Eur J Nutr (2010) 49:111–117
DOI 10.1007/s00394-009-0055-5

ORIGINAL CONTRIBUTION

Very high plant stanol intake and serum plant stanols and non-cholesterol sterols

Helena Gylling · Maarit Hallikainen · Markku J. Nissinen · Piia Simonen · Tatu A. Miettinen

Received: 25 May 2009 / Accepted: 5 September 2009 / Published online: 23 September 2009
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Abstract
Background Today, consumers meet abundant supply of functional foods with plant stanol increments for serum cholesterol lowering purposes. However, efficacy and safety of plant stanols intake beyond 4 g/day have remained unexplored.
Aim of the study We evaluated the effects of very high daily intake of plant stanols (8.8 g/day) as esters on cholesterol metabolism, and serum levels of plant sterols and stanols.
Methods In a randomized, double-blind, parallel study of 49 hypercholesterolemic subjects (mean age 62 years, range 41–73) consumed a test diet without (control, $n = 24$), and with added plant stanol esters (staest, $n = 25$) over 10 weeks followed by 4 weeks on home diet. Serum lipids, lipoprotein lipids, and non-cholesterol sterols were determined at baseline, during intervention, and 4 weeks afterwards. Cholesterol precursor sterol lathosterol reflected cholesterol synthesis, and serum plant sterols and cholestanol mirrored cholesterol absorption.
Results When compared with controls, 8.8 g/day of plant stanols reduced serum and LDL cholesterol by 12 and 17% ($P < 0.01$ for both). Synthesis marker lathosterol was increased by 30%, while absorption markers decreased up to 62% when compared with controls ($P < 0.001$ for both). Serum plant stanols increased slightly, but significantly compared with controls (serum sitostanol during intervention, controls: 16 ± 1 μg/dL, staest: 37 ± 2 μg/dL, serum campestanol during intervention, controls: 0.5 ± 0 μg/dL, staest: 9 ± 1 μg/dL, $P < 0.001$ for both). Changes in serum cholesterol, non-cholesterol sterols, and plant stanols were normalized during post-treatment weeks.
Conclusions Serum plant stanol levels remained at comparable low levels as in studies with daily intake of 2–3 g, and were normalized in 4 weeks suggesting that daily intake of 8.8 g of plant stanols might not increase systemic availability of plant stanols, but reduces effectively serum cholesterol and plant sterol levels.

Keywords Plant stanol ester · Sitostanol · Campestanol · Sitosterol · Cholesterol

H. Gylling (✉) · M. Hallikainen
Department of Clinical Nutrition, University of Kuopio, P.O. BOX 1627, 70211 Kuopio, Finland
e-mail: helena.gylling@uku.fi

H. Gylling
Department of Medicine, Kuopio University Hospital, Kuopio, Finland

M. J. Nissinen
Division of Gastroenterology, Department of Medicine, University of Helsinki, Helsinki, Finland
e-mail: markku.nissinen@dlc.fi

P. Simonen · T. A. Miettinen
Division of Internal Medicine, Department of Medicine, University of Helsinki, Helsinki, Finland

Introduction

Studies dealing with the effects of plant sterol and stanol-enriched diets on serum cholesterol level have shown that the reduction in LDL cholesterol (10–15%) increases up to an intake of about 4 g/day of plant stanols and sterols as esters [10]. Cater et al. [1] showed that a daily intake of 2, 3, and 4 g of plant stanols as their esters reduced LDL cholesterol by 12, 13, and 14%, respectively. Studies with plant sterol esters providing up to 6.6 g/day of plant sterols

revealed up to 12.6% lowering of LDL cholesterol [2], but in another study, the intake of plant sterols up to 9 g/day failed to change LDL cholesterol level [3]. Accordingly, the efficacy of large plant sterol intake is controversial, and respective plant stanol studies are lacking.

The absorption of dietary plant sterols (campesterol and sitosterol) is low when compared with cholesterol, but that of plant stanols (campestanol and sitostanol) is even lower from plant sterols. Even in long-term daily consumption, their serum levels remained relatively low, about 60 μg/dL compared with 30 μg/dL in controls [7]. For comparison, serum campesterol level was 694 μg/dL at baseline, and 399 μg/dL after 1-year study with plant stanol intake of 1.6–2.8 g/day [14]. Consumption of plant stanol ester spread (about 3 g/day of plant stanols) for over 15 years showed only a minor increase in serum plant stanols versus marked reductions in the respective plant sterol and cholesterol values [5]. However, it is not known whether high daily intake of plant stanols could lead to further increased serum plant stanol levels or to enhanced cholesterol synthesis as compared to smaller daily intake of plant stanols in the range of 2–3 g. A high daily intake of plant stanols did not result in undesired effects on serum fat-soluble vitamins and antioxidants or had any harmful effects on safety variables [4]. Thus, hypercholesterolemic subjects consumed plant stanols 8.8 g/day as fatty acid esters, and serum lipids and sterols were recorded before and during the 10-week treatment period. To record the normalization of serum plant stanols, serum samples were analyzed also 4 weeks after the discontinuation of the consumption of plant stanol esters.

Subjects and methods

Subjects

Eighty-four subjects were screened for the study from announcements in a local newspaper in North Savo, Finland. The inclusion criteria were serum cholesterol concentration 4.5–7.5 mmol/L, age 18–75 years, and normal liver, kidney, and thyroid function. The presence of unstable coronary heart disease, inflammatory gastrointestinal disease, diabetes, lipid-lowering medication, or consumption of functional food products were exclusion criteria. Fifty-one subjects were selected for the study. One subject in the intervention group and one in the control group dropped out at the beginning of the study because of infeasibility to use the test drink, and because of starting of cholesterol lowering medication. Altogether, 49 subjects completed the study. The detailed description of the study population has been presented earlier [4]. Briefly, one subject had stable coronary heart disease and six subjects had hypertension. Four subjects used hormone-replacement therapy, and two hormonal contraceptives. Two subjects had beta-blocking agents, two calcium channel blockers, and three angiotensin converting enzyme—or angiotensin-receptor blocking agents for hypertension, and three had beta-blocking agents for arrhythmia. Two were smokers. The subjects gave their written informed consent for the study. The study protocol was approved by the Ethics Committee of the University of Kuopio, Finland.

Study design

The study was randomized, double-blind, placebo-controlled with parallel design with an intervention ($n = 25$) and a control ($n = 24$) group (Table 1). Intervention group consumed vegetable oil-based spread and oat-based drink enriched with plant stanol esters (staest) for 10 weeks, and controls consumed the same products without added plant stanols. The intervention was followed by 4 weeks on home diet.

Routine laboratory measurements were taken to ensure normal health before entry. On weeks 0, 9, 10, and 14 blood samples were drawn after 12 h of fast, and the subjects were weighted.

Diet

The subjects were advised to continue their habitual diet otherwise unchanged, but to replace 20 g/day of their regular fat intake with the test spread (3 g of plant stanols), and to replace 2–4 dL/day of juices, soups, or porridges with fruits or berries with 2.5 dL/day of the test drink (6 g of plant stanols). The daily amount of plant stanols was 8.8 g in the staest products. The staest and control spreads contained small amounts of natural plant sterols (about 0.1 g/daily dose of spread). The oat-based drink contained practically no β-glucan. The detailed composition of the test products was presented earlier [4].

Laboratory measurements

Body weight was measured with a digital scale. Safety variables including blood count, plasma bilirubin and haptoglobin, liver enzymes, plasma glucose and thyroid-stimulating hormone, and fat-soluble vitamins and carotenoids in serum were analyzed and the results are published elsewhere [4]. Serum total, LDL and HDL cholesterol, and serum triglycerides were analyzed using enzymatic methods (Roche Diagnostics, Mannheim, Germany). Serum cholesterol, cholesterol precursor sterol (lathosterol), plant sterols (sitosterol, avenasterol, campesterol), plant stanols (sitostanol and campestanol) and cholestanol, a metabolite of cholesterol, were quantified from non-saponifiable

Table 1 Characteristics of the study population and serum and lipoprotein lipids at baseline and during the study (mean values of weeks 9 and 10)

Variables	Controls ($n = 24$)		Plant stanol ester ($n = 25$)		P^a
	Baseline	Intervention	Baseline	Intervention	
N (M/F)	8/16		9/16		
Age (years)	60.7 ± 1.7		62.9 ± 1.5		
BMI (kg/m^2)	24.1 ± 0.6	24.2 ± 0.7	26.7 ± 0.7[c]	26.8 ± 0.7[c]	0.184
Serum cholesterol (mmol/L)	5.58 ± 0.13	5.52 ± 0.12	5.73 ± 0.14	4.98 ± 0.12[b,c]	<0.001
LDL cholesterol (mmol/L)	3.24 ± 0.08	3.24 ± 0.09	3.44 ± 0.12	2.84 ± 0.11[b,c]	<0.001
HDL cholesterol (mmol/L)	1.75 ± 0.11	1.74 ± 0.10	1.61 ± 0.09	1.64 ± 0.08	0.976
Serum triglycerides (mmol/L)	1.10 ± 0.16	1.18 ± 0.12	1.15 ± 0.08	1.25 ± 0.08	0.739

Mean ± SE

[a] Group by time interaction (repeated measured variance of analysis (general linear model) with adjustment for baseline BMI). Baseline values (except BMI) did not differ significantly between the groups

[b] $P < 0.05$ from baseline

[c] $P < 0.05$ from controls

serum material by capillary gas–liquid chromatography (GLC) (Agilent 6890N Network GC System, Agilent Technologies, Wilmington, DE, USA) equipped with a 50-m long Ultra 2 capillary column (5% phenyl-methyl siloxane) (Agilent Technologies, Wilmington, DE, USA) [12]. The serum values were expressed as concentrations (μg/dL), but also in terms of 10× mmol/mol of cholesterol (called ratio in the text) by dividing the concentrations, with the cholesterol value of the same GLC run to eliminate the changing concentrations of sterol transporters. The ratios to cholesterol of serum cholesterol precursors reflect whole-body cholesterol synthesis, and those of plant sterols and cholestanol cholesterol absorption. Baseline serum cholestanol to cholesterol ratio was divided into tertiles in the whole study population depicting low to high cholesterol absorption.

Statistical analyses

Statistical analyses were performed with SPSS for Windows 14.0 statistics program (SPSS, Chicago, IL, USA). Normality and homogeneity of variance were checked before further analyses. Univariate analysis of variance was used to compare the baseline values and the changes between groups. The analysis of variance for repeated measurements (GLM) was used to analyze the interaction of time and group, changes over time, and the effect and gender in between-group comparisons followed by post hoc comparisons with Bonferroni corrections. At baseline, BMI significantly differed between the groups, so that the adjustment for BMI was performed in all analyses. Pearson, Spearman, or partial correlation coefficients were calculated. Variables not normally distributed even after different transformations, non-homogenous in variance, or non-continuous were tested with non-parametric methods. The results are given as mean ± SE.

Results

Lipid levels did not vary between gender; so that the results were combined. There were no significant differences in any of the essential clinical variables (Table 1) or in the frequencies of diseases, medications, smoking habits, physical activity, or alcohol consumption between the study groups (data not shown) except that BMI was higher in the staest group when compared with controls. After adjustment for BMI, only waist circumference was greater in the staest group compared with controls. BMI was not changed during the treatment (Table 1), and it was not associated with changes in serum lipids and sterols during the study.

Nutrient intakes did not differ between the study groups [4]. The consumption of the test drinks increased flatulence ($P < 0.05$) in both the groups probably because of added polydextrose to test drinks. The actual mean daily intake of plant stanols and sterols was 8.90 ± 0.05 and 0.14 ± 0.00 g in the staest and control groups, respectively. The actual mean daily intake of plant stanols was 8.76 ± 0.04 g (7.18 ± 0.04 g sitostanol and 1.55 ± 0.00 g campestanol) in staest and 0 g in controls.

Serum lipids and lipoproteins

In the staest group, serum and LDL cholesterol concentrations were reduced by 12.8 and 17.3% from baseline and by 12.0 and 17.1% from controls, respectively ($P < 0.001$ for all, Table 1). The higher the baseline serum cholesterol

Table 2 Serum non-cholesterol sterols and stanols

Variables	Controls ($n = 24$)		Plant stanol ester ($n = 25$)		P^a
	Baseline	Intervention	Baseline	Intervention	
μg/dL					
Lathosterol	256 ± 17	255 ± 17	265 ± 20	300 ± 20[b]	0.001
Campesterol	574 ± 42	666 ± 57[b]	540 ± 39	255 ± 20[b,c]	<0.001
Campestanol	0.0 ± 0.0	0.5 ± 0.2	0.0 ± 0.0	9.2 ± 0.9[b,c]	<0.001
Sitosterol	323 ± 26	325 ± 29	283 ± 20	130 ± 9[b,c]	<0.001
Sitostanol	16.8 ± 1.0	16.3 ± 0.8	17.2 ± 1.0	37.4 ± 1.9[b,c]	<0.001
Avenasterol	95 ± 6	101 ± 6	85 ± 3	58 ± 2[b,c]	<0.001
Cholestanol	325 ± 13	309 ± 14[b]	314 ± 13	260 ± 11[b]	0.001
10^2 mmol/mol of cholesterol					
Lathosterol	128 ± 8	130 ± 9	130 ± 9	166 ± 11[b]	<0.001
Campesterol	288 ± 22	337 ± 28[b]	264 ± 20	140 ± 11[b,c]	<0.001
Campestanol	0.0 ± 0.0	0.3 ± 0.1	0.0 ± 0.0	5.1 ± 0.6[b,c]	<0.001
Sitosterol	162 ± 13	164 ± 14	138 ± 9	71 ± 4[b,c]	<0.001
Sitostanol	8.3 ± 0.5	8.2 ± 0.4	8.3 ± 0.4	20.9 ± 1.1[b,c]	<0.001
Avenasterol	47 ± 3	51 ± 3[b]	41 ± 1	32 ± 1[b,c]	<0.001
Cholestanol	163 ± 6	157 ± 6	153 ± 5	143 ± 4	0.360

Mean ± SE

[a] Group by time interaction with adjustment for baseline BMI. Baseline values did not differ significantly between the groups

[b] $P < 0.05$ from baseline

[c] $P < 0.05$ from controls

level, the higher was its absolute reduction ($r = -0.471$, $P = 0.034$) with staest. LDL cholesterol was reduced in 23 out of 25 subjects with staest. No significant changes in HDL cholesterol or serum triglyceride concentrations were found in either group.

Serum non-cholesterol sterols

Concentrations

In the staest group, synthesis marker lathosterol was increased from baseline (Table 2). Plant sterols and cholestanol were decreased from baseline, and plant sterols also from controls. Campestanol and sitostanol were ninefold and twofold increased from baseline and controls. In controls, campesterol was increased and that of cholestanol decreased from baseline.

Ratios to cholesterol

In the staest group, cholestanol ratio remained unchanged during the study, while that of lathosterol was increased by 32% from baseline (Tables 2, 3).

In the staest group, plant sterol ratios were decreased by 22–46% from baseline (Tables 2, 3). Campesterol ratio was increased by 17% in controls indicating that the control-related reduction of campesterol ratio by staest was 62%. At 4 weeks of post-treatment, campesterol ratio was still increased by 8.6 ± 3.3% from baseline in controls ($P < 0.05$).

Table 3 Percentage changes from baseline of serum non-cholesterol sterols and stanols

Variables	Controls ($n = 24$)	Plant stanol ester ($n = 25$)	P^a
Lathosterol	1.8 ± 3.2	31.8 ± 4.9	<0.001
Campesterol	17.1 ± 2.6	−44.9 ± 3.1	<0.001
Sitosterol	2.2 ± 1.9	−46.2 ± 2.6	<0.001
Sitostanol	3.1 ± 5.7	157.9 ± 15.0	<0.001
Avenasterol	9.0 ± 2.1	−22.0 ± 2.4	<0.001
Cholestanol	−3.8 ± 1.0	−6.2 ± 1.3	0.439

Percentage of changes based on ratios to cholesterol, 10^2 mmol/mol of cholesterol

Mean ± SE

[a] Difference between groups (BMI as covariate)

Campestanol and sitostanol ratios were increased with staest from baseline and from controls (Table 2). At 4 weeks of post-treatment, sitostanol concentration was higher in the staest group compared with controls (19 ± 1 vs. 15 ± 1 μg/dL, $P < 0.05$), but did not differ from baseline (Fig. 1). Sitostanol ratio was higher at 14 weeks than at baseline in the staest group, but the ratio did not differ any more from controls (9.4 ± 0.5 vs. 7.8 ± 0.4 mmol/mol of cholesterol, $P < 0.05$ from baseline). No differences in campestanol values were found at week 14 (Fig. 1).

In the two subjects with practically no change in LDL cholesterol during staest, lathosterol ratios were increased by a mean of 27%, and those of campesterol were decreased by a mean of 42% indicating good compliance.

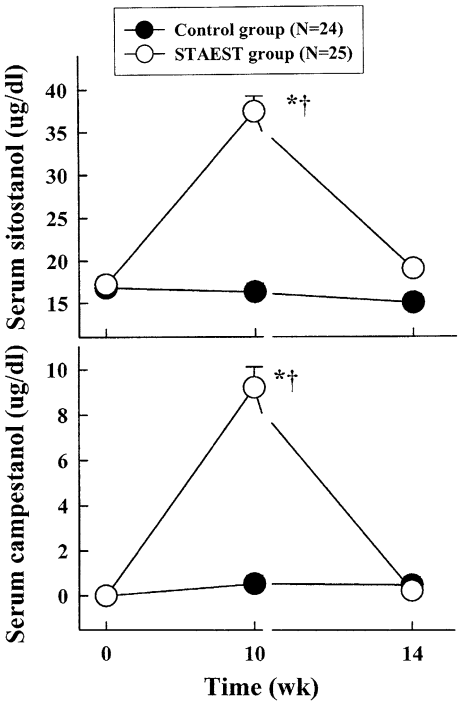

Fig. 1 Serum concentrations of sitostanol (*upper part*) and campestanol (*lower part*) during the study. *Filled circles* test products without plant stanol ester (controls). *Open circles* test products with plant stanol ester. The products were used for 10 weeks followed by regular home diet for 4 weeks

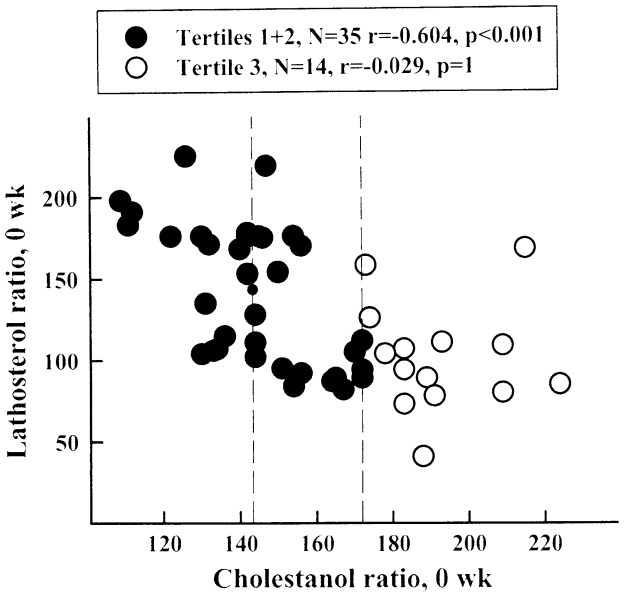

Fig. 2 Correlations between baseline ratios to cholesterol of serum lathosterol and cholestanol. *Filled circles* cholestanol tertiles 1 + 2. *Open circles* cholestanol tertile 3. *Vertical lines* baseline cholestanol to cholesterol tertiles (10^2 mmol/mol of cholesterol)

Correlations

The higher the baseline ratios of sitosterol and avenasterol to cholesterol, the higher were the staest-induced reductions of serum cholesterol levels ($r = -0.494$; $P = 0.028$, $r = -0.502$; $P = 0.024$, respectively), even when the values were adjusted for the difference in initial body weight**.** Changes in non-cholesterol sterols were of general negatively related to their baseline values in the staest group, but less significantly in controls. Thus, statistically significant weight-corrected correlation coefficients were found for lathosterol, sitosterol, and avenasterol (P range from <0.05 to <0.001) in the staest group, and for avenasterol ($P < 0.01$) in controls. At baseline, lathosterol ratio was related to that of cholestanol in the whole population, but in the third cholestanol tertile (high absorbers), the correlation was non-significant, despite the negative correlation in the 1 + 2 tertiles (low absorbers) (Fig. 2). During intervention, lathosterol ratio was related to that of cholestanol in both groups, but in the third control tertile the values were not interrelated.

Discussion

The major findings were that very high intake (8.8 g/day) of plant stanols reduced serum levels of cholesterol and plant sterols, but increased the precursor sterols and slightly, but significantly the plant stanols. As compared to earlier studies with plant stanol intake within 2–3 g/day, the changes in cholesterol and non-cholesterol sterols were somewhat higher. Owing to the lack of side effects on safety variables [4] and the relatively small increase in serum plant stanols and their rapid normalization on home diet, the present findings support an increase in plant stanol dose according to needs from the earlier accepted upper dose of 3 g/day even up to 8.8 g/day.

LDL cholesterol reduction (17%) was somewhat higher than in the 1-year study with 2.6 g/day of plant stanols (LDL cholesterol, 14%) [14]. The present plant stanol dose was about 3.4 times higher than earlier (8.8 vs. 2.6 g), which in view of the relatively small difference in LDL cholesterol lowering between the two studies indicates some interference in cholesterol lowering activity of increased plant stanol consumption. In the present series, serum campesterol was reduced by 62% and sitosterol 48% compared with controls. The respective reductions were less, 42 and 16%, with smaller plant stanol intake [7]. This means up to a three times higher effect with the current plant stanol intake compared with the previous study with lower intake, suggesting that cholesterol absorption was inhibited more effectively in the current study. It is interesting to note that treatment with ezetimibe, a drug inhibiting cholesterol absorption, results in almost similar LDL cholesterol, and serum plant sterol reductions as 8.8 g/day of plant stanols [17].

Similar calculations for cholesterol synthesis evaluated by means of changes in serum lathosterol ratio suggest higher stimulation of cholesterol synthesis by the high (+30%) (present study) than low (+10%) [7] plant stanol consumption. Interpretation of this finding would mean that higher cholesterol lowering would be contributed by higher inhibition of cholesterol absorption, despite an enhanced compensatory cholesterol synthesis. Similar findings, shown in Fig. 3, were obtained when the present 8.8 g/day intake was compared with 2 g/day of a 4-week study [8]. Relative lowering of total and LDL cholesterol concentrations and serum campesterol and sitosterol (reflecting cholesterol absorption), and relative increase in serum lathosterol (reflecting cholesterol synthesis) were more marked in this high current plant stanol intake study.

In the present study, the higher the baseline cholesterol concentration, the higher was its lowering with plant stanol ester. Furthermore, the best serum cholesterol reduction was obtained in those with highest baseline absorption markers [7, 14]. In the present series, only high serum sitosterol and avenasterol ratios predicted enhanced reduction in serum cholesterol with plant stanol ester consumption. Correspondingly, most of the changes in non-cholesterol sterols, both synthesis and absorption markers, were negatively related to their baseline values. This would mean that high baseline synthesis of cholesterol is increased less than the respective low one, while high baseline absorption of cholesterol is decreased more than the respective low baseline value.

The cholestanol tertiles divide the study population to low, intermediate, and high absorbers of cholesterol. Because of the homeostasis of cholesterol metabolism, it is generally acknowledged that in low absorbers cholesterol synthesis is high and in high absorbers low, respectively. However, the present study suggests that the homeostasis may not be present in every situation. The lacking correlation of lathosterol (synthesis marker) to cholestanol (absorption marker) in the highest tertile of cholestanol (high absorbers) (Fig. 2) indicates that homeostasis between cholesterol synthesis and absorption is detectable only within high cholesterol synthesis and low absorption, but no more at high cholesterol absorption. This observation is in agreement with an earlier study showing that in normal adolescent male population the correlation of synthesis markers to those of absorption is detectable only at high cholesterol synthesis [13].

There was a small increase in serum concentrations of campestanol (+9 μg/dL) and sitostanol (+20 μg/dL) during plant stanol ester consumption. In the 1-year study, the respective increments were 4 and 26 μg/dL [7]. In addition, in the rest of the studies with serum plant stanol quantification during daily consumption of 2.4–3 g of plant stanols the increase in serum plant stanols was up to 70 μg/dL [5, 6, 8, 11] indicating that despite three times higher plant stanol consumption, the increments of serum plant stanol levels were not higher in the present versus earlier studies. As a whole, serum plant stanol concentrations remained at low levels. Even though the intestinal absorption of campestanol is higher than that of sitostanol [16], their serum

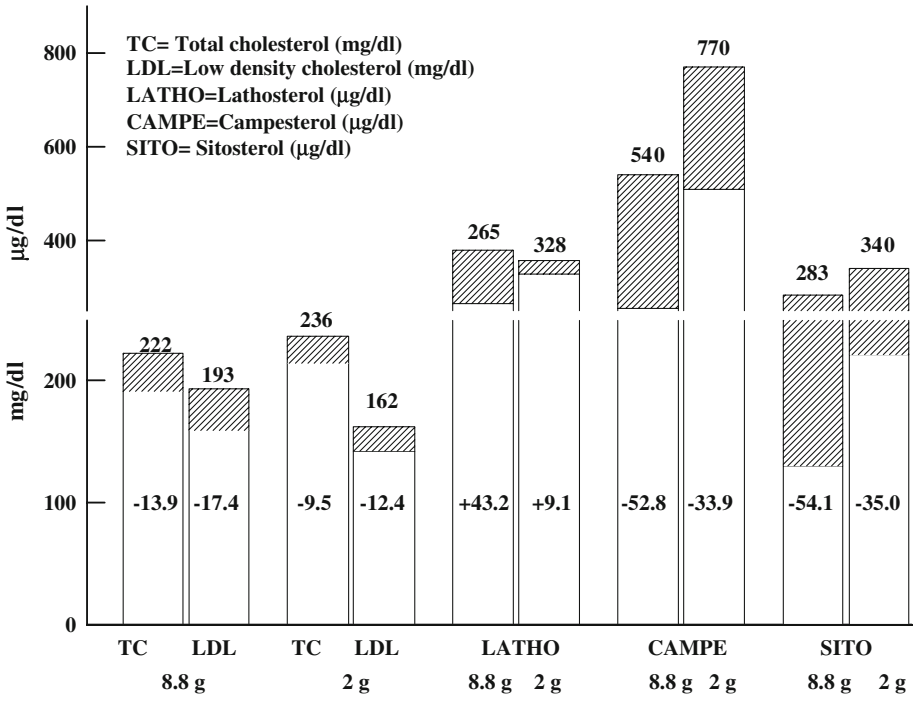

Fig. 3 Concentrations (*on top of each column*) of total and LDL cholesterol, and serum lathosterol, campesterol, and sitosterol during consumption of large (8.8 g/day; the current study) and small (2 g/day; [8]) doses of plant stanols as esters. Absolute decrements of cholesterol and plant sterols, and increments of lathosterol are shown by *black column areas*, and relative percent changes with figures in the columns

ratio is not detectably changed despite increasing the ratio of fed campestanol/sitostanol to 23/77 in a previous study [6] as compared to the present one of 18/82. Biliary secretion of plant stanols is effective [15], and the increased serum plant stanol values were rapidly normalized. In fact, the present data revealed normal cholestanol and unchanged sitostanol and campestanol concentrations at 4 weeks after discontinuation of staest consumption. It is not known, how selectively plant stanols are incorporated to tissues, especially to arterial plaques. The long-term consumption of plant stanols 3 g/day for more than 15 years in a patient stabilized serum sitostanol level to 30 μg/dL [5], and in aortic valve to levels 0.2 mg/100 g tissue (unpublished observations, Gylling and Miettinen 2008), comparable with that of 0.1 mg/100 g tissue found in patients with aortic valve replacement without preoperative consumption of plant stanol-enriched products [9]. A diet supplementation with plant sterol esters over a much shorter period of time (2–4 years) may have a greater impact on plant sterol concentrations in aortic valves (fivefold increase) [18].

In conclusion, very high daily intake of plant stanols increased serum plant stanol levels within respective concentrations found in studies with one-third of the daily plant stanol intake from the present one, and the values returned to baseline within 4 weeks post-treatment. Serum plant sterols were markedly decreased depicting efficient inhibition in cholesterol absorption, and despite increased cholesterol precursor sterol, LDL cholesterol was reduced by 17%. The results suggest that a very high intake of plant stanols is effective with respect to serum profiles of lipids and plant sterols and might not increase systemic availability of plant stanols.

Acknowledgment This work was supported by Raisio Nutrition Ltd. [grant number CL2007_011].

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