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Injected phytosterols/stanols suppress plasma cholesterol levels in hamsters

Catherine A. Vanstone, Mahmoud Raeini-Sarjaz, Peter J.H. Jones*

School of Dietetics and Human Nutrition, Faculty of Agriculture and Environmental Sciences, McGill University, Montreal H9X 3V9, Canada

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Abstract

Although plant sterols are known to suppress intestinal cholesterol absorption, whether plasma and hepatic lipid levels are influenced through non-gut related internal mechanisms has not been established. To examine this question 50 male hamsters were divided into 5 groups and fed semi-purified diets containing 20% energy as fat and 0.25% (w/w) cholesterol *ad libitum* for 60 days. The control group (i) received diet alone, while four additional groups consumed the diet plus one of four equivalent phytosterol mixtures (5 mg/kg/day) given either as (ii) tall oil phytosterols/stanols mixed with diet (oralSA), (iii) tall oil phytosterols/stanols subcutaneously injected (subSA), (iv) soybean oil phytosterols alone mixed with diet (oralSE), or (v) soybean oil subcutaneous injected phytosterols alone (subSE). The control group and both orally supplemented groups also received placebo subcutaneous sham injections. Neither food consumption, body weight, nor liver weight differed across treatment groups. Subcutaneous administration of SA and SE decreased plasma total cholesterol levels by 21% and 23% ($p < 0.0001$) and non-apolipoprotein-A cholesterol concentrations by 22% and 15% ($p < 0.0002$), respectively, compared to control. HDL cholesterol and TG concentrations remained unchanged across all groups, except for a decline of 25% ($p < 0.0001$) in HDL concentration in the subSE group versus control. Plasma campesterol levels were lower ($p < 0.05$) in the subSA group relative to all other groups. Plasma campesterol:cholesterol and campesterol:sitosterol ratios were, however, higher ($p < 0.0001$) for both the oral and subSE groups. Hepatic cholesterol levels were higher ($p < 0.0001$) in the oral and subSE phytosterol groups by 30% and 31%, respectively, relative to control. We conclude that low doses of subcutaneously administered plant sterols reduce circulating cholesterol levels through mechanisms other than inhibiting intestinal cholesterol absorption.

Keywords: Hamster; Phytosterol; Plasma cholesterol; Sitostanol; Injection

1. Introduction

Phytosterols, found abundantly in plant material [1], are structurally similar to cholesterol [2]. Consumption of unsaturated phytosterol mixtures rich in beta-sitosterol has been shown to moderately lower plasma total and LDL cholesterol levels in animals [2–5] and humans [6–12]. Similarly, oral administration of phytostanols, plant sterol mixtures rich in the 5 alpha-saturated derivative of beta-sitosterol, sitostanol, has also been shown to be effective in reducing circulating cholesterol concentrations [7,12–18]. It has been suggested that phytosterols and stanols lower circulating cholesterol concentrations by either direct competitive blocking of intestinal cholesterol absorption [7,14,16, 19,20], displacing cholesterol from bile salt micelles [21], increasing bile salt excretion [22], or hindering cholesterol esterification rate in the intestinal mucosa [19]. Unlike cholesterol, phytosterols are poorly absorbed [23] and almost completely absent from tissues, suggesting that these external mechanisms involving reduction of intestinal cholesterol absorption are most likely responsible for lowering circulating cholesterol levels.

Although such external intestinal mechanisms have been most widely cited as responsible for cholesterol-lowering actions of phytosterols/stanols, animal studies in rats [24, 25] and chickens [26] have suggested that intraperitoneal and subcutaneous injection of beta-sitosterol lower circulating cholesterol concentrations. It was speculated that phytosterols intrinsically affect circulating cholesterol concentration, possibly by altering enzymes involved in cholesterol

Abbreviations: SE, phytosterols; SA, phytosterols/stanols; TC, total cholesterol; HDL, high-density lipoprotein; Non-apo-A, non-apolipoprotein-A; lipoprotein; TG, triglyceride; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; GLC, gas liquid chromatography.

* Corresponding author. Tel.: +1-514-398-7842; fax: +1-514-398-7739.

E-mail address: jonesp@agradm.lan.mcgill.ca (P.J.H. Jones).

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Table 1
Composition of basal semi-purified diet

Ingredients	% (wet weight)
Casein	20.0
Corn Starch	28.0
Sucrose	36.3
Corn Oil	5.0
Cellulose	5.0
D1-methionine	0.5
Mineral Mixture	4.0
Vitamin Mixture	1.0
Choline Bitartrate	0.2
Cholesterol	0.25
Beta Hydroxy Toluene	0.02

metabolism [25,27]. Phytosterols are also differentially distributed across individual lipoprotein classes, suggesting internal discrimination and compartmentalization [28]. These findings are not consistent with currently accepted hypotheses of mechanism of action and raise questions as to additional mechanisms of cholesterol lowering by phytosterols/stanols. The objective of this study was therefore to determine whether phytosterols/stanols influence cholesterol concentrations via an internal mechanism by comparing the cholesterol lowering efficacy and action of sitostanol- and sitosterol-containing phytosterols on circulating plant sterol levels when provided in identical quantities by oral and subcutaneous administration.

2. Materials and methods

Fifty male out-bred Golden Syrian hamsters weighing 80–100 g were randomized into five groups of ten and housed individually in stainless steel mesh cages. Hamsters were acclimatized for 3 days to an air-conditioned room (20–22°C) with a 12 hr light period beginning at 17:00, and were given free access to plain rodent chow and water. Following acclimatization, all groups consumed *ad libitum* a basal semi-purified diet produced *de novo* from primary ingredients each week (Table 1). Hamsters were fed semi-purified diets containing 20% energy as fat and 0.25% (w/w) cholesterol *ad libitum* for 60 days. The control group (i) received diet alone. Four additional groups consumed the diet plus one of four equivalent phytosterol mixtures (5 mg/kg/day) given either as (ii) tall oil phytosterols/stanols mixed with diet (oralSA), (iii) tall oil phytosterols/stanols subcutaneously injected (subSA), (iv) soybean oil phytosterols mixed with diet (oralSE), or (v) tall oil phytosterols subcutaneously injected (subSE). The phytosterol/stanol (SA) blend was obtained from tall oil and the phytosterols (SE) were from soybean oil, both were supplied by Forbes Medi-Tech Inc. Table 2 summarizes the dietary regimen and subcutaneous injection treatment of each group. The phytosterol mixtures were supplemented at a level of 0.00625% (w/w), which corresponded to 5 mg/kg body weight per day. Subcutaneous phytosterol injections were administered weekly at a level of 3.5 mg/100 g body weight. The vehicle for the subcutaneous injection was 0.6 ml of an olive oil: ethanol mixture (6:1 ratio). The control group and orally supplemented plant sterol groups were also sham injected weekly with a subcutaneous placebo of 0.6 ml of olive oil:ethanol. SA and SE phytosterols were analyzed by gas liquid chromatography (GLC) and results of their relative composition listed in Table 3. Food intake was monitored every 3 days by weighing food cups before and after each feeding period and weekly averages were determined. Body weight was monitored on a weekly basis.

Table 3
Composition of phytosterol sources

	Tall oil	Soybean
β-sitosterol (%)	51.7	54.5
Campesterol (%)	18.3	33.2
Sitostanol (%)	21.4	—
Dihydrobrassicasterol (%)	—	10.9

After 60 days of diet consumption, hamsters were deprived of food and water for 1 hr prior to anesthetization with halothane and sacrifice by cardiopuncture. Blood samples were withdrawn and centrifuged at 1500 rpm for 15 min to obtain plasma. Tissue samples including liver and small intestine were removed, weighed, frozen in liquid nitrogen, and stored at -80°C for subsequent analysis. Plasma total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG) concentrations were mea-

Table 2
Dietary supplementation and subcutaneous injection treatment for each group

Group (n=10)	Dietary Sterol Supplementation[a]			Subcutaneous Injection[b]	
	Cholesterol	Phytosterols/stanols	Phytosterols	Phytosterols/stanols	Phytosterols
Control	0.25	—	—	—	—
OralSA	0.25	0.00625	—	—	—
SubSA	0.25	—	—	0.5	—
OralSE	0.25	—	0.00625	—	—
SubSE	0.25	—	—	—	0.5

[a] Dietary supplementation expressed as percent wet weight of diet.
[b] Dose of subcutaneous injection expressed as mg/d of phytosterol per day per 100g body weight.

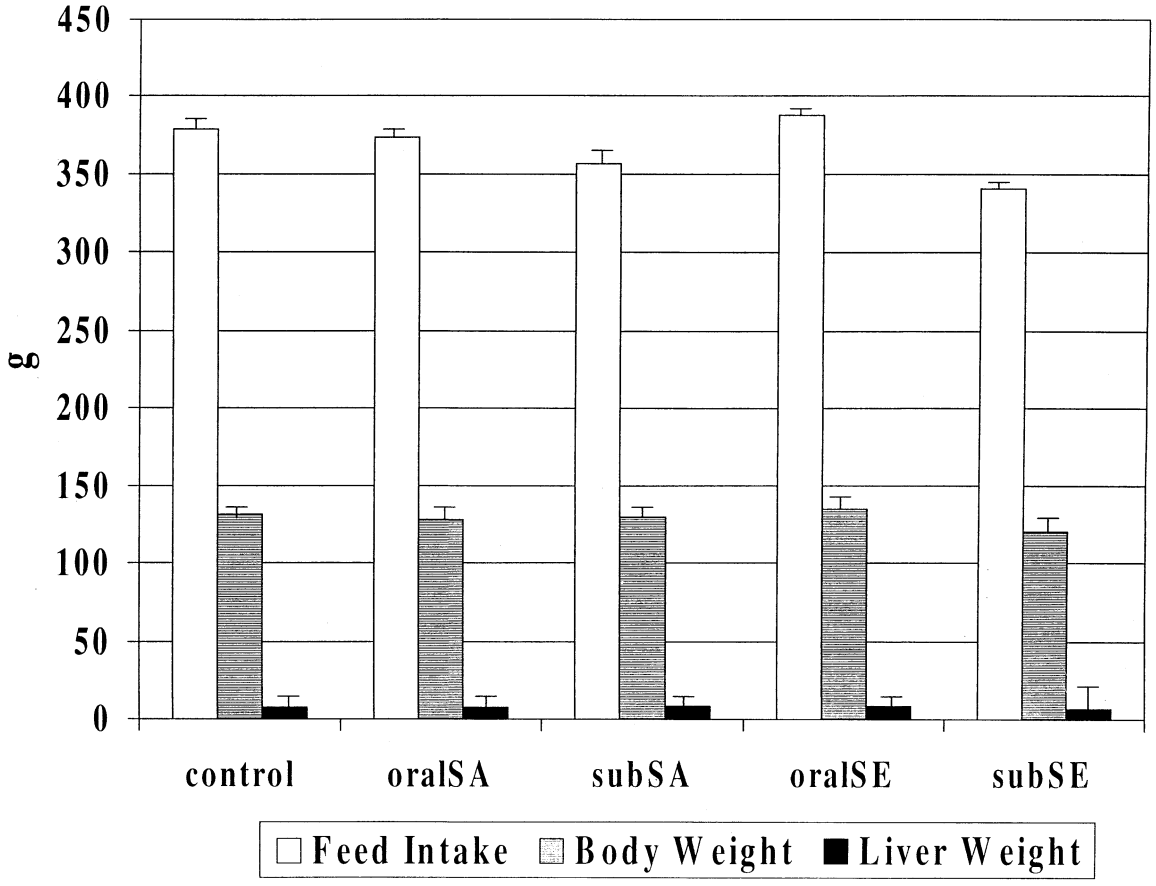

Fig. 1. Food intake, final body weight, and liver weight expressed in grams (g). Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols.

sured using a VP Autoanalyzer and commercial enzymatic kits utilizing appropriate reference standards (Abbott Diagnostics, Montrèal, Québec). The concentration of non-apolipoprotein-A (non-apo-A) cholesterol was calculated as total cholesterol minus HDL cholesterol. Non-apo-A cholesterol levels were reported in place of low-density lipoprotein (LDL) cholesterol, as the use of the Friedewald equation [29] may be considered inappropriate in the hamster model due to the skewed distribution of lipids across lipoprotein groups.

Plasma and hepatic phytosterols were extracted and quantified by gas liquid chromatography (GLC) as previously described by Ntanios and Jones [30]. Briefly, 5-alpha-cholestane, used as an internal standard (Sigma-Aldrich Canada Ltd., Oakville, Ont.), was added to each sample of liver. Non-saponified materials were then extracted after addition of 0.5 M methanolic KOH for 2 h at 100°C using petroleum ether. Samples were dried, dissolved in chloroform and injected into a GLC (HP 5890 Series II), equipped with flame ionization detector and auto-injector system. Separation was achieved on a 30 m capillary column, 0.25 mm ID, 0.25 μm thickness (SAC-5, Sigma-Aldrich Canada Ltd., Oakville, Ont.). Samples were injected at 285°C. Isothermal running conditions were maintained for 42 min. The injector and detector were set at 300°C and 310°C, respectively. The carrier gas (helium) flow rate was 1.0 ml/min with the inlet splitter set at 100:1. Campesterol and sitosterol peaks were identified using authentic standards (Sigma-Aldrich Canada Ltd., Oakville, Ont.) and appropriate detector response factors.

Hepatic total cholesterol was extracted and quantified by GLC, using the same method described above. Using this method a response factor was determined for hepatic cholesterol as well as for each phytosterol/stanol. These factors were then used to calculate the absolute values of each component.

3. Statistics

Data are expressed as means ± SEM. The data across treatment groups were analyzed using one-way analysis of variance (ANOVA). Where a significance of $P < 0.05$ was achieved, specific group differences were evaluated using the LSD test.

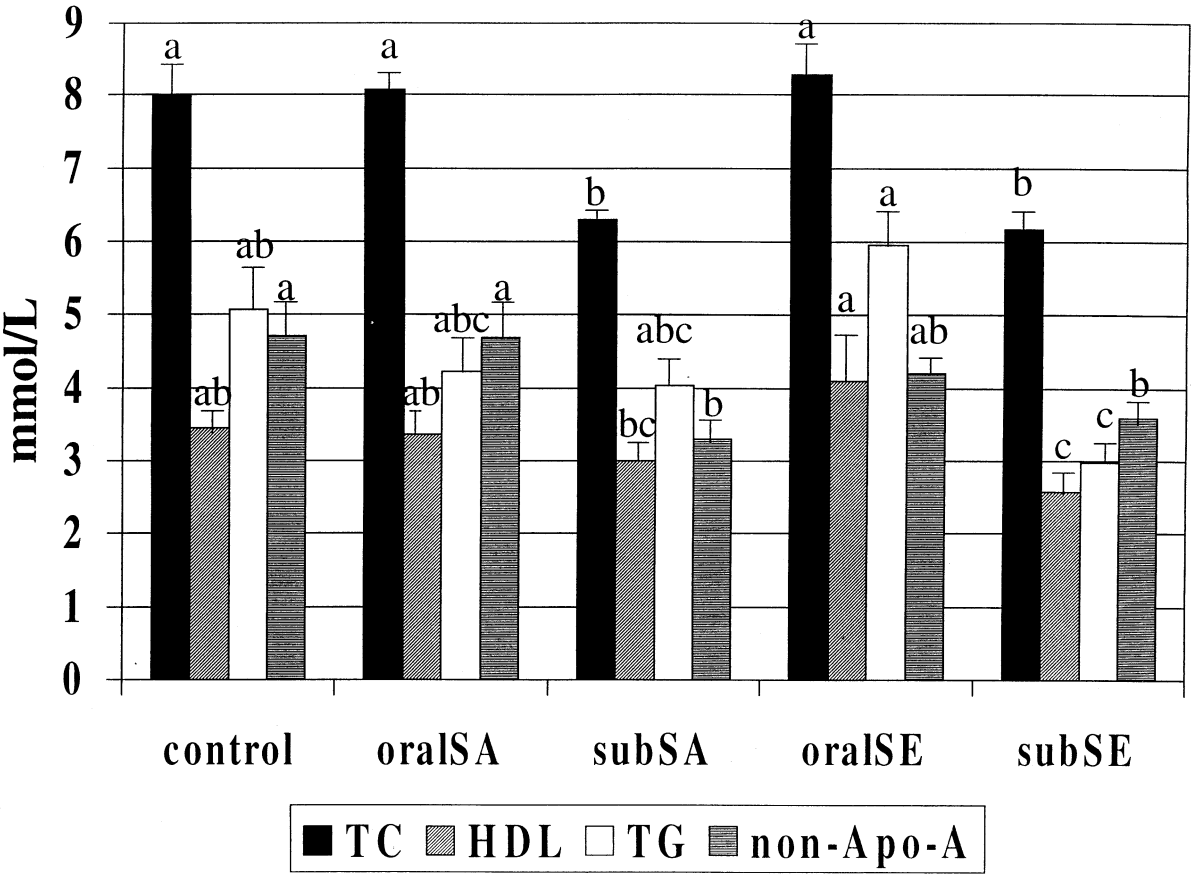

Fig. 2. Plasma lipid concentrations for treatment groups expressed in mmol/L. Tot-C, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Non-Apo-A, non-Apolipoprotein A. Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols. Different letters represent significant differences between treatment groups.

4. Results

Food consumption, body weights, and liver weights did not differ across treatment groups (Figure 1). Histopathological examination of the testis, liver, duodenum, and liver showed no negative action by either oral or subcutaneous administration of SA or SE phytosterols/stanols (data not shown).

Mean plasma total cholesterol level with consumption of the cholesterol control diet was 8.0 ± 0.5 mmol/L. Oral supplementation of SA phytosterols produced no change in total cholesterol level. However, when SA phytosterols were administered subcutaneously, total cholesterol level (6.3 ± 0.3 mmol/L) decreased ($p < 0.0001$) by 21%, compared to control. The same pattern of response was observed with SE-derived phytosterols. Oral administration of SE phytosterols produced no change in total cholesterol level, whereas, subcutaneously administered SE phytosterols invoked a 23% decrease ($p < 0.0001$) in total cholesterol (6.2 ± 0.3 mmol/L), compared to control, which was similar to the decrease observed with subcutaneously administered SA phytosterols (Figure 2).

The pattern of response of non-apo-A containing lipoproteins to treatments was similar to that of total cholesterol levels (Figure 2). Mean plasma non-apo-A cholesterol level attained 4.7 ± 0.4 mmol/L after consumption of the atherogenic control diet. Neither the oralSA or oralSE phytosterol supplemented groups experienced any significant change in non-apo-A cholesterol levels, compared to control. However, when SA phytosterols were injected subcutaneously, non-apo-A cholesterol levels (3.3 ± 0.3 mmol/L) decreased ($p < 0.02$) by 30%, compared to control. A similar pattern of response was observed with SE-derived phytosterols. When SE phytosterols were given subcutaneously, a decrease of 24% in non-apo-A cholesterol level (3.6 ± 0.2 mmol/L) was observed, compared to control. Non-apo-A cholesterol levels did not differ significantly for each administration route between SA and SE phytosterols.

Mean plasma HDL cholesterol concentration was 3.4 ± 0.3 mmol/L in the control group. Supplementation of either oral or subcutaneous SA phytosterols did not significantly influence plasma HDL cholesterol concentrations (3.4 ± 0.2 and 3.0 ± 0.3 mmol/L, respectively), compared to control. Supplementation of oral SE phytosterols exhibited a trend towards increased plasma HDL cholesterol levels (4.1 ± 0.4 mmol/L), compared to control; while subcutaneous injec-

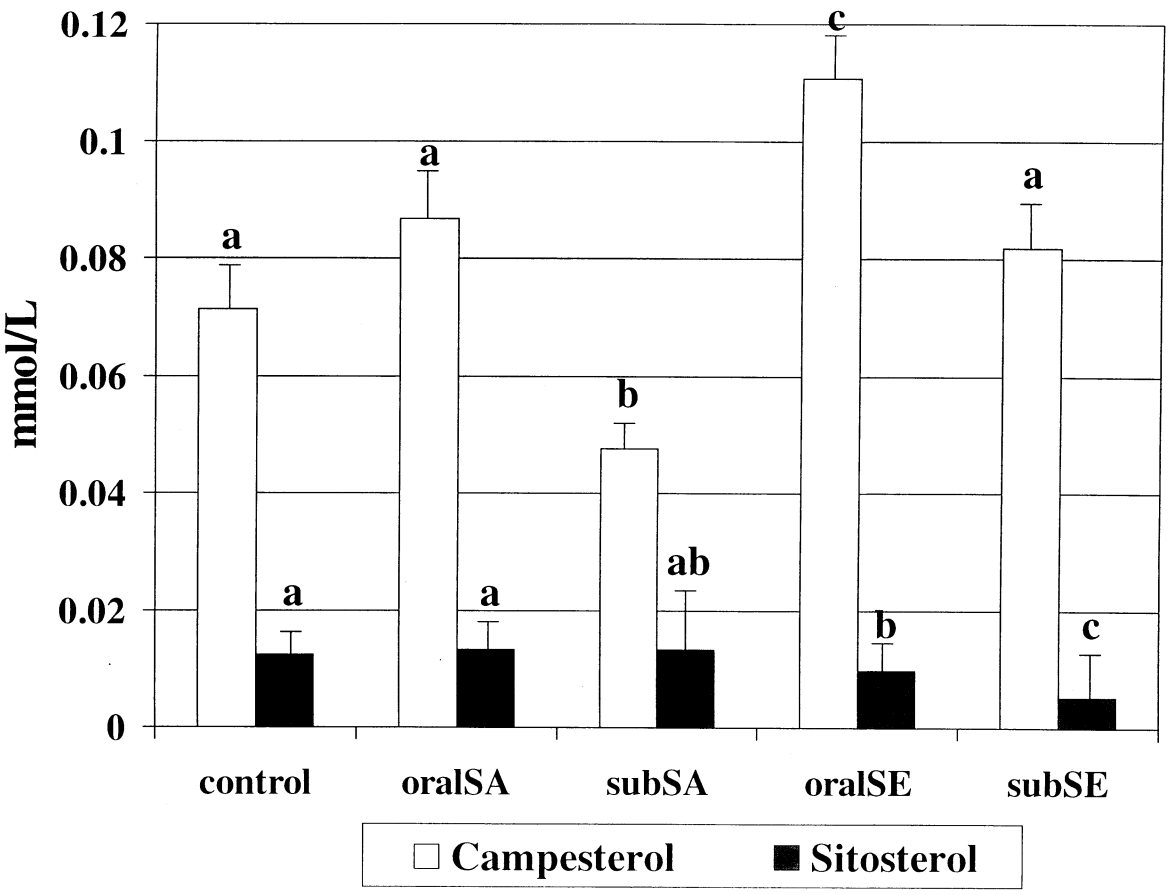

Fig. 3. Plasma phytosterol concentrations expressed in mmol/L. Campesterol and sitosterol concentrations are shown for each treatment group. Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols. Different letters represent significant differences between treatment groups.

tion of SE phytosterols resulted in a 25% decrease ($p < 0.001$) in HDL cholesterol levels (2.6 ± 0.2 mmol/L), relative to the cholesterol control group (Figure 2).

Mean plasma triglyceride concentration in the atherogenic control group was 5.1 ± 1.0 mmol/L, which did not differ from values observed after either oral (4.2 ± 0.5 mmol/L) or subcutaneous (4.0 ± 0.7 mmol/L) administration of SA phytosterols. Oral administration of SE phytosterols produced no significant effect (5.9 ± 0.9 mmol/L), however, subcutaneous injection of SE phytosterols decreased ($p < 0.05$) triglyceride levels (2.9 ± 0.4 mmol/L) by 42%, compared to the control group (Figure 2).

Plasma campesterol levels were unchanged in the oral SA phytosterol group and the subcutaneously injected SE phytosterol group, relative to control. However, plasma campesterol levels were lower ($p < 0.05$) in the subcutaneously injected SA phytosterol group and higher ($p < 0.05$) in the oral SE phytosterol group, relative to control (Figure 3).

Plasma phytosterol:cholesterol ratios (mmol:mol) are displayed in Figure 4. The plasma campesterol:cholesterol ratio was 9.1 ± 1.1 mmol:mol for the cholesterol control diet. When SA phytosterols were orally supplemented, the ratio showed no change relative to the cholesterol control group (10.4 ± 1.3 mmol:mol), whereas, subcutaneous administration of SA phytosterols tended to be lower (7.6 ± 0.8 mmol:mol) than the cholesterol control diet but the difference was not statistically significant. Both oral (14.0 ± 1.7 mmol:mol) and subcutaneous (14.6 ± 1.7 mmol:mol) administration of SE phytosterols resulted in an approximate 40% increase ($p < 0.0001$) in the campesterol:cholesterol ratio, relative to the control group. Plasma campesterol:sitosterol ratio for the cholesterol control group was 6.5 ± 1.2 mmol:mol. The ratios for the oral and subcutaneously injected SA phytosterol groups remained unchanged relative to the cholesterol control group. Ratios increased ($p < 0.0001$) for the groups orally (15.5 ± 2.5 mmol:mol) and subcutaneously (14.8 ± 1.9 mmol:mol) supplemented with SE phytosterols (Figure 4).

Hepatic cholesterol concentration for the cholesterol control group was 61.7 ± 4.4 mmol/kg (Figure 5). Cholesterol levels were unchanged for both the oral (65.0 ± 5.0 mmol/kg) and subcutaneously injected (65.8 ± 7.5 mmol/kg) SA phytosterol groups, whereas, both the oral (80.2 ±

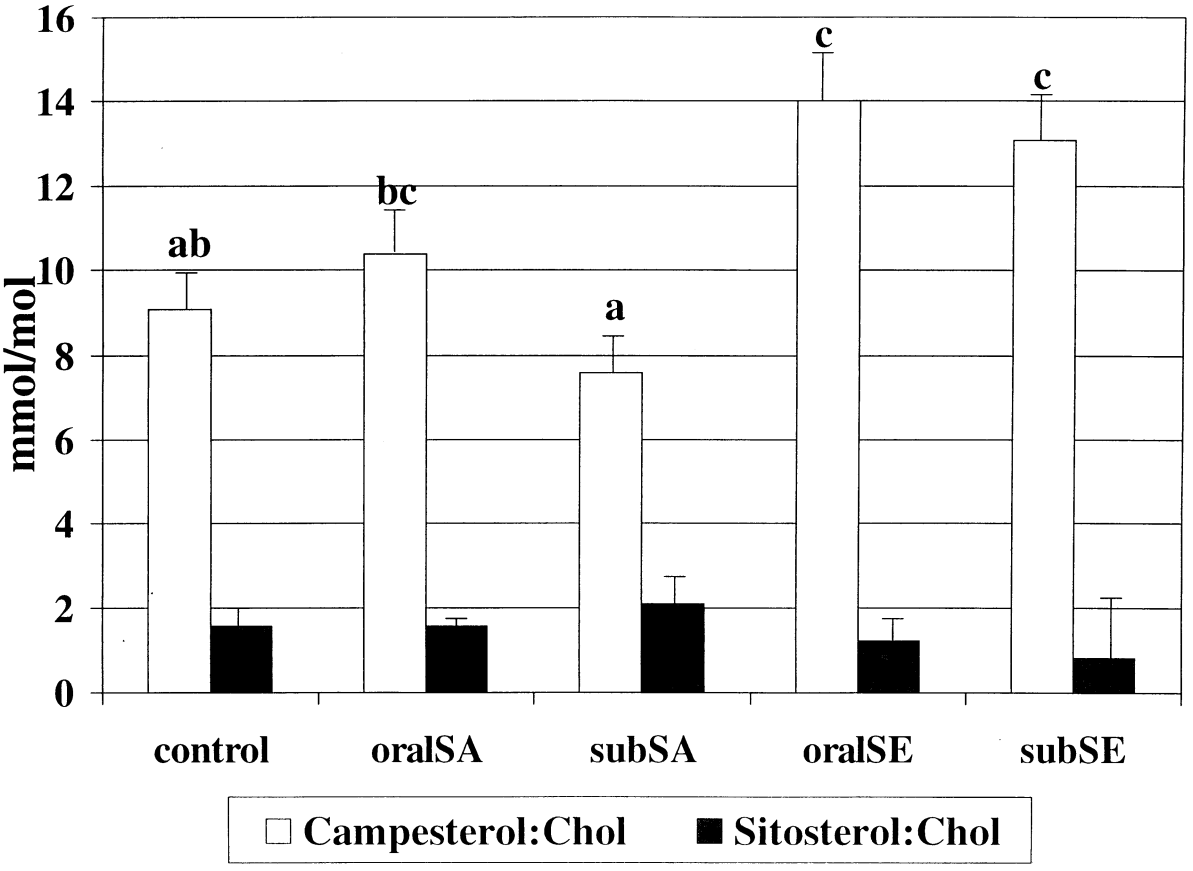

Fig. 4. Plasma phytosterol:cholesterol ratios expressed as mmol/mol. Camp:Chol, campesterol:cholesterol; Sitos:Chol, sitosterol:cholesterol. Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols. Different letters represent significant differences between treatment groups.

5.5 mmol/kg) and subcutaneously injected (80.9 ± 5.9 mmol/kg) SE phytosterol groups showed higher ($p < 0.0001$) levels (30 and 31%, respectively, relative to the control group).

Hepatic campesterol levels were lower ($p < 0.05$) across all groups relative to the cholesterol control (Figure 6). The mean hepatic campesterol:cholesterol ratio was 8.1 ± 0.6 mmol:mol in the cholesterol control group. When SA phytosterols were provided, the mean ratio decreased ($p < 0.001$) to 5.3 ± 0.2 mmol:mol and 3.7 ± 0.2 mmol:mol for oral and subcutaneous administration, respectively. The mean ratio also decreased ($p < 0.0001$) in both the oral and subcutaneously injected SE phytosterol groups, 4.6 ± 0.2 mmol:mol and 3.5 ± 0.2 mmol:mol, respectively (Figure 7).

5. Discussion

The present data show for the first time perturbations in plasma lipid and phytosterol levels in response to subcutaneous injection of small quantities of sitostanol-containing and sitostanol-free phytosterol mixtures; changes, which were not, observed when identical amounts of the same phytosterol mixtures were provided orally. Results indicate the presence of an intrinsic influence of phytosterols, which is likely mediated in a manner other than that of blocking intestinal absorption. Non-absorptive, hypocholesterolemic effects of plant sterols have been suggested previously in animals to include modification of hepatic acetyl-CoA carboxylase [31], 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase [32] and cholesterol-7-hydroxylase [33]. However, direct comparison of oral and intravenous plant sterol mixtures varying in composition had not been previously carried out. Phytosterols were obtained from two sources; tall oil and soybean oil. The difference in their relative compositions of sterols and the proportion of sitostanol (21%) in the tall oil phytosterol mixture is likely the reason for the differences observed between the groups.

Although the extent of lowering of non-apo-A cholesterol, the surrogate for human LDL-C, was similar between injected SA and SE plant sterols, other circulating lipids were differentially altered as a function of phytosterol composition when these plant sterols were given by injection. HDL-C showed a decrease in response to the SE but not SA mixtures, resulting in a more favorable LDL/HDL ratio with the sitostanol-containing, versus sitostanol-free mixture. On

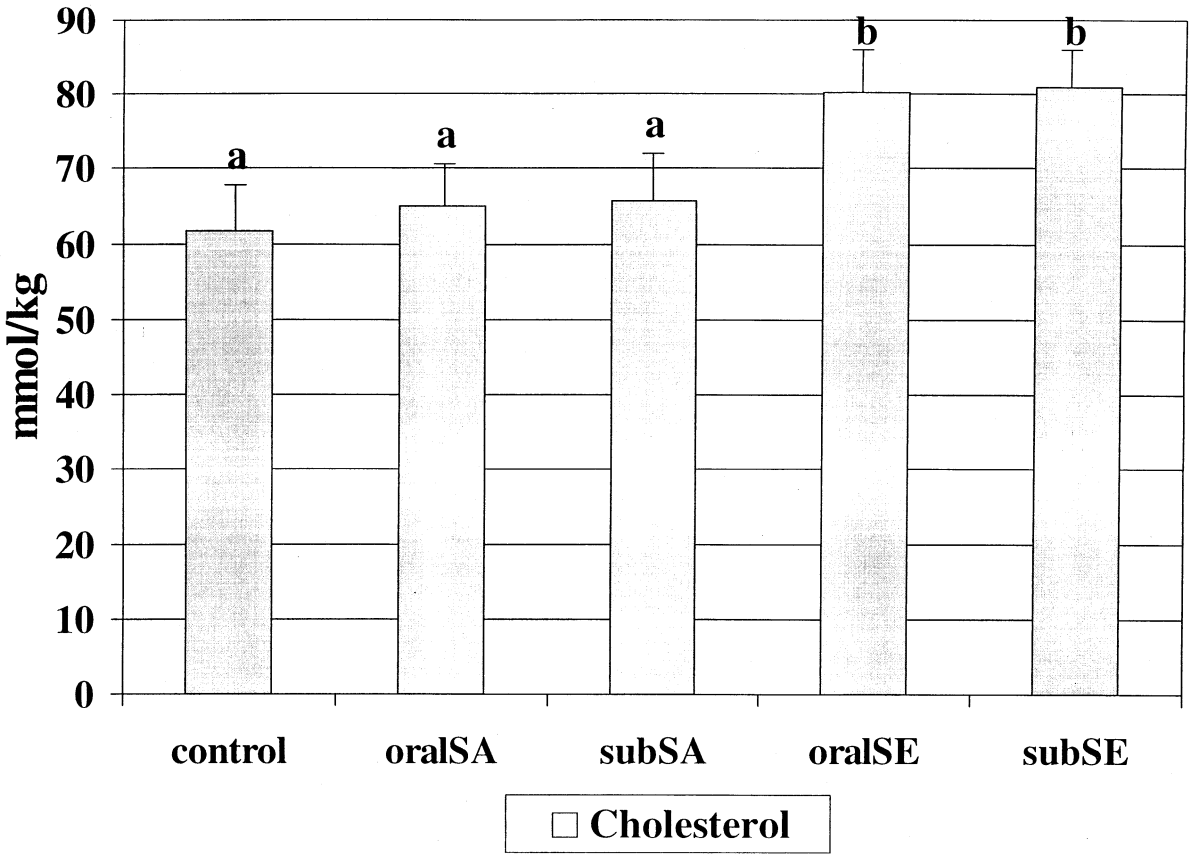

Fig. 5. Hepatic cholesterol concentrations expressed as mmol/kg. Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols. Different letters represent significant differences between treatment groups.

the other hand, the sitostanol-free phytosterols showed the best TG lowering effect when injected subcutaneously. This difference in lipid patterning due to the presence of sitostanol in the mixture strongly indicates a structure-specific modality of endogenous plant sterol action, in contrast to similar lipid-lowering effects when stanols versus sterols are provided orally to human subjects [34,35]. However, the hamster model does appear to show a response to increasing sitostanol level in a manner that is not consistent with results in humans. Ntanios and Jones showed that as the proportion of dietary sitostanol increases in a plant sterol mixture, the cholesterol-lowering efficacy improves in a step-wise fashion [30].

How phytosterols/stanols produce an intrinsic non-apo-A lipoprotein lowering action is not completely clear. It can be assumed that when phytosterols/stanols are subcutaneously injected, they are rapidly shunted to the liver and have a more rapid turnover rate than cholesterol as has been shown previously with ingested plant sterols [35]. β-sitosterol is absorbed from the intestine only about one tenth as effectively as cholesterol and is secreted into the bile more rapidly than cholesterol [35]. The very low normal circulatory levels of plant sterols and stanols seen in humans [36] and animals [12] provide further support for their fast clearance. As these molecules are eliminated through the bile there is most likely a "sterol drag" effect, which essentially pulls cholesterol, particularly LDL-C, along with the phytosterols out of the blood and increases their excretion. As the phytosterol/cholesterol rich bile enters the intestine, endogenous cholesterol may be further blocked from being re-absorbed, contributing to the lower circulating cholesterol levels. Stanols and sterols may exhibit different rates of elimination, explaining the differential action on circulatory LDL-C and TG levels. Such a differential in elimination rates may also explain why hepatic cholesterol levels responded to treatment in a manner dependent on phytosterol composition. The ability of sitostanol-free mixtures to increase hepatic total cholesterol contents, relative to controls, may exist in response to a sequestering into liver of cholesterol secondary to the clearance of the injected phytosterol material. Hepatic cholesterol content was also quite high in the control group. The basal diet contained corn oil and it has been shown that phytosterol concentrations in corn oil exceed those of most other oil types [37]. Therefore the inclusion of corn oil may have accounted for the elevated levels observed in control animals. Why hepatic cholesterol levels increased with oral feeding of these very low

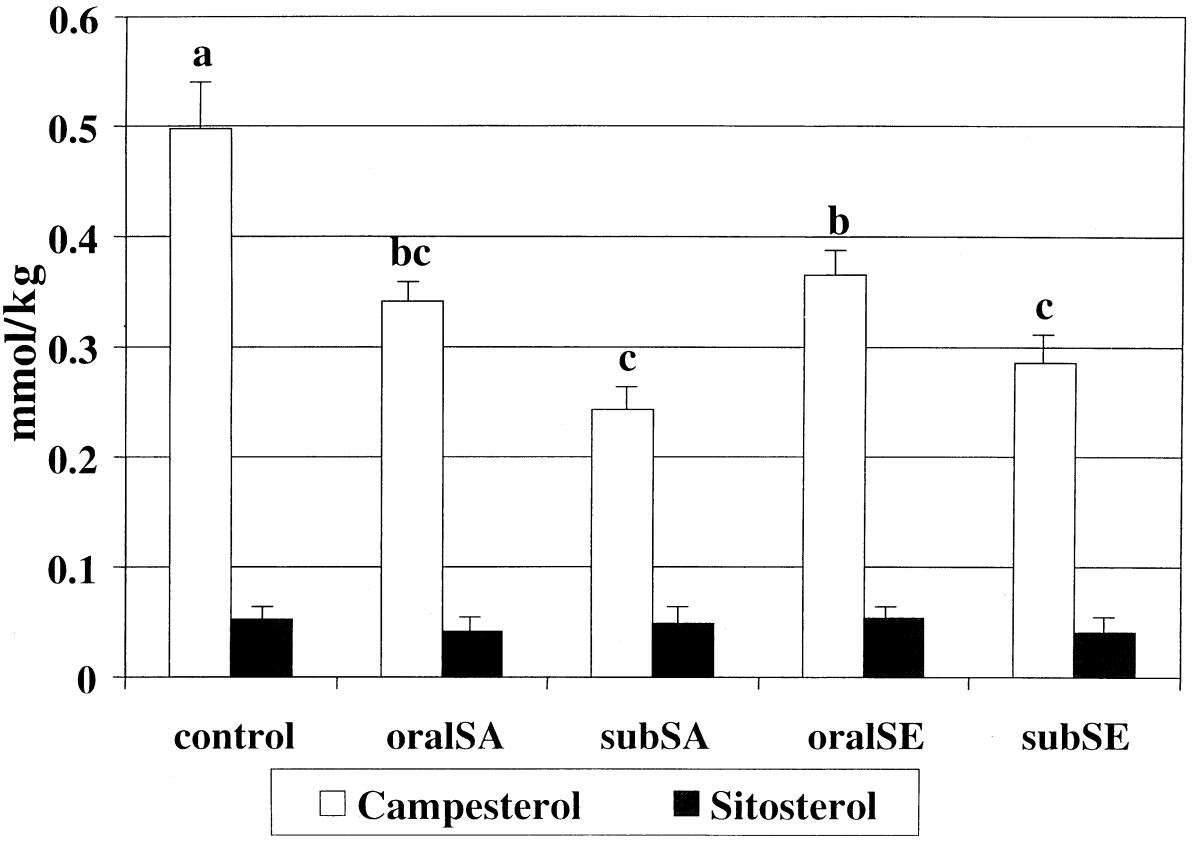

Fig. 6. Hepatic phytosterol concentrations expressed in mmol/kg. Campesterol and sitosterol concentrations are shown for each treatment group. Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols. Different letters represent significant differences between treatment groups.

levels of sitostanol-free plant sterols is not readily explainable.

In the present study, plasma campesterol level was the lowest for the group subcutaneously injected with SA phytosterols. In humans, changes in plasma campesterol levels and campesterol:cholesterol ratios have been used as markers of cholesterol absorption rates [38,39]. It has been suggested that variations in circulating campesterol levels may occur as a result of a change in HMG-CoA reductase activity [40]. It has also been shown that when HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, activity is inhibited a resultant lowering in circulating cholesterol concentrations occurs [41]. Presently the reduced plasma campesterol level in the group subcutaneously injected with SA phytosterols may indicate a more aggressive reduction in cholesterol absorption compared with SE phytosterols in the hamster model. Alternatively, as the campesterol content of the SE mixture was greater than that of the SA mixture, the higher levels could potentially reflect the greater plasma contribution of the injectate. Similarly, ratios of campesterol:cholesterol in liver for both the SA and SE subcutaneously injected groups were the lowest of all groups due to the decrease in campesterol levels. This finding suggests that subcutaneously injected phytosterols inhibit cholesterol absorption through some indirect process. Although the levels provided were much lower than normally required to produce a direct gut effect, it cannot be excluded that injected plant sterols are readily excreted through bile into the intestinal lumen where they interfere with normal cholesterol absorption. Figure 7 shows little change in the profile of campesterol:cholesterol or sitosterol:cholesterol ratios across the SE and SA treatments. It is not known why in all groups campesterol:cholesterol ratio fell relative to the control animals. Since the control animals were treated in every way identically to those of the 4 groups given sterols or stanols, it is difficult to speculate on a mechanism of action underlying this effect. Given the small amount of phytosterols provided, however, it is more likely that some internal action of injected phytosterols is responsible for the shifts in lipid profile.

In summary, present data provide some evidence for an intrinsic influence of phytosterols/stanols on cholesterol metabolism *in vivo*, auguring for a mechanism which is beyond the level of the gut. The variable response of circulating HDL-C and TG levels, as well as hepatic cholesterol concentrations and circulating plant stanol levels, indicate the structure dependent nature of the intrinsic action. It is concluded that plant sterols and stanols, provided at levels well

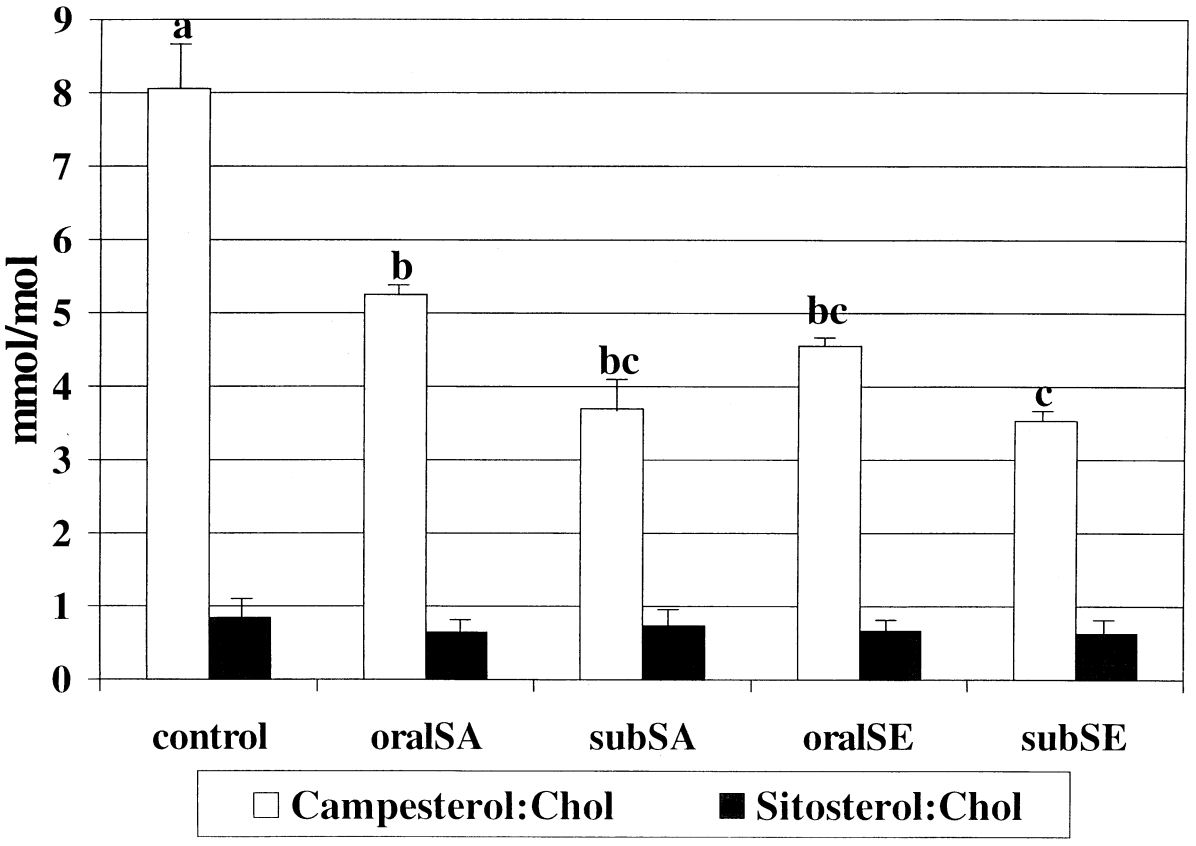

Fig. 7. Hepatic phytosterol:cholesterol ratios expressed as mmol/mol. Camp:Chol, campesterol:cholesterol; Sitos:Chol, sitosterol:cholesterol. Control, cholesterol control group; oralSA, tall oil phytosterols/stanols mixed with diet; subSA, subcutaneously injected tall oil phytosterols/stanols; oralSE, soybean oil phytosterols mixed with diet; subSE, subcutaneously injected soybean oil phytosterols. Different letters represent significant differences between treatment groups.

below the threshold required to cause favorable improvements in lipid profile, exert actions which result in a reduction in disease risk in the hamster model of atherosclerosis. Further research is required to fully delineate the role for intrinsically administered sterols/stanols as a strategy for cholesterol lowering and heart disease risk reduction.

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