Nutrition 29 (2013) 96–100

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Lipid effects of a dietary supplement softgel capsule containing plant sterols/stanols in primary hypercholesterolemia

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ARTICLE INFO

Article history:
Received 23 December 2011
Accepted 9 May 2012

Keywords:
Plant sterols
Plant stanols
Phytosterols
Dietary supplements
Hypercholesterolemia
Low-density lipoprotein cholesterol
Non–high-density lipoprotein cholesterol

ABSTRACT

Objective: This randomized, placebo-controlled, crossover trial assessed the lipid-altering efficacy of a softgel capsule dietary supplement, providing esterified plant sterols/stanols 1.8 g/d, in 28 participants (~75% women) with primary hypercholesterolemia (fasting low-density lipoprotein cholesterol [LDL-C] levels ≥130 and <220 mg/dL), a mean age of 58.4 y, and a mean body mass index of 27.9 kg/m^2.

Methods: After a 5-wk National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and a single-blinded placebo lead-in, subjects received double-blinded placebo or sterol/stanol softgel capsules for 6 wk and then crossed over to the opposite product for 6 wk while continuing the TLC diet. Fasting lipids were assessed in duplicate at the end of the diet lead-in (baseline) and the end of each treatment.

Results: The mean baseline lipid concentrations (milligrams per deciliter) were 223 for total cholesterol (TC), 179 for non–high-density lipoprotein cholesterol (non-HDL-C), 154 for low-density lipoprotein cholesterol, 44 for HDL-C, 125 for triacylglycerols, and 5.2 for TC/HDL-C. Differences from the control responses (plant sterol/stanol minus control) in the per-protocol sample were significant ($P < 0.05$) for LDL-C (−9.2%), non-HDL-C (−9.0%), TC (−7.4%), TC/HDL-C (−5.4%), and triacylglycerols (−9.1%). The HDL-C responses were not significantly different between treatments.

Conclusion: The incorporation of softgel capsules providing esterified plant sterols/stanols 1.8 g/d into the NCEP TLC diet produced favorable changes in atherogenic lipoprotein cholesterol levels in these subjects with hypercholesterolemia.

Introduction

Plant sterols and stanols (sterols containing additional hydrogen) occur naturally and have a similar structure to cholesterol [1,2]. Plant sterols/stanols have been shown to decrease cholesterol absorption by competing with cholesterol for incorporation into micelles in the intestinal lumen and for transport across the brush border by Niemann Pick C1-like 1 transporters [3–5]. Plant sterol/stanol accumulation in the enterocyte also appears to trigger the greater production of transporters (adenosine triphosphate binding cassette transporters G5 and G8), which move sterols out of the enterocyte and into the intestinal lumen [3,5]. The net result is increased fecal cholesterol excretion [5,6], leading to decreased hepatic cholesterol content that in turn stimulates the upregulation of hepatic low-density lipoprotein (LDL) receptor number, thus increasing the removal of LDL and other apolipoprotein B–containing lipoproteins from the circulation [5]. Plant sterols/stanols also have been reported to have an antioxidant effect against the lipid peroxidation of LDL in laboratory and animal studies [7].

In a typical Western diet, approximately 150 to 400 mg of plant sterols/stanols is consumed daily in food, and this level of intake does not substantially affect blood cholesterol concentrations [8,9]. However, at higher intakes, the consumption of plant sterols or stanols lowers total cholesterol (TC), non–high-density lipoprotein cholesterol (non-HDL-C), and LDL

This trial was funded by Pharmavite, LLC, Northridge, California.
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0899-9007/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
doi:10.1016/j.nut.2012.05.002

cholesterol (LDL-C) concentrations [2,10–13]. Meta-analyses of data from plant sterol and stanol trials have suggested that LDL-C is decreased by approximately 4% to 5% with each gram of plant sterol or stanol consumed in the range of 1 to 3 g/d, and higher baseline LDL-C levels typically have been associated with larger decreases [2,12,13].

Commercially available products containing plant sterols and/or stanols, in their free and ester forms, include margarine-type spreads, yogurt and yogurt-based drinks, orange juice, and dietary supplement tablets and capsules. Most clinical examinations of the effects of plant sterols/stanols on lipid concentrations have used food vehicles, and fewer have investigated the effects of plant sterols or stanols administered in tablets and capsules [1,2,12–24]. Results from these investigations have suggested that food and supplement forms are successful in lowering circulating cholesterol concentrations. However, the use of plant sterol/stanol-containing tablets or capsules is particularly appealing because of the ease of incorporating these into a cholesterol-lowering regimen compared with the dietary adjustments necessary to incorporate food products [2,13].

This trial was undertaken to assess the efficacy of the consumption of softgel capsules providing esterified plant sterols/stanols 1.8 g/d, incorporated into the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet [11], for improving the lipid profile of men and women with primary hypercholesterolemia. Previously, non-esterified sitostanol-containing phytosterols 1.7 and 1.8 g/d administered in margarine and chocolate have been shown to decrease LDL-C by up to 15.5% [14,15].

Materials and methods

Study design

This was a randomized crossover study conducted from September 2009 to February 2010, consisting of a 5-wk diet plus a single-blinded placebo softgel capsule lead-in, followed by two double-blinded 6-wk treatment periods during which subjects received softgel capsules providing esterified sterol/stanols 2.9 g/d (equivalent to non-esterified plant sterol/stanols 1.8 g/d) or control softgel capsules. Subjects completed three screening/lead-in/baseline visits (weeks −5, −1, and 0) and four treatment visits (weeks 5, 6, 11, and 12). The study was conducted at two clinical research centers (Biofortis-Provident Clinical Research in Addison, IL and Bloomington, IN, USA) according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and the US 21 Code of Federal Regulations. Signed written informed consent for the study was obtained from all subjects before the protocol-specific procedures were carried out and the subjects were informed of their right to withdraw from the study at any time.

Subjects

Men and women 21 to 79 y of age, inclusive, each with a fasting LDL-C level from at least 130 to lower than 220 mg/dL and in good general health based on medical history and routine laboratory tests, were eligible for the study. Individuals were excluded from participation if they had a body mass index higher than 42.0 kg/m^2, a fasting blood glucose level of at least 126 mg/dL or diabetes mellitus, a resting systolic blood pressure of at least 160 mmHg and/or a diastolic blood pressure of at least 100 mmHg, or coronary heart disease or a coronary heart disease risk equivalent [11]. Additional exclusion criteria included a history of extreme dietary habits, eating disorders, alcoholism, cancer, or any clinically important cardiovascular disorders. The use of any medications, dietary supplements, or fortified foods with lipid-altering effects, including sterol and stanol products, was excluded for at least 4 wk before study entry (week −1), as was use of weight-loss drugs or programs and a recent body weight change greater than 4.5 kg.

Study products and diet instruction

After the diet and single-blinded control study product lead-in, the subjects were randomly assigned to receive, in a double-blinded manner, esterified sterol/stanol softgel capsules (0.45 mg/capsule) or control softgel capsules (matched placebo that contained soybean oil and medium-chain triacylglycerols [TGs] from coconut oil) for 6 wk (first treatment period) and then crossed over to receive the opposite study product for 6 wk (second treatment period). The softgel capsules contained 81% plant sterol (predominantly sitosterol) and 19% plant stanol (predominantly sitostanol). Subjects were instructed to swallow whole, with water or another beverage, four softgel capsules daily (two with each of two meals) at consistent times each day. Compliance with the active and control softgel capsules was assessed by counting the unused study product returned to the clinic. In addition, subjects were instructed to maintain their usual physical activity patterns throughout the trial.

Beginning at week −5 and throughout the study, subjects were counseled to follow the weight-maintenance version of the TLC diet created by the NCEP and handouts were provided to reinforce the diet instructions [11]. To evaluate compliance with the TLC diet, diet records were completed on 3 consecutive days (2 weekdays and 1 weekend day) at baseline and the end of each treatment period. Daily intakes of energy and selected nutrients were calculated from these records using Food Processor SQL 10.4 (ESHA Research, Salem, OR, USA). In addition, subjects were instructed to maintain their usual physical activity patterns throughout the study period.

Laboratory measurements

Clinical laboratory measurements in fasting (9–15 h) blood samples 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) were conducted by the Elmhurst Memorial Hospital Laboratory (Elmhurst, IL, USA) according to the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute. Lipoprotein lipid assessments (milligrams per deciliter) included TC, LDL-C, HDL-C, non-HDL-C (calculated as TC minus HDL-C), TG, and the TC/HDL-C ratio. The LDL-C concentration was calculated according to the Friedewald equation as: LDL-C = TC − HDL-C − TG/5 [25]. Because this equation is not valid when the TG concentration is above 400 mg/dL, the LDL-C values were not calculated in the few instances when subjects had values in this range.

Statistical analyses

Statistical analyses were completed in SAS 9.2 (SAS Institute, Cary, NC, USA). Analyses were performed on an efficacy evaluable sample that included all subjects who were randomized and provided at least one fasting lipid profile during each treatment condition after randomization. Per-protocol analyses also were performed in a subset of the efficacy evaluable sample that excluded subjects with poor compliance, significant protocol violations, or circumstances during the study that could confound the evaluation of the study product. All decisions about exclusion from the per-protocol sample were documented before breaking the treatment code. The per-protocol results are described in this report, except where indicated otherwise. A sample of 24 evaluable subjects was calculated to provide 90% power to detect a difference between the active and control treatment conditions of 7% in LDL-C change from baseline with a two-tailed α level of 0.05, assuming a pooled standard deviation of 10% for the LDL-C response. A larger sample of 34 subjects was randomized to allow for subject attrition and non-compliance.

Baseline characteristics for subjects in the two treatment sequences were compared using unpaired t tests (continuous variables) or the Fisher exact test (categorical variables). Repeated measures analysis of covariance was used to compare lipids and dietary intake responses (changes or percentages of change from baseline) for the two treatment conditions (active and control) using the baseline value as a covariate. The initial model included the subject as a random effect and terms for treatment condition, sequence, site and treatment-by-site and treatment-by-sequence interactions. If an interaction term for a variable was not statistically significant ($P > 0.05$), it was dropped from the final model. The examination of responses by sequence suggested that no material differences were present that would bring into question the appropriateness of pooling data from the two sequence groups. Residuals from the final model were examined to assess normality; if clear evidence of non-normality was present, rank transformations were used in the final models.

An additional analysis of covariance was conducted using the results of the equation of Yu et al. [26] for estimating changes in lipid concentrations in response to a dietary alteration according to the diet record results, with and without an adjustment for dietary cholesterol intake based on the dietary cholesterol term in the equation of Hegsted et al. [27]. This was done to assess possible confounding by dietary changes during the treatment periods.

Safety analyses were performed on the sample that included all subjects who were randomized and consumed at least one dose of the study product. Safety assessments included an evaluation of treatment-emergent adverse events compared between the two treatment conditions using the McNemar test, and changes in vital sign measurements were analyzed with a repeated measures analysis of covariance as described earlier.