A Softgel Dietary Supplement Containing Esterified Plant Sterols and Stanols Improves the Blood Lipid Profile of Adults with Primary Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Replication Study

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ABSTRACT

A well-controlled clinical trial previously demonstrated the efficacy of a novel softgel dietary supplement providing 1.8 g/day esterified plant sterols and stanols, as part of the National Cholesterol Education Program Therapeutic Lifestyle Changes diet, to improve the fasting lipid profile of men and women with primary hypercholesterolemia (fasting low-density lipoprotein [LDL] cholesterol ≥130 and <220 mg/dL [≥3.37 and <5.70 mmol/L]). The purpose of this randomized, double blind, placebo-controlled crossover study (conducted July 2011 to January 2012) was to support these previous findings in a similar, but independent, sample with a different lead investigator and research site. Repeated measures analysis of covariance was used to compare outcomes for sterol/stanol and placebo treatment conditions using the baseline value as a covariate. Forty-nine subjects were screened and 30 (8 men and 22 women) were randomized to treatment (all completed the trial). Baseline (mean±standard error of the mean) plasma lipid concentrations were: total cholesterol 236.6±4.2 mg/dL (6.11±0.11 mmol/L), high-density lipoprotein (HDL) cholesterol 56.8±3.0 mg/dL (1.47±0.08 mmol/L), LDL cholesterol 151.6±3.3 mg/dL (3.92±0.09 mmol/L), non-HDL cholesterol 179.7±4.6 mg/dL (4.64±0.12 mmol/L), and triglycerides 144.5±14.3 mg/dL (1.63±0.16 mmol/L). Mean placebo-adjusted reductions in plasma lipid levels were significant ($P<0.01$) for LDL cholesterol (−4.3%), non-HDL cholesterol (−4.1%), and total cholesterol (−3.5%), but not for triglycerides or HDL cholesterol. These results support the efficacy of 1.8 g/day esterified plant sterols/stanols in softgel capsules, administered as an adjunct to the National Cholesterol Education Program Therapeutic Lifestyle Changes diet, to augment reductions in atherogenic lipid levels in individuals with hypercholesterolemia.
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ELEVATED TOTAL CHOLESTEROL, LOW-DENSITY lipoprotein (LDL) cholesterol, and non–high-density lipoprotein (non-HDL) cholesterol are risk factors for coronary disease that are modifiable with dietary intervention. A large body of evidence supports increasing daily consumption of plant sterols and stanols as an effective adjunct to the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet to lower circulating cholesterol concentrations.[1-4] Plant sterols and stanols are commercially available in food products[5-10] and dietary supplements in tablet or capsule form[11-15] in amounts sufficient (1 to 3 g/day) to lower blood cholesterol levels.

A previous randomized, placebo-controlled clinical trial[15] demonstrated the efficacy of a novel softgel dietary supplement providing 1.8 g/day esterified plant sterols/stanols, incorporated into the NCEP TLC diet, to improve the lipid profile of men and women with primary hypercholesterolemia. Although the results from that study were promising, reproducible clinical data are particularly useful for guiding health care professionals in making lifestyle recommendations to their patients.[16] Thus, the objective of our trial was to support the results from a prior placebo-controlled, randomized clinical trial[15] showing that plant sterol and stanol esters delivered in a softgel capsule would lower plasma levels of cholesterol in atherogenic lipoprotein fractions.

METHODS

Study Design

Our randomized, double-blind, placebo-controlled crossover study utilized the same design and sterol/stanol ester softgel capsule as a previous trial[15] conducted at other research sites with a different principal investigator. Briefly, participants completed a 5-week lead-in period during which they consumed the weight maintenance version of the NCEP TLC diet for 5 weeks along with placebo softgel capsules (single blind) for at least 2 weeks (there was an unexpected delay in the delivery of the placebo to the research clinic, resulting in some participants not receiving the placebo for the full lead-in period). The lead-in period was followed by two 6-week double-blind treatment periods: four softgel capsules providing a total of 1.8 g/day esterified plant sterols/stanols (~2.9 g/day sterol/stanol ester) or four placebo softgel capsules. Participants completed three lead-in visits (Weeks −5, −1, and 0) and four treatment visits (Weeks 5, 6, 11, and 12). No washout period was employed because previous research has shown that 6 weeks should be sufficient to establish a new steady state for plasma lipid concentrations.[17] This study was conducted from July 2011 to January 2012 by National Clinical Research, Inc, and data management/analysis was conducted by Biofortis Clinical Research according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and the US Code of Federal Regulations. The Schulman Associates Institutional Review Board approved this study and all participants signed a written informed consent form.

Participants

Men and women with hypercholesterolemia (fasting LDL cholesterol level ≥130 mg/dL [3.4 mmol/L] and <220 mg/dL [5.7 mmol/L]), aged 21 to 79 years, and in good general health were eligible to participate. Exclusion criteria have been described previously.[15]

Study Products and Diet Instruction

The active softgel capsules contained 0.45 g sterol/stanol (Reducol, Forbes Medi-Tech, Inc) per capsule (81% plant sterols [predominantly sitosterol] and 19% plant stanols [predominantly sitostanol]). The sterol/stanol and placebo softgel capsules were provided by Pharmavite, LLC. Participants were instructed to take four softgel capsules (two with each of two main meals) at consistent times each day, and to swallow the capsules whole with water or another beverage. All unused study product was returned to the research site where it was counted, and compliance was calculated based on the difference between the number of capsules dispensed and those returned accompanied by subject query to verify that all of the capsules not returned were consumed.

Participants were instructed to follow a weight maintenance version of the NCEP TLC diet throughout the study (including the 5-week lead-in period) and handouts were provided to reinforce diet instructions.[4,18] Participants were also instructed to avoid consuming foods or supplement products containing added sterols or stanols. To evaluate dietary compliance, daily energy and macro/micronutrient intakes were calculated (Food Processor SQL software, version 10.9, 2011, ESHA Research) from 3-day diet records (2 weekdays and 1 weekend day) completed during the week just before randomization (start of double-blind treatment) and during the final week of each treatment period. In addition, participants were instructed to maintain habitual physical activity patterns throughout the study and were queried about changes in physical activity at each visit.

Laboratory Measurements

Fasting (9 to 15 hours) blood samples were collected in duplicate at baseline (Weeks −1 and 0) and at the end of each treatment period (Weeks 5 and 6, Weeks 11 and 12). Routine clinical laboratory measurements were conducted as described previously.[15] Lipoprotein lipid assessments included total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol (calculated as total cholesterol−HDL cholesterol), triglycerides, and the total cholesterol to HDL cholesterol ratio. LDL cholesterol concentration in milligrams per deciliter was calculated according to the Friedewald equation: LDL cholesterol=Total cholesterol−HDL cholesterol−triglycerides/5.[18]

Statistical Analyses

SAS version 9.2 (2002-2008, SAS Institute Inc) was used in the conduct of all statistical analyses. The primary outcome was the percent change from baseline in LDL cholesterol and secondary outcomes were other parameters of the lipoprotein profile. A sample of 28 participants was expected to provide 80% power to detect an effect size of 0.44 standard deviations for the difference between treatments in LDL cholesterol response, using a two-sided α=.05. Assuming a pooled standard deviation of 9% for the percent change from baseline in LDL cholesterol, based on results from previous trials,[13,15,17] this would translate into a 4% difference between treatments in response. Because the standard deviations for responses of other lipoprotein cholesterol values (secondary outcomes) have generally been observed to be similar to that for LDL cholesterol, the power to detect changes in these would have been approximately the same as for the primary outcome. Because triglyceride response typically has a larger standard deviation (~25%), the study had roughly 80% power to detect a difference of 11% between treatments in triglyceride level response.[13,15,17]

Nonpaired *t* tests and Fisher's exact test were used to compare baseline characteristics for participants in the two treatment sequences. Repeated measures analysis of covariance was used to compare changes (dietary variables) or percent changes (lipoprotein lipid variables) in continuous variables for the sterol/stanol and placebo treatment conditions, with baseline value as a covariate in each model. Values for baseline and end of treatment were calculated as the average from two samples collected at weeks −1 and 0 for baseline, Weeks 5 and 6 for the end of Treatment 1, and Weeks 11 and 12 for the end of Treatment 2. Initial models each included participant as a random effect and terms for treatment condition, sequence, and treatment by sequence interactions. If an interaction term was not statistically significant ($P>0.05$), it was dropped from the final model. No material differences in responses by treatment sequence were present that would bring into question the appropriateness of pooling data from the two sequence groups. Evidence of non-normality was present in model residuals for HDL cholesterol (Shaprio-Wilk $P<0.01$)[19]; therefore, rank

transformations were employed in the final models for this variable.[20]

Results for continuous variables are presented as mean±standard error of the mean, including HDL cholesterol because mean and median values were not materially different. Frequencies of adverse events are presented as numbers and percent of subjects experiencing each type of event and comparisons between treatment conditions were assessed using McNemar's test.

RESULTS AND DISCUSSION

Forty-nine individuals were screened and 30 (8 men and 22 women) were randomized (placebo followed by sterol/stanol n=14; sterol/stanol followed by placebo n=16); all 30 participants completed the study. The primary reason for screen failure was LDL cholesterol outside of the range required for qualification. All participants completed both treatment phases and were included in the analyses. Demographic and baseline characteristics of participants are presented in Table 1. No statistically significant differences were observed between treatment sequence groups for baseline characteristics. As shown in Table 2, significant reductions were observed in atherogenic plasma lipid levels in the sterol/stanol condition (LDL cholesterol −4.3%, non-HDL cholesterol −4.1%, total cholesterol −3.5%) compared with placebo. Triglycerides, HDL cholesterol, and total cholesterol/HDL cholesterol level responses were not significantly different between treatment conditions.

Table 1. Subject characteristics at baseline in a study to demonstrate the efficacy of a novel softgel dietary supplement providing 1.8 g/d esterified plant sterols and stanols, as part of the National Cholesterol Education Program Therapeutic Lifestyle Changes diet (N=30)[a]

Characteristic	Result
	n (%)
Men	8 (27)
Women	22 (73)
Race/ethnicity	
Non-Hispanic white	24 (80)
Asian or Pacific Islander	1 (3)
Black/African American	5 (17)
Smoking status	
Nonsmoker	20 (67)
Current smoker	4 (13)
Past smoker	6 (20)
	mean±standard error of the mean
Age (y)	58.7±1.5
Weight (kg)	73.4±2.6
Body mass index	26.7±0.9
Systolic blood pressure (mm Hg)	127.6±2.5
Diastolic blood pressure (mm Hg)	77.1±1.6
Fasting glucose (mg/dL)[b]	96.3±1.7

[a]Results for both treatment sequences were pooled and values shown are for the efficacy evaluable analysis sample.

[b]To convert mg/dL glucose to mmol/L, multiply mg/dL by 0.0555. To convert mmol/L glucose to mg/dL, multiply mmol/L by 18. Glucose of 70 mg/dL=3.89 mmol/L.

These results support similar, statistically significant findings from a prior study[15] that was conducted at two research clinics in Indiana and Illinois (Biofortis-Provident Clinical Research), independent of the current study site (National Clinical Research in Richmond, VA), that used the same design, methods, and formulation of the sterol/stanol supplement. In that study, statistically significant placebo-adjusted reductions in atherogenic lipid levels (−9.2% for LDL cholesterol, −9.0% for non-HDL cholesterol, and −7.4% for total cholesterol) were observed in a similar sample of adults with hypercholesterolemia. Although the directions of the changes observed in the two studies were the same, the magnitudes of the reductions in LDL cholesterol, non-HDL cholesterol, and total cholesterol in our study were somewhat smaller than those observed in the previous trial. The authors view random variation as the most likely explanation for the differences in responses, because the study protocols and the active and placebo test products employed were essentially identical. Our validation of the earlier study, in conjunction with the published literature, provides support for health care professionals to recommend the option of a sterol/stanol supplement as an adjunct to the NCEP TLC diet for the management of hypercholesterolemia.

The dietary supplement used in our trial and the previous trial[15] was composed of a blend of plant sterols and stanols previously shown to lower LDL cholesterol levels when administered in food forms such as margarine[6] and chocolate.[5] Indeed, the cholesterol-lowering properties of plant sterols/stanols in fortified food forms have been extensively documented,[1-3] but relatively few investigators have studied the efficacy of plant sterols/stanols administered in tablets or capsules. It is important to recognize that fortified foods containing plant sterols/stanols may be challenging for some individuals to incorporate into a cholesterol-lowering diet on a consistent basis. Some individuals may find it easier to incorporate a dietary supplement into their daily regimen. Compliance was high in this trial as it was in the previous study,[15] with 94.3%±1.2% and 96.2%±1.1% of expected doses consumed during the sterol/stanol and placebo treatment periods, respectively (P=0.223). In addition, all randomized participants completed both treatment periods.

It is unlikely that the beneficial changes in the atherogenic lipid profile observed with sterol/stanol supplementation occurred due to changes in background diet because there were no significant changes from baseline (after the diet lead-in) during sterol/stanol and placebo treatments for percentages of intake from saturated fatty acids (10.8%±0.6% vs 11.2%±0.8% and 10.9%±0.4%; P=0.470), polyunsaturated fatty acids (4.1%±0.3% vs 3.7%±0.3% and 4.4%±0.4%; P=0.105), monounsaturated fatty acids (7.9%±0.7% vs 7.8%±0.6% and 8.6%±0.7%; P=0.304), cholesterol (220.7±19.9 mg/day vs 252.0±20.5 mg/day, and 223.7±20.1 mg/day; P=0.274), and dietary fiber (16.4±1.2 g/day vs 16.2±1.5 g/day and 16.5±1.4 mg/day; P=0.619). There were also no significant changes from baseline during sterol/stanol and placebo treatments for total energy intake; percentages of intake from carbohydrate,

Table 2. Fasting lipid levels at baseline and end of treatment, along with percent changes from baseline and differences in responses between treatments, in a study to demonstrate the efficacy of a novel softgel dietary supplement providing 1.8 g/d esterified plant sterols and stanols, as part of the National Cholesterol Education Program Therapeutic Lifestyle Changes diet[a]

Parameter	Baseline, (mg/dL)[bc]	End of Treatment, Control (mg/dL)[cd]	End of Treatment, Sterol/Stanol (mg/dL)[cd]	Control, %Δ[e]	Sterol/Stanol, %Δ[e]	% Difference in Response (mean)[f]	*P* value
	←——————*mean±standard error of the mean*——————→						
LDL[g] cholesterol	151.6±3.3	150.5±4.8	143.9±4.5	−1.1±1.9	−5.4±1.8	−4.3	0.008
Non-HDL[h] cholesterol	179.7±4.6	177.1±5.4	169.8±5.4	−1.5±1.8	−5.7±1.6	−4.1	0.006
Total cholesterol	236.6±4.2	236.0±5.5	227.5±4.9	−0.3±1.5	−3.8±1.3	−3.5	0.003
HDL cholesterol	56.8±3.0	58.9±3.2	57.7±3.1	4.4±2.3	2.1±1.7	−2.3	0.206
Triglycerides	144.5±14.3	133.3±13.2	130.0±11.3	−3.0±4.2	−6.2±3.2	−3.2	0.397
Total cholesterol/HDL cholesterol	4.5±0.2	4.3±0.2	4.2±0.2	−3.5±1.9	−5.2±1.5	−1.7	0.291

[a]Results for both treatment sequences were pooled (N=30, efficacy evaluable sample). Adjusting for differences in dietary intake did not significantly alter results.
[b]Baseline=Average of values at weeks −1 and 0.
[c]To convert mg/dL cholesterol to mmol/L multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 200 mg/dL=5.17 mmol/L. To convert mg/dL triglycerides to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.6. Triglycerides of 160 mg/dL=1.8 mmol/L.
[d]End of Treatment=Average of values at the final 2 weeks of each treatment period (Weeks 5 and 6, and Weeks 11 and 12).
[e]% Δ=Percentage change from baseline to end of each treatment period (average of values at Weeks 5 and 6, and Weeks 11 and 12).
[f]% Difference in Response=Active % change−Control % change.
[g]LDL=low-density lipoprotein.
[h]HDL=high-density lipoprotein.

protein, or total fat; and intake of soluble fiber (data not shown). The intake of saturated fat and cholesterol, on average, did not reach the targets of the NCEP TLC diet of <7% of energy from saturated fat and <200 mg/day cholesterol, but participants did follow a diet that is lower in these dietary components than a typical American diet. This reflects what likely occurs in clinical practice, because free-living people given dietary counseling are often unable to attain the relatively stringent TLC diet recommendations.[21] Also, because reported dietary intakes did not differ between treatment periods, this is unlikely to have affected the comparisons of lipoprotein levels between treatment periods.

There was an increase in mean dietary cholesterol intake during the sterol/stanol treatment period (~14% increase relative to baseline); however, it should be noted that the standard deviation around the mean cholesterol intake during the sterol/stanol treatment period was high (~115 mg) and, thus, this increase cannot be reliably separated from chance. Using the Hegsted equation[22] to estimate the effect of a 31 mg/day increase in dietary cholesterol indicates that the predicted effect on total cholesterol would be ~1.2 mg/dL (0.03 mmol/L) and, with the assumption that the contribution to LDL cholesterol would be two thirds of this value, a difference of ~0.8 mg/dL (0.02 mmol/L) in LDL cholesterol. Given the baseline LDL cholesterol concentration of 151.6 mg/dL (3.92 mmol/L), this translates into an increase of ~0.5% in LDL cholesterol during the sterol/stanol condition potentially contributed by the increase in dietary cholesterol, which could have partially offset the LDL cholesterol reduction produced by the sterol/stanol supplement. Sensitivity analyses that adjusted for the predicted differences in circulating LDL cholesterol concentration attributable to differences in dietary fatty acid and cholesterol intakes did not suggest significant confounding by dietary differences between baseline and the two treatment periods (data not shown).

There were no significant changes from baseline in mean body weight (<0.1 kg) or systolic and diastolic blood pressures (<3 mm Hg) during either treatment period. No significant differences in adverse events were noted between treatment conditions. Adverse events assessed at each clinic visit after randomization were reported by four participants (13.3%) during the sterol/stanol treatment (weight gain n=1 and upper respiratory tract infection n=3), and four participants (13.3%) during the placebo treatment (upper respiratory tract infections n=2, urinary tract infection n=1, and eczema n=1). The study physicians classified all adverse events as mild or moderate in severity and not related or unlikely to be related to the study products. No severe adverse clinical effects associated with the consumption of the study products were reported.

A small segment of the general population (one patient in 1 million) is homozygous for a genetic disorder (beta sitosterolemia), which occurs due to the absence or dysfunction of two adenosine triphosphate-binding cassette (ABC) transporters (ABCG5 and ABCG8) that facilitate the transport of sterols, including plant sterols, from the enterocytes into the intestinal lumen. This results in overabsorption of plant sterols with resulting high blood levels that may damage the arterial wall, enhancing risk for the development of atherosclerosis.[23] A recent meta-analysis[24] failed to find any evidence of an association between blood levels of plant sterols and increased risk of cardiovascular disease with more

modest levels of plant sterols, as might be observed in those consuming diets high in plant sterols or taking dietary supplements.

Some investigators have observed reductions in serum carotenoid levels with sterol or stanol consumption[10,25-27]; however, reduced serum carotenoids can be counteracted with increased consumption of carotene-rich foods.[17] This premise was tested in a study of 46 participants with hypercholesterolemia who were instructed to consume margarine containing 2.5 g/day plant sterols or stanols and five or more servings of fruits and vegetables, of which one or more servings were to include carotenoid-rich foods (eg, carrots, sweet potatoes, pumpkins, tomatoes, apricots, spinach, or broccoli).[8] Results indicated a significant decrease in LDL cholesterol and a significant increase in plasma beta carotene concentrations. Nevertheless, the potential for reduced carotenoid bioavailability resulting from sterol/stanol consumption is a valid concern, and additional research is needed to further clarify the magnitude of this effect with different formulations of sterol/stanol-containing supplements or foods, as well as potential clinical significance of such reductions.

Our study does have some limitations. The 6-week treatment period with the sterol/stanol product focused on relatively short-term changes in surrogate markers of cardiovascular disease. Although short-term reductions in cardiovascular disease risk factors appear favorable, it remains to be determined whether continued long-term consumption of the sterol/stanol product would ultimately reduce major cardiovascular disease outcomes (eg, myocardial infarction). In addition, although study entry criteria were based on the presence of hypercholesterolemia and did not prespecify a fixed ratio of women to men, women accounted for 73% of the study sample. Post hoc analyses of pooled results from our trial and the previous trial[15] do not indicate a treatment by sex interaction in response. Moreover, results from prior studies of sterols and stanols have not indicated a treatment by sex interaction in responses. Thus, we believe that the results herein should be generalizable to both sexes.

Our results support previous findings that a novel sterol/stanol softgel dietary supplement lowers atherogenic lipoprotein levels. This is important because coronary event risk may be reduced by ~3% for each 1% lower level of LDL cholesterol if the reduced LDL cholesterol level is maintained over decades, which is larger than the coronary event risk reduction observed in clinical trials of cholesterol-lowering drug therapies over periods of 5 to 6 years (~1% risk reduction for each 1% reduction in LDL cholesterol).[28-30] Future research studies with focus on outcome trials will provide greater understanding of the benefits of phytosterols for dietary management of cardiovascular disease risk long term.

CONCLUSIONS

The results of our trial support those of a previous study demonstrating cholesterol-lowering effects of the ingestion of 1.8 g/day esterified plant sterol and stanols given as four dietary supplement softgel capsules (two capsules with each of two main meals).[28] For the practicing health care professional, these results provide further support for the use of plant sterols/stanols as an adjunct to the NCEP TLC diet. This supplement may be particularly useful for those clients or individuals who desire the flexibility of a dietary supplement due to the ease of incorporation into a cholesterol-lowering dietary regimen, and the consistency of delivering a sufficient dose to affect blood cholesterol levels.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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