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.


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Efecto a largo plazo de los estanoles vegetales en el perfil lipídico de pacientes con hipercolesterolemia. Ensayo clínico aleatorizado

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...
INTRODUCCIÓN

Aunque diversas guías clínicas y estudios aleatorios han indicado que los niveles séricos de LDL-C en individuos con hipercolesterolemia, una alta proporción de pacientes tiene valores más altos que el objetivo recomendado en ambos grupos y con el segundo tratamiento se observó una reducción significativa (ligeramente superior al 10%) de las concentraciones de colesterol unido a lipoproteínas de baja densidad en sujetos con hipercolesterolemia. Se realizó un ensayo clínico aleatorizado de corta duración y placebo-controlado con participantes recién diagnosticados con hipercolesterolemia. Los resultados confirmaron que la administración de estanol 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. Registra el ensayo (www.ClinicalTrials.gov): Current Controlled Trials NCT01406106. © 2014 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

**Abreviaturas**

CVR: riesgo cardiovascular
LDL-C: bajo-density lipoprotein cholesterol
TC: colesterol total

**MÉTODOS**

Este estudio consistió de un ensayo clínico aleatorizado y placebo-controlado. Los participantes fueron seleccionados de 9 familias de servicios de salud en el área de Albacete, España. Los individuos mayores de 18 años que asistieron a los servicios de salud se incluyeron si habían sido diagnosticados con hipercolesterolemia (TC, 200-249 mg/dL) o hipercolesterolemia (TC, 250 mg/dL) y si habían sido diagnosticados con hipercolesterolemia. La eficacia se evaluó a través de la pérdida de 2 g/día de estanol y del consumo de productos lácteos con estanol. Todos los participantes firmaron un consentimiento informado después de una explicación suficientemente detallada del estudio. El estudio fue aprobado por el Comité de Ética para Investigación en el Cuartel General de Albacete y se ajustó a las directrices éticas de la declaración de Helsinki. El tamaño muestral de acuerdo con un cálculo de potencia se calcularía para lograr una reducción significativa (ligeramente superior al 10%) de la concentración de colesterol unido a lipoproteínas de baja densidad en sujetos con hipercolesterolemia. El personal de la clínica y los participantes fueron informados de que los resultados se documentarían de manera anónima. Los participantes que participaron en el estudio fueron remunerados con una cantidad fija.

**Conclusiones**

Los resultados confirmaron que la administración de estanol 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. Registra el ensayo (www.ClinicalTrials.gov): Current Controlled Trials NCT01406106. © 2014 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.
provide samples for analysis. At the initial visit, participants were randomized to 1 of the 2 groups, data were obtained on medical history, analytics, and physical examination, and the corresponding yogurt drink was dispensed (subsequent deliveries were made according to the expiration date). Follow-up visits were conducted after 1, 3, 6, and 12 months to record analytical and physical examination parameters, as appropriate. The primary end point was the difference in LDL-C levels after 12 months. The lipid profile was measured (TC, LDL-C, HDL-C [high-density lipoprotein cholesterol], and triglycerides) after 3 and 12 months. Analytical measurements were made using blood vein samples taken following a fast of at least 12 h; the plasma concentrations of TC and LDL-C were determined using the CHODPAP and Friedewald methods, respectively. These measurements were made in the reference laboratory (Complejo Hospitalario Universitario de Albacete), which is accredited by the Spanish Society of Clinical Biochemistry. Other variables analyzed included sociodemographic characteristics (age, sex, marital status, education level, and social class), therapeutic adherence using the Morisky-Green test (adherence was considered good if patients responded adequately to the 4 dichotomous questions of the questionnaire, concerning forgetting to drink the yogurt and adherence to the regimen), adverse events, adherence to dietary recommendations, dietary intake (lifestyle questionnaire), cardiovascular events (ischemic heart disease, atherothrombotic cerebrovascular disease, and peripheral artery disease), anthropometric data (weight, height, and body mass index), physical activity, smoking habits, systolic and diastolic blood pressure, CVR (SCORE [Systematic Coronary Risk Evaluation] tables for countries with low CVR and REGICOR [Registre Gironı´ del Cor]), health problems (International Classification of Primary Care-2 of WONCA [World Organization of National Colleges, Academies, and Academic Associations of General Practitioners/Family Physicians]), follow-up of the lipid-lowering drug therapy, and use of

**Figure.** Study flowchart.
other medications. The following events were considered study end points: completion of the observation period, death, protocol violation, a severe adverse event, an intercurrent disease precluding dietary ingestion, and patient abandonment or withdrawal of consent. No changes were made to the protocol during the course of the study.

For the statistical analysis, a description was made of the baseline characteristics of the 2 groups (measures of central tendency and spread). Subsequently, the participants in both groups were classified into different levels of LDL-C and TC reductions and a crude analysis was performed to evaluate the following parameters and their 95% confidence intervals (95% CIs): absolute benefit increase, relative benefit increase, and number of patients needed to treat. Moreover, the incidences of the outcome variables were described and compared in the 2 groups (comparison of proportions via a chi-square test or comparison of means via a Student t test or Mann-Whitney U test, with an alpha error of 5%). Changes in the parameters of each group were analyzed using a repeated measures t test. The possible existence of confounding factors and the effects of other variables on the relationship between the proposed intervention and the outcome variables were analyzed using logistic regression models (dependent variable: level of reduction of the lipid parameters). Multiple linear regression was used to analyze the possible variables related to a greater reduction in LDL-C levels in the intervention group and in all participants, by including the following variables in the model: sex, age, marital status, social class, number of health problems, number of medications taken, tobacco consumption, performance of physical activity, plasma levels of LDL-C and TC, weight and body mass index, CVR determined with SCORE, and adherence to the lipid-lowering diet at the beginning of the study. An effectiveness analysis was performed by intention to treat and all participants were maintained in their originally assigned group. All participants analyzed at 3 and 12 months were included in this analysis, regardless of their adherence to the yogurt consumption. The LDL-C value was determined in the corresponding visit. Analyses were performed with SPSS v.20.0.

RESULTS

Of the 182 individuals who began the study, 79 and 77 completed follow-up in the intervention and control groups, respectively. There was no difference in the percentage of individuals completing the study (86.8% vs 84.6%; P = .672). The distribution of patients lost to follow-up is shown in the Figure.
Table 2
Changes in Lipid Parameters and Differences Between the Intervention and Control Groups in the Reduction of These Parameters After 3 and 12 Months

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>3 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change from baseline (mg/dL), mean (95%CI)</td>
<td>Difference in reduction (mg/dL), stanols vs placebo</td>
</tr>
<tr>
<td></td>
<td>Mean (95CI)</td>
<td>P</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanol group</td>
<td>–20.9 (–28.7 to –13.0)</td>
<td>15.5 (5.3 to 25.8)</td>
</tr>
<tr>
<td>Control group</td>
<td>–5.3 (–12.0 to 1.3)</td>
<td>1.7 (–4.9 to 8.3)</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanol group</td>
<td>–21.0 (–28.2 to –13.7)</td>
<td>13.3 (3.8 to 22.8)</td>
</tr>
<tr>
<td>Control group</td>
<td>–7.7 (–13.9 to –1.5)</td>
<td>–4.1 (–11.3 to 3.1)</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanol group</td>
<td>2.2 (–0.7 to 5.1)</td>
<td>–0.4 (4.8 to 4.0)</td>
</tr>
<tr>
<td>Control group</td>
<td>2.6 (–0.8 to 6.0)</td>
<td>2.5 (–0.5 to 5.5)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanol group</td>
<td>–1.3 (–8.0 to 1.0)</td>
<td>–10.2 (–22.3 to 1.9)</td>
</tr>
<tr>
<td>Control group</td>
<td>8.9 (1.1 to 16.7)</td>
<td>6.8 (–2.1 to 15.7)</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; LDL-C, high-density lipoprotein cholesterol; HDL-C, low-density lipoprotein cholesterol; NS, not significant.
*p Significant difference in the mean reduction between the intervention and control groups (P < .05).

The mean (standard deviation) age of the participants was 54.3 (10.6) years. The baseline characteristics of the 2 groups are shown in Table 1. At the beginning of the study, 31 (34.1%) and 27 (29.7%) individuals were taking statins in the intervention and control groups, respectively. In the intervention group, 18, 10, 2, and 1 participants were taking simvastatin, atorvastatin, rosvastatin, and pravastatin, respectively. In the control group, 17, 8, 1, and 1 participants were taking simvastatin, atorvastatin, pravastatin, and fluvastatin, respectively. The 2 groups showed similar dietary habits regarding the frequency of the consumption of oil, vegetables, salads, meat, fish, and other foods.

Table 2 shows the differences between the intervention and control groups in the lipid parameters at 3 and 12 months of follow-up. Comparison of the changes in the values of the various lipid parameters between the 2 groups during follow-up revealed a greater mean reduction in TC in the intervention group at both 3 months (15.5 [95% CI, 5.3-25.8] mg/dL; P = .003) and 12 months (18.1 [95% CI, 8.1-28.2] mg/dL; P < .001). The decrease in LDL-C was also greater in participants taking stanols at both 3 months (13.3 [95% CI, 3.8-22.8] mg/dL; P = .006) and 12 months (13.7 [95% CI, 3.2-24.1] mg/dL; P = .011). There were no statistically significant differences between the groups in HDL-C, triglycerides, TC/HDL-C, and LDL-C/HDL-C.

At 12 months, the mean reduction in LDL-C from baseline was significantly greater in the intervention group than in the control group (11.0% vs 0.9%; 95%CI, 2.1%-18.1%; P = .014). The reduction in TC was also greater (6.1% vs 1.3%; 95%CI, 3.0%-11.7%; P = .001).

The proportion of participants with reduced LDL-C levels was significantly greater in the intervention group at both 3 months (relative risk [RR] = 1.38; 95%CI, 1.10-1.74) and 12 months (RR = 1.47; 95%CI, 1.13-1.91). A 10% reduction in LDL-C levels was achieved by a significantly higher proportion of participants in the intervention group than in the control group at both 3 months (RR = 1.74; 95%CI, 1.16-2.62) and 12 months (RR = 1.72; 95%CI, 1.11-2.65). After 12 months, the absolute benefit increase for achieving a 10% LDL-C reduction was 20% (95%CI, 5%-34%), the relative benefit increase was 42% (95%CI, 10%-62%), and the number of patients needed to treat was 5. A 10% reduction in TC levels at 12 months was also achieved by significantly more patients in the intervention group (RR = 2.57; 95%CI, 1.38-4.77).

Adverse effects were seen in 7 patients (7.7%) in the intervention group and in 6 (6.7%) in the control group, without statistically significant differences between the groups (P = .733). All adverse effects were gastrointestinal (epigastric pain, feeling of fullness, bloating).

At 3 and 12 months, 73.0% (95% CI, 65.7%-80.2%) and 72.2% (95%CI, 64.7%-79.7%), respectively, of all the participants showed adequate adherence to the yogurt drink. No significant differences between the groups were seen in adherence at 3 months (68.7% vs 77.6%) and 12 months (68.8% vs 75.5%).

At both 3 and 12 months, no significant differences between the groups were seen in statin use and adherence to the dietary recommendations. At 12 months, 28 patients in the intervention group (35.4%) and 25 in the control group (32.9%) were taking statins. During follow-up, statins were prescribed to 2 patients in the intervention group and 2 patients in the control group. No modification was made to the statin dosage or type in any members of either group during follow-up.

There were no significant differences between the 2 groups in changes in anthropometric parameters, blood pressure, or CVR during follow-up.

In the linear multiple regression, the factors related to the greatest reduction in LDL-C at 12 months are shown in Table 3 for all participants and in Table 4 for those consuming stanols. The variables related to a greater reduction in LDL-C values at 12 months in all participants were, apart from the treatment type

Table 3
Multiple Linear Regression Model for Variables Related to the Higher Reduction in Low-density Lipoprotein Cholesterol Levels in All Participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>β (95%CI)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>–124.66</td>
<td>–163.25 to –86.07</td>
<td>–</td>
</tr>
<tr>
<td>Older age</td>
<td>0.786</td>
<td>0.34-1.22</td>
<td>3.52</td>
</tr>
<tr>
<td>Statin use</td>
<td>9.26</td>
<td>0.14-18.38</td>
<td>2.01</td>
</tr>
<tr>
<td>Higher baseline level of plasma LDL-C</td>
<td>0.59</td>
<td>0.40-0.77</td>
<td>6.16</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; LDL-C, low-density lipoprotein cholesterol.
DISCUSSION

Studies of the effectiveness of stanols in combating hypercholesterolemia show wide variation in design, with differences in consumption duration, the product administered, sample size, and the epidemiological characteristics of the population. In the present study, daily ingestion of 2 g of plant stanols was associated with a > 10% decrease in the plasma levels of LDL-C from baseline at both 3 months and 12 months of consumption. This 10% reduction in LDL-C could reduce cardiovascular disease risk.8,9,19

Our results match those of a recent meta-analysis evaluating the effects of phytosterols incorporated in 9 distinct food types and consumed for different durations.20 Previous studies with stanols administered in yogurt form have shown similar21 or inferior22 LDL-C and TC reductions to those of our study. A similar decrease has also been seen upon supplementation of other foods with stanols.23 As in previous studies, our study failed to show changes in HDL-C and triglycerides.12,21

Our study shows the long-term effects of stanols, whereas few previous studies exceeded 4 weeks and almost all of those studies were shorter than 2 months.24–26 In addition, this effect on LDL-C was demonstrated in a large sample of primary care patients with hypercholesterolemia treated according to standard clinical practice treatment guidelines adapted to the Spanish population. Moreover, the adverse effects seen after stanol consumption for 12 months were similar to those described elsewhere.18,24

Our results agree with the available evidence and suggest consideration of stanols in patients in primary prevention whose CVR does not justify statin administration27,28 and in those requiring simultaneous treatment with statins.6,26,29 Thus, stanols could be useful in both primary and secondary6 prevention to allow use of lower statin doses, avoiding their possible adverse effects.

Age and baseline LDL-C concentrations were associated here with a greater LDL-C reduction. Similar results have been found in various meta-analyses,22,28 although the effect of age was explained by the initial LDL-C values. In contrast, in our study, the effect of age was maintained after exclusion of baseline LDL-C from the regression model. These results could be related to the age distribution of our sample.

Limitations

One of the limitations of our study is that changes in diet or statin use could alter the results; however, there were no significant changes in either parameter from baseline, so it is unlikely that the lipid profile reductions were due to dietary or statin changes. Moreover, there were no differences between the intervention and control groups in lipid-lowering agent use and diet. Another possible limitation is that statol consumption could affect statin adherence, but previous studies have shown that daily statol consumption does not modify adherence.31 The characteristics of the study setting could be a limitation restricting extrapolation of our results; however, the present study was a randomized clinical trial of dyslipidemic patients attending primary care health clinics, whose characteristics should be similar to those of other patients with hypercholesterolemia.

Given the demonstrated effectiveness of plant stanols in reducing TC and LDL-C concentrations after 12 months, new controlled studies of longer durations should be performed to determine the effectiveness of stanols in reducing the frequency of cardiovascular events,4 because no data are available on the effectiveness of stanols in preventing cardiovascular disease.9 Also required are new studies specifically designed to determine the factors associated with the degree of the LDL-C reduction following long-term statol consumption. These studies of longer-term statol consumption could also determine if the development of adverse effects is modified.9 Moreover, new studies are required that examine statol adherence and possible associated factors, such as the type of food supplemented, the daily dose, and the number of doses per day.

CONCLUSIONS

Our results show the effectiveness of plant stanols on LDL-C reduction in individuals with hypercholesterolemia: in this randomized and placebo-controlled study, daily ingestion of 2 g of plant stanols for 12 months was associated with a higher decrease in plasma LDL-C than the consumption of stanol-free yogurt. This reduction exceeded 10% with respect to the baseline values at both 3 and 12 months of consumption and could be clinically relevant. Our results suggest that daily consumption of plant stanols can be considered in patients with hypercholesterolemia, given their effectiveness, adequate adherence, and few adverse effects.

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CONFLICTS OF INTERESTS

None declared.

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