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REVIEW

Plant sterols for adults with hypercholesterolemia treated with or without medication (statins)

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KEYWORDS

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Phytosterols;
Plant Sterols;
Functional Food;
Hydroxymethylglutaryl-CoA Reductase Inhibitors;
Statins

ABSTRACT

Hypercholesterolemia is the most common coronary risk factor among the Spanish population; 37.4% of the Spanish adult population have cholesterol levels between 190 and 240 mg/dl. Foods enriched with plant sterols (PS) can effectively reduce plasma cholesterol in patients with high levels. However, its effectiveness and safety in adults with moderate hypercholesterolemia who are on medication (statins) or not has been less studied. The aim of this review is to establish the possible role of plant sterols in the control of hypercholesterolemia, as well as how safe they are for people with moderate hypercholesterolemia treated with statins. The main studies were looked at, regardless of design, language or publication date which studied the connection between "plant sterols" and "hypercholesterolemia", using Pubmed/Medline, SCOPUS and Google Scholar databases. The studies brought together in this review show that an intake of between 2 and 3g/day of plant sterols effectively reduces plasma cholesterol levels in patients with hypercholesterolemia. Both clinical studies and available meta-analyses do not indicate any problems related to the drug-nutrient interaction associated with the use of plant sterol-enriched foods. In patients with moderate hypercholesterolemia where the use of statins is not justified a healthy diet, exercise and foods high in PS can provide the best therapeutic approach.

Esteroles vegetales para adultos con hipercolesterolemia tratada con o sin fármacos (estatinas)

PALABRAS CLAVE

Hipercolesterolemia;
Fitoesteroles;
Esteroles Vegetales;
Alimento Funcional;
Inhibidores de
Hidroximetilglutaril-
CoA Reductasa;
Estatinas

RESUMEN

La hipercolesterolemia es el factor de riesgo cardiovascular más frecuente en la población española. El 37,4% de la población adulta española presenta niveles de colesterol de entre 190 y 240 mg/dl. Los alimentos enriquecidos con esteroles vegetales (EV) pueden disminuir de forma efectiva el colesterol plasmático en pacientes con niveles elevados, sin embargo su efecto y seguridad en adultos con hipercolesterolemia moderada, tratados o no con fármacos (estatinas) ha sido menos estudiada. El objetivo de la presente revisión es establecer el posible papel de los esteroles vegetales en el control de la hipercolesterolemia, así como su seguridad en personas con hipercolesterolemia moderada tratada con estatinas. Se revisaron los principales estudios, sin limitación de diseño, lengua o fecha de publicación que relacionara "esteroles vegetales" e "hipercolesterolemia", explotando las bases de datos Pubmed/Medline, SCOPUS y Google Scholar. Los estudios recuperados en la presente revisión muestran que el aporte de entre 2 y 3g/día de esteroles vegetales disminuyen de forma efectiva los niveles de colesterol plasmático en pacientes con hipercolesterolemia. Tanto los estudios clínicos como los metaanálisis disponibles no muestran problemas relacionados con la interacción fármaco-nutriente asociada al uso de alimentos enriquecidos con EV. En pacientes con hipercolesterolemia moderada en que no esté justificado el uso de estatinas, una alimentación saludable, actividad física y alimentos con EV, puede constituir el mejor acercamiento terapéutico.

CITA

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INTRODUCTION

Hypercholesterolemia is a metabolic imbalance characterised by the presence of high levels of cholesterol in the blood. In general hypercholesterolemia is diagnosed when cholesterol values are equal to or above 240 mg/dl^{1,2}, although there is no universally accepted criteria to define this disorder^{3,4}. In this respect there are entities who differentiate between primary prevention (patients who have not clinically shown ischemic vascular disease) and secondary (patients who have clinically shown ischemic vascular disease). The Catalan Health Institute, for instance, considers that hypercholesterolemia exists when the total cholesterol is equal to or over 200 mg/dl in primary prevention, while in secondary prevention hypercholesterolemia is defined

when values of cholesterol linked to low density proteins (cLDL) are equal to or above 100 mg/dl⁵. In any case, there is no definite cut-off point between normal and abnormal cholesterol levels and this is why doctors interpret patients' readings in relation to other health conditions and risk factors of coronary heart disease.

It is well established that high total cholesterol and LDL cholesterol is associated with a clearly increased risk in developing coronary heart disease⁶. In fact, high levels of cholesterol are one of the main factors of coronary heart disease⁷ to the extent that high cholesterol increases the risk of ischemic heart disease in an independent, severe and continual way^{3,8,9}. This can be observed even among populations with low coronary heart disease risk^{3,10}. Moreover, the association between cholesterol levels and

ischemic disease is not only lineal but it can begin to be visible in values of 150 mg/dl⁵.

Hypercholesterolemia is the most common cardiovascular risk factor among the Spanish population. Between 17–50% (depending on the cut-off point used) of Spanish people suffer from hypercholesterolemia^{1,3,4}. It is estimated that hypercholesterolemia is the cause of one fifth of coronary events in Spain, where coronary heart disease is the first cause of hospitalisation and death. In 2008 it was the cause of over 122,000 deaths and over 5 million hospital stays¹.

According to statistics from the ENRICA study, 37.4% of the Spanish adult population have cholesterol levels between 190 and 240 mg/dl. Applying this prevalence among the Spanish population of 18 years of age and older, approximately 14.5 million Spanish men and women have cholesterol levels within this range³.

The only research that has been found to evaluate the approximate number of Spanish people with moderate hypercholesterolemia and who are also being treated with statins was a cross sectional study which included 804 patients aged between 35–74, randomly selected from two Spanish health centres. According to this study, approximately 9.5% of patients without high cardiovascular risk were treated with statins¹¹. Although the extrapolation of results in other populations should be conducted with caution, given that this is not a strict multicentre study, if these statistics were confirmed for the rest of the Spanish adult population, they may generate the hypothesis that about 1.4 million Spanish adults are unjustifiably being treated with statins.

In this respect, the French High Authority of Health observes a certain abuse in the prescription of statins in primary prevention in France¹². No data has been found on the number of Spanish people with moderate hypercholesterolemia who habitually ingest foods enriched with plant sterols. The aim of this review is to establish what is known about the role of plant sterols in the control of hypercholesterolemia, and to find out if there are studies which evaluate the safety of the use of plant sterols, especially in people with hypercholesterolemia who are on medication. The main studies were reviewed without limitations of design, language or publication date which linked “plant sterols” and “hypercholesterolemia”, using the databases of Pubmed/Medline, SCOPUS and Google Scholar.

PLANT STEROLS AND HYPERCHOLESTEROLEMIA

Plant sterols (also called phytosterols), are organic compounds from the plant kingdom which have a structure and cell function equivalent to that of cholesterol in vertebrates^{13–15}. This similarity is of paramount importance when it comes to justifying their role in the control of cholesterol in humans as this means that both dietary and bile cholesterol compete with the plant sterols in the intestine to be absorbed. In this way the plant sterols reduce the amount of cholesterol that enters the blood stream. Furthermore, the absorption rate of plant sterols in humans is very low, something which does not happen with cholesterol. These reasons explain why plant sterols reduce cholesterol in humans^{13,16–19}.

Oils, cereals, pulses, fruit and vegetables are the main dietary sources of plant sterols in the Spanish diet. It is estimated that they provide an average of 276 mg/day²⁰. Nevertheless, this figure does not show significant reductions in cholesterol levels. In this sense functional foods enriched with plant sterols are designed to provide between 1 and 3 g/day of these substances, a figure which is between 2 to 10 times higher than that which is usually achieved through diet²¹.

Several rigorous studies conclude that foods enriched with plant sterols may effectively reduce plasma cholesterol in patients with hypercholesterolemia^{22–25}. The *National Heart, Lung and Blood Institute* of the United States considers that foods enriched with plant sterols reduce levels of LDL cholesterol between 6–15%²⁶. Current American guidelines on the management of cholesterol in adults include recommendations about ingesting ~2 g/day of plant sterols in order to reduce total cholesterol in patients with hypercholesterolemia⁶. The European Food Safety Authority (EFSA), associated to the European Commission and the European Parliament, and whose advisory council is represented by the Spanish Food and Nutrition Safety Agency in Spain (AESAN), considers there to be a cause-effect relationship (in the form of dose-dependency) between the intake of foods enriched with plant sterols and the reduction in LDL cholesterol^{27–30}. More recently, in 2011, the American Diabetes Association recommended all patients with diabetes to increase their intake of plant sterols in order to improve their lipid profile³¹. One year later European guidelines^{32,33} on the prevention of cardiovascular disease pointed out that functional foods containing plant sterols are effective in reducing LDL cholesterol. Two meta-analysis published in 2011 and 2014, also indicated that these foods do so by approximately 6–12% when taken in a

dose of 2–3 g/day^{34,35}. It indicated that their effectiveness is added to that provided by statins^{32,33}.

POSSIBLE SIDE EFFECTS OF PLANT STEROLS

In spite of the possible effect of plant sterols on the absorption or metabolism of certain nutrients, in particular liposoluble ones²¹, the evidence available shows that plant sterols have no significant effect on the absorption and metabolism of vitamins A, D, E, alpha-carotene or lycopene²⁶. There are doubts, however, about a possible interference from plant sterols on the absorption of beta-carotenes. The scientific literature includes tests which indicate that levels of beta-carotenes may be slightly reduced, although it would seem that this would not produce any side effects²⁶. In any case, it is recommended that the continual intake of foods enriched with plant sterols is accompanied by a diet high in fruit and vegetables which are high in beta-carotene and liposoluble vitamins, or that these nutrients are added to foods that contain plant sterols⁶.

Gupta *et al.* (International Centre for Circulatory Health, National Heart & Lung Institute, Imperial College London) point out that both clinical tests and available meta-analyses do not indicate any problems related to the drug-nutrient interaction associated with the use of foods enriched with plant sterols³⁶. Likewise, Mailonwski and Gehret consider that plant sterols in the doses recommended in enriched foods have little interaction with drugs³⁷. Available clinical tests (and meta-analyses) have not indicated any important safety issues (side effects)³⁶. A recent study has confirmed, moreover, the stability of plant sterols in functional foods³⁸.

The intake of plant sterols is accompanied by slight increases in plasma concentrations of plant sterols, and certain studies have suggested that this increase could increase the risk of coronary heart disease³⁹. However, a study carried out among the Spanish population within the framework of the EPIC study showed that plasma levels of sitosterol, the main plant sterol in the diet, was associated with a lower risk of coronary heart disease⁴⁰. In any case, a recent meta-analysis (2012) concluded that this increase would not be relevant for coronary heart disease risk⁴¹.

The Scientific Committee on Food of the European Commission considers that people with inherited metabolic disorders must be aware of the presence of high levels of phytosterols in foods enriched with plant sterols⁴². In any case, despite the fact that the intake of plant sterols is not recommended for people who suffer from homozygous sitosterolemia, a recent study has shown that in heterozygous sitosterolemia the intake of plant sterols would be safe⁴³. In any event, the prevalence of this pathology is very low among the population in general.

The European Commission considers that the use of foods enriched with plant sterols, in compliance with the information in Table 1 is safe, although an intake of plant sterols above 3 g/day is not recommended^{42,44,45}.

DRUGS OR COMBINATIONS OF DRUGS AND HYPERCHOLESTEROLEMIA

Statins are the first choice of medication in the treatment of hypercholesterolemia, due to their proven efficacy based on scientific evidence^{46–49}. Nevertheless, it should be specified,

Table 1. Conditions for use in the EU of health declaration approved for plant sterols^{62–64}.

Conditions for use in the EU health declaration approved for plant sterols.

- Information to the consumer that the beneficial effect is obtained with a daily intake of 1.5-2.4 g of plant sterols/stanols.
- Reference to the magnitude of the effect of yellow fat spreads, dairy products and salad dressings, mayonnaise enriched with plant sterols.
- When referring to the magnitude of the effect, the reduction in cholesterol will range between 7 and 10%, and the duration to obtain the effect of 2-3 weeks must be communicated to the consumer.

as the European Association of Cardiovascular Prevention and Rehabilitation points out, that there are other drugs or combinations of drugs which the doctor may evaluate when treating this disease. Therefore, in the case of intolerance to statins, a first option should be to consider prescribing bile acid sequestrants or nicotinic acid.

As a second option the use of cholesterol absorption inhibitors should be evaluated, either on their own or in combination with bile acid sequestrants and nicotinic acid. However, if treatment with statins does not have the desired effect as stipulated by the doctor in relation to cholesterol readings, a prescription of a combination of statins with a cholesterol absorption inhibitor or a bile acid or nicotinic acid sequestrant is recommended⁵⁰.

Statins and/or plant sterols for patients with hypercholesterolemia and high risk of heart disease

It is well established that patients with hypercholesterolemia and a high risk of coronary heart disease benefit, in terms of reducing mortality, from the first choice drug: statins⁵¹. Nevertheless, most patients with a high risk of coronary heart disease who are treated with statins in Spain fail to achieve the recommended lipid targets⁵².

With respect to the combination of hypocholesterolemic medication (statins) with foods enriched with statins, far from being harmful, they are in fact beneficial in the control of plasma cholesterol^{22,26,53}, as is recognised by the European Society of Cardiology^{32,33}. This fact has been confirmed by a recent meta-analysis carried out by Scholle JM *et al.*⁵⁴. In any case The European Authority on Food Safety has indicated that people with high cholesterol and who are already taking medication for their cholesterol should only consume foods enriched with statins under medical supervision^{28,29}.

Statins and/or plant sterols for patients with moderate hypercholesterolemia

Although statins are justified in patients with hypercholesterolemia and high coronary heart disease risk, as far as primary prevention is concerned (patients who have not clinically shown any ischemic vascular disease) there are doubts about the risk-benefit balance of using these drugs. The French High Authority of Health points out that statins should be reserved for patients who are at high risk, that is, who combine several risk factors such as diabetes, hypertension, smoking, etc.¹². These ideas are shared by the American Heart Association⁵⁵ and the American Diabetes Association³¹.

Similarly, a meta-analysis carried out by Cochrane *et al.* in 2011 showed that evidence of benefits in terms of life

quality in using statins in primary prevention in patients with low risk of coronary heart disease is limited. Cochrane therefore recommends precaution when prescribing these drugs in primary prevention for patients with low risk of coronary heart disease⁵¹. It should not be overlooked that the prescription of statins has undergone an important increase in recent years. The efficacy of statins in primary prevention in women and people over 65 has not been well established¹¹.

Although statins are well tolerated as a whole, and serious side effects are rarely reported, their widespread use magnifies these events. Among the risks of unjustified use of statins type 2 diabetes stands out (a risk which is compensated if the medication is justified, by the reduction of coronary heart disease), myopathy (especially in people with complex medical conditions and/or who are prescribed a lot of medication, or in the elderly), myalgia (between 5–10%), elevated transaminases and drug interactions. Moreover, an inter-individual variation in response to statin therapy has been observed, as well as the incidence of side effects^{50,56}. In any case, as the European Association for Cardiovascular Prevention and Rehabilitation points out, the clinical conditions of the patients, concomitant treatments and tolerance to the drug will play an important role in determining the final choice of drug and dosage⁵⁰. Patients should not discontinue treatment without first consulting their doctor if they are concerned about this and should ask their doctor at their next appointment.

Top organisations recommend that in low risk patients the use of statins should not be considered as the first option and that these patients should opt for a healthy diet and plant sterols before starting treatment with prescribed drugs^{6,57}.

CONCLUSIONS

Taking into account the abovementioned data, there would appear to be a clear consensus which justifies the usage of plant sterols in lowering the risk of coronary heart disease in patients with hypercholesterolemia, where this usage has few side effects and where rigorous studies show that prescribing statins for primary prevention for low risk coronary heart disease patients should be done with caution^{51,56}.

Consequently, it is to be considered that a balanced diet together with functional foods with sufficient amounts of plant sterols is the most recommendable way to treat hypercholesterolemia in patients with measurements

between 190 and 240 mg/dl, except where clinical judgement is to the contrary.

Health professionals can feel confident when prescribing foods enriched with plant sterols for the treatment of moderate hypercholesterolemia (except, as has been mentioned, where clinical judgement is to the contrary)⁵⁸.

In this way, it is expected that each reduction of 1 mg/dL in LDL serum cholesterol can correspond to a 1% reduction in the risk of developing heart disease⁵⁷. The abovementioned meta-analysis show that plant sterols in doses of 1–3 g/day can reduce LDL cholesterol by between 12 and 24 mg/dL²³⁻²⁵, which would represent a reduction of 12–24% in the risk of heart disease. It is without a doubt a clinically relevant benefit. One meta-analysis showed that the addition of 2 g of plant sterols to a daily portion of margarine can produce a reduction in LDL cholesterol which would mean up to a 25% reduction in the risk of coronary heart disease. This is a better than expected effect for people who reduce their intake of saturated fats²².

The European Society of Cardiology has recently indicated that the daily intake of functional foods containing about 2 g of plant sterols reduces cholesterol readings by 10%^{32,33}. Foods enriched with plant sterols may therefore play an important role in the protection against atherosclerosis and coronary heart disease in patients with hypercholesterolemia^{28,29}.

Likewise, it is expected that the intake of plant sterols by people with moderate hypercholesterolemia who take statins reduces potential side effects. It is also expected that a large number of Spanish people can benefit from this recommendation with respect to the reduction in the risk of coronary heart disease. As was previously stated, a

theoretical figure of 1.4 million Spanish adults could see a reduction in plasma cholesterol readings. A simulation carried out in the United Kingdom showed that the daily intake of foods enriched with plant sterols represented an 11.8% reduction in coronary events. Its conclusion was that a “universal” therapy using these foods could lead to a very significant decrease in coronary disease rates⁵⁹. It is important to note that the European Society of Cardiology has recently indicated that the positive effect on the reduction of coronary risk that is noted after the decrease in cholesterol levels is independent of the method used to achieve this reduction (drugs, plant sterols, diet or changes in lifestyle)^{32,33}.

Both the European Society of Cardiology^{32,33}, as well as data from well-designed studies⁶⁰ confirm that the combination of the intake of foods enriched with plant sterols together with a healthy diet has a synergic effect.

The European Union Register on nutrition and health⁶¹ points out that the authorised declaration of health within the framework of the European Community associated with foods enriched with plant sterols is the following: “Plant sterols and plant stanol esters have been proven to reduce cholesterol in the blood. High cholesterol is a risk factor in the development of heart disease”. The conditions of use of this health declaration are stated in Table 1⁶²⁻⁶⁴.

New scientific advice on plant sterols points out that as well as previously approved health statements, there is sufficient evidence to conclude that the intake of 3 g daily of plant sterols or plant stanols (range 2.6–3.4 g/day) in the matrices approved by Regulation (EC) n° 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings)⁶³, lowers LDL cholesterol by 11.3%. The minimum length of

Table 2. Interventions for reducing cholesterol levels and expected degree of efficacy that they produce, according to the European Association for Cardiovascular Prevention and Rehabilitation⁵⁰.

Intervention	Degree of efficacy
■ Reduce intake of saturated fats	+++
■ Reduce intake of trans fatty acids	
■ Use functional foods enriched with plant sterols	
■ Increase intake of foods rich in dietary fibre	++
■ Reduce intake of dietary cholesterol	
■ Reduce excess body weight	+
■ Increase regular exercise	

time necessary in order to achieve the maximum effect of plant sterols and stanols in the reduction of cholesterol would be from two to three weeks⁶⁵.

Therefore, it is considered that the treatment with foods containing plant sterols should include a daily minimum of 1.5 g and a maximum of 3 g/day. Continual monitoring and counselling are crucial as this kind of therapy is only effective if it is properly followed^{58,66}.

A change in lifestyle is one of the keys to success in all treatments that aim to reduce blood lipids. Nutritional

intervention should improve diet, encourage exercise, weight loss (where necessary) and the giving up of smoking. Nutritional intervention should be adapted to suit each patient, their age and other medical conditions as well as the information set out in Table 2. It is important to point out that the reduction in the intake of foods rich in saturated fats together with an intake of foods enriched with plant sterols may reduce LDL by as much as 20%²⁶. Tables 2–4 sum up food and nutrition advice and lifestyle recommendations from the authors.

Table 3. Dietary recommendations for lowering cholesterol, adapted from the European Association for Cardiovascular Prevention & Rehabilitation, 2011⁵⁰.

Dietary recommendations for reducing cholesterol

	Preferable	To be consumed in moderation	To be consumed occasionally and in small amounts
Cereals	Whole grain	Refined grains or derivatives: bread, rice, pasta or processed breakfast cereal	Pastries, croissants, etc.
Vegetables	Raw or cooked vegetables		Vegetables prepared with creams or butter
Pulses	All		
Fruit	Fresh or frozen	Dried, preserved, jams and marmalades, sorbets, in syrup, etc.	
Sugars and sweeteners	Calorie-free sweeteners	Saccharine, honey, fructose, glucose, chocolate, sweets	Cakes and ice-creams
Meat and fish	White and oily fish, skinless free-range poultry	Lean cuts of beef, lamb, pork, seafood	Sausages, salami, bacon, hotdogs, offal
Dairy products and eggs	Skimmed milk, low-fat yoghurts, egg white	Semi-skimmed milk, low-fat cheese or other dairy products	Cheese, cream, egg yolk, full-cream milk and yoghurt
Cooking oils and dressings	Vegetable oils, vinegar, ketchup, mustard, fat-free dressings, margarines containing plant sterols†	Soft margarines, salad dressings, mayonnaise	Butter, hard, margarines*, coconut and palm oil, lard, dressings containing egg yolk
Dried fruit and nuts/seeds		All	Coconut
Cooking procedures	Stews, boiled, steamed	Stir-fried, roasted	Fried

† In adults con hypercholesterolemia. Intake in patients who are on take hypocholesterolemic medication, children, pregnant and breastfeeding women should only do so under medical supervision; *Not commercially available in Spain.

Table 4. Summary of measures related to lifestyle and healthy diet in order to reduce coronary heart risk, adapted from the European Association for Cardiovascular Prevention & Rehabilitation⁵⁰.**Summary of measures related to lifestyle and healthy diet choices for reducing coronary heart disease risk**

- Dietary recommendations should take into account local habits, although interest should be promoted in healthy diets from other cultures.
- A healthy diet should be based on a varied intake of foods of mainly plant origin.
- The calorific intake should be adjusted to prevent excess weight and obesity.
- Intake of saturated fat should be reduced and should not surpass 7% of the daily calorific intake. Dietary cholesterol should not be above 300 mg/day. Limiting intake of red meat, cold meats and processed meat as well as full-fat dairy products will help to achieve this goal.
- Salt intake should be less than 5 g/day. Not placing the salt cellar on the dining table, adding less during cooking and especially reducing the intake of cold meats, cheese and bread containing salt as well as ready-made meals will help to reach this target.
- If you suffer from hypertriglyceridemia you should avoid drinking alcoholic beverages. For the rest of the adult population the message from the World Health Organisation in this respect is the most adequate: *"the less alcohol, the better"*.
- The intake of drinks and foods with added sugar should be limited, especially soft drinks.
- A minimum of 30 minutes physical exercise should be done a day.
- The use of and exposure to tobacco should be avoided.

COMPETING INTERESTS

The authors state that they are working in a company that commercialize a functional food with plant sterols.

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