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Original article

Long-term Effects of Plant Stanols on the Lipid Profile of Patients With Hypercholesterolemia. A Randomized Clinical Trial

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ABSTRACT

Introduction and objectives: Plant stanol consumption may improve long-term cholesterol control. The aim of the present study was to evaluate the effectiveness of 2 g/day of plant stanols in reducing low-density lipoprotein cholesterol levels in patients with hypercholesterolemia.
Methods: This randomized, double-blind, and placebo-controlled study included 182 adults diagnosed with hypercholesterolemia. A yogurt drink containing 2 g of plant stanols was administered to 91 participants in the intervention group; 91 participants in the control group received unsupplemented yogurt. The primary end point was the change in the lipid profile at 12 months.
Results: Low-density lipoprotein cholesterol levels at 12 months were significantly more reduced in the stanol intervention group than in the control group: 13.7 (95% confidence interval, 3.2-24.1) mg/dL ($P = .011$). A reduction of more than 10% in low-density lipoprotein cholesterol was achieved by a significantly higher proportion of participants in the intervention group (relative risk = 1.7; 95% confidence interval, 1.1-2.7). In this group, the mean (standard deviation) level of low-density lipoprotein cholesterol decreased by 11.0% (23.9%).
Conclusions: Our results confirm that administration of plant stanols at a dosage of 2 g/day for 12 months significantly reduces (by slightly more than 10%) the concentrations of low-density lipoprotein cholesterol in individuals with hypercholesterolemia.
Trial registration (www.ClinicalTrials.gov): Current Controlled Trials NCT01406106.
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Efecto a largo plazo de los estanoles vegetales en el perfil lipídico de pacientes con hipercolesterolemia. Ensayo clínico aleatorizado

Palabras clave:
Hipercolesterolemia
Fitosteroles
Atención primaria de salud
Ensayo clínico

RESUMEN

Introducción y objetivos: El consumo de estanoles vegetales puede contribuir a un mejor control a largo plazo del colesterol. El objetivo es evaluar la eficacia del aporte de estanoles vegetales, a dosis de 2 g/día, en la reducción de las cifras de colesterol unido a lipoproteínas de baja densidad de los pacientes con hipercolesterolemia.
Métodos: Se realizó un ensayo clínico aleatorizado, a doble ciego y controlado con placebo, en el que se incluyó a 182 sujetos adultos diagnosticados de hipercolesterolemia. Se administró yogur líquido con 2 g de estanoles vegetales a 91 sujetos del grupo intervención y yogur no suplementado a 91 del grupo control. La variable principal fue la variación del perfil lipídico a los 12 meses.
Resultados: En comparación con el placebo, a los 12 meses se observó una disminución significativamente superior del colesterol unido a lipoproteínas de baja densidad en el grupo que tomó estanoles: 13,7 (intervalo de confianza del 95%, 3,2-24,1) mg/dl (p = 0,011). En este grupo fue significativamente superior la proporción de sujetos que redujeron en más del 10% sus cifras de colesterol unido a

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lipoproteínas de baja densidad (riesgo relativo = 1,7; intervalo confianza del 95%, 1,1-2,7). En el grupo tratado, el colesterol unido a lipoproteínas de baja densidad descendió, en promedio, un 11,0 ± 23,9%.
Conclusiones: Los resultados confirman que la administración de estanoles vegetales en dosis de 2 g/día durante 1 año produce una reducción significativa (ligeramente superior al 10%) de las concentraciones de colesterol unido a lipoproteínas de baja densidad en sujetos con hipercolesterolemia.
Registro del ensayo (www.ClinicalTrials.gov): Current Controlled Trials NCT01406106.
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Abbreviations

CVR: cardiovascular risk
LDL-C: low-density lipoprotein cholesterol
TC: total cholesterol

INTRODUCTION

Although various clinical practice guidelines are aimed at reducing total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in individuals with hypercholesterolemia, a high percentage of patients have values higher than the recommended targets in both primary and secondary prevention.[1–3]

Low dosages of lipid-lowering drugs can be sufficient in some people with elevated cardiovascular risk (CVR) if they make sufficient changes to their usual diet.[4] One dietary method that reduces TC and LDL-C is daily consumption of stanols.[5] Moreover, the combination of stanols and statins provides an additional effect on lipid reduction.[6] However, controversy surrounds the recommendation of dietary phytosterol supplementation.[7]

Although the available evidence on the effectiveness of phytosterols has been included in various clinical practice guidelines,[4,8–11] fewer guidelines recommend their consumption.[8,11]

Despite publication of various studies on this topic, they have often been short in duration and with small numbers of patients.[12–14] Moreover, most of the studies on the effectiveness of stanols have been performed outside Spain, probably in populations with life style and dietary habits different from ours. Accordingly, rigorous and longer-lasting studies in our setting are required to accurately quantify the magnitude of the long-term effects of stanols. Thus, the aim of the present study was to evaluate the effectiveness of 2 g/day of plant stanols in reducing LDL-C levels in patients diagnosed with hypercholesterolemia. We also quantified the effect of daily stanol intake on other lipid profile parameters, evaluated the presence of adverse effects, and identified the factors associated with a greater reduction in LDL-C levels.

METHODS

This study consisted of a randomized, double-blind, placebo-controlled clinical trial. Participants were selected from 9 family medicine clinics from 3 health care centers of the health services area of Albacete, Spain. Individuals ≥ 18 years attending the participating centers were included if they had been diagnosed with borderline (TC, 200-249 mg/dL) or definite (TC ≥ 250 mg/dL) hypercholesterolemia with LDL-C ≥ 130 mg/dL. Exclusion criteria were as follows: known hypersensitivity or contraindication for stanols or other components of the yogurt drink, triglyceride levels ≥ 400 mg/dL, physical incapacity to participate, or severe chronic disease, whether organic or psychiatric, that restricted the patient's ability to attend the clinic or consume lactate products. All participants signed a written informed consent form after sufficient explanation of the study. The trial was approved by the Ethics Committee for Clinical Research in the Health Care Area of Albacete and adhered to the pertinent ethical guidelines for clinical trials (Spanish Royal Decree 223/2004) and the Declaration of Helsinki.

Sample size calculation was based on an expected mean (standard deviation) LDL-C level of 190 (36) mg/dL[15] in the participants and an expected demonstration of a 10% reduction in LDL-C in those consuming stanols for 12 months. To obtain a power of 90% with an alpha error of 0.05 (bilateral hypothesis), 152 individuals were required (76 in the intervention group and 76 in the control group). With an assumed rate of loss to follow-up of 20%, 182 individuals distributed between 2 equal-sized groups (91 per group) were selected to achieve maximum statistical power. Of the 189 individuals evaluated for selection, 7 declined to participate in the study (acceptance rate, 96.3%) (Figure). The recruitment period was from March 2010 to February 2011.

The 182 remaining individuals were randomly and equiprobably assigned to the intervention or control group. The patient were assigned to groups by computer using a sequence of random numbers and following a 4×4 block system (ensuring that in a short interval there would be a similar number of patients in both groups). The assignment was performed in a centralized manner by a researcher of the Pharmacy Department of the *Gerencia de Atención Primaria* of Albacete who was not involved in the interviews or analysis. The information with the patient identification number and the assigned product number was kept in the pharmacy department in sealed, opaque, and numbered envelopes. The yogurt containers (with or without stanols) were delivered in a blind manner to the patients. To protect the blinding, the placebo and stanol-supplemented products had an identical appearance and were only identifiable via a code whose assignment was unknown to patients and researchers. Patients, researchers, and those responsible for data analysis were blinded to group assignments to guarantee objectivity when analyzing the results.

The intervention consisted of a yogurt drink, commercially available in Spain, containing 2 g of the following plant stanol esters per container: sitostanol and campestanol (recommended dose of the American Heart Association, 1.5-3.0 g). Both the supplemented product and the placebo had the same characteristics (composition, external appearance, and taste) but the placebo contained no stanol esters. The yogurt drink was administered in a daily container and consumed after the main meal for 12 months. Each container had the following composition: protein, 1.8 g; carbohydrate, 9.8 g; fat (except stanols), 1.4 g; plant stanols, 2 g; vitamin B_6, 0.6 mg; folic acid, 60 μg. All participants continued with previous and any newly prescribed lipid-lowering therapies. All participants were recommended to follow the therapeutic guidelines most suitable in each case (lifestyle modifications or lipid-lowering medication, according to the recommendations of the European guidelines on cardiovascular disease prevention).[16] Physical exercise was advised (at least 30 min/day for 4-5 days/weak), as well as the general characteristics of the Mediterranean diet (type and quantity of fats, carbohydrates, and proteins).

The follow-up duration was 12 months. Once consent was obtained, patients were scheduled for the initial visit and to

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