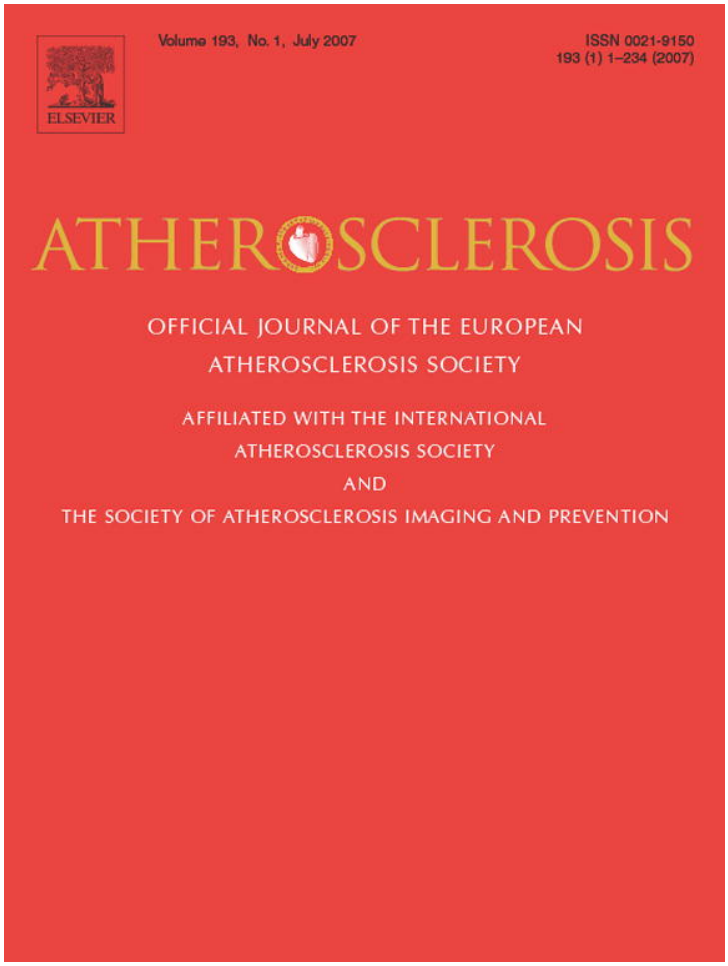

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A new compound-specific pleiotropic effect of statins: Modification of plasma gamma-tocopherol levels☆

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Abstract

Gamma tocopherol (γ-T) is a recognized peroxynitrite scavenger, reputedly metabolized via the cytochrome P450 3A4 (CYP3A4). In this study, we assessed whether equipotent LDL-lowering doses of statins with or without inhibitory activity on CYP3A4 differently affect γ-T metabolism. Patients with ATP III criteria for statin use ($n = 35$) were randomly allocated to treatment with simvastatin 20 mg/day or pravastatin 40 mg/day. Plasma lipids, α-tocopherol (α-T), γ-T as well as the urinary excretion of the γ-T metabolite 2,7,8-trimethyl-2-(2′carboxyethyl)-6-hydroxychroman (γ-CEHC), were determined at baseline and after 6 weeks of treatment. Pravastatin and simvastatin equally reduced LDL-C (-42.8 ± 2.9 and $-42.1 \pm 3.0\%$) and α-T levels (-17.5 ± 4.2 and $-12.2 \pm 4.1\%$), and increased the α-T/LDL-C ratios (51.4 ± 14.6 and $60.4 \pm 15\%$). Conversely, pravastatin did not affect whereas simvastatin significantly augmented plasma γ-T levels ($22 \pm 7.9\%$, $p = 0.009$, between groups $p = 0.0045$). Moreover, the γ-T/LDL-C ratio increased significantly more with simvastatin than with pravastatin (124 ± 23 versus $61.3 \pm 22.1\%$, $p = 0.05$ between groups). In addition, pravastatin but not simvastatin increased the urinary excretion of γ-CEHC ($34.3 \pm 17.3\%$, $p = 0.056$; between groups $p = 0.046$). In conclusion, simvastatin and pravastatin produced distinct effects on γ-T metabolism, presumably as a result of different statin-CYP interactions.

Keywords: Statins; Gamma-tocopherol; Cytochrome P450; Pleiotropic effect

1. Introduction

Some statins are metabolized by the cytochrome P450 superfamily of enzymes [1]. The isoform CYP450 3A4 (CYP3A4) participates in the biotransformation of lovastatin, simvastatin, atorvastatin and many other pharmaceutical compounds, some of which also inhibit its enzymatic activity [2]. Even a short-term consumption of drugs such as azole antifungals, macrolide antibiotics or cyclosporine may reduce the catabolic rate of CYP3A4-metabolized statins, increasing their levels to toxic ranges with substantial risk of a potentially life-threatening episode of rhabdomyolysis. Ample divulgation of this aspect of the statin-CYP3A4 interaction has probably reduced the utilization of iatrogenic drug associations and saved many serious adverse events. Yet, the statin-CYP3A4 interaction may also be considered from a different angle. In in vitro studies, Cohen et al. [3] demonstrated that some statins show an inhibitory effect on CYP3A4 activity, which raises the possibility that these specific compounds increase the concentration of endogenous substances eliminated, at least partly, via this enzyme, such as gamma-tocopherol (γ-T) [4–8].

Even being a minor fraction of circulating tocopherols, γ-T produces distinct antioxidant and anti-inflammatory effects

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not shared by α-tocopherol (α-T) [9–14]. These specific actions of γ-T, and the lack of benefit associated with α-T supplementation in controlled trials [15], shifted the interest from the α-T to the γ-T potential so much to encourage the proposal of γ-T as the new vitamin E [16].

We therefore conducted a prospective investigation of the effect of equipotent LDL-lowering doses of statins, either with (simvastatin) or without (pravastatin) inhibitory effect on CYP3A4, on plasma levels of γ-T and urinary excretion of its CYP3A4-metabolized product 2,7,8-trimethyl-2-(2′carboxyethyl)-6-hydroxychroman (γ-CEHC) [17].

2. Methods

Potential participants were men and women, 35–70 years of age, attending the Clinic for Atherosclerosis Prevention (Centro Cardiologico Monzino, Milan, Italy) who required statin therapy according to the ATP III criteria after a 2-month trial of life-style modifications. Exclusion criteria were: treatment with lipid-lowering compounds in the last 2 months prior to randomization, treatment with other compounds known to modify the activity of CYP3A4 [2], history of statin intolerance, chronic liver disease, serum creatinine > 1.5 mg/dL, serum triglycerides > 350 mg/dL, uncontrolled thyroid disease, primary myopathy or serum CPK > twice the upper limit of normal, and use of any kind of vitamin supplement or antioxidant. The local scientific and ethics committees approved the study and all patients gave written informed consent. Eligible patients were randomly assigned to open-labeled treatment with simvastatin 20 mg/day or pravastatin 40 mg/day for 6-weeks. After baseline determinations, participants were instructed to take one pill/day of the assigned treatment at bedtime and keep constant their diet and level of physical activity throughout the study. At baseline and after 6 weeks of treatment, venous blood and urine were collected after an overnight fast. Serum, EDTA-plasma and urine samples were frozen at −80 °C until analyzed.

Lipid levels were measured by standard methods. Alpha-tocopherol and γ-T plasma concentrations were detected by HPLC, modified from Perugini et al. [18], after previous organic extraction. Briefly, 100 μL of plasma sample were precipitated with ethanol 50% and α- and γ-T were extracted with 1 mL of *n*-hexane. After evaporation to dryness under nitrogen stream of 600 μL of organic extract, the residue was dissolved in ethanol (200 μL). An aliquot (25 μL) was separated using a Discovery C18, 3.5 μm RPcolumn (4.6 mm × 250 mm) (Supelco, USA) eluted with methanol (100%) as mobile phase at flow rate of 1 mL/min. Analysis was carried out by Jasco (Japan) FP15-20 fluorescent detector (λ_{ecc} 292 nm, λ_{em} 335 nm). ESA commercial software was used for the chromatograms integration. Data were obtained after comparison with calibration curves using α- and γ-T pure standard solutions (Sigma, USA). The intra-assay and the inter-assay CV for plasma α-T were 3.3 and 4.0%, respectively; LOQ 0.38 μmol/L. The corresponding values for γ-T were 3.3 and 4.7%, respectively; LOQ 0.014 μmol/L. We assessed the effect of the treatments on indexes of LDL-tocopherol content by calculating changes in α-T/LDL-C and γ-T/LDL-C ratios. Urinary γ-CEHC levels were determined by HPLC modified from Jiang and Ames [11], after previous enzymatic hydrolysis and organic extraction. Briefly, 2.5 mL urine samples were incubated with β-glucuronidase (1 mg/mL) for 4 h at 37 °C. After stopping the reaction (HCl 6N at 4 °C) the samples were extracted with ethyl acetate (4 mL) (3500 rpm × 10′ at 15 °C). After evaporation to dryness under nitrogen stream, the residue was dissolved in ethanol (400 μL) to concentrate the sample. An aliquot (20 μL) was injected onto Simmetry C_{18}, 5 μm RP column (3.9 mm × 150 mm) (Waters, USA) eluted at 30 °C with a mobile phase (10 mM acetate buffer, 32% acetonitrile, and adjusted to pH 4,3 with acetic acid) at a flow rate of 1 mL/min. Analysis was carried out by ESA 5011 cell detector with electrodes settled at +300, +0 mV. ESA commercial software was used for the chromatograms integration. Data were obtained after comparison with calibration curves using γ-CEHC pure standard solution (Sigma, USA). The intra-assay and the inter-assay CV were 7.0 and 7.9%, respectively; LOQ 206.2 nmol/L.

Variables are summarized as means ± SEM, unless otherwise specified. Data were analyzed as percent changes versus baseline. The two treatment groups were compared by analysis of covariance (ANCOVA) adjusting for baseline values. Associations between changes in study parameters were assessed by linear regression and Pearson correlation coefficients. Differences between slopes in the two groups were assessed by ANCOVA. All analyses were two-sided and p values below 0.05 were considered statistically significant. All analyses were performed using the SAS statistical package v.8 (SAS Institute, Cary, North Carolina).

3. Experimental results

A total of 349 patients were screened between September 2003 and April 2005. Candidates were selected among a majority of patients in secondary prevention, mostly on polypharmacy. Forty-four patients were deemed eligible. Two patients prematurely dropped out due to minor side effects. In seven participants, protocol violations were recognized at the final visit: undeclared use of sexual hormones at baseline ($n = 1$) or during the study ($n = 1$), undeclared use of OTC poly-vitamins ($n = 1$), vitamin E ($n = 1$), lanzoprazol ($n = 1$) or diltiazem ($n = 2$). Thus, 35 patients (17 on simvastatin and 18 on pravastatin) were considered assessable *per protocol*. Compliance to study treatments, assessed by pill count, was 98 ± 5% with simvastatin and 96 ± 6% with pravastatin and drug tolerability was acceptable.

Patients assigned to treatment with simvastatin or pravastatin were similarly distributed in terms of age, gender, proportion of subjects in secondary prevention and number

Table 1
Baseline characteristics

	Simvastatin ($n=17$)	Pravastatin ($n=18$)
Age (years)	59.9 ± 9.3	58.7 ± 8.3
Females *N* (%)	5 (29.4)	6 (33.3)
Hypertension *N* (%)	8 (47)	4 (22.2)
Diabetes mellitus *N* (%)	2 (11.7)	4 (22.2)
Smoking status		
Ex-smoker *N* (%)	7 (41.2)	5 (27.8)
Current smoker *N* (%)	3 (17.6)	3 (16.7)
Body mass index (kg/m^2)	25.6 ± 2.9	25.2 ± 2.4
Secondary prevention *N* (%)	6 (35.2)	10 (55.5)
Number of concomitant drugs	2.2 ± 1.9	1.9 ± 2
Total cholesterol (mg/dL)	262 ± 42	250 ± 35
LDL-cholesterol (mg/dL)	181 ± 39	170 ± 30
HDL-cholesterol (mg/dL)	53 ± 13	54 ± 9
Triglycerides (mg/dL)	136 ± 51	131 ± 55
α-Tocopherol (μg/mL)	15 ± 3.5	13.8 ± 2.6
γ-Tocopherol (μg/mL)	0.4 ± 0.17	0.36 ± 0.16
γ-CEHC (ng/mL)	151.0 ± 68.7	111.3 ± 58.0

Numerical variables are reported as means ± S.D.

of concomitant drugs used. Relevant parameters, including baseline plasma levels of LDL-C, HDL-C, triglycerides, α-T, γ-T and γ-CEHC did not significantly differ between groups (Table 1).

Simvastatin 20 mg/day and pravastatin 40 mg/day significantly reduced total cholesterol (TC) and LDL-C levels to a similar extent (−31 ± 2.2 and −33.5 ± 2.2%; −42.1 ± 3.0 and −42.8 ± 2.9%, respectively, $p<0.0001$ versus baseline for all changes, $p>0.44$ between groups for both parameters). Minor changes in HDL-C and triglycerides were observed, without significant differences between groups.

Plasma α-T levels were equally reduced by pravastatin and simvastatin (−17.5 ± 4.2%, $p=0.0002$ and −12.2 ± 4.1%, $p=0.006$, respectively; between groups $p=0.38$). Pravastatin did not significantly affect plasma γ-T levels whereas simvastatin produced a significant increase (−11.9 ± 7.7%, $p=0.13$ and 22 ± 7.9%, $p=0.009$, respectively; between groups $p=0.0045$) (Fig. 1). Opposite changes were induced by pravastatin and simvastatin on the urinary excretion of γ-CEHC (34.3 ± 17.3%, $p=0.05$ and −11.1 ± 18%, $p=0.55$, respectively; between groups $p=0.046$) (Fig. 1).

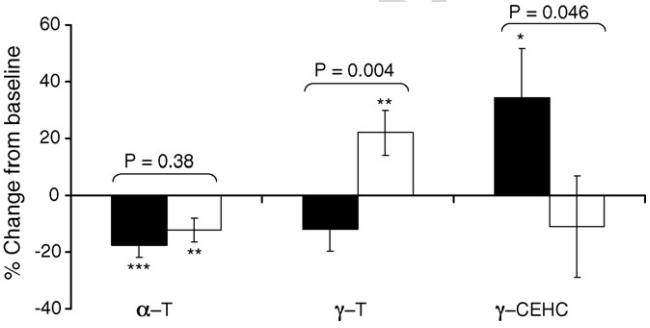

Fig. 1. Effect of pravastatin and simvastatin on plasma level of α-tocopherol (α-T) and gamma-tocopherol (γ-T) and urinary excretion of 2,7,8-trimethyl-2-(2′carboxyethyl)-6-hydroxychroman (γ-CEHC). Solid bars: pravastatin ($n=18$); empty bars: simvastatin ($n=17$). Mean percent changes ± SEM; $^{*}p=0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ vs. baseline.

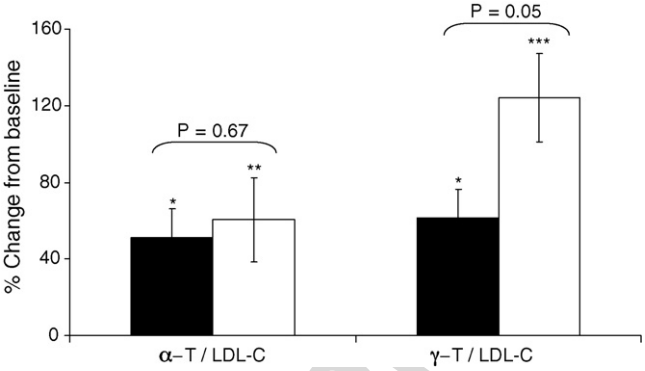

Fig. 2. Effect of pravastatin and simvastatin on the α-tocopherol/LDL-cholesterol (α-T/LDL-C) and the gamma-tocopherol/LDL-cholesterol (γ-T/LDL-C) ratios. Solid bars: pravastatin ($n=18$); empty bars: simvastatin ($n=17$). Mean percent changes ± SEM; $^{*}p<0.01$, $^{**}p<0.001$ and $^{***}p<0.0001$ vs. baseline.

Both compounds increased the α-T/LDL-C ratio to a similar extent (simvastatin 60.4 ± 15%, $p=0.0003$; pravastatin 51.4 ± 14.6%, $p=0.0013$; between groups $p=0.67$). Both statins also increased the γ-T/LDL-C ratio, although simvastatin was significantly more effective than pravastatin (simvastatin 124 ± 23%, $p<0.0001$; pravastatin 61.3 ± 22.1%, $p=0.0091$; between groups $p=0.05$) (Fig. 2).

No significant correlations were found between LDL-C changes and either α-T or γ-T changes in any group. Besides, a negative correlation was observed between changes in plasma levels of γ-T and changes in the urinary excretion of γ-CEHC only in the pravastatin group, although not reaching statistical significance ($r=-0.42$, $p=0.09$). However, the slopes of the regression lines diverged significantly between the two groups (pravastatin $b=-0.98\pm0.58$; simvastatin $b=0.02\pm0.36$, $p=0.035$) (Fig. 3).

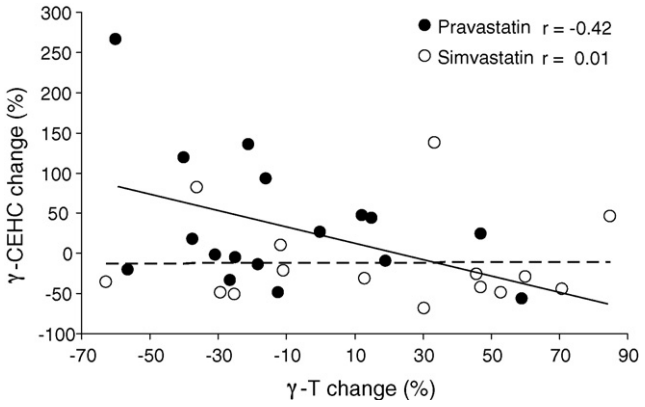

Fig. 3. Correlations between changes in plasma levels of gamma-tocopherol (γ-T) and changes in urinary excretion of 2,7,8-trimethyl-2-(2′carboxyethyl)-6-hydroxychroman (γ-CEHC). Solid line and filled circles: pravastatin; dotted line and empty circles: simvastatin; $p=0.035$ between slopes.

4. Discussion

Statins are effective and well tolerated lipid-lowering compounds that significantly reduce the risk of cardiovascular events and total mortality in high-risk patients [19]. If the antiatherosclerotic efficacy of statins is solely ascribed to their hypocholesterolemic activity or also related to pleiotropic effects is still a matter of intensive debate. The biochemical basis for several pleiotropic effects of statins is the reversible inhibition of mevalonate synthesis, which decreases the concentration of intermediates (isoprenoids) responsible for the modulation of many proteins with relevant cellular functions [20].

We herein describe that simvastatin (but not pravastatin) augment γ-T levels, a new potential pleiotropic effect presumably based on the drug-CYP3A4 interaction. In fact, numerous metabolic studies indicate that γ-T is mostly eliminated by CYP-mediated catabolism [4–8] and, at least in vitro, simvastatin but not pravastatin inhibit CYP 3A4 activity [3]. According to previous studies, drug-mediated CYP inhibition occurs early during administration of inhibitory compounds such as erythromycin or diltiazem [21,22]. Therefore, we speculated that 6 weeks of treatment could be sufficient to detect a potential effect mediated by statin-CYP inhibition. Although theoretically both statins may augment the liver uptake of γ-T, which is transported into endogenous lipoproteins [23,24], γ-T may be promptly eliminated through CYP-mediated catabolism in patients treated with pravastatin, which does not affect CYP activity. On the contrary, the inhibition of CYP 3A4 by simvastatin may drive γ-T from catabolism to recirculation [25], leading to an increase in γ-T levels in plasma. Although kinetic studies are necessary to corroborate this mechanism, both the augmented urinary excretion of the γ-T metabolite γ-CEHC and the negative correlation between changes in plasma γ-T and urinary γ-CEHC with pravastatin but not with simvastatin support this possibility. Moreover, the direction of changes induced by simvastatin in plasma γ-T and urinary γ-CEHC reproduce the effects of the CYP3A4 inhibitor ketoconazole observed in animal studies (8).

Previous studies [26] reported a 20–40-fold greater γ-T concentration in tissues than in plasma. Therefore, even modest changes in plasma γ-T levels, as those observed in this study, might be an index of substantial changes in γ-T tissue concentration, where its antioxidant action could be more physiologically important. The absence of significant correlations between LDL-C changes and γ-T changes with either compound as well as the contrasting effects of equipotent doses of pravastatin and simvastatin, in terms of LDL reduction, suggest that the effects of statins on γ-T metabolism are independent of the lipid-lowering efficacy of the specific drug. Actually, independence of LDL modification is a feature observed with many other pleiotropic effects of statins. Although the different physicochemical properties of the compounds used in this study (i.e. lipophilicity) or other unexplored features apart from the statin-CYP3A4 interaction might explain the contrasting effects on γ-T observed with the two statins considered, our results suggest that simvastatin may modulate CYP3A4 activity in vivo, affecting the metabolism of γ-T and possibly other CYP3A4 substrates. Yet, additional investigations are required to assess in vivo the effect of different statins on CYP 3A4 activity and to substantiate the role of CYP 3A4 inhibition on the changes observed with simvastatin in γ-T metabolism.

Oppositely to their diverging effect on γ-T, both statins similarly reduced the total α-T plasma concentration, which may be explained by the different hepatic fate of tocopherol isoforms. In fact, metabolic studies demonstrate that α-T has a much higher affinity than γ-T for the liver protein tocopherol transfer protein (TTP) [27], which preferentially salvages α-T from catabolism, promoting its incorporation into nascent VLDL and its recirculation. The presence of these different tocopherol pathways is supported by recent in vivo studies in humans with deuterium-labeled tocopherols, showing that whereas γ-T is rapidly metabolized to γ-CEHC, α-T is maintained in the plasma and little is metabolized to α-CEHC [17]. Thus, whereas CYP inhibition results in a significant shift of γ-T from catabolism to recirculation, α-T catabolism is less affected, which may explain the similar effects of simvastatin and pravastatin on total α-T levels.

Both treatments increased the α-T/LDL-C ratio, indicating an enrichment of LDL with α-T, reportedly associated with an augmented resistance of LDL to oxidative modification [28]. Similar effects of statins on α-T have been observed in previous studies [29,30]. Both statins also increased the γ-T/LDL ratio, indicative of an enrichment of LDL with γ-T. However, this effect was significantly higher with simvastatin than with pravastatin. To our knowledge, just two recent studies dealt with the effect of statins on plasma γ-T levels with contrasting results [29,31].

Epidemiological data [32,33] and experimental studies in animals and humans [9–14] showing unique antioxidant and anti-inflammatory actions of γ-T suggest that the changes induced by statins on plasma γ-T levels observed in the present investigation might be clinically relevant. As repeatedly acknowledged, the role of the different pleiotropic effects of statins in the prevention of cardiovascular events has not been thus far fully established [34]. Including the combined measurement of γ-T, indexes of inflammation and markers of oxidative damage in ongoing or future large-scale trials with different statins might help to substantiate the present findings and to assess their association with clinical outcomes.

In conclusion, we show in this study that pharmacological doses of simvastatin but not pravastatin augment γ-T levels, seemingly through the inhibition of the CYP3A4 activity. The herein reported data put forward a new perspective about the statin-CYP3A4 interaction, complementing its well-known role in the rise of statin concentrations up to toxic levels in the context of inappropriate drug associations with a new potentially favorable pleiotropic effect at statin levels within the therapeutic range.

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