Short-Term Administration of Tall Oil Phytosterols Improves Plasma Lipid Profiles in Subjects With Different Cholesterol Levels

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To assess the short-term cholesterol-lowering potential of sitostanol-containing tall oil plant sterols, 22 subjects consumed fixed-food diets over two 10-day periods with or without 21.2 mg/kg body weight/d tall oil phytosterols (sitosterol 62%, sitostanol 21%, campesterol 16%, and campestanol 1%) in a randomized crossover study design. On day 10 of each diet, plasma lipoprotein cholesterol levels, plasma phytosterol concentrations, and cholesterol biosynthesis rates were determined. Total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels were lower ($P < .01$) after administration of tall oil phytosterol (4.7 ± 0.3 and 3.0 ± 0.3 mmol/L, respectively) versus placebo (5.0 ± 0.3 and 3.2 ± 0.3 mmol/L, respectively). Tall oil treatment had no effect on the plasma high-density lipoprotein (HDL) cholesterol level (1.1 ± 0.1 mmol/L) versus placebo (1.1 ± 0.1 mmol/L). Similarly, plasma triglyceride (TG) levels did not differ between tall oil (1.3 ± 0.2 mmol/L) and placebo (1.4 ± 0.2 mmol/L) treatments. Plasma campesterol (15.8 ± 3.7 mmol/mol cholesterol) and sitosterol (6.0 ± 2.1 mmol/mol cholesterol) levels were not different after tall oil treatment versus placebo treatment (15.4 ± 2.3 and 6.4 ± 2.0 mmol/mol cholesterol, respectively). Plasma sitostanol levels were essentially undetectable. No difference was observed in cholesterol biosynthesis between tall oil (0.045 ± 0.004 pools/d) and placebo (0.034 ± 0.004 pools/d) treatments; however, the effect of treatments in subjects with different cholesterol levels varied. In subjects with lower cholesterol values, the red blood cell cholesterol fractional synthesis rate (FSR) increased from 0.0291 ± 0.0054 pools/d after placebo to 0.0509 ± 0.0049 pools/d ($P < .05$) after phytosterol treatment. In subjects with higher cholesterol values, the red blood cell cholesterol FSR did not change significantly after treatment. These results demonstrate the short-term efficacy of tall oil plant sterols as cholesterol-lowering agents.

THE CHOLESTEROL-LOWERING actions of sitosterol- and campesterol-containing plant sterol mixtures following oral administration have been well defined.[1-5] However, the high doses required to produce this action have limited their practical use. More recently, sitostanol, a saturated derivative of sitosterol, has been shown to be as effective to decrease cholesterol with doses much lower than those of nonsaturated plant sterol mixtures.[6-10] Sitostanol ester administered at 1.8 g/d over 12 months to mildly hypercholesterolemic individuals was shown to produce a reduction in total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol of 10.2% and 14.1%, respectively.[10] Plant sterols, particularly sitostanol, interfere with cholesterol absorption from the intestinal tract by competing with micellar incorporation, uptake into the enterocyte, or reesterification within the enterocyte of cholesterol.[2,6] Margarine containing sitostanol ester is commercially available as a lipid-lowering food in Europe; however, its cost is substantial due to the labor-intensive hydrogenation process.

An abundant source of natural sitostanol is tall oil, a by-product of the pulping industry. Tall oil phytosterols contain 20% to 30% sitostanol. Such mixtures, if effective for decreasing lipids, offer the potential advantages of economy and availability over synthetic sitostanol. However, at present, tall oil phytosterol mixtures have not been systematically investigated for cholesterol-modulating ability in normal or hyperlipidemic humans, nor has the safety of tall oil phytosterols been entirely established.

The objective of this study was therefore to examine the efficacy and mechanisms through which tall oil phytosterols modify lipoprotein cholesterol levels in normolipidemic and mildly hyperlipidemic individuals consuming fixed diets naturally low in phytosterol. Specifically, it was hypothesized that short-term oral administration of tall oil phytosterols results in no change in plasma lipoprotein cholesterol and TG concentrations, plasma β-sitosterol, campesterol, and sitostanol concentrations, or fractional synthesis rates (FSRs) of free cholesterol.

SUBJECTS AND METHODS

Subjects

Prior to entry to the study, subjects received a complete physical examination and provided a thorough medical history. Twenty-two healthy, free-living volunteers were verbally screened for chronic illness, including hepatic, renal, thyroid, and cardiac dysfunction, before admission to the study. Fasting blood and urine samples were collected for serum chemistry, hematology, and urine analyses. Subjects refrained from drug treatment for hypercholesterolemia for at least 8 weeks before study and reported no other prescription medication use. They reported being free of atypical sleep, activity, and exercise patterns. To test the overall effects of tall oil phytosterol treatment, subjects were pooled as an entire group. However, to test for effects related to screening cholesterol levels, we also compared normocholesterolemic individuals with initial plasma cholesterol less than 5 mmol/L against hypercholesterolemics with levels greater than 5 mmol/L. All subjects provided informed written consent to participate prior to study commencement. Procedures were approved by the Human Ethical Review Committee of McGill University.

Experimental Design

Over each of two 10-day periods, 22 subjects consumed a basal diet containing 33%, 52%, and 15% of total energy as fat, carbohydrate, and protein, respectively. Two thirds of dietary fat was provided as extra virgin, cold-pressed olive oil (Bertolli Canada, Laval, Quebec, Canada). The olive oil was blended into baked goods to enhance palatability. Diets were designed to meet individual energy needs and were fed at a

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level estimated to satisfy individual energy requirements,[11] using a factor of 1.7 to compensate for additional energy needs of healthy individuals. The basal diet was provided as a 2-day rotating menu of three solid-food meals per day that were isocaloric in energy and fat. The basal diet was supplemented with 21.2 mg/kg body weight/d of either tall oil phytosterol (Forbes Medi-Tech, Vancouver, British Columbia, Canada) or a corn starch placebo. Daily phytosterol and placebo supplements were administered in equal amounts mixed with the oil portion of the breakfast, lunch, and supper meals. Allocation of subjects to the treatment or placebo periods was made using a randomized crossover design. The two 10-day diet cycles were separated by at least 14 days of habitual eating. The starch placebo provided approximately 6 kcal/d as carbohydrate energy, a level considered insignificant in relation to the mean total carbohydrate (385 g/d) and caloric intake (2,968 kcal/d). Ingestion of energy-containing substances other than the prescribed diet was prohibited. Meals were prepared and consumed under supervision in the Clinical Nutrition Research Unit, McGill University. Meals were occasionally prepackaged for take-out. Tall oil phytosterol composition was analyzed by gas-liquid chromatography. The tall oil phytosterol diet contained 16.1% campesterol, 0.9% campestanol, 62.0% β-sitosterol, and 21.1% sitostanol.

Subjects were instructed to maintain typical and consistent sleep and exercise patterns during study. Each subject's energy balance was monitored by daily prebreakfast measurement of body weight. On day 1 of each diet cycle, a 10-mL blood sample was drawn to measure plasma cholesterol and TG levels. Fasting blood samples were also collected on days 9 and 10 of each diet cycle to measure plasma cholesterol, phytosterol, and TG levels, as well as plasma and red blood cell deuterium enrichment. Following blood sample collection on day 9, at 8 AM of the same day, subjects consumed 0.7 g/kg estimated body water of deuterium oxide (99.8% atom percent excess; CDN Isotopes, Montreal, Quebec, Canada). Body water weight was estimated to be 60% of body weight. Over the following 24 hours, drinking water labeled with deuterium oxide 1.4 g/kg water was consumed ad libitum to maintain plateau enrichment.

Macronutrient Analysis of Basal Diet

Homogenized mixtures of each meal for the basal diet were chemically analyzed for macronutrient content. Moisture, ash, crude fat, and protein content of the homogenized food mixtures were analyzed in accordance with Association of Official Analytical Chemists guidelines.[12] Proximate compositions are reported as grams of macronutrient per 100 g wet weight. The carbohydrate content of food samples was calculated by subtracting the sum of moisture, protein, crude fat, and ash values from 100 g. Final values are presented as percent of total energy in Table 1.

Circulating Cholesterol and TG Determination

Plasma TC, high-density lipoprotein (HDL) cholesterol, and TG levels were measured in duplicate using a VG Autoanalyzer with commercial enzymatic kits (Abbott Diagnostics, Montreal, Quebec, Canada). The concentration of LDL cholesterol was determined using the Friedewald equation.[13]

Circulating Phytosterol Determinations

Plasma phytosterols were extracted and quantified by gas-liquid chromatography in duplicate. Briefly, 5-α-cholestane, used as an internal standard (Sigma Chemical, St Louis, MO), was added to approximately 1 mL plasma, and the lipids were extracted. The lipid extract was saponified with 50% KOH and methanol (6:94 vol/vol) for 2 hours at 100°C. Sterols were then extracted three times with petroleum ether, dried, dissolved in hexane, and injected into the chromatograph (HP 5890 Series II, equipped with flame ionization detection and autoanalyzer system; Hewlett-Packard, Palo Alto, CA). Separation was achieved on a SAC-5 capillary column (30 m length, 0.25 mm ID, 0.25 μm thickness; Supelco, Sigma-Aldrich Canada, Mississauga, Ontario, Canada). Samples were injected at 275°C. Isothermal running conditions were maintained for 42 minutes. The injector and detector were both set at 300°C. The carrier gas (helium) flow rate was 1.0 mL/min with the inlet splitter set at 50:1. Phytosterol (campesterol, sitosterol, and sitostanol) peak identification was confirmed using authentic standards (Sigma Chemical). The coefficient of variation between replicate analyses was less than 10%.

Table 1. Composition of the Basal Diet

Component	Value
Carbohydrate*	52.4 ± 3.9
Protein*	15.0 ± 1.4
Fat*	32.7 ± 2.8
Fatty acids†	
Saturated	7.4
C8:0	0.1
C10:0	0.2
C12:0	0.5
C14:0	0.6
C16:0	4.6
C18:0	1.5
MUFA	20.9
C16:1n7	0.5
C18:1n9	20.4
PUFA	4.3
C18:2n6	3.9
C18:3n3	0.4
Cholesterol (mg/1,000 kcal)	128.9

Abbreviations: MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

*Percent of total energy (mean ± SD).

†Percent of total fat.

Red Blood Cell Cholesterol Synthesis Determination

Deuterium enrichment was measured in free cholesterol in red blood cells and in plasma water in duplicate.[14] Approximately 3 g red blood cells were mixed with hexane:chloroform (4:1 vol/vol). The mixture was shaken mechanically and centrifuged at 1,500 rpm, and the supernatant was collected. The extraction procedure was then repeated, and solvent layers were combined. The extract was dried under nitrogen, and the residue was chromatographed on silica plates. Plates were developed in hexane:ethyl ether:acetic acid (70:30:1) for 60 minutes and air-dried. Free cholesterol bands were visualized in iodine vapor and identified according to a corresponding co-chromatographed standard. Cholesterol bands were scraped from the plates and eluted from the silica by hexane:chloroform:diethyl ether (5:2:1 vol/vol/vol). Extracts containing approximately 2 mg cholesterol were transferred to Pyrex combustion tubes (18 cm × 6 mm, Vycor; Corning Glass Works, Corning, NY). Cupric oxide (0.5 g) and a 2-cm length of silver wire were added, and the tubes were sealed under vacuum. Cholesterol samples were combusted for 4 hours at 520°C, and the water generated was vacuum-distilled into Pyrex tubes containing 60 mg zinc reagent (Biogeochemical Laboratories, Indiana University, Bloomington, IN).

To measure deuterium enrichment of body water, plasma samples were diluted sevenfold with water to reduce the enrichment to within the normal analytical range. Baseline samples were not diluted. Plasma samples were vacuum-distilled in Pyrex tubes that contained zinc. Cholesterol and plasma samples were reduced to hydrogen gas at 520°C for 30 minutes. Deuterium enrichment of cholesterol and plasma samples was determinated using a triple-inlet differential isotope ratio mass spectrometer (VG Isomass 903D; VG Isogas, Cheshire, UK).

FSR, calculated as pools per day, were derived from the increase in red blood cell cholesterol deuterium abundance in relation to that of the precursor body water pool, adjusted for the fraction of hydrogens of cholesterol derived from labeled substrate.[14] Mean internal and external precision levels of the mass spectrometer were 0.17 and 2.1 per mil (‰), respectively, for mean enrichment changes of about 150 ‰. The sample H_3^+ contribution was checked daily, and appropriate corrections were applied. The instrument was calibrated against water standards of known isotopic enrichment. Samples for each subject were analyzed concurrently using a single set of standards.

Statistical Analysis

Results are expressed as the mean ± SD for descriptive data and the mean ± SEM for inferential data. The data for tall oil phytosterol and placebo treatments were pooled using a paired Student's *t* test. The means between normocholesterolemic and hypercholesterolemic subgroups were separated by an unpaired Student's *t* test. Significance was determined at P less than .05.

RESULTS

Subject Parameters, Caloric Intake, and Phytosterol Intake

The mean subject age was 35 ± 14 years (mean ± SD). The mean weight and height were 78 ± 13 kg and 174 ± 8 cm, respectively, and caloric intake was 2,968 ± 342 kcal/d. The mean dosage of tall oil phytosterol administered during the corresponding diet treatment was 1.6 g/d. Based on a purity of 94%, tall oil phytosterols provided a mean intake over the basal diet of 0.27, 1.04, and 0.35 g/d of campesterol, sitosterol, and sitostanol, respectively. Individual and mean data for subject age, weight, height, body mass index (BMI), caloric intake, and phytosterol intake are reported in Table 2.

Plasma Cholesterol and TG Levels

Plasma TC levels of subjects after consumption of the diet supplemented with tall oil or placebo are reported in Table 3 and illustrated in Fig 1. The mean tall oil treatment plasma TC level (4.7 ± 0.3 mmol/L) was lower ($P < .05$) than the placebo treatment level (5.0 ± 0.3 mmol/L). Furthermore, when subjects were divided according to the initial circulating cholesterol level, 10 individuals had plasma cholesterol less than 5 mmol/L and 12 had plasma cholesterol higher than 5 mmol/L. After treatment with tall oil versus placebo, plasma TC decreased ($P < .05$) in both the normocholesterolemic group (3.2 ± 0.2 and 3.5 ± 0.2 mmol/L, respectively) and moderately hypercholesterolemic group (5.9 ± 0.2 and 6.2 ± 0.2 mmol/L, respectively).

Plasma LDL cholesterol levels of subjects after consumption of the diet supplemented with tall oil or placebo are listed in Table 3 and shown in Fig 1. Mean plasma LDL cholesterol level was lower ($P < .05$) after tall oil treatment (3.3 ± 0.3 and 3.0 ± 0.3 mmol/L). For normocholesterolemic and hypercholesterolemic subjects, tall oil treatment plasma LDL cholesterol levels (1.7 ± 0.2 and 4.1 ± 0.2 mmol/L) were lower ($P < .05$) than with placebo treatment (2.0 ± 0.2 and 4.3 ± 0.1 mmol/L).

Plasma HDL cholesterol levels of subjects after consumption of the diet supplemented with tall oil sterols or placebo are displayed in Table 3 and Fig 1. After tall oil and placebo treatment, plasma HDL cholesterol levels were 1.1 ± 0.1 and 1.1 ± 0.1 mmol/L, respectively. There were no significant differences in HDL cholesterol levels between tall oil and placebo treatment in two different initial plasma TC subgroups. The HDL/LDL cholesterol ratio (0.471 ± 0.063 and 0.400 ± 0.044 for tall oil and placebo treatment, respectively) showed an effective treatment effect ($P < .05$). However, in the hypercholesterolemic group, there were no significant changes in the HDL/LDL cholesterol ratio (0.258 ± 0.019 and 0.259 ± 0.017 for tall oil and placebo treatment, respectively), which differs from the treatment effect observed ($P < .05$) in

Table 2. Demographic Data of the Subjects

Subject No.	Gender	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m²)	Caloric Intake (kcal/d)	Phytosterol Intake (g/d)
1	M	35	104	170	36	2,940	2.2
2	M	48	76	175	25	2,505	1.6
3	M	28	87	187	25	3,300	1.9
4	M	53	74	183	22	3,300	1.6
5	M	50	94	176	30	2,565	2.0
6	M	58	66	165	24	2,970	1.2
7	M	49	94	173	31	3,150	2.0
8	M	54	85	181	26	2,765	1.8
9	M	52	94	169	33	3,060	2.1
10	M	36	73	171	25	2,940	1.6
11	M	34	76	177	24	3,150	1.6
12	M	42	79	174	26	2,910	1.7
13	M	24	75	179	23	3,270	1.6
14	M	23	69	177	22	3,090	1.5
15	M	24	85	183	25	3,390	1.8
16	M	20	76	170	20	3,210	1.6
17	M	27	82	181	27	3,420	1.8
18	M	25	90	183	25	3,405	1.9
19	F	21	65	179	20	2,700	1.4
20	F	20	59	160	23	2,400	1.3
21	F	20	57	173	19	2,550	1.2
22	F	20	59	152	25	2,310	1.3
Mean ± SD		35 ± 14	78 ± 13	174 ± 8	25 ± 4	2,968 ± 342	1.6 ± 0.3

Table 3. Plasma Cholesterol, Lipoprotein, and TG Levels of the Subjects

	TC (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)		HDL:LDL (mmol/mmol)		TG (mmol/L)	
	PS	Placebo	PS	Placebo	PS	Placebo	PS	Placebo	PS	Placebo
1	6.5	6.5	4.9	4.9	1.0	1.0	0.204	0.204	1.1	1.1
2	6.0	6.4	4.5	4.8	0.9	0.9	0.200	0.188	1.4	1.4
3	6.8	7.9	3.5	3.7	0.6	0.7	0.171	0.189	5.9	7.6
4	5.9	6.1	3.9	4.0	1.5	1.5	0.385	0.375	1.1	1.2
5	4.7	5.1	3.4	3.6	0.9	0.9	0.265	0.250	1.0	1.3
6	5.7	6.4	3.9	4.4	1.3	1.3	0.333	0.300	1.2	1.6
7	6.5	6.4	4.6	4.7	0.9	0.9	0.196	0.192	2.1	1.7
8	6.8	6.8	5.0	4.6	1.2	1.4	0.240	0.304	1.4	1.7
9	5.3	5.5	3.7	3.9	0.9	0.9	0.243	0.231	1.6	1.6
10	5.4	5.9	4.0	4.2	1.0	1.3	0.250	0.310	0.9	1.0
11	5.1	5.3	3.5	3.5	0.9	1.0	0.257	0.286	1.6	1.7
12	6.4	6.6	4.3	4.7	1.5	1.3	0.349	0.277	1.3	1.3
13	3.6	3.7	2.2	2.3	0.9	1.1	0.388	0.455	1.0	0.7
14	3.0	3.0	1.6	1.8	1.1	0.9	0.649	0.496	0.7	0.7
15	2.8	3.2	1.1	1.5	1.3	1.2	1.176	0.835	0.8	1.1
16	2.7	3.0	1.3	1.7	1.0	1.0	0.795	0.603	0.9	0.7
17	3.7	4.0	2.2	2.8	1.3	0.9	0.579	0.305	0.5	0.8
18	2.9	3.3	1.7	2.2	0.9	0.9	0.526	0.403	0.6	0.5
19	2.5	3.0	1.0	1.4	0.9	1.2	0.944	0.836	1.1	0.9
20	3.8	3.6	1.7	1.9	1.7	1.3	0.983	0.687	0.7	0.7
21	3.1	3.5	1.6	1.8	1.3	1.2	0.814	0.675	0.6	0.9
22	3.8	4.6	2.5	2.8	1.0	1.1	0.410	0.398	0.6	1.5
Mean ± SEM	4.7 ± 0.3	5.0 ± 0.3	3.0 ± 0.3	3.3 ± 0.3	1.1 ± 0.1	1.1 ± 0.1	0.471 ± 0.063	0.400 ± 0.044	1.3 ± 0.2	1.4 ± 0.3

Abbreviation: PS, phytosterol.

the normocholesterolemic group (0.726 ± 0.082 and 0.569 ± 0.059 for tall oil and placebo treatment, respectively).

Plasma TG levels of subjects after consumption of the diet supplemented with tall oil or placebo are reported in Table 3 and illustrated in Fig 1. Treatment plasma TG levels were 1.3 ± 0.2 and 1.4 ± 0.3 mmol/L following tall oil and placebo treatment, respectively. There were no significant differences in plasma TG levels in response to treatment between subgroups.

Plasma Phytosterol Levels

Group mean and individual plasma phytosterol levels following consumption of the tall oil phytosterol and placebo diets are reported in Fig 2. Plasma campesterol and sitosterol levels in the overall groups were, respectively, 15.8 ± 3.7 and 6.0 ± 2.1 mmol/mol cholesterol following tall oil treatment and 15.4 ± 2.3 and 6.4 ± 2.0 mmol/mol cholesterol following placebo treatment. In the normocholesterolemic subgroup, plasma

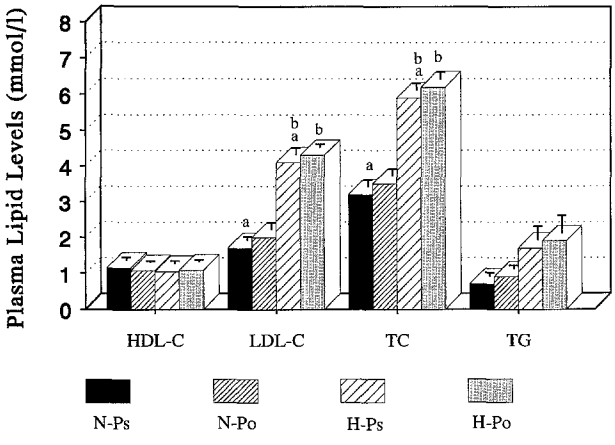

Fig 1. Plasma levels (mmol/L) of HDL-C, LDL-C, TC, and TG in subjects (N = 22) supplemented with either phytosterol (Ps) or placebo (Po) in normocholesterolemic (N) and hypercholesterolemic (H) subgroups. Results are expressed as the mean ± SEM. [a]Significantly different from Po group, $P < .05$ (paired Student's t test); [b]significantly different from N subgroup, $P < .05$ (unpaired Student's t test).

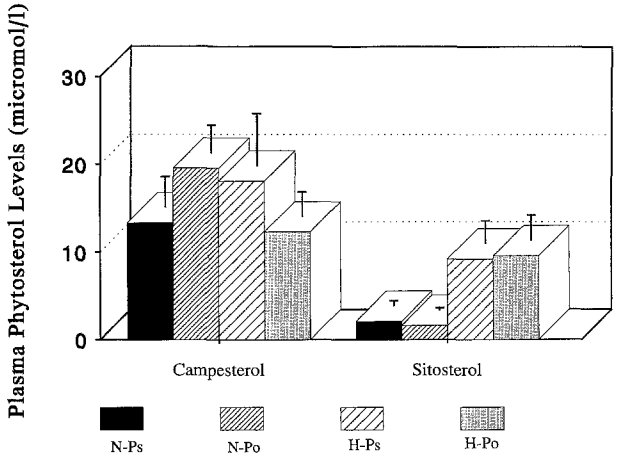

Fig 2. Effect of treatment on the phytosterol to cholesterol ratio (mmol/mol) in subjects (N = 22) supplemented with either phytosterol (Ps) or placebo (Po) in normocholesterolemic (N) and hypercholesterolemic (H) subgroups. Results are expressed as the mean ± SEM. There was no significant difference between treatment groups, $P > .05$ (paired and unpaired Student's t test).

campesterol and sitosterol levels were 13.3 ± 3.5 and 2.1 ± 0.6 mmol/mol cholesterol after tall oil treatment and 19.6 ± 3.2 and 1.6 ± 0.3 mmol/mol cholesterol after placebo treatment. In the hypercholesterolemic group, plasma campesterol and sitosterol levels were 18.1 ± 6.0 and 9.2 ± 2.7 mmol/mol cholesterol after tall oil treatment and 12.3 ± 2.8 and 9.6 ± 3.0 mmol/mol cholesterol after placebo treatment. No significant treatment effects were observed following both treatments; plasma sitostanol levels were essentially undetectable in all subjects.

Red Blood Cell Cholesterol FSR

Individual FSRs of free cholesterol in red blood cells following consumption of the olive oil diet supplemented with phytosterol or placebo are reported in Fig 3. The group mean FSR tended to be higher when subjects received tall oil phytosterols (0.045 ± 0.004 pools/d) versus placebo (0.034 ± 0.004 pools/d), but this difference did not achieve statistical significance. Nevertheless, when the group was stratified, the normocholesterolemic group tall oil treatment FSR (0.0509 ± 0.0049 pools/d) was higher ($P < .05$) than for placebo treatment (0.0291 ± 0.0054 pools/d). In the hypercholesterolemic group, the FSR was not elevated with tall oil phytosterol (0.0385 ± 0.0052 pools/d) versus placebo (0.0354 ± 0.0061 pools/d).

DISCUSSION

A lifetime reduction in cholesterol levels may decrease the risk of coronary heart disease (CHD). A long-term 10% reduction of TC levels decreases the risk of CHD 50% if begun by age 40.[15,16] Beneficial cholesterol-lowering effects of plant sterols have been recognized for several decades; however, the amount of nonsaturated plant sterols required to elicit a cholesterol-lowering response ranges from 4 to 30 g/d.[1-5] These larger doses, compared with other, more modern cholesterol-lowering agents, have limited the practical pharmaceutical use of plant sterols. More recently, purified sitostanol has been shown to possess cholesterol-lowering efficacy at more manageable doses of 1.5 to 3g/d,[6-10] although these effects are not without exception.[17] Unfortunately, pure sitostanol produced through catalytic hydrogenation of sitosterol is expensive, potentially limiting its large-scale use as a cholesterol-lowering agent. The present data indicate that tall oil, which is easily available, inexpensive and contains a mixture of saturated and unsaturated phytosterols, may possess advantages for use as a cholesterol-lowering agent.

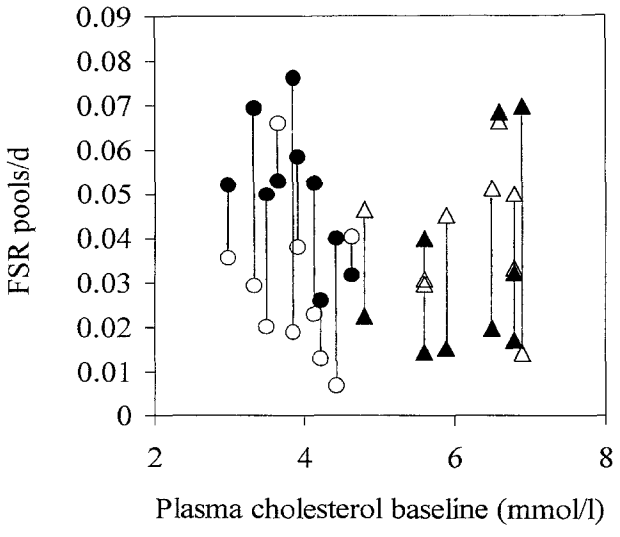

Fig 3. Effect of treatment with either phytosterol or placebo on FSRs in subjects with different baseline plasma cholesterol levels. FSRs of the group with a normal plasma cholesterol level differ significantly after treatment, $P < .05$ (paired t test). Normocholesterolemic subjects (n = 10) treated with placebo (○) or phytosterol (●); hypercholesterolemic subjects (n = 9) treated with placebo (△) or phytosterol (▲).

The extent of the cholesterol-lowering action of tall oil phytosterols in the present study was a reduction of 10% of the plasma TC level. This effect was generally modest; however, the feeding period was brief. Generally, the degree of efficacy varies depending on the type of individual studied, the composition of the mixture used, and the dose and duration provided.[9,10,18,19] By comparison, sitostanol ester administration at levels of 1.8 and 2.6 g/d to hyperlipidemic individuals resulted in a TC decrease of 10% to 12%,[10] although others have seen no effect from a similar dosage.[17] On the basis of these experiments showing a significant cholesterol-lowering action, the present mixture containing about 20% sitostanol, with the remainder of the composition being nonsaturated sterols such as campesterol and sitosterol, produced effects consistent with what would be expected given the relative potency of each constituent. The effect identified may have been indistinguishable had the controlled diet not been applied. Use of the standardized diet enabled fat, cholesterol, and other nutrient intakes to be kept consistent across placebo and treatment periods, thus minimizing biological variations in treatment response.

The diet used herein contained olive oil as the major source of added fat, in keeping with the notion that higher-fat diets rich in monounsaturated fatty acids may be more desirable than those low in fat but high in carbohydrate. Olive oil is naturally low in plant sterols,[20] resulting in plant sterol intakes for our placebo diet that are less than the current North American normal values. Whether the effects of adding tall oil plant sterols on the lipid profile are similar when the diet already contains substantial levels of plant sterols, as would the North American diet, remains to be determined. The existence of a similar threshold effect on circulating lipoprotein cholesterol levels has been suggested when cholesterol is added to diets varying in the amount of existing cholesterol.[21]

Sitostanol levels in plasma were virtually absent, indicating the very poor absorption of this saturated phytosterol seen previously.[6,18,22,23] The low absorbability of sitostanol is thought to be responsible for its greater inhibition of cholesterol absorption compared with either sitosterol or campesterol.[9,23] Campesterol and sitosterol levels were not significantly different between the two treatment groups, although marginally higher values were observed during tall oil phytosterol treatment. These data suggest that circulating phytosterol levels are largely resistant to shifts in intake over a short-term period. Other studies have shown that over longer periods, the plasma plant sterol levels are significantly influenced by the dietary concentrations.[9,11,18,22,24]

We observed in this study a desuppression of cholesterol biosynthesis in normolipidemics, similar to what has been reported previously in animals[18] and humans,[19,25-27] but not in individuals in the higher category of screening cholesterol levels, with tall oil feeding. Previous results have suggested that biosynthesis is upregulated due to the phytosterol-induced decrease in cholesterol absorption. The failure to observe a significantly increased biosynthesis of cholesterol in 12 individuals with higher cholesterol values on the tall oil sterol diet may be due to a difference in the response of cholesterol homeostasis due to the circulating level. Perhaps cholesterogenesis in the 10 normolipidemics exhibits greater flexibility to changes in external cues. Alternatively, a simpler explanation is that there was insufficient time for any effect of plant sterols to become manifest, due to larger body cholesterol pools in individuals with higher lipid levels.

In summary, these results suggest that tall oil phytosterol consumption over the short-term produces a moderate but significant improvement in plasma cholesterol profiles in individuals with a range of lipid concentrations. It is concluded that tall oil sitostanol mixtures may be useful low-cost adjuncts to the diet to provide an improvement in circulating cholesterol levels and a reduction in cardiovascular disease risk.

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