PLANT STEROL ESTERS/STEROLS
MAY REDUCE THE RISK OF HEART DISEASE

Coronary heart (artery) disease is the leading cause of death not only in Western and Westernized nations, but now also across the globe. In the U.S. alone, the economic cost of cardiovascular disease and stroke combined is estimated to be $351.8 billion in 2003, according to the American Heart Association and the National Heart, Lung and Blood Institute (American Heart Association website: www.americanheart.org). While male gender and a family history of premature heart disease are uncontrollable risk factors for heart disease, several diet-related and lifestyle activities are recognized as risk factors that can be modified. These include high blood cholesterol, cigarette smoking, high blood pressure, diabetes mellitus, obesity and physical inactivity. Extensive research has demonstrated that lowering blood cholesterol, especially the "bad" LDL-cholesterol, can have a significant impact on lowering one's risk of heart attack or stroke. More than 50 years of research has proven that natural plant sterols or "phytosterols", can effectively lower cholesterol.

The leading cause of death*

- Cardiovascular disease (CVD) is the world's leading cause of death, killing more than 16 million people per year, equivalent to about one third of all deaths.
- In the United States, nearly 946,000 people died from CVD in 2000, accounting for almost 40 percent of all deaths.
- In Europe, CVD is associated with the yearly loss of over 4 million lives each year, equivalent to about 50 percent of all deaths.
- Coronary heart disease (CHD) alone, is the most common cause of death in both the US and Europe, contributing to about half of the deaths from CVD.
- High blood cholesterol is estimated to cause more than 4 million deaths, globally, per year
- Poor dietary choices play a role in heart disease; low intakes of fruits and vegetables contribute 31 percent of CHD.

* 2003, American Heart Association web site: www.americanheart.org

Plant sterol esters/sterols – a safe, natural and highly effective intervention

Plant sterols or phytosterols and their esters are a class of natural, fat-like compounds whose chemical structures are very similar to cholesterol. Figure 1. They are found in everyday foods such as vegetables, fruit, legumes, nuts, grains, and cooking oils (including corn, soy, and olive oils). The most common plant sterols are sitosterol, campesterol and stigmasterol. A plant-based diet
rich in phytosterols likely accounts for at least part of the cholesterol-lowering effect of vegetables and polyunsaturated (PUFA) vegetable oils. However, studies have shown that relatively few people in Western nations eat sufficient amounts of fruits and vegetables. In addition, consumers on low-fat diets may be limiting their consumption of naturally occurring sterols.

Extensive human clinical research indicating that plant sterol esters/sterols substantially and consistently lower blood levels of total and low-density lipoprotein (LDL) cholesterol has led to the marketing of these compounds in foods and dietary supplements. Since the late 1990s when phytosterol esters achieved GRAS status (Generally Recognized As Safe), they began being added to food products such as margarine-type spreads, as part of a cholesterol lowering strategy that includes a diet low in saturated fat and cholesterol. In 2000, the U.S. Food and Drug Administration (FDA) approved a specific health claim for reducing the risk of heart disease by manufacturers of sterol ester-containing vegetable oil spreads and salad dressings. Recently, the FDA publicly acknowledged an extension of this health claim for a variety of foods and dietary supplements containing phytosterols and their esters. ("FDA Letter Regarding Enforcement Discretion With Respect to Expanded Use of an Interim Health Claim Rule About Plant Sterol/Stanol Esters and Reduced Risk of Coronary Heart Disease," Feb 14, 2003; www.cfsan.fda.gov/~dms/lab-hlth.html).

In 2000, the European Union (EU) Commission, through the Novel Foods regulations, approved the use of specific phytosterol ester-containing yellow spreads for reducing cholesterol. The product’s label includes a statement that they are intended for people who want to lower their blood cholesterol levels (Official Journal of the European Communities, 8.8.2000, L200/59). Recently, the Scientific Committee on Food (SCF), the health advisory board, expressed their general view on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources. Their conclusion was that phytosterols could be used in other types of food if management measures are provided to avoid sterol intakes exceeding a range of 1-3 g/day.

*Figure 1: Sterol Structures*
U.S. FDA approves heart disease health claim

- “Foods containing at least 0.65 g per serving of vegetable oil sterol esters, eaten twice a day with meals for a daily intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.” (Federal Register Vol. 65, No. 175, September 8, 2000 Rules and Regulations).

- To be eligible for using the health claim, products must provide a minimum of two servings with at least 0.65 grams of plant sterol esters per serving for a total of 1.3 grams of sterol esters.

- These levels represent the lowest effective cholesterol lowering dose from published research studies.

- The health claim also must recommend that the sterol esters/sterols be consumed as part of a diet low in saturated fat and cholesterol.

- 80% of the total sterol content must be composed of sitosterol, campesterol, and stigmasterol.

- In February 2003, the FDA stated it would exercise “enforcement discretion” with regard to the use of the approved health claim on additional phytosterol-containing products. In essence, this was an acknowledgement of expanding the health claim to a variety of foods and supplements with added sterols, stanols and their esters.

How sterol esters/sterols reduce cholesterol levels

Blood cholesterol levels are derived from two sources: endogenous synthesis (made by the body) and animal products in the diet. Normally, the liver produces about 1 gram of cholesterol per day, while our diets typically contribute less than half that amount. Some of the endogenous cholesterol is released with bile into the intestine, where it can be reabsorbed. Phytosterol esters/sterols work by reducing absorption of both cholesterol sources dietary cholesterol and endogenous cholesterol. Phytosterol esters/sterols have chemical structures very similar to cholesterol and interfere with cholesterol absorption.

- Sterol esters are broken apart or cleaved during digestion to deliver free sterols to the intestine, where they compete with cholesterol for absorption.

- Small amounts (0.1–0%) of phytosterols are absorbed into the bloodstream, depending on the specific sterol, compared with an average of about 50% absorbed dietary cholesterol.

- Blood levels of cholesterol are about 100 times greater than blood levels of phytosterols.

- Reduced dietary cholesterol absorption and endogenous resorption lead to lower blood levels of total cholesterol and LDL cholesterol, thereby reducing the risk of coronary heart disease.

- Some research indicates that phytosterol esters/sterols can serve as adjunct therapy to cholesterol-lowering medications, such as fibrates or statins, because they act in a different manner. The use of dietary phytosterol esters/sterols along with statins has been shown to have an additive effect on cholesterol reduction. One study found that statins reduced LDL cholesterol by 32%, and added phytosterol esters further reduced LDL cholesterol by 7 percent, for a total cholesterol reduction of 39 percent. (Simons LA. Am J Cardiol. 2002;90:737).
Highlights of research on esterified sterols

- Researchers have known for more than 50 years that phytosterols can reduce blood cholesterol levels in humans.
- Dozens of clinical studies have found that esterified plant sterols can lower total cholesterol by an average of 6 to 10% and LDL cholesterol by 8 to 15%.
- Esterified plant sterols do not appreciably lower levels of the "good" high-density lipoprotein (HDL) cholesterol. There is no information about desirable ratios.
- In cases of mild to moderate hypercholesterolemia, phytosterols make an ideal first choice for cholesterol management.

**PHYTOSTEROL ESTERS IN MARGARINE-TYPE SPREADS**

**STUDY 1. EFFECTS OF DOSE ON CHOLESTEROL LOWERING**

**Design**
- 100 healthy men and women with normal or slightly elevated cholesterol
- 4 of 5 spreads consumed by each subject in cross-over fashion for 3.5 weeks
- Butter, commercial margarine-type spread, margarine-type spread with 0.83, 1.61 or 3.24 g sterols (1.3, 2.6 or 5.2 g as esters) per day

**Results**
- All three sterol ester-fortified margarines reduced total and LDL cholesterol by 5-10%.
- There were no significant differences in cholesterol lowering between the three doses; therefore, the lowest effective dose was 0.83 g sterols (1.3 g sterol esters) per day.
- HDL cholesterol was unaffected, contributing to improved LDL/HDL ratio.
- Blood levels of lipid-standardized vitamin E and vitamins K and D were unaffected, but some carotenoids were reduced.


**STUDY 2. EFFECT OF PHYTOSTEROL SOURCE ON CHOLESTEROL LOWERING**

**Design**
- 95 healthy men and women with normal or slightly elevated cholesterol
- 4 of 5 spreads consumed by each subject in cross-over fashion for 3.5 weeks
- Commercial margarine-type spread (control), commercial margarine-type spread with stanol esters, test spreads with sterol esters from soybean oil, rice bran oil or sheanut oil.
- 1.5 to 3.3 g sterols (approx. 2.4 to 5.3 g sterol esters) per day

**Results**
- Stanol esters and soybean sterol esters reduced total and LDL cholesterol by 8-13%.
- Spreads made with sterol esters from rice bran oil or sheanut oil were not significantly different from the control spread.
- HDL cholesterol was unaffected, contributing to improved LDL/HDL ratio.
- Blood levels of some carotenoids were reduced.

STUDY 3. EFFECTS IN CHILDREN AT RISK OF PREMATURE HEART DISEASE

Design
- 38 children, ages 7 to 12 years, with familial hypercholesterolemia
- 2 spreads consumed by each subject in cross-over fashion for 8 weeks
  - Margarine-type spread (control) or spread with 1.6 g sterols (2.6 g sterol esters) per day

Results
- Esterified plant sterols reduced total cholesterol levels by 7.4% and LDL cholesterol levels by 10.2%.
- HDL cholesterol was unaffected, contributing to improved LDL/HDL ratio.
- Triglycerides were unaffected, but lipid-standardized vitamins A and E were elevated.
- Blood levels of some carotenoids were reduced.

Comment: Familial hypercholesterolemia is an inherited condition caused by a mutation in the LDL receptor gene. Esterified plant sterols were found to modify high cholesterol levels associated with this genetic risk factor.


STUDY 4. EFFECT OF LONG-TERM USE

Design
- 185 healthy men and women with fasting cholesterol levels less than 310 mg/dL
- 1 of 2 spreads consumed by each subject in parallel fashion for 1 year
  - Margarine-type spread (control) or spread with 1.6 g sterols (2.6 g sterol esters) per day

Results
- Sterol esters in spreads reduced total and LDL cholesterol levels by 4% and 6%, respectively, compared to the control spread.
- Cholesterol reduction was sustained throughout the whole year for both men and women.
- HDL cholesterol, triglycerides and lipoprotein (a) were unaffected.
- Blood levels of some carotenoids were reduced.
- There was no difference between groups in observed adverse events.

Comment: "This study therefore indicates that daily consumption of 1.6 g of plant sterol in the long-term, consistently lowers blood cholesterol levels and does not appear to have any adverse health effects."

PHYTOSTEROLS AND THEIR ESTERS IN FOODS OTHER THAN MARGARINE

STUDY 5. EFFECT OF A SINGLE DAILY DOSE INCORPORATED IN LOW-FAT GROUND BEEF ON CHOLESTEROL LOWERING

Design
- 34 males with elevated total and LDL cholesterol levels
- 2.7 g sterols (4.3 g sterol esters) in ground beef consumed once per day (lunch) by each subject for 4 weeks

Results
- Total and LDL cholesterol levels decreased by 9.3% and 14.6%, respectively, similar to multiple daily doses.
- HDL cholesterol was unaffected, contributing to improved LDL/HDL ratio; triglycerides also were unaffected.
- LDL particle size was unaffected, but the percentage of larger HDL particles was enhanced, which may offer greater protection against atherosclerosis.


STUDY 6. EFFECTS OF FORTIFIED LOW-FAT GRAINS AND SPREADS ON CHOLESTEROL LOWERING

(A) Design
- 22 men and women with elevated cholesterol levels
- Subjects already on low fat, low cholesterol diets
- 2.4 g total sterols (3.8 g sterol esters) or non-esterified stanols as part of three foods (cereal, bread, and margarine), consumed 2 or 3 times per day for 4 weeks.

(A) Results
- Sterol esters significantly reduced total cholesterol by 8.5% compared to 3.5% by stanols.
- Both sterol esters and stanols significantly reduced LDL cholesterol by 13.6% and 8.3%, respectively.
- HDL cholesterol and triglycerides also were unaffected.
- Carotenoid levels were unaffected, but alpha- and gamma- tocopherol levels increased with sterol ester consumption.

(B) Design
- 15 of the same subjects from A
- Subjects already on low fat, low cholesterol diets
- 2 spreads consumed by each subject in cross-over fashion for 4 weeks
- Dairy spread (mixture of butter and oil blends) (control), or dairy spread with 2.4 g sterols (3.8 g sterol esters) per day

(B) Results
- Total and LDL cholesterol levels increased by about 6% with consumption of the dairy spread
- Sterol esters added to the dairy spread reduced total and LDL cholesterol levels by 8.5% and 12.2%, respectively
- While HDL cholesterol levels were unaffected by treatment, triglyceride levels increased with the dairy spread.

Comment: Phytosterols were shown to blunt the cholesterol-raising effect of butter.

STUDY 7. EFFECTS OF ENRICHED LOW-FAT YOGHURT ON CHOLESTEROL LOWERING

(A) Design
- 30 patients with moderately elevated blood cholesterol levels
  - Low fat, low cholesterol diet (AHA Step 1 diet) for 8 weeks before intervention
  - 2 yoghurt-based drinks consumed by each subject in cross-over fashion for 4 weeks
    - Low-fat, low-lactose yoghurt drink (control) or the same drink with 1 g sterols per day

(B) Design
- 11 (of original 30) patients with moderately elevated cholesterol levels
  - Continued low fat, low cholesterol diet (AHA Step 1)
  - Yoghurt drink with 2 g sterols per day consumed for 8 weeks (open study)

Results
- Sterol-fortified low-fat yoghurt drink significantly reduced total and LDL-cholesterol in a dose-response manner.
  - 1 gram/day of sterols reduced total cholesterol by 7% and LDL-cholesterol by 11%
  - 2 grams/day of sterols reduced total cholesterol by 11% and LDL-cholesterol by about 16%
- HDL-cholesterol and triglyceride levels were unaffected by sterols.

Comment: The researchers noted that the cholesterol lowering was similar to the results of some lipid-lowering drugs.


Further Reading:


"The aim of the present review is to examine effects of plant sterol and stanol consumption on absorption, plasma concentration, and excretion of cholesterol and phytosterols in humans. Potential mechanisms of action and toxicity will also be briefly described.*


"Current literature suggests that phytosterols are safe when added to the diet, and measured absorption and plasma levels are very small. Increasing the aggregate amount of phytosterols consumed in a variety of foods may be an important way of reducing population cholesterol levels and preventing coronary heart disease."

"Functional foods enriched with plant sterols and stanols are widely sold. Due to their structural similarity with cholesterol, these additives lower intestinal absorption of both dietary and biliary cholesterol, so that endogenous cholesterol synthesis and LDL-receptor expression increase, whereas LDL production decreases. The overall effect is a reduction in serum LDL-C of 10-15% at daily intakes of 2-3 g of plant sterols or stanols, which are also effective as part of a cholesterol-lowering diet and in combination with a cholesterol-lowering drug."


**Glossary of Terms (from American Heart Association):**

**Arteriosclerosis:** "a variety of conditions that cause artery walls to thicken and lose elasticity." Otherwise known as "hardening of the arteries."

**Atherosclerosis:** "a form of arteriosclerosis in which the inner layers of artery walls become thick and irregular due to deposits of fat, cholesterol and other substances." This "plaque" causes narrowed arteries which reduces blood flow.

**Cardiovascular:** "pertaining to the heart and blood vessels."

**Cardiovascular disease:** high blood pressure, coronary heart disease and stroke.

**Coronary arteries:** "Two arteries arising from the aorta that arch down over the top of the heart, branch and provide blood to the heart muscle."

**Coronary artery disease (CAD):** "Conditions that cause narrowing of the coronary arteries, reducing blood flow to the heart muscle. A type of atherosclerosis."

**Coronary heart disease (CHD):** "Disease of the heart caused by atherosclerotic narrowing of the coronary arteries likely to produce angina pectoris or heart attack."

**Heart attack:** "Death or damage to part of the heart muscle due to an insufficient blood supply. The medical term for heart attack is myocardial infarction. It's also sometimes called a coronary thrombosis or coronary occlusion."

**HDL cholesterol:** "Often called ‘good’ cholesterol because a high level of it seems to protect against heart attack. People with a low HDL cholesterol level (less than 40 mg/dL) have a higher risk of heart disease."

**High Density Lipoprotein (HDL):** "A type of protein believed to transport cholesterol away from the tissues and to the liver, where it can be removed from the bloodstream."

**Hypercholesterolemia:** "High levels of blood cholesterol, a major risk factor for coronary heart disease, heart attack and stroke."
**Hypertriglyceridemia:** "High levels of triglycerides in the blood. A high triglyceride level combined with low HDL cholesterol or high LDL cholesterol seems to speed up atherosclerosis (fatty buildups of plaque in the arteries)."

**Low Density Lipoprotein (LDL):** "A type of protein that transports ‘harmful’ cholesterol in the blood." It’s the major cholesterol carrier in the blood.

**LDL-cholesterol:** Often called ‘bad’ cholesterol. "A high level of LDL cholesterol (160 mg/dL and above) reflects an increased risk of heart disease and stroke."

**Stanols:** the saturated (no double bonds) form of sterols. Hydrogenation of sitosterol transforms this compound into sitostanol.

**Triglyceride:** "The most common type of fat in the body. The body gets triglyceride directly from some foods (fatty acids) and makes it in the liver from other energy sources (carbohydrates, alcohol, and some cholesterol)."

According to the US FDA: "The term ‘phytosterols’ is used as a collective term for plant sterols, and their hydrogenated stanol forms, whether used in the free sterol form or esterified with fatty acids. Phytosterol is a term commonly used by manufacturers and distributors of these substances."

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