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Phytosterol capsules and serum cholesterol in hypercholesterolemia: A randomized controlled trial

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ABSTRACT

Objective: Phytosterols are recommended in combination with diet therapy to reduce elevated LDL-cholesterol level. Meta-analyses indicate a 10% reduction in LDL-cholesterol from intake of approximately 2 g phytosterols/d incorporated into fat-based foods. However, the cholesterol lowering effect from capsules containing phytosterols is less documented. The pre-specified primary endpoint of the present study was to investigate the effect of capsules with phytosterols on circulating LDL-cholesterol in patients with mild to moderate hypercholesterolemia.

Methods: In a double-blinded, randomized, placebo-controlled crossover study, 41 men and women were randomized into two four-weeks intervention periods with softgel capsules containing either phytosterols (2.0 g/d) or sunflower oil. There was a three-weeks washout period between the intervention periods.

Results: No significant difference in total- or LDL-cholesterol between the phytosterol and the placebo period were observed after four weeks intervention (0.0 mmol/L (95%CI: −0.3 to 0.2), $P = 0.74$ and −0.1 mmol/L (95%CI: −0.3 to 0.1), $P = 0.32$, respectively).

Conclusion: Daily intake of capsules containing 2 g phytosterols did not reduce total- or LDL-cholesterol significantly in a highly relevant target group for the use of phytosterol products. The present results may emphasize the importance of choosing a suitable dosage-delivery system in order to achieve optimal cholesterol lowering effect.

The study was registered at www.clinicaltrials.gov, IDno:NCT00485095.

1. Introduction

Foods added with 2 g plant stanol or sterol esters have shown approximately 10% decrease in LDL-cholesterol level [1–3]. In particular, it is well documented that phytosterol esters reduces LDL-cholesterol when added to fat based food such as margarine [3–7]. Capsules with phytosterols are commercially available, but very few randomized placebo-controlled trials with phytosterol capsules are accessible [8–14].

Meta-analyses have shown that LDL-cholesterol is affected differently when phytosterols are incorporated in different food matrixes; high fat vs. low fat content, and solid vs. liquid form [2–4]. However, the different dietary guidelines that recommend phytosterols in the treatment of elevated LDL-cholesterol, do not distinguish between intake of margarine, capsules or other delivery forms [15–17]. The current recommendation is approximately 2 g phytosterols/d [15–17]. The proposed mechanism for the cholesterol lowering effect is that phytosterols displace cholesterol (biliary and dietary cholesterol) from micelles in the duodenum, thereby inhibiting the intestinal cholesterol absorption [18].

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Phytosterols have shown an additive effect both to diet therapy [19] and to statin treatment [20,21].

The Food and Drug Administration (FDA) in the US and the EU Commission have authorized a health claim for reduced cholesterol from intake of foods containing phytosterols [22]. Thus, capsules containing phytosterols do not require efficacy or safety evaluation before being marketed.

Capsules with phytosterols are widely commercially available and marketed towards people with elevated blood cholesterol level. We have carried out a randomized placebo-controlled study in subjects with mild to moderate hypercholesterolemia; a highly relevant target group for the use of phytosterol products. The aim of the present study was to investigate the effect of four weeks daily intake of capsules with phytosterols on plasma LDL-cholesterol level.

2. Materials and methods

2.1. Subjects

This study was conducted at the Lipid Clinic, Rikshospitalet, Oslo-University Hospital in Norway from January 2007 to July 2007. The subjects were recruited through newspaper advertisement. Men and women of 18–80 years of age with total cholesterol 4.7–7.7 mmol/L and with fasting triglycerides $\leq$ 4.0 mmol/L were included. Exclusion criteria for the study were diagnosis of familial hypercholesterolemia (FH), secondary hyperlipidemia, diabetes, chronic rheumatoid disease, coronary-, periphery- or cerebral-vascular disease within the previous three months of inclusion, any diseases known to affect C-reactive protein (CRP), body mass index (BMI) $\geq$ 35 kg/m^2, hypertension ($\geq$170/100), pregnancy, lactation and planning to reduce weight in the near future and change in hormone replacement therapy or oral contraceptives during the last 3 months. Use of any phytosterol (e.g. functional foods added phytosterols), drugs or supplements that are known to interfere with plasma cholesterol, such as soluble fiber and red yeast rice were not allowed during the four weeks prior to the intervention period or during the entire intervention period. Statins was permitted, but only those with a stable statin dose during the last three months prior to inclusion were allowed to participate. In the present study, eight subjects (20%) used a stable dose of statins, either simvastatin (20 or 40 mg), atorvastatin (10 mg) or pravastatin (20 or 40 mg). No change in statin treatment was made during the study period.

The study was approved by the Regional Committee of Medical Ethics and by the Norwegian Social Science Data Services. It was registered at www.clinicaltrials.gov (IDno. NCT00485095). Written informed consent for participation was obtained from each participant and it complied with the Declaration of Helsinki.

2.2. Design, randomization and blinding

The study was conducted as a randomized double-blind placebo-controlled crossover study comprising two four-weeks intervention periods with capsules containing phytosterols (2 g/d) in one period and capsules containing sunflower oil (2 g/d) in the other. There was a four weeks run-in period prior to randomization, and a three-weeks washout period between each intervention period. Each subject met for a screening visit and a visit before and after each intervention period. Height, body weight, blood pressure, pulse, and waist- and hip-circumference were registered at all visits. The capsules were identical in size and color, and both capsules were delivered in closed containers of identical appearance. The containers were marked with a digit code blinded for the study investigators and a pharmacist at the local pharmacy. Compliance was assessed by the pharmacist through capsule count. The subjects were randomly assigned for phytosterol or placebo in the first intervention period by equal allocation (1:1) to two groups according to a randomization list made by an external part. The randomization code was concealed from the study investigators until the primary endpoint analysis were completed. The subjects were instructed to take four capsules per day, two with the first main meal and two with dinner. In order to check for a stable diet during the intervention, the subjects completed a validated qualitative questionnaire; SmartDiet®, at visit one, two and five [23]. At each visit the subjects were instructed by an experienced nurse or dietitian on how to keep their weight and diet stable during the study.

2.3. Capsules

Each placebo capsule contained 1 g sunflower oil, and each intervention capsule contained 1 g sunflower oil of which 0.8 g was phytosterol esters. Phytosterols (Vegapure®95E, Cognis GMBH, Germany) originated from pine and rapeseed were used. Free sterols were esterified with fatty acids from sunflower oil and mixed with tocopherols (0.04% final concentration). The amount of phytosterol esters and sterol oxides in test-capsules (phytosterols and placebo capsules) was analyzed after saponification by gas chromatography (GC) and mass spectrometry (MS) at the Department of Applied Chemistry and Microbiology at University of Helsinki, Finland, according to the method of Toivo et al. [24]. Concentrations of phytosterol esters and sterol oxides were based on duplicate analyses, and the total phytosterol content was found to be 50.5 g/100 g and 0.4 g/100 g in phytosterol and placebo capsules, respectively (Table 1). The content of sterol oxides in the phytosterol capsules was 17.8 mg/100 g indicating that the degree of oxidation was negligible.

Softgel-capsules (Eurocaps Ltd, Wales, UK) were made of bovine gelatin (0.3 g) and glycerol (0.1 g). The digestibility of the softgel-capsules (phytosterols and placebo) was measured at Nofima Mat, Norway in an in vitro human stomach and duodenum model system.

2.4. Compliance and side effects

During the study, two adverse advents were reported in the phytosterol period (more frequent defecation), and one adverse event was reported in the placebo period (abdominal discomfort). Data on compliance is missing for two subjects in the placebo period and for one subject in the phytosterol periode. For the remaining participants, average compliance for the phytosterol and placebo period was 94 $\pm$ 6% (n = 40) and 95 $\pm$ 11% (n = 39),

Table 1
Phytosterol composition of phytosterols from Vegapure®95E and of sunflower oil capsules.

Sample	Campe-sterol	Campe-sterol	Stigma-sterol	Sito-sterol	Sito-stanol	Brassica-sterol	Other sterols	Total phyto-sterols
	Phytosterols (g/100 FW)							
Phytosterol capsules	8.0	0.5	0.4	35.2	3.7	1.4	1.2	50.5
Sunflower oil capsules	(−)	(−)	<0.1	0.2	(−)	(−)	0.2	0.4

(−) means <0.05.