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Plant sterol-enriched fermented milk enhances the attainment of LDL-cholesterol goal in hypercholesterolemic subjects

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Abstract *Background* The number of hypercholesterolemic individuals who do not meet their cholesterol recommended targets is inappropriately high. The use of plant sterol-enriched foods could help in this clinical setting. *Aim of the study* To evaluate the efficacy and side effects of plant sterol-enriched fermented milk in reducing LDL-cholesterol and increasing the number of patients who attain their therapeutic targets. *Methods* This was a multicentre, randomised, double-blind, placebo-controlled, parallel clinical trial. Eighty-three hypercholesterolemic patients that were not at therapeutic goals were studied. The patients received one 100 ml serving of either plain (control) low-fat or phytosterol enriched (1.6 g of free sterol equivalents) drinkable yogurt per day along with the main meal for 42 days. The principal variables were variation on LDL cholesterol (LDL-C) concentration and the number of patients achieving therapeutic goals after intervention. *Results* Patients on phytosterols attained an average LDL-C reduction of more than 10% (12.2% after 3 weeks; 10.6% after 6 weeks) ($P = 0.001$; 95% CI: 4.03–19.00) regardless of statin therapy compared to the control group. About 50% of the subjects on phytosterols, as compared to 20% of controls, attained their LDL-C target values (<3.3 or <2.6 mmol/l for primary and secondary prevention, respectively) at the end of the study ($P < 0.001$). HDL-cholesterol (HDL-C) did not change and triglycerides (TG) were decreased by 14% ($P < 0.018$). The plasma sterols/total cholesterol ratio increased. *Conclusions* Plant sterol-enriched fermented milk significantly reduced LDL-C and increased the number of moderately hypercholesterolemic patients achieving therapeutic targets.

Key words LDL-cholesterol – coronary disease – plant sterols – fermented milk

Introduction

Many scientific bodies have established medical guidelines in order to reduce the number of individuals with elevated cholesterol concentrations [4]. Dietary recommendations and lifestyle advice are the cornerstone of cardiovascular disease prevention. The development of functional foods, including components with cholesterol-lowering capacity, has increased the tools available to control cholesterol levels. Among them, the use of phytosterol-enriched aliments is widely accepted. Phytosterols decrease

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cholesterol absorption rate, by displacing cholesterol from intestinal micelles and thus preventing cholesterol absorption. Phytosterols can enter the enterocyte, but are immediately released to the intestinal lumen through the ABCG5/G8 molecular system. The western diet contains about 150–400 mg of phytosterols and stanols per day [23]. By increasing this amount by threefold to fivefold, a clinically significant cholesterol-lowering effect can be observed. At least 1 g of phytosterols per day is necessary to obtain a significant 5–8% LDL cholesterol reduction [30]. This effect is dosage-dependent until reaching a plateau of around 2 g per day [23, 26, 46]. Dietary phytosterol supplements are usually prescribed to moderately hypercholesterolemic patients; therefore it may be better to incorporate them in low-fat aliments along with low-fat, cholesterol poor, diets [21]. Additionally, the food matrix that contains phytosterols plays a role in their lipid lowering potency. In recent years, non- or low-fat matrices able to contain phytosterols have been developed. However, their lipid-lowering effects have not been fully studied [10, 11, 22, 28].

Epidemiological data clearly have shown that higher cholesterol levels correlate with higher cardiovascular risk [47]. Subsequent intervention trials have demonstrated that by lowering the plasma LDL-cholesterol (LDL-C) level, the number of cardiovascular events is reduced both in primary and secondary prevention [2, 40]. In a recent meta-analysis, it was calculated that the cardiovascular risk was reduced by 20% [8, 38] by each 1 mmol/l of LDL-C reduction, independent of the therapy. The Adult Treatment Panel (ATP) III recommend the following LDL-C targets: for individuals in primary prevention with no additional risk factors, <4.1 mmol/l; with two or more non-lipid risk factors, <3.3 mmol/l; for patients with a first vascular accident or diabetes, <2.6 mmol/l mg/dl or below 1.8 mmol/l in patients with diabetes and cardiovascular disease (CVD). In spite of the clear scientific support for these recommendations, the number of individuals who do not meet these targets is inappropriately high (approaching 50%) [1, 3, 6, 15, 44, 45]. The reasons for this are many but may be due to concern over adverse effects of lipid-lowering drugs that are dosage-dependent. This is especially true when patients are very close to targets and physicians are reluctant to double statin doses to obtain just a 6% incremental cholesterol reduction. The addition of about 2 g of phytosterols induces a LDL reduction of about 10% [5, 12, 23, 25, 28–30, 32, 39] and doses above 2 g add very little [23]. The introduction of drinkable phytosterol-enriched fermented skim milk may be advantageous in controlling high cholesterol. However, its clinical effects must be verified, preferably with a low-fat diet background. In this work, we studied the effect of daily consumption of low-fat fermented milk, enriched with plant sterols, on LDL-C plasma concentrations and the overall impact of this product on increasing the number of patients attaining the LDL-C targets in a group of moderately hypercholesterolemic subjects.

Subjects and methods

This was a multicentre, randomised, double-blind, placebo-controlled, parallel clinical study. There were two groups of intervention: control and low-fat tested product containing 1.6 g equivalent of free sterols. The recruitment was performed in six primary healthcare centres and the external dispensary of a tertiary centre. The latter was the coordinating site where plasma lipid determinations for the study were centralised. After being enrolled, study subjects followed a single-blind 4-week run-in period under a standard Mediterranean diet, which has been demonstrated to reduce cardiovascular risk parameters [13] (34% of calories derived from fat; 7% saturated, 7% polyunsaturated and 20% monounsaturated, mainly from olive oil; 15% from proteins; 51% from carbohydrates; cholesterol <300 mg/day) while receiving one serving of low-fat (1.2%) drinkable yogurt. Afterwards, 84 subjects were randomised and entered the experimental period for 42 days. Forty-four patients were allocated to the plant sterol-enriched fermented milk and 40 to the control product. Randomisation was stratified by the presence of concomitant statin therapy. The Mediterranean diet was maintained during the experimental period. The diet was assessed by dietary frequency questionnaires and 24-hour recall tests for 3 days, four times throughout the study. In each visit, dietary advice was given to maintain compliance on the Mediterranean diet. During the study, the patients attended five medical appointments where physical examinations, cardiovascular risk status, and four dietician visits were performed to assess the dietary adherence. The compliance with the study product was assessed as percentage of scheduled servings consumed determined by interview and counting the unopened bottles returned to the clinic. Less than 80% consumption throughout the duration of the study was defined as non-compliance. Data from physical examination, anthropometrics parameters and blood pressure were recorded and monitored across the study. Plasma analyses were performed prior to the beginning and after 3 and 6 weeks of tested product consumption. Basal and final values of the main lipid variables were calculated as the mean of two determinations from blood samples taken 2–4 days apart before and after the study. An additional sample was

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obtained after 3 weeks of intervention. The blood samples were taken after a 12 h overnight fast. Global cardiovascular risk was calculated using the Framingham score. Patients with CVD were considered at high (>20%) global cardiovascular risk.

Study subjects

Hypercholesterolemic subjects aged between 18 and 75 years with plasma LDL-C concentration above 3.3 mmol/l (10-year risk ≤20% and without ischemic heart disease) or above 2.6 mmol/l (10-year risk >20% or ischemic heart disease) not receiving or receiving statin (nine in each group) were selected. Subjects with a body mass index (BMI) higher than 30 kg/m^2, diabetes, symptomatic CVD within the prior 6 months, hypertriglyceridemia (>4 mmol/l), severe digestive disorders or receiving lipid-lowering drugs other than statins, antiacids or corticosteroids were excluded. Patients were considered to be on therapeutic targets when their LDL-C was <3.3 or 2.6 mmol/l, for lower and higher risk groups, respectively. All participants provided a written informed consent to participate and the study protocol was reviewed and approved by an independent ethical committee.

Study products

The control product was low-fat (1.2%) fermented milk (milk fermented with *L. delbruekii bulgaricus* and *S. thermophilus*) without plant sterols. The tested product was the same low-fat fermented milk enriched with ester of plant sterols at a dose-equivalent mass of 1.6 g of free sterol. The major components of the enriched-products were β-sitosterol (approximately 80%) and campesterol (approximately 10%). The remaining 10% included β-sitostanol, campestanol, stigmasterol and brassicasterol. The fermented milk consumed by both groups contained (per 100 g) 3.2 g of protein; 11.2 g carbohydrates; 1.2 g of fat (7% of saturated fatty acids, 63% of mono-unsaturated fatty acids and 30% of polyunsaturated fatty acids) for a total energy of 68 kilocalories. The study products were all packaged in 100 ml bottles. Participants ingested one unit per day after lunch, for the course of the study period.

Study assessments

The variation of plasma LDL-C from baseline to day 42 and the proportion of patients that attained target LDL-C levels fitted to their risk levels according to ATP III recommendations were the primary efficacy criterion. Variation of total cholesterol (TC), HDL-C and TG concentrations were also determined. Side effects and cholesterol metabolism parameters included the variation of β-carotene, retinol, lathosterol, campesterol, β-sitosterol, plasma concentrations, and lathosterol/total-cholesterol, campesterol/total-cholesterol, β-sitosterol/total-cholesterol, and β-carotene/LDL-cholesterol ratios. Plasma samples were analysed for TC, HDL-C and TG concentrations by standard methods in the same run for each subject and visit. LDL-C concentration was calculated with the Friedewald equation [14]. Plasma β-sitosterol, campesterol, and lathosterol concentrations were determined by a mass spectrometric-gas chromatography procedure. Plasma concentrations of β-carotene and vitamin A were determined by reverse phase high-pressure liquid chromatography. Serum C-reactive protein (CRP) concentration was measured by a highly sensitive turbidimetric immunoassay [9].

Statistical analyses

The sample size was calculated at 42 subjects per group to provide 80% statistical power to detect a difference between the values of the primary efficacy criterion (LDL-C variation) equal or greater than 0.4 mmol/l between both groups, assuming a common standard deviation of 0.6 mmol/l mg/dl and a drop-out rate of 10% [26, 28, 30, 35, 36].

The primary null hypothesis was that the active products were neither more effective than the control in reducing LDL-C plasma concentrations nor increasing patients at therapeutic targets. All analyses were performed according to the intention-to-treat principle. To test the differences between the two groups, univariate analyses based on the generalised linear models were performed to adjust for any systematic contribution to the changes from baseline including the baseline values, the study product received and the presence of concomitant statin pharmacotherapy. Specific Tukey–Kramer post hoc contrasts were defined for pairwise comparisons between study products. The parameters not accepting parametric description were analysed by means of Kruskal–Wallis tests. Secondary efficacy criteria based on categorical variables were analysed by means of Mantel–Haenszel χ^2 tests stratified by the cardiovascular risk category (≤20% versus <20%).

Results

Subject characteristics: Eighty-four subjects were enrolled in the study. One patient was excluded due to

Table 1 Demographic and clinical characteristics at baseline

Variable	*n*	Phytosterol (1.6 g/day) group mean (SD)	*n*	Control group mean (SD)
Age (years)	43	51.8 (10.19)	40	50.9 (12.03)
BMI (kg/m^2)	43	26.5 (2.52)	40	26.9 (2.68)
SBP (mm Hg)	43	124.0 (14.21)	40	122.5 (15.55)
DBP (mm Hg)	43	77.3 (7.85)	40	78.0 (8.13)
Heart rate (bpm)	43	72.1 (7.87)	40	73.1 (7.95)
Serum LDL-cholesterol (mmol/l)	43	3.79 (0.66)	40	3.70 (0.79)
Serum total cholesterol (mmol/l)	43	5.94 (0.79)	40	5.94 (0.95)
Serum HDL-cholesterol (mmol/l)	43	1.46 (0.28)	40	1.48 (0.32)
Serum triacylglycerol (mmol/l)	43	1.55 (0.63)	40	1.62 (0.70)
	n	Frequency (%)	*n*	Frequency (%)
Concomitant statins	9	20.9	9	22.5
Cardiovascular risk >20%	13	30.2	12	30.0
Gender (proportion of males)	17	39.5	17	42.5

Table 2 Initial (baseline), intermediate (Day 21) and final (Day 42) plasma lipids concentration and absolute and relative mean changes (Day 42 minus baseline)

	After 3 weeks of consumption (Day 21)				*P* value	After 6 weeks of consumption (Day 42)				*P* value*
	1.6 g/day		Control			1.6 g/day		Control		
	n	Mean (SD)	*n*	Mean (SD)		*n*	Mean (SD)	*n*	Mean (SD)	
LDL-cholesterol										
Baseline (mmol/l)	43	3.79 (0.66)	40	3.70 (0.79)	–	43	3.79 (0.66)	40	3.70 (0.79)	–
Absolute change (mmol/l)	43	−0.41 (0.49)	40	0.05 (0.56)	<0.001*	43	−0.43 (0.47)	40	−0.07 (22.93)	0.001*
Relative change (%)	43	−10.15 (12.31)	40	2.02 (15.46)	<0.001*	43	−10.49 (12.55)	40	0.14 (15.69)	<0.001*
Total-cholesterol										
Baseline (mmol/l)	43	5.94 (0.79)	40	5.94 (0.95)	–	43	5.94 (0.79)	40	5.94 (0.95)	–
Absolute change (mmo/l)	43	−0.43 (0.60)	40	−0.18 (0.70)	0.002*	43	−0.50 (0.55)	40	−0.14 (0.71)	0.004*
Relative change (%)	43	−6.90 (9.96)	40	0.91 (12.56)	0.002*	43	−7.99 (9.15)	40	−1.30 (11.99)	0.002*
HDL-cholesterol										
Baseline (mmo/l)	43	1.46 (0.28)	40	1.48 (0.32)	–	43	1.46 (0.28)	40	1.48 (0.32)	–
Absolute change (mmo/l)	43	−0.03 (0.18)	40	0.00 (0.17)	0.167*	43	−1.03 (5.76)	40	−0.05 (0.20)	0.404[a]
Relative change (%)	43	−1.69 (12.60)	40	0.82 (13.12)	0.365*	43	−1.00 (10.86)	40	−2.83 (12.97)	0.477[a]
Triacylglycerol										
Baseline (mmo/l)	43	1.55 (0.63)	40	1.62 (0.70)	–	43	1.55 (0.63)	40	1.62 (0.70)	–
Absolute change (mmo/l)	43	−0.01 (0.50)	40	0.03 (0.60)	0.517[a]	43	−0.13 (0.35)	40	0.07 (0.57)	0.077[a]
Relative change (%)	43	−2.02 (26.09)	40	6.66 (34.92)	0.236[a]	43	−6.58 (18.38)	40	7.69 (29.28)	0.018[a]

*ANCOVA adjusted by baseline values
[a]Kruskal-Wallis test

low compliance. The two groups produced by randomisation were homogeneous in terms of demographic and clinical characteristics (Table 1). No differences were observed between centres.

Participants followed identical dietary recommendations in both groups. No gross violations of dietary advice leading to withdrawal were observed by the dieticians. Changes in body weight during the experimental period were not statistically significant. Compliance was above 80% in all participants included in the final analyses.

LDL-cholesterol and other lipid parameters: The absolute mean changes of TC, LDL-C and HDL-C and TG from baseline to day 21 and 42 are summarised in Table 2. The LDL-C lowering effect observed at the end of the intervention period was −0.43 (0.47) mmol/l with a significant mean change over control of 10.6% ($P < 0.001$). This difference was already present at the intermediate visit (after 3 weeks of product consumption) with a mean change from a baseline of −0.41(0.49) mmol/l, a change over the control of 12.2% ($P = 0.001$). A similar significant 10.6% LDL-C decrease was observed when comparing subjects under statin treatment (nine per group) after 6 weeks of intervention ($P = 0.034$). The effects were similar for men and women and were not influenced by age. TC

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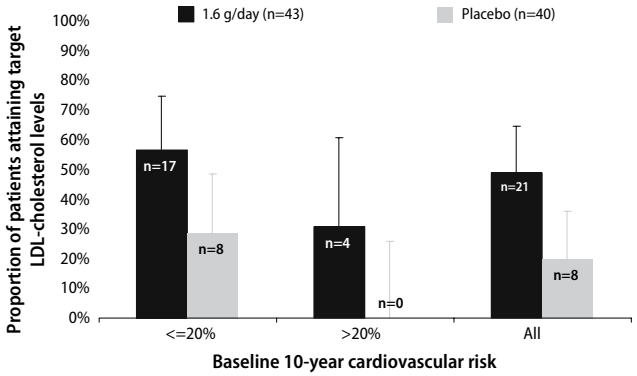

Fig. 1 Proportion of patients meeting their target LDL-cholesterol levels on the final visit (Day 42) in the whole sample and stratified by Framingham 10-year cardiovascular risk score. *Figures* in the bars are the absolute number of patients achieving therapeutic targets in each group regarding treatment

concentrations were also significantly decreased by 7.8 and 6.7% after 3 and 6 weeks, respectively ($P < 0.002$). HDL-C plasma concentrations were unchanged during the study, whereas TG concentrations were decreased by 14% with respect to the control group ($P = 0.018$) after 6 weeks of product consumption (Table 2).

LDL-cholesterol targets: Twenty-one out of 43 (48.8%) subjects in the plant sterol enriched-product group attained target LDL-C levels suited to their 10-year cardiovascular risk (χ^2 $P = 0.044$), compared to 8 out of 40 (20.0%) in the control group. Among patients in the low-risk group, 56.6% on active product versus 28.6% in the control group achieved the LDL targets ($P < 0.001$), while among those in high cardiovascular risk, 69.2% of those on active product were on target and none on the control product reached their target (Fig. 1).

Plant sterols and cholesterol precursors: The lathosterol/cholesterol ratio was not significantly increased (12.56%; $P = 0.228$). We observed a significant increase in β-sitosterol/cholesterol and campesterol/cholesterol ratios in the group receiving enriched product (38.8 and 26.7%, respectively; $P \leq 0.002$ in both cases) (Table 3). CRP, β-carotene and retinol variations did not show any statistical differences between the groups.

Table 3 Initial (baseline) and final (Day 42) plasma campesterol, beta-sitosterol related to total cholesterol and absolute and relative mean changes (Day 42 minus baseline)

	1.6 g/day		Control		*P* value*
	n	Mean (SD)	*n*	Mean (SD)	
Campesterol/total cholesterol					
Baseline (μg/mg)	43	0.82 (0.39)	40	0.65 (0.22)	–
Final (μg/mg)	42	1.05 (0.54)	39	0.68 (0.30)	–
Absolute change (μg/mg)	42	0.22 (0.34)	39	0.03 (0.23)	0.001[a]
Relative change (%)	42	33.08 (44.41)	39	6.33 (30.32)	0.002*
Beta-sitosterol/total cholesterol					
Baseline (μg/mg)	43	1.47 (0.70)	40	1.18 (0.44)	–
Final (μg/mg)	42	1.98 (0.97)	39	1.10 (0.45)	–
Absolute change (μg/mg)	42	0.49 (0.64)	39	−0.07 (0.37)	<0.001[a]
Relative change (%)	42	41.25 (39.58)	39	−2.44 (27.29)	<0.001*

*ANCOVA adjusted by baseline values
[a]Kruskal–Wallis test

Discussion

In this study, we confirm the LDL-C reduction efficacy of a low dosage (1.6 g/day) of plant sterols in a low-fat matrix (less than 1.5% fat) in combination with a low-fat, cholesterol-poor background diet. Only a few studies have demonstrated the LDL-C lowering effect of plant sterol-enriched low-fat dairy products. Our results are similar to other studies using different matrices such as yogurt, spread margarine, cheese, bread and cereals, among others [10, 16, 20, 25, 33]. The results confirm the cholesterol lowering effect of plant sterol-enriched low-fat drinkable yoghurt. Recent studies show that phytosterol-enriched fermented milk has a significant LDL cholesterol-lowering efficacy when used in either a multiple or single-dose drinkable or spoon yogurt. The reductions of LDL-C are in the range of 5% [32, 39, 46] to 10% [5, 19, 24] greater when the phytosterol-enriched products are taken along with a meal [12]. Most works have been done using doses up to 2 g/day because higher doses add very little to the LDL lipid-lowering effect [23]. In our study, this percentage reduction was due to an absolute mean LDL-C lowering of about 0.5 mmol/l in the active group. Two recent meta-analyses [8, 38] demonstrate that for each 1 mmol/l of LDL-C reduction, the CVD risk is reduced by 20%. Extrapolating these data to our results, it is suggested that by taking a daily dose of the product, the mean relative risk reduction would be about 10%. Statins are the cornerstone of hypercholesterolemia treatment and it is well-established that these drugs reduce LDL-C by 20 to 50% and relative cardiovascular risk by an average of 30% [2]. Doubling the statin dose induces just an additional 6–8% LDL-C decrease [42]. In our study, the addition of fermented milk enriched with phytosterols resulted in cholesterol lowering capacity greater than 10%, even in those patients under statin treatment in accordance with observations by Katan et al. [23]. The most striking finding in this study was that when we stratified the patients according to their cardiovascular risk, the number of individuals attaining the predefined LDL-C targets was more than doubled, from 20% in the control group to about 50% in the intervention group including those on statins. This observation is of great clinical importance because we have much data showing that the percentage of people

at high cardiovascular risk and not on target is inappropriately high in Spain and abroad; exceeding 50% and being even worse in those groups at very high risk [1, 3, 6]. We can assume that these moderately hypercholesterolemic patients were close to the targets. In this clinical situation, physicians are reluctant to increase pharmacological treatment to force patients into goals due to concern over dosage-dependent adverse effects. The use of this widely consumed food, enriched with phytosterols, could help patients obtain the therapeutic objectives. During the experimental phase, plant sterols were well-accepted and clinical, anthropometric parameters, blood pressure, and body mass index, were unchanged. Since plant sterols inhibit part of cholesterol absorption, they might also interfere with the absorption of other fat-soluble compounds such as β-carotene or vitamin A. In our study, the β-carotene/LDL cholesterol concentrations were unchanged between groups. These observations are consistent with previous studies [17, 24, 27, 43]. The results of a few studies have suggested a slight reduction of plasma carotenoid concentrations [18, 36, 37, 41]. It seems that providing the appropriate diet including carotenoid-rich foods [31] can minimise or compensate carotenoid-lowering effects. Plasma sitosterol and campesterol concentrations increased independently of cholesterol variations in the active group by 26.7 and 38.8%, respectively. This effect is in accordance to the product composition. It has been reported that 2 g daily of phytosterols can increase plasma campesterol and sitosterol up to 50% regardless of cholesterol variations [23]. In our patients, the final values of plasma phytosterol were well within normal ranges [23]. In the rare disease referred to as sitosterolemia, the sitosterol plasma concentrations are increased from 20 to 100 times the normal ranges and lead to increased cardiovascular risk. Although it has been suggested that moderately elevated plasma sterol levels could also be associated to cardiovascular risk [7], recent data show no correlations [48] or even a protective effect [34] between plasma sterols within normal ranges and cardiovascular risk. The daily use of this plant sterol-enriched fermented milk was associated with a 10.6% reduction in LDL-C concentrations compared to the control group and a twofold to threefold increase of people attaining the LDL-C goals, regardless of any adverse effect.

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References

1. (2003) (Characteristics of the patients with heart disease in a health area of A Coruna province. Barbanza 2000 study). Rev Clin Esp 203:570–576
2. (1994) Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389
3. (2000) (Secondary prevention of ischemic heart disease in the Cuidad Real Province, Spain. Effectiveness of lipid-lowering therapy in primary health care). Med Clin (Barc) 115:321–325
4. (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106:3143–3421
5. Algorta Pineda J, Chinchetru Ranedo MJ, Aguirre Anda J, Francisco Terreros S (2005) Hypocholesteremic effectiveness of a yogurt containing plant stanol esters. Rev Clin Esp 205:63–66
6. Alvarez-Sala LA, Suarez C, Mantilla T, Franch J, Ruilope LM, Banegas JR, Barrios V (2005) [PREVENCAT study: control of cardiovascular risk in primary care]. Med Clin (Barc) 124:406–410
7. Assmann G, Cullen P, Erbey J, Ramey DR, Kannenberg F, Schulte H (2006) Plasma sitosterol elevations are associated with an increased incidence of coronary events in men: results of a nested case-control analysis of the Prospective Cardiovascular Munster (PROCAM) study. Nutr Metab Cardiovasc Dis 16:13–21
8. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366:1267–1278

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9. Bertran N, Camps J, Fernandez-Ballart J, Murphy MM, Arija V, Ferre N, Tous M, Joven J (2005) Evaluation of a high-sensitivity turbidimetric immunoassay for serum C-reactive protein: application to the study of longitudinal changes throughout normal pregnancy. Clin Chem Lab Med 43:308–313
10. Clifton PM, Noakes M, Sullivan D, Erichsen N, Ross D, Annison G, Fassoulakis A, Cehun M, Nestel P (2004) Cholesterol-lowering effects of plant sterol esters differ in milk, yoghurt, bread and cereal. Eur J Clin Nutr 58:503–509
11. Davidson MH, Maki KC, Umporowicz DM, Ingram KA, Dicklin MR, Schaefer E, Lane RW, McNamara JR, Ribaya-Mercado JD, Perrone G, Robins SJ, Franke WC (2001) Safety and tolerability of esterified phytosterols administered in reduced-fat spread and salad dressing to healthy adult men and women. J Am Coll Nutr 20:307–319
12. Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA (2006) Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. Eur J Clin Nutr 60:325–333
13. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, Fiol M, Gomez-Gracia E, Lopez-Sabater MC, Vinyoles E, Aros F, Conde M, Lahoz C, Lapetra J, Saez G, Ros E (2006) Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 145:1–11
14. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
15. Garcia Ruiz FJ, Marin Ibanez A, Perez-Jimenez F, Pinto X, Nocea G, Ahumada C, Alemao E, Yin D (2004) Current lipid management and low cholesterol goal attainment in common daily practice in Spain. The reality study. Pharmacoeconomics 22(Suppl3):1–12
16. Goldberg AC, Ostlund RE, Jr, Bateman JH, Schimmoeller L, McPherson TB, Spilburg CA (2006) Effect of plant stanol tablets on low-density lipoprotein cholesterol lowering in patients on statin drugs. Am J Cardiol 97:376–379
17. Hallikainen MA, Sarkkinen ES, Gylling H, Erkkila AT, Uusitupa MI (2000) Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet. Eur J Clin Nutr 54:715–725
18. Hallikainen MA, Sarkkinen ES, Uusitupa MI (1999) Effects of low-fat stanol ester enriched margarines on concentrations of serum carotenoids in subjects with elevated serum cholesterol concentrations. Eur J Clin Nutr 53:966–969
19. Hansel B, Nicolle C, Lalanne F, Tondu F, Lassel T, Donazzolo Y, Ferrieres J, Krempf M, Schlienger JL, Verges B, Chapman MJ, Bruckert E (2007) Effect of low-fat, fermented milk enriched with plant sterols on serum lipid profile and oxidative stress in moderate hypercholesterolemia. Am J Clin Nutr 86:790–796
20. Jauhiainen T, Salo P, Niittynen L, Poussa T, Korpela R (2006) Effects of low-fat hard cheese enriched with plant stanol esters on serum lipids and apolipoprotein B in mildly hypercholesterolaemic subjects. Eur J Clin Nutr
21. Jones PJ, Ntanios FY, Raeini-Sarjaz M, Vanstone CA (1999) Cholesterol-lowering efficacy of a sitostanol-containing phytosterol mixture with a prudent diet in hyperlipidemic men. Am J Clin Nutr 69:1144–1150
22. Judd JT, Baer DJ, Chen SC, Clevidence BA, Muesing RA, Kramer M, Meijer GW (2002) Plant sterol esters lower plasma lipids and most carotenoids in mildly hypercholesterolemic adults. Lipids 37:33–42
23. Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R (2003) Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc 78:965–978
24. Korpela R, Tuomilehto J, Hogstrom P, Seppo L, Piironen V, Salo-Vaananen P, Toivo J, Lamberg-Allardt C, Karkkainen M, Outila T, Sundvall J, Vilkkila S, Tikkanen MJ (2006) Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. Eur J Clin Nutr 60:633–642
25. Lau VW, Journoud M, Jones PJ (2005) Plant sterols are efficacious in lowering plasma LDL and non-HDL cholesterol in hypercholesterolemic type 2 diabetic and nondiabetic persons. Am J Clin Nutr 81:1351–1358
26. Law M (2000) Plant sterol and stanol margarines and health. BMJ 320:861–864
27. Lichtenstein AH (2002) Plant sterols and blood lipid levels. Curr Opin Clin Nutr Metab Care 5:147–152
28. Mensink RP, Ebbing S, Lindhout M, Plat J, van Heugten MM (2002) Effects of plant stanol esters supplied in low-fat yoghurt on serum lipids and lipoproteins, non-cholesterol sterols and fat soluble antioxidant concentrations. Atherosclerosis 160:205–213
29. Moruisi KG, Oosthuizen W, Opperman AM (2006) Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. J Am Coll Nutr 25:41–48
30. Nguyen TT (1999) The cholesterol-lowering action of plant stanol esters. J Nutr 129:2109–2112
31. Noakes M, Clifton P, Ntanios F, Shrapnel W, Record I, McInerney J (2002) An increase in dietary carotenoids when consuming plant sterols or stanols is effective in maintaining plasma carotenoid concentrations. Am J Clin Nutr 75:79–86
32. Noakes M, Clifton PM, Doornbos AM, Trautwein EA (2005) Plant sterol ester-enriched milk and yoghurt effectively reduce serum cholesterol in modestly hypercholesterolemic subjects. Eur J Nutr 44:214–222
33. O'Neill FH, Brynes A, Mandeno R, Rendell N, Taylor G, Seed M, Thompson GR (2004) Comparison of the effects of dietary plant sterol and stanol esters on lipid metabolism. Nutr Metab Cardiovasc Dis 14:133–142
34. Pinedo S, Vissers MN, von Bergmann K, Elharchaoui K, Lutjohann D, Luben R, Wareham NJ, Kastelein JJ, Khaw KT, Boekholdt SM (2007) Plasma levels of plant sterols and the risk of coronary artery disease: the prospective EPIC-Norfolk Population Study. J Lipid Res 48:139–144
35. Plat J, Mensink RP (2000) Vegetable oil based versus wood based stanol ester mixtures: effects on serum lipids and hemostatic factors in non-hypercholesterolemic subjects. Atherosclerosis 148:101–112
36. Plat J, van Onselen EN, van Heugten MM, Mensink RP (2000) Effects on serum lipids, lipoproteins and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. Eur J Clin Nutr 54:671–677
37. Richelle M, Enslen M, Hager C, Groux M, Tavazzi I, Godin JP, Berger A, Metairon S, Quaile S, Piguet-Welsch C, Sagalowicz L, Green H, Fay LB (2004) Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. Am J Clin Nutr 80:171–177
38. Robinson JG, Smith B, Maheshwari N, Schrott H (2005) Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol 46:1855–1862

39. Seppo L, Jauhiainen T, Nevala R, Poussa T, Korpela R (2007) Plant stanol esters in low-fat milk products lower serum total and LDL cholesterol. Eur J Nutr 46:111–117
40. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 333:1301–1307
41. Sierksma A, Weststrate JA, Meijer GW (1999) Spreads enriched with plant sterols, either esterified 4,4-dimethylsterols or free 4-desmethylsterols, and plasma total- and LDL-cholesterol concentrations. Br J Nutr 82:273–282
42. Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, Lipka L, Suresh R, Maccubbin D, Veltri E (2004) Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 148:447–455
43. Thomsen AB, Hansen HB, Christiansen C, Green H, Berger A (2004) Effect of free plant sterols in low-fat milk on serum lipid profile in hypercholesterolemic subjects. Eur J Clin Nutr 58:860–870
44. Van Ganse E, Laforest L, Alemao E, Davies G, Gutkin S, Yin D (2005) Lipid-modifying therapy and attainment of cholesterol goals in Europe: the Return on Expenditure Achieved for Lipid Therapy (Reality) study. Curr Med Res Opin 21:1389–1399
45. Vanuzzo D, Pilotto L, Ambrosio GB, Pyorala K, Lehto S, De Bacquer D, De Backer G, Wood D (2000) Potential for cholesterol lowering in secondary prevention of coronary heart disease in europe: findings from EUROASPIRE study. European Action on Secondary Prevention through Intervention to Reduce Events. Atherosclerosis 153:505–517
46. Volpe R, Niittynen L, Korpela R, Sirtori C, Bucci A, Fraone N, Pazzucconi F (2001) Effects of yoghurt enriched with plant sterols on serum lipids in patients with moderate hypercholesterolaemia. Br J Nutr 86:233–239
47. Wilson PW, Castelli WP, Kannel WB (1987) Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol 59:91G–94G
48. Wilund KR, Yu L, Xu F, Vega GL, Grundy SM, Cohen JC, Hobbs HH (2004) No association between plasma levels of plant sterols and atherosclerosis in mice and men. Arterioscler Thromb Vasc Biol 24:2326–2332