mg (n=17), add-on-statin extended release nicotinic acid (ER-NA)/laropiprant (LRPT) (1000/20 mg first four weeks and 2000/40 mg thereafter) (n=14), or add-on-statin micronized fenofibrate (200 mg) for three months. The endpoint for this analysis was between-group difference in changes in 25(OH)VitD levels.

Results: Serum 25(OH)VitD levels did not significantly change in any group. In the switch to the highest dose of rosuvastatin group and the add-on-statin ER-NA/LRPT group there was an insignificant decrease in 25(OH)VitD levels {-4.7% [from 16.8 (3.2-37) to 16.0 (7.9-51.6)] and -14.8% [from 12.8 (2.0-54.8) to 10.9 (2.4-34)], respectively]}, while in the add-on-statin fenofibrate group there was an insignificant increase [+13% (from 14.5 (1.0-42) to 16.4 (4.4-30.4) ng/mL)]. No significant difference between groups was found.

Conclusion: In patients already on a conventional statin dose, neither switching to high-dose rosuvastatin (40 mg) nor add-on-statin ER-NA/LRPT or fenofibrate were associated with significant changes in 25(OH)VitD serum levels.
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Keywords: vitamin D, cardiovascular disease, statins, rosuvastatin, fenofibrate, nicotinic acid, laropiprant

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Introduction

During the last decade a substantial amount of evidence has highlighted the role of vitamin D (VitD) in multiple functions other than bone metabolism and calcium homeostasis. Additionally, VitD deficiency {25-hydroxy-vitamin D [25(OH)VitD] levels <20 ng/mL}, which is very common even in sunny areas, has been associated with various chronic diseases. Among others, VitD deficiency has emerged as a novel cardiovascular disease risk factor, being implicated in the pathophysiology of metabolic syndrome and its components and overall mortality[1,2].

Based on earlier observations linking statin use with fewer hip fractures and improved hip bone mineral density[3], several studies have associated various statins with increases in 25(OH)VitD levels[4-10]. However, the effect of other lipid lowering drugs on serum 25(OH)VitD levels remains largely unknown. In previous studies we showed that high-dose rosuvastatin monotherapy, and the usual-dose rosuvastatin plus fenofibrate, or omega-3 fatty acids were associated with significant and similar increases in 25(OH)VitD levels[11]. In another study, simvastatin 40 mg was associated with a greater increase in 25(OH)VitD levels compared with simvastatin/ezetimibe 10/10 mg[12].

So far there are no data on the effect of switching to the highest dose of the most potent statin, rosuvastatin, from a standard statin dose on 25(OH)VitD levels, or on the effect of add-on-statin nicotinic acid or fenofibrate. Therefore, we aimed to compare the effect of switching to rosuvastatin 40 mg versus add-on-statin extended release nicotinic acid with laropiprant (ER-NA/LRPT) versus add-on-statin micronized fenofibrate (200 mg) in patients with mixed dyslipidemia not at treatment goals despite treatment with a statin at a standard dose. The

endpoint for this analysis was the between-group difference in changes in 25(OH)VitD levels after 3 months of treatment.

Material and Methods

Study population

This was a prespecified analysis of a previously published study[13]. In brief, the participating patients in this study were treated for minimum 3 months with a standard statin dose (10-40 mg simvastatin or 10-20 mg atorvastatin or 5-10 mg rosuvastatin) but their low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C) levels did not reach treatment targets[14]. Exclusion criteria were the existence of chronic kidney or liver disease and triglyceride (TG) levels >500 mg/dL (5.65 mmol/L). Patients with hypertension and/or diabetes could participate in the study only if they were on stable medication for at least three months and had normalized their blood pressure and glucose serum levels. Patients were randomly distributed (without a wash-out phase) to switch to open-label high-dose rosuvastatin (40 mg/ day) or to add-on-statin treatment with ERNA/LRPT (1000/20 mg/day for the first four weeks followed by 2000/40 mg/day for the next eight weeks) or to add-on-statin micronised fenofibrate (200 mg/day) for three months. The study design relates to everyday clinical practice, since usually patients can not achieve lipid targets when treated with a conventional statin dose, thereby raising concerns to the attending physician for the appropriate modification of the treatment regimens. Similar dietary advice was given to all patients according to National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines[14]. Moreover, adherence to treatment and lifestyle habits were assessed by tablet count and an appropriate questionnaire, respectively. Before enrolment, all study participants gave their written informed consent.

For the present analysis we randomly selected 44 patients (22 men and 22 women) to test for 25(OH)VitD serum levels at study onset and end. We took care that all specimens for evaluation were collected during the same season of the year (from late spring till late summer) so as to exclude any sunlight effect on 25(OH)VitD levels (the duration of sunlight is approximately similar during this season in Greece). The study protocol was approved by the Ethics Committee of the University Hospital of Ioannina.

Laboratory measurements

All laboratory assays were performed after an overnight fast and were blindly assessed regarding treatment allocation at baseline and 12 weeks after study onset. The quantitative determination of serum 25(OH)VitD levels was carried out by an enzyme immunoassay method using the reagents from DRG Instruments GmbH kit (DRG, Marburg, Germany). This method has a sensitivity of 3.2 nmol/L (1.28 ng/mL) and an intra- and inter assay variation of 7% for each at the level of 72 and 84 nmol/L (28.8 and 33.6 ng/mL), respectively.

Statistical Analyses

The evaluation of the distribution of each variable (Gaussian or not) was achieved through the use of the Kolmogorov-Smirnoff test. Data are presented as mean and standard deviation apart from the variables with a non-Gaussian distribution, which are presented as median (range). Non-parametric tests were used for variables that did not follow the normal distribution. In order to assess the effect of treatment in each group the paired samples t-test (or the Wilcoxon Signed Ranks test, when required) was used. For comparisons between treatment groups the analysis of covariance (ANCOVA), or the Kruskal-Wallis test for non-parametric variables, adjusted for baseline values, was used appropriately. The significance was designated as $p < 0.05$. The SPSS 18.0 statistical package for Windows (SPSS Inc., 1989-2004, Chicago, IL) was used for the performed analyses.

Results

Originally 100 patients were recruited. Of them, forty-four patients (22 men and 22 women, mean age of 60 ± 10 years) were randomly selected for this analysis. Patients were divided in 3 groups: the switch to high-dose of rosuvastatin (n=17), the add-on-statin ER-NA/LRPT (n=14) and the add-on-statin fenofibrate group (n=13). No significant differences in baseline characteristics were noted among the three groups, including initial 25(OH)VitD levels and estimated glomerular filtration rate (eGFR) (Table 1).

Serum 25(OH)VitD levels did not significantly change in all study groups after three months (Table 2). Specifically, in the switch to high-dose rosuvastatin and add-on-statin ER-NA/LRPT groups, there were non-significant decreases in 25(OH)VitD levels (-4.7% and -14.8%, respectively), while in the add-on-statin fenofibrate group there was a non-significant increase (+13%). Neither the changes in 25(OH)VitD, nor eGFR follow up levels did differ significantly between groups. There was no relationship between 25(OH)VitD changes and eGFR levels.

The high-dose rosuvastatin monotherapy, as well as the add-on-statin ER-NA/LRPT were related to similar decreases in non-HDL-C levels, which were greater in comparison with the add-on-statin fenofibrate treatment. Likewise, high-dose rosuvastatin monotherapy and add-on-statin ER-NA/LRPT were associated with the biggest reduction in LDL-C levels, while add-on-statin fenofibrate was not associated with any change in LDL-C. Notably, add-on-statin ER-NA/LRPT and add-on-statin fenofibrate were found to lead to the greatest TG reduction, while add-on-statin ER-NA/LRPT was also associated with the largest HDL-C levels increment (Table 2).

Discussion

In this analysis, to our knowledge, we showed for the first time that neither the switch to high-dose rosuvastatin, nor add-on-statin ER-NA/LRPT or fenofibrate was associated with significant changes in 25(OH)VitD levels

Table 1: Baseline characteristics of the 44 patients with mixed dyslipidemia not at treatment goal despite treatment with simvastatin 10-40 mg or atorvastatin 10-20 mg or rosuvastatin 5-10 mg. These patients were randomized to switching to high-dose rosuvastatin or add-on-statin nicotinic acid or add-on-statin fenofibrate. The primary end point was between group difference in changes of 25(OH)VitD serum levels after three months of treatment. No significant difference was noted across the three treatment groups regarding baseline characteristics.

	Switch to high-dose rosuvastatin	Add-on-statin ER-NA/LRPT	Add-on-statin fenofibrate	p
N (males/females)	17 (8/9)	14 (7/7)	13 (7/6)	NS
Age (years)	59 ± 11	61 ± 5	59 ± 12	NS
Current smokers (%)	43	50	46	NS
Body weight (kg)	79 ± 10	81 ± 12	88 ± 14	NS
BMI (kg/m^2)	29 ± 2	29 ± 3	31 ± 4	NS
WC (cm)	98 ± 12	98 ± 7	103 ± 12	NS
SBP (mm Hg)	131 ± 11	130 ± 11	129 ± 12	NS
DBP (mm Hg)	78 ± 6	82 ± 10	80 ± 13	NS
LDL-C (mg/dL)	121 ± 40	115 ± 35	112 ± 32	NS
TGs (mg/dL)	190 (173-210)	213 (190-254)	210 (189-260)	NS
HDL-C (mg/dL)	50 ± 9	47 ± 12	45 ± 11	NS
Non-HDL-C (mg/dL)	157 ± 40	156 ± 37	155 ± 34	NS
Glucose (mg/dL)	94 ± 12	98 ± 20	98 ± 12	NS
eGFR (mL/min/1.73 m^2)	86 ± 28	90 ± 29	95 ± 29	NS
25(OH)VitD (ng/mL)	16.8 (3.2-37)	12.8 (2.0-54.8)	14.5 (1.0-42)	NS

BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL-C: low-density lipoprotein cholesterol, TGs: triglycerides, HDL-C: high-density lipoprotein cholesterol, non-HDL-C is calculated as TC minus HDL-C, TC: total cholesterol, eGFR: estimated glomerular filtration rate, 25(OH)Vit D: 25-hydroxy vitamin D. To convert values for triglycerides to mmol/L multiply by 0.01129. To convert values for cholesterol to mmol/L multiply by 0.02586. To convert values for glucose to mmol/L multiply by 0.05551. To convert values for 25(OH)Vit D to nmol/L multiply by 2.5.

Table 2: Serum metabolic parameters at baseline and after three months of drug treatment of the 44 patients with mixed dyslipidemia not at treatment goal despite treatment with simvastatin 10-40 mg or atorvastatin 10-20 mg or rosuvastatin 5-10 mg. These patients were randomized to switching to high-dose rosuvastatin or add-on-statin nicotinic acid or add-on-statin fenofibrate. The primary end point was between group difference in changes of 25(OH)VitD serum levels after three months of treatment. Serum 25(OH)VitD levels did not significantly change in any group and no significant difference between groups was found

	Baseline	**3 months**	**Change %**
TGs (mg/dL)			
Switch to high-dose rosuvastatin	190 (173-210)	152 (140-184)	-20‡
Add-on-statin ER-NA/LRPT	213 (190-254)	128 (119-178)	-40‡,§
Add-on-statin fenofibrate	210 (189-260)	142 (118-170)	-32‡,§
HDL-C, mg/dL (mmol/L)			
Switch to high-dose rosuvastatin	50±9	51±10	+2†
Add-on-statin ER-NA/LRPT	47±12	53±11	+13$^{\dagger,\S,\#}$
Add-on-statin fenofibrate	45±11	48±10	+7‡,§
LDL-C (mg/dL)			
Switch to high-dose rosuvastatin	121±40	93±24	-23$^{\ddagger,\#}$
Add-on-statin ER-NA/LRPT	115±35	93±34	-19$^{\ddagger,\#}$
Add-on-statin fenofibrate	112±32	116±33	+4
Non-HDL-C (mg/dL)			
Switch to high-dose rosuvastatin	157±40	123±23	-22$^{\ddagger,\#}$
Add-on-statin ER-NA/LRPT	156±37	117±34	-25$^{\ddagger,\#}$
Add-on-statin fenofibrate	155±34	144±36	-7†
eGFR (mL/min/1.73 m^2)			
Switch to high-dose rosuvastatin	86±28	85±26	-0.01
Add-on-statin ER-NA/LRPT	90±29	90±26	0
Add-on-statin fenofibrate	95±29	99±27	+0.04
25(OH)VitD (ng/ml)			
Switch to high-dose rosuvastatin	16.8 (3.2-37)	16.0 (7.9-51.6)	-4.7
Add-on-statin ER-NA/LRPT	12.8 (2.0-54.8)	10.9 (2.4-34)	-14.8
Add-on-statin fenofibrate	14.5 (1.0-42)	16.4 (4.4-30.4)	+13.0

TGs: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, non-HDL-C is calculated as TC minus HDL-C, TC: total cholesterol, eGFR: estimated glomerular filtration rate, 25(OH)Vit D: 25-hydroxy vitamin D, $^{\dagger}p < 0.01$ versus baseline levels, $^{\ddagger}p < 0.001$ versus baseline levels, $^{\S}p < 0.01$ versus the switch to rosuvastatin 40 mg group, $^{\#}p < 0.01$ versus the add-on-statin fenofibrate group.

in patients with mixed dyslipidemia not at goal while on treatment with a conventional statin dose.

The possible effect of statins on 25(OH)VitD levels has been previously studied, since the publication of a study which for the first time associated statin use with fewer hip fractures and improved hip bone mineral density[3]. Indeed, several statins were found to increase 25(OH)VitD levels[4-10], which is in contrast to the initial concern that the synthesis of steroids dependent on the cholesterol synthetic pathway, including vitamin D production, would be blocked by statins[15]. On the other hand, other studies found no effect of simvastatin 40 mg[16] or fluvastatin 80 mg[5] on 25(OH)VitD levels compared with placebo. According to our previously published findings, both simvastatin[12] and rosuvastatin[11] were related to increases in 25(OH)VitD serum levels. This observation (i.e. the increase in 25(OH)VitD concentrations with statin therapy) was attempted to be explained by several potential mechanisms. At first, it was proposed that the cause for the increased 25(OH)VitD levels observed in patients on statin treatment is the competition in the cytochrome P450 3A4 (CYP3A4) catabolic pathway, which both catabolises 25(OH)VitD in the liver and intestine[17], as well as extensively metabolizes statins. If this is indeed a potential mechanism for statin's ability to raise vitamin D levels, the least likely statins to increase 25(OH)VitD levels may be the non-CYP3A4 statins (such as pravastatin, rosuvastatin, and pitavastatin). Additionally, studies showed that atorvastatin may be exceptionally good at raising 25(OH)VitD levels, even when compared to simvastatin[4,10]. Another possible mechanism is that the inhibition of the 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase by statins, may lead to an increase in the 7-dehydrocholesterol levels, which is the common precursor of cholesterol and 25(OH)VitD. Thereby this might lead to an accumulation of an abundance of substrate (i.e. 7-dehydrocholesterol) which could subsequently lead to an increased synthesis of 25(OH)VitD by ultraviolet sun radiation of the skin[18].

In our study, the switch to high-dose rosuvastatin (40 mg) from a standard statin dose was not associated with significant changes in serum 25(OH)VitD levels. Previous studies by Yavuz et al[6] and Ertugrul et al[5] have examined the effect of rosuvastatin at 10 and 20 mg daily on 25(OH)VitD levels after eight weeks of treatment and found significant increases in 25(OH)VitD concentrations by 159% and 198%, respectively. These increases were much greater than the ones found in our previous study, in which rosuvastatin 40 mg was associated with a 53% increase in 25(OH)VitD levels after three months of treatment[11]. Additionally, monotherapy with rosuvastatin 40 mg was related to increases of the same degree in 25(OH)VitD levels when compared with rosuvastatin 10 mg plus fenofibrate 200 mg or rosuvastatin 10 mg plus omega-3 fatty acids (2 g), (53%, 64% and 61% respectively)[11]. In the present analysis, the switch to the highest dose of rosuvastatin was not associated with any change in 25(OH)VitD levels. Therefore, the possible positive effect of rosuvastatin on 25(OH)VitD levels may be dose-independent. We have previously showed that simvastatin 40 mg was associated with a more than twice increment in 25(OH)VitD levels as compared to simvastatin/ezetimibe 10/10 mg[12], but it remained inconclusive if this was due to a dose-dependent effect of simvastatin on raising 25(OH)VitD levels or to an extra reduction of VitD intestinal absorption by ezetimibe or maybe both. In the present study, the initial treatment of all patients with either simvastatin 10-40 mg or atorvastatin 10-20 mg or rosuvastatin 5-10 mg may have already affected 25(OH) VitD levels so that the switch to the maximum dose of rosuvastatin caused no further change. However, data from direct comparisons of several statins at various dosages are lacking and safe conclusions cannot be reached.

Moreover, we found that the addition of fenofibrate (200 mg) to a standard statin dose was not associated with significant changes in 25(OH)VitD levels, although there was a trend for increase. Taking into consideration our previous findings, i.e. that the combined treatment with rosuvastatin 10 mg plus fenofibrate 200 mg was related to a 64% increase ($p=0.001$) in 25(OH)VitD levels[11], one may speculate that fenofibrate has limited effect on 25(OH)VitD levels and that the observed increase could be attributed to rosuvastatin alone. However, only studies with fenofibrate monotherapy could answer this question.

Furthermore, the addition of ER-NA/LRPT to a standard statin dose did not significantly affect 25(OH)VitD levels. There are no other data about the effect of ER-NA/LRPT on 25(OH)VitD concentration in the literature. Of note, ER-NA/LRPT has been withdrawn from the market due to a plethora of serious nonfatal side effects[19].

Raising 25(OH)VitD serum levels by lipid-lowering treatment could be clinically important, since VitD deficiency has emerged as a cardiovascular risk factor[20]. Results from large, cross-sectional studies [National Health and Nutrition Examination Survey (NHANES) III][21], as well as from prospective studies[22], have linked 25(OH) VitD deficiency with increased rate of myocardial infarction, and reduced survival, while supplementation may decrease overall mortality[23,24]. Notably, both add-on-statin ER-NA/LRPT[25,26] and fenofibrate studies[27] did not show any clear additional clinical profit compared with statin monotherapy.

The effect of lipid-lowering treatments on 25(OH) VitD serum levels merits further investigation with suitably designed studies to clarify possible benefits in cardiovascular and overall health. Whether optimizing 25(OH)VitD serum status through other ways (for example through sun exposure or prescription of supplements) can prevent or ameliorate various chronic diseases is currently under debate. The Vitamin D and Omega-3 Trial (VITAL), a 5-year, randomized, placebo-controlled trial, involving 20,000 U.S. people, is currently underway in order to examine whether VitD (2000 IU/d) with or without the addition of omega-3 fatty acids 1 gram could prevent cardiovascular disease and cancer in the primary prevention setting[28].

Study limitations and strengths

This is a prespecified analysis of a previous study with an open-label design. A major limitation of this study is that we included no group receiving monotherapy with ER-NA/LRPT or fenofibrate, as statin use must be the basis of any lipid-lowering treatment. Also, study participants did not have identical baseline 25(OH)VitD levels, but they were taken into account as covariates in statistical analysis. Last, the number of patients analyzed is rather small.

On the other hand, this is a clinically relevant study, conferring novel results on the effect of switching to the highest dose of rosuvastatin from a standard statin dose or adding-on-statin nicotinic acid or fenofibrate on 25(OH)VitD levels.

Conclusions

In patients on conventional dose statin neither the switch to the highest dose of rosuvastatin (40 mg) nor the add-on-statin ER-NA/LRPT or fenofibrate were associated with significant changes in 25(OH)VitD serum levels. Larger, prospective studies should establish the exact effect of these lipid lowering regimens on 25(OH)VitD levels. The clinical relevance of improving VitD status in dyslipidemic populations remains to be determined.

Conflict of interest

Authors report no conflict of interest.

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