

Dietary Plant Sterols and Cholesterol Metabolism

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Plant sterols, naturally occurring in foods of plant origin, reduce cholesterol absorption. Experimental studies show plant sterols to be an important part of the serum-cholesterol lowering effect of certain diets and dietary components. Epidemiological data show that individuals with higher intakes of plant sterols from their habitual diets have lower serum-cholesterol levels. To date, the role of naturally occurring plant sterols for lowering serum cholesterol has probably been underestimated. The consumption of dietary plant sterols should be a part of dietary advice to patients with hypercholesterolemia and the general public for the prevention and management of coronary heart disease.

Key words: cholesterol, diet, plant sterols

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INTRODUCTION

The coronary mortality rate has declined in the United States and Europe during the last decades, although it remains the most common cause of early death in the Western world. Improvements in medical care and preventive measures such as changes in lifestyle and dietary pattern as well as increased use of lipid-lowering medications could explain the reduced incidence of cardiovascular disease. Therapeutic lifestyle changes such as diet, exercise, smoking cessation, and weight control have recently been emphasized in the US National Cholesterol Education Program.¹ A diet rich in unsaturated fatty acids, including adequate amounts of ω -3 fatty acids, whole-grain cereals, fruits, and vegetables, provides significant protection against coronary heart dis-

ease.² Such a diet usually results in an increased intake of dietary plant sterols. The aim of this review is to provide evidence that, although plant sterols have previously been overlooked as serum cholesterol-lowering agents, the protective effect of diet on heart disease may partly be an effect of the concurrent increased intake of dietary plant sterols.

DIET AND SERUM CHOLESTEROL

High serum cholesterol due to a high LDL cholesterol concentration is a well-established risk factor for coronary heart disease.³ Cholesterol metabolism is mainly regulated in the small intestine and the liver. This in turn affects the distribution of cholesterol between the liver and the blood. Lower uptake of cholesterol or bile acids from the small intestine gives lower concentrations of cholesterol in the hepatocytes. This leads to a compensatory hepatic up-regulation of LDL receptors, which in turn increases hepatic uptake of LDL from the circulation, and therefore LDL and total cholesterol levels decrease.

Dietary content of fat and fiber, as well as fat quality, have traditionally been considered to be the cornerstone of dietary effects on serum cholesterol. When assessing food items with a high dietary fiber content, two different actions can be distinguished: one that reduces the reabsorption of bile acids and another that reduces cholesterol absorption. In order to precisely assess the excretion of bile acids and cholesterol from the small intestine, we have used metabolic balance trials with controlled dietary intake to study excretion in ileostomy contents in volunteers after colectomy due to ulcerative colitis.⁴ From such ileostomy studies it has been demonstrated that foods with viscous dietary fiber, such as pectin⁵ or beta-glucans,⁶ bind bile acids in the intestine and decrease the reabsorption of bile acids in the small intestine. This results in an increased production of bile acids in the liver, which is detectable by the high concentration of the 7- α -hydroxy-4-cholesten-3-one cholesterol metabolite in serum.⁷ A lower inflow of bile acids in the liver circulation leads to an up-regulation of LDL receptors and thus lower serum cholesterol levels.

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Fats containing saturated fatty acids, mainly lauric acid (12:0), myristic acid (14:0), and palmitic acid (16:0), increase serum LDL cholesterol levels, while unsaturated fats such as oleic acid (18:1), linoleic acid (18:2), and linolenic acid (18:3) decrease serum LDL cholesterol.⁸ Several studies in ileostomy subjects have demonstrated that diets high in monounsaturated fatty acids⁹ and polyunsaturated fatty acids¹⁰ increase the excretion of sterols (cholesterol and/or bile acids) from the small bowel, as do diets with reduced amounts of saturated fatty acids.^{11,12}

The physiologic effects of diet overall on serum cholesterol are not entirely known. An optimal diet to prevent coronary heart disease has been suggested to be based on three strategies: 1) substitute nonhydrogenated, unsaturated fats for saturated and trans-unsaturated fats, 2) increase consumption of ω -3 fatty acids, and 3) increase the consumption of fruits, vegetables, nuts, and whole grains (to replace refined grains).² An increased intake of these foods leads to a lower proportion of saturated fats and a higher intake of unsaturated fatty acids and dietary fiber,¹³ which work together in decreasing serum cholesterol levels. However, recent research in this area has increased our understanding of how other substances, such as plant sterols, can further reduce serum cholesterol concentration. Foods with a high proportion of unsaturated fatty acids (e.g., vegetable oils) and foods high in dietary fiber (e.g., vegetables and whole grain bread) are also rich in plant sterols, so some of the effect may actually come from the sterols rather than from the fatty acids and dietary fiber.^{14,15} In a well-controlled Danish study, an olive oil-rich diet resulted in somewhat higher LDL cholesterol levels than diets rich in either rapeseed (canola) oil or sunflower oil.¹⁶ We have recently reported a higher cholesterol excretion and lower cholesterol absorption with rapeseed oil compared with olive oil in ileostomy subjects.¹⁷ The fatty acid compositions of these oils are similar, although not identical, and are shown in Table 1; olive oil is considerably lower in plant sterols than rapeseed oil.

A compilation of results from several studies of fat and fiber carried out in our laboratory with patients with an ileostomy shows that higher excretion of cholesterol correlates with more plant sterols in the diet.¹⁸ We have also shown that cholesterol absorption correlates with the plant sterol content of foods consumed.¹² This supports the idea that plant sterols are important in the cholesterol-lowering effects of the diet, and that naturally occurring plant sterols contribute to the dietary effects on serum cholesterol. The effect of dietary plant sterols can have greater significance for serum cholesterol than the effect of viscous dietary fiber, which is normally available in limited amounts in foods of the urban Western diet.

Table 1. Plant Sterol Content* in a Selection of Foods	
Food	Sterol Content†
	<i>mg/100 g edible</i>
Fruits and Vegetables	
Broccoli, frozen	44
Green peas, frozen	25
Orange	24
Apple	13
Cucumber	6
Tomato	5
Cereals	
Wheat bran	200
Swedish knackebrot	89
Wholemeal bread	53
Rolled oats	39
Wheat bread	29
Fats and Oils	
Corn oil	912
Rapeseed (canola) oil	668
Liquid margarine	522
Sunflower oil	213
Spreadable butter	153
Olive oil	154
* Analyzed at the Department of Clinical Nutrition, the Sahlgrenska Academy at the University of Göteborg. ^{36,37,40}	
† Total plant sterols are the sum of β -sitosterol, campesterol, and stigmasterol, together with β -sitostanol and campestanol.	

PHYSIOLOGICAL EFFECTS OF PLANT STEROLS

Plant sterols are found in all foods of plant origin. In plants, these sterols function as structural components of the cell membrane. They have a chemical structure similar to that of cholesterol but contain one or two methyl or ethyl groups in the molecule's side-chain. They are biologically comparable to cholesterol in animals, which is an essential part of the cell membrane. The most important function of plant sterols in plants is to influence permeability and fluid exchange in the cell.

Plant sterols in foods compete with cholesterol absorption in the intestines, mainly during the building of micelles by reducing the solubility of cholesterol. Despite increased endogenous cholesterol synthesis, the concentration of serum cholesterol is reduced due to a concurrent increase in LDL-receptor synthesis, which occurs in response to the decreased intestinal cholesterol absorption.¹⁹ Plant sterols reduce serum cholesterol even if there is no cholesterol in the diet, since the uptake of both endogenous cholesterol from the bile and exogenous cholesterol from the diet are inhibited.²⁰ The same effect on serum cholesterol is achieved whether the plant

sterols are consumed only in the morning or if the intake is spread throughout the day.²¹

Cholesterol absorption is usually about 50%, but recent studies have shown that there are large individual variations, and absorption figures between 30% and 80% have been reported.²² On the other hand, the absorption of plant sterols is very low, varying between 0.1% and 5% depending on the molecular structure of the specific plant sterol.²³

PHARMACOLOGICAL EFFECTS OF PLANT STEROLS

For the past 50 years, it has been known that plant sterols in pharmacological doses can lower serum cholesterol. Early trials in man, however, had shown poor effect, probably due to limited enteral solubility. The esterification of plant sterols with fatty acids or emulsification with phospholipids increases solubility 10-fold, which has made it possible to add plant sterols in food processing in gram doses, for example, in “functional foods.”

Margarines enriched with plant sterol esters have been commercially available in Finland since 1995, and their cholesterol-lowering effect has been well documented.²⁴ Plant sterols affect LDL cholesterol but not HDL cholesterol or triglyceride levels.²⁵ The addition of 2 g of plant sterols per day reduces LDL cholesterol by 10% according to a recent meta-analysis of 41 studies.²⁶ The effect levels out with higher doses (>3 g/d). Margarine and dairy products enriched with plant sterols are currently available in many countries. There is also an increasing range of products based on yogurts and meat products.

It has been under debate whether esterified, saturated plant sterols (plant stanols) are more effective than esterified, unsaturated plant sterols. There are several published comparisons showing that the forms are equally effective.^{27,28} In our ileostomy trials, the effect on cholesterol absorption was equivalent between esterified plant sterols and esterified plant stanols.²⁹

The safety of plant sterols in gram doses such as those used in functional foods has also been under debate. In general, margarines enriched with plant sterols/plant stanols have been well tolerated. No side effects were reported in a 1-year, placebo-controlled study of approximately 100 persons receiving 1.8 to 2.6 g of sitostanol-ester enriched margarine.³⁰ Safety aspects of plant sterol enrichment have been discussed in a recent review article, which concluded that since their inception in the marketplace in 1995, no report of any serious side effects of plant sterols has been published.³¹

Finnish researchers have speculated an increased risk for atherosclerosis with high intakes of unsaturated

plant sterols. This is based on observations that individuals with the rare illness sitosterolaemia have high levels of plant sterols in the blood and concurrently show signs of atherosclerosis. A recently published study of 2542 individuals did not find any association between serum concentration of plant sterols and atherosclerosis measured as calcium deposits in the coronary artery.³²

Some researchers have expressed concern over a theoretical risk for increased plant sterol concentrations in the bloodstream, as well as decreased concentrations of fat-soluble vitamins and other bioactive substances in the serum due to uptake inhibition. The serum concentration of fat-soluble carotenoids such as α -carotene, β -carotene, and lycopene decreases somewhat with high plant sterol intake; however, the fat-soluble vitamins A, D, and E (retinol, cholecalciferol, and α -tocopherol) are not similarly affected. The negative effect on the concentration of certain carotenoids may be countered by an increased intake of fruits and vegetables.³³

DIETARY PLANT STEROLS IN EPIDEMIOLOGICAL STUDIES

Together with British researchers, we have recently examined the effects of naturally occurring plant sterols on serum cholesterol in the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) population study in Norfolk, England. This study is comprised of more than 22,000 men and women in the age range of 39 to 79 years.³⁴ A database of plant sterol content in approximately 350 food items and food dishes was used to study the relation between intake of plant sterols from the habitual diet (based on a food frequency questionnaire) and serum cholesterol concentration. The study found an inverse relationship between intake of plant sterols and both total and LDL serum cholesterol corrected for age, body mass index, and energy intake. The relationship remained even after adjusting for intake of dietary fiber and saturated fat.

Based on these results, an increased intake of 200 mg of naturally occurring plant sterols from food would lower serum cholesterol by about 3% in man. The average daily intake of plant sterols in the British population under study was about 300 mg/d for both men and women, with a range of 100 to 700 mg, which is in agreement with a previous study in a Dutch population.³⁵ The difference in total and LDL cholesterol between men and women remained across all quintiles of plant sterol intake and was thus independent of plant sterol intake. It therefore appears that the relatively low amount of plant sterols consumed in our daily diets does in fact have an effect on cholesterol level.

PLANT STEROLS IN OUR DIET

Traditionally, the plant sterol content of foods has not been attributed any great significance for possible effects on the concentration of serum cholesterol. With this article we argue that this is a simplified interpretation of reality. All foods of plant origin contain varied amounts of plant sterols. Over 40 different plant sterols have been identified, with the unsaturated sterols sitosterol, stigmasterol, and campesterol being the most common. In foods, sterols are found mostly as free sterols or bound to fatty acids (esterified plant sterols) or carbohydrates (plant sterol glycosides).

The plant sterol content of a large number of food items is now available.³⁶⁻⁴⁰ The highest amounts are found in various oils of plant origin. Corn oil and rapeseed oil contain high amounts of plant sterols (Table 1). Bread, due its being a base food in many cultures, is an important source of plant sterols. The content of plant sterols in vegetables varies widely. For example, broccoli is a good source of plant sterols, while peas contain considerably lower amounts. Margarine, fruits, and nuts are also relatively good sources of plant sterols. The total average daily intake of plant sterols in a Western diet is estimated to be between 200 and 400 mg/d (considerably higher for vegetarians).

It is not yet clear to what extent the amount of naturally occurring plant sterols in our diet affects serum cholesterol. The effect of products enriched with plant sterols in the diet has been examined in many studies and compared with the same diet without added plant sterols.²⁶ In such a comparison, the plant sterol content of the habitual diet has been disregarded, a factor that has been pointed out by Ostlund.⁴¹ In studies from his group, the cholesterol absorption was found to increase by 40% when plant sterols were removed from wheat germ and corn oil, and when sterols were repleted, cholesterol absorption decreased by 10% to 30%.^{42,43} The amount of plant sterols depleted and repleted was 150 to 300 mg, approximately equal to the daily Western dietary intake. Therefore, the effect of plant sterols in the habitual diet has been previously underestimated. The food industry refines many foods that contain plant sterols, which could reduce their content. Processing edible vegetable oils by bleaching, deodorization, deacidification, and other manipulations may decrease sterol content by 10% to 70%.³⁹ On the other hand, plant sterols do not appear to be affected by food preparation such as cooking.³⁷

The addition of plant stanols to statin treatment has shown an amplification of the lipid-lowering effect of these drugs.⁴⁴ This supports the speculation that even plant sterols occurring naturally in foods give an additive cholesterol-lowering effect when a plant sterol-rich diet is consumed in combination with statin therapy. This diet

requires knowledge of the available food sources of plant sterols. In a recent study, 34 patients with hyperlipidemia were given a diet combining several food items with a very low content of saturated fatty acids or cholesterol but high in dietary fiber with nuts, soy-based protein, and plant sterol-enriched margarine. This diet was associated with an impressive 30% reduction in serum cholesterol in just 4 weeks.⁴⁵ This is directly comparable to the effect of taking 20 mg of lovastatin, and is considerably better than the effect of the reduction of saturated fat intake alone. Unfortunately, the naturally occurring plant sterol content of the test diet was not analyzed but it was likely to be higher than a common Western diet. Epidemiological data indicate that even a minor change, such as exchanging a food item with low plant sterol content with a food that contains higher amounts of plant sterols, can have a meaningful effect on public health. Data from prospective studies is needed to elucidate the importance of plant sterol intake for morbidity and mortality. Such studies are under way, with results expected in the coming years.

PLANT STEROL CONSUMPTION AS PART OF DIETARY COUNSELING

General dietary advice to prevent cardiovascular disease is built on a few principles that can be adapted to increase daily plant sterol intake. This should especially be considered if the LDL-C concentration is the main problem in the cardiovascular disease risk profile.

One of the key messages of “Dietary Guidelines for Americans”⁴⁶ is based on a recommendation to consume a variety of foods and beverages of the basic food groups while choosing foods that limit the intake of saturated and trans fats, cholesterol, added sugars, salt, and alcohol. For example, individuals should consume 6 to 11 servings of the bread, cereal, rice, and pasta group and 5 to 9 servings of vegetables and fruits each day. The general dietary approach would be to choose fiber-rich alternatives, while the specific plant sterol advice would be to increase intake of cereal-based foods such as fiber-rich rye bread or sourdough pumpernickel bread, and to choose fruits and vegetables with higher content of plant sterols.

Table 2 illustrates a classification of regular heart-healthy foods, which of course also includes plant sterol-rich foods, but where the latter have been specifically categorized in the column furthest to the right. A person with a suboptimal or even high LDL-cholesterol concentration who has followed a heart-healthy diet for more than a month may want to choose more of the plant sterol-enriched foods described in the table. Individuals can replace regular white bread with whole wheat or rye bread, change their spread based on butter or olive oil to

Food Group	Recommended Servings per Day	Regular Heart-Healthy Foods	Plant Sterol-Rich Foods
Bread, cereal, rice, pasta	6–11	Regular bread, cereal, rice and pasta	Bread from buckwheat, whole wheat, and/or rye, wheat bran
Vegetables	3–5	Cabbage, carrot, celeriac, fennel, kale, leek, onion, pepper, tomato, turnip	Broccoli, brussel sprouts, cauliflower, olives, wheat germ
Fruits	2–4	Apple, banana, clementine, grapefruit, honeydew melon, kiwi, peach, pear	Passion fruit, figs, orange, pineapple
Milk, yogurt, cheese	2–3	Low-fat alternatives	N/A*
Meat, poultry, fish, dry beans, eggs, nuts	2–3	Low-fat alternatives of meat and poultry, fatty fish, cholesterol reduced eggs/egg whites, cashew nuts, hazelnuts, peanuts, pumpkin seeds, walnuts	Most types of dried beans, almonds, flax seeds, pistachio nuts, sesame seeds, sunflower seeds
Fats, oils, sweets	Use sparingly	Oils and/or spreads based on grape seed and olives	Oils, margarines and/or spreads based on corn, flax, rapeseed (canola), sesame seed, soy, sunflower, and wheat germ

* There are a number of dairy foods enriched with plant sterols, but only natural foods are described here.

something based on corn oil or rapeseed oil, fry in the mentioned oils while cooking, try to consume beans a few times a week, change from walnuts and peanuts as snacks or as salad ingredient to almonds or pistachio nuts, add 1 tablespoon of wheat germ to their morning cereal or at dinner. The combination of these approaches can increase the daily plant sterol intake by a few hundred milligrams.

CONCLUSION

With this article we have provided support that, based on experimental studies on cholesterol metabolism and epidemiological evidence, plant sterols in the diet lower serum cholesterol concentration. Information about dietary sources of plant sterols should be incorporated in dietary counseling for hypercholesterolemia and in non-pharmacological treatment and prophylactic advice in the prevention of heart disease. It should also be considered in the processing of plant sterol-rich foods by the food industry, as an increased intake of plant sterols will help the many hypercholesterolemic subjects in Western populations to reach their blood lipid targets.

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