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Additive effects of plant sterols supplementation in addition to different lipid-lowering regimens

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OBJECTIVE: Plant sterol (PS) supplementation has been widely used alone or combined with lipid-lowering therapies (LLTs) to reduce low-density lipoprotein (LDL) cholesterol. The effects of PS added to high-intensity LLT are less reported, especially regarding the effects on cholesterol synthesis and absorption.

METHODS: A prospective, randomized, open-label study, with parallel arms and blinded end points was designed to evaluate the effects of addition of PS to LLT on LDL cholesterol, markers of cholesterol synthesis, and absorption. Eighty-six patients of both genders were submitted to a 4-wk run-in period with atorvastatin 10 mg (baseline). Following, subjects received atorvastatin 40 mg, ezetimibe 10 mg, or combination of both drugs for another 4-wk period (phase I). In phase II, capsules containing 2.0 g of PSs were added to previous assigned treatments for 4 wk. Lipids, apolipoproteins, plasma campesterol, β-sitosterol, and desmosterol levels were assayed at all time points. Within and between-group analyses were performed.

RESULTS: Compared with baseline, atorvastatin 40 mg reduced total and LDL cholesterol (3% and 22%, respectively, $P < .05$), increased β-sitosterol, campesterol/cholesterol, and β-sitosterol/cholesterol ratios (39%, 47%, and 32%, respectively, $P < .05$); ezetimibe 10 mg reduced campesterol and campesterol/cholesterol ratio (67% and 70%, respectively, $P < .05$), and the combined therapy decreased total and LDL cholesterol (22% and 38%, respectively, $P < .05$), campesterol, β-sitosterol, and campesterol/cholesterol ratio (54%, 40%, and 27%, $P < .05$). Addition of PS further reduced total and LDL cholesterol by ∼7.7 and 6.5%, respectively, in the atorvastatin therapy group and 5.0 and 4.0% in the combined therapy group ($P < .05$, for all), with no further effects in absorption or synthesis markers.

CONCLUSIONS: PS added to LLT can further improve lipid profile, without additional effects on intestinal sterol absorption or synthesis.

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Introduction

Plant sterols (PSs) supplementation reduces intestinal cholesterol absorption by competition of PS with cholesterol for micelle formation, reducing the transport of cholesterol to the enterocyte by the Niemann-Pick C1 Like1 protein.[1] Other mechanisms involve upregulation of ABCG5/G8 transporters, and transintestinal cholesterol excretion, increasing fecal loss of neutral sterols.[2] These mechanisms result in reduction in intestinal cholesterol absorption and lead to increase in the liver expression of low-density lipoprotein (LDL) receptors. Compared with cholesterol, PSs are not good substrates for ACAT2 esterification, and plasma levels of PS are not significantly changed after PS supplementation.[2] Based on systematic reviews and meta-analyses, the expected reduction on serum LDL cholesterol levels after an ingestion of 1.6-2.0 g/d of PS is ~10%,[3,4] and they are more effective when given with meals.[5] PS supplementation is either effective in food preparations or consumed as capsules.[6] Because the recommended ingestion of 2.0 g/d is not feasible on an average diet,[7–9] supplementation with phytosterol-enriched foods or encapsulated can be an alternative for LDL cholesterol reduction. Added to a statin, PS supplementation is equivalent to doubling the statin dose with regard to LDL cholesterol lowering.[10]

Moderate increases in markers of cholesterol absorption, mainly β-sitosterol, have been associated with increased incidence of coronary artery events (myocardial infarction and sudden coronary death) or incident coronary artery disease in 2 prospective studies.[11,12] Phytosterol intake can result in increased plasma levels in individuals with the high-absorption phenotype,[13,14] especially under therapies with potent statins.[15,16] However, a recent meta-analysis has shown that these augments are likely to be clinically unimportant and correspond to less than 1% of plasma total sterols.[17]

As a result of evidence from clinical trials, high-dose statin therapy has been recommended to reduce levels of LDL cholesterol.[18] Nevertheless, high-intensity statin therapy may not be tolerated or sufficient for some patients and the concomitant use of ezetimibe has proven that additional reduction of LDL cholesterol further reduced cardiovascular outcomes, when compared with statin alone.[19,20] Statins appear related to increased intestinal absorption of sterols, both cholesterol and PSs.[15,16] Ezetimibe has an important synergism with statins in LDL cholesterol reduction and is able to prevent the increase in intestinal sterols absorption, but can also increase cholesterol synthesis.[19]

Although changes in lifestyle, including a prudent diet,[18,21] have been widely recommended for primary or secondary prevention of cardiovascular disease, the effect of phytosterols added to different regimens of lipid-lowering therapies, is less reported, not only for the achievement of lipid goals, but also to their effects on cholesterol synthesis and absorption.

Materials and methods

Design and study population

A prospective, randomized, open-label study, with parallel arms and blinded end points was performed. Patients were recruited from the outpatient unit of dyslipidemias of our university between February 2009 and March 2010. The trial protocol was conducted in accordance with the ethical standards of the institution on human experimentation, following the procedures as formulated in the Helsinki Declaration of 1975 (revised 1983). The trial protocol was approved by the local ethics committee, and a written informed consent was obtained from all participants before inclusion. Eligible patients were men and women, aged 30 to 75 years, in primary or secondary prevention of coronary heart disease, who had an indication for lipid-lowering therapy in accordance with the National Cholesterol Education Program/Adult Treatment Panel III guidelines.[21] Eighty-six subjects completed the study protocol. Patients with liver, renal or gastrointestinal disease, malignancies, and uncontrolled metabolic disorder that might affect the tolerability or safety of the treatments were excluded. Exclusion criteria during the study were low adherence (less than 85%) either to the lipid-lowering regimen or to the phytosterol supplement. The major characteristics of the study population are presented in Table 1.

After an initial clinical evaluation, eligible patients had prior lipid-lowering therapy discontinued, received nutrition counseling, and simultaneously initiated a 4-wk run-in period with atorvastatin 10 mg, to homogenize the sample population at baseline. Baseline blood samples were obtained at the end of the run-in period for laboratory analyses. After confirming the eligibility criteria, patients were randomized to receive atorvastatin 40 mg, ezetimibe 10 mg, or combination of atorvastatin 40 mg and ezetimibe 10 mg daily for another 4-wk period (phase I). Furthermore, the patients received capsules containing 2.0 g of PSs (as free sterols) to achieve the recommended target of 2.0 g/d, divided into 2 daily doses administered with meals, for additional 4 wk (phase II) and added to the previous lipid-lowering therapies. Lifestyle changes were reinforced and adherence to the study drugs and to PS supplements was evaluated monthly. Study design and procedures are shown in Figure 1.

Study drugs and phytosterol

Atorvastatin (Lipitor, IPR Pharmaceuticals, Porto Rico), and ezetimibe (Zetia, Schering-Plough Products, Las Piedras, Porto Rico) were provided by Pfizer and Merck Co, respectively. The nonsterified PS, as water-dispersible powder (Vegapure F 40 WDP E), was purchased from Cognis Nutrition and Health (Illertissen, Germany), in 20-kg fiber drum packages, containing 400 mg/g of free PSs. Specific PS composition is presented in Table 2. The