International Heart
and Vascular Disease Journal • Volume 1, Number 1, August 2013
Journal of the Cardioprogress Foundation

Phytosterols: another way to reduce LDL cholesterol levels

Bitzur R.*

Author:

Rafael Bitzur, MD, The Bert W Strassburger Lipid Center; Sheba Medical Center; Tel Hashomer, Israel

Summary

Phytosterols are sterols found naturally in various oils from plants. Phytosterols compete with cholesterol for a place in the mixed micelles, needed for cholesterol absorption by the small intestine. As a result, cholesterol absorption, either from food or from bile salts is lowered by about 50%, leading to a lowering of about 10% of blood cholesterol level, despite an increase in hepatic cholesterol synthesis. This reduction is achieved when phytosterols are given both as monotherapy, and in addition to statin therapy. The average Western diet contains about 400–800 mg of phytosterols per day, while the dose needed for lowering the blood cholesterol level is about 2–3 grams per day. Therefore, for the purpose of reducing blood cholesterol, they should be given either as phytosterol-enriched food or as supplements. The reduction in the level of low-density lipoprotein (LDL) cholesterol achieved with phytosterols may reduce the risk of coronary disease by about 25%. For this reason the American Heart Association has recommended the consumption of phytosterols, as part of a balanced diet, for lowering blood cholesterol levels.

High levels of LDL cholesterol is a well known risk factor for atherosclerosis, which is the main cause of mortality in Western countries [1]. Statins are the drugs of choice for people who are at high risk of developing cardiovascular diseases, and who have LDL cholesterol levels higher than recommended [2]. Following recent studies, low LDL cholesterol target levels have been set for high-risk patients. Such target levels mandate the use of high doses of potent statins in many cases [2]. Some of these high-risk patients fail to reach LDL cholesterol target levels even with intensive statin therapy. Moreover, 10–20% of statin-treated patients develop side effects (mainly myopathy), which limit the ability to use intensive statin therapy [3]. Potential therapies in such cases include ezetimibe, bile acid sequestrants and niacin [2]. Another treatment option which gathered renewed interest in recent years is the use of phytosterols. Phytosterols are plant-derives sterols that inhibit the intestinal absorption of cholesterol. This review covers current knowledge on cholesterol absorption and the available data concerning phytosterols efficacy and safety.

Keywords

Phytosterols, sterols, stanols, cholesterol

* Corresponding author. Tel. +972-3-5303486, fax. +972-3-5304431, e-mail: Rafael.Bitzur@sheba.health.gov.il

The mechanism of intestinal cholesterol absorption

The human body contains about 140 grams of cholesterol, and is able to produce its daily need of about 1200 mg [4]. A typical Western diet contains about 300–500 mg of cholesterol per day. Bile acids present another 800–1300 mg of cholesterol daily to the intestine. About half of the cholesterol reaching the intestine from these two sources is absorbed and transferred to the liver [5].

Cholesterol absorption starts with the formation in the intestinal lumen of mixed micelles, which contain cholesterol, bile salts, fatty acids, phospholipids and monoacylglycerols [4]. The micelles enable fatty molecules to cross the hydrophilic layer and reach the brush border, where they are absorbed by the enterocytes. Cholesterol molecules not entering these micelles will not be absorbed.

The second phase of cholesterol absorption involves the selective entrance of cholesterol molecules into the enterocytes, via a sterol transporter. This transporter was recently identified as the Nieman-Pick C1 Like 1 protein (NPC1L1) [6,7]. This protein, which contains a sterol-sensing domain, is expressed mainly in proximal jejunum cells, where most of the cholesterol absorption takes place. This protein is the target of ezetimibe, a drug that inhibits cholesterol absorption [7]. Other sterols, such as phytosterols, are also taken up by the enterocytes using NPC1L1.

Cholesterol absorbed by the enterocytes enters the endoplasmic reticulum, where it is esterified by the enzyme acyl-Coa: cholesterol acyltransferase (ACAT) [8]. The formed cholesterol-ester molecules are packed into chylomicrons and secreted to the lymphatics on their way to the liver. Unlike cholesterol, phytosterols are of no use to the body, and therefore are secreted back to the intestinal lumen. This process is carried out by a heterodimer of two adenosine triphosphate (ATP) binding cassette transporters, ABCG5 and ABCG8 [9]. For this reason, the plasma concentration of phytosterols is lower by several orders of magnitude than that of cholesterol [10].

Phytosterols and their use as cholesterol absorption inhibitors

Phytosterols are plant-specific phytochemicals that are essential components of cell membranes. Phytosterols and their saturated forms (saturation of the double bond at carbon-5), termed phytostanols, are structurally related to cholesterol, although they differ in the complexity of their side chain which is attached to the steroid ring. They are not synthesized by animals and humans and, therefore, always originate from the diet. There are two types of phytosterols: sterols, which have a double bond in the sterol ring; and stanols, which do not have that double bond.

Lipid-rich plant foods such as nuts, legumes and seeds contain a relatively high amount of phytosterols. Over 40 phytosterols have been identified. Of those identified, campesterol, stigmasterol and β-sitosterol account for more than 95% of total phytosterol dietary intake. The typical Western diet contains 400–800 mg of phytosterols per day, of which only a minute amount is absorbed [11]. Because of the low bioavailability of unesterified phytosterols they should be given as esters of fatty acids [12].

Phytosterols have been known to reduce plasma levels of cholesterol since 1953 [13]. The mechanism of cholesterol absorption inhibition by phytosterols involves competition for a place in the mixed micelles, required for intestinal cholesterol absorption, since phytosterols are more hydrophobic and have higher affinity for micelles than cholesterol. As a result, cholesterol absorption (both exogenous from food and endogenous from bile salts) is reduced by about 50%. Reduction of cholesterol absorption leads to reduction of plasma levels of cholesterol, despite a compensatory increase in cholesterol synthesis by the liver [14].

Supplementation with phytosterols in the form of functional foods (margarine, yogurt) or in tablet form reduces plasma LDL cholesterol levels by 10–15%. High-density lipoprotein (HDL) cholesterol and triglyceride levels are unaffected by phytosterols supplementation. The required phytosterols dose to produce a maximal effect on LDL cholesterol levels is 2–3 grams per day, and higher doses do not produce further reductions in LDL cholesterol levels [11,14]. Supplementation with phytosterols is effective when added both to a typical Western diet and to a low-fat diet [14]. For example, in a study of 194 subjects with moderate hypercholesterolemia (LDL cholesterol between 130 and 190 mg/dL), supplementation with 1.6 grams per day of phytosterols in the form of a phytosterols-enriched yogurt reduced LDL cholesterol levels by 9.5% compared to supplementation with a regular yogurt [19].

Addition of phytosterols to patients treated with statins enables a further reduction of LDL cholesterol levels by 7–11% [15–18], a reduction similar to that achieved by doubling the dose of the statin [20]. This further reduction enables more patients to reach their LDL cholesterol target levels. In a study of 84 subjects (both with and without coronary heart disease), supplementation with 1.6 grams per day of phytosterols in the form of a phy-

tosterols-enriched yogurt reduced LDL cholesterol levels by 10% compared to supplementation with a regular yogurt, including in statin-treated patients. About 50% of the subjects treated with phytosterols achieved their LDL cholesterol target levels (less than 130 mg/dL for subjects without and less than 100 mg/dL for subjects with coronary heart disease) compared with only 20% of subjects treated with a regular yogurt [21].

The effect of phytosterols on reduction of cholesterol levels was found to be similar in many subgroups of patients at high risk of cardiovascular morbidity and mortality, such as diabetics [22] and postmenopausal women [27].

A dietary portfolio of cholesterol-lowering foods containing a margarine enriched in phytosterols (providing 1.0 g plant sterols per 1000 kcal) was found to significantly reduce the levels of apolipoprotein B (apo B) and the ratio of apo B to apo A-I, both considered risk factors for atherosclerosis [23].

Recent evidence suggests that inhibition of cholesterol absorption may not be the only mechanism through which phytosterols affect cholesterol levels and atherogenesis [24], since phytosterols do not need to be present in the intestinal lumen simultaneously with cholesterol to inhibit its absorption.

Liver X Receptors (LXRs) α and β are broadly expressed in the body and act as a global regulator of cholesterol homeostasis, mainly by preventing excess cholesterol accumulation in tissues. These LXRs are expressed in the intestine, which suggests that these transcription factors may play a role in intestinal cholesterol metabolism. The induction of LXR by ligand binding enhances the transcription of several members of the ABC gene family such as ABCA1 and ABCG5/ABCG8. Phytosterols have been shown to act as LXR ligands, suggesting that cholesterol metabolism within the enterocytes may change as a result of LXR agonist activity induced by these compounds. Transcriptional ABCA1 activation has been proposed as a mechanism to explain the reduction in intestinal cholesterol absorption induced by phytosterols. Mixed micelles enriched with sitostanol were found to be potent inducers of ABCA1 expression in a model of human intestinal cells. LXR activation may also reduce intestinal cholesterol absorption independently of ABCA1, probably by increasing the intestinal transcription of ABCG5 and ABCG8. Therefore, activation of these efflux transporters could also explain the phytosterol-mediated inhibition of intestinal cholesterol absorption. However, in other studies, transcriptional changes in intestinal ABCA1, ABCG5 and ABCG8 did not correlate with an intestinal cholesterol absorption decrease in phytosterol-treated mice and hamsters, so the question of the significance of this mechanism remains open.

Other studies have proposed that phytosterols may act through an effect on cholesterol esterification and lipoprotein assembly (ACAT), or cholesterol internalization (NPC1L1), but conclusive evidence for these proposed mechanisms is lacking.

Consumption of phytosterols may also reduce oxidative stress, which may exert another beneficial effect on the development of atherosclerosis. Subjects consuming a phytosterols-enriched yogurt had a grater reduction in the levels of the highly atherogenic oxidized LDL compared to control subjects [19]. Phytosterols have also been shown to reduce plasma levels of 8-isoprostane, a measure of oxidative stress [25].

Phytosterols may also have an anti-inflammatory effect. In one study, supplementation with a phytosterols-enriched margarine resulted in a 42% reduction in the level of C-reactive protein (CRP), a marker of inflammation considered by some to be a risk factor for atherosclerosis [26].

In animal models, phytosterols have an anti-atherogenic effect. In a model of transgenic LDL-receptor deficient mice, phytosterols reduced the formation and may even have regressed atherosclerotic plaques [27]. This effect was even noted in mice treated with atorvastatin.

The effect of phytosterols on the incidence of cardiovascular events in humans was not tested. However, other methods of cholesterol absorption inhibition were associated with a reduction in cardiovascular events. In the Program on the Surgical Control of the Hyperlipidemia (POSCH) trial, reduction of cholesterol absorption by a partial intestinal bypass was associated with a reduction in cardiovascular events in patients after a myocardial infarction [28]. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), reduction of cholesterol absorption with cholestyramine was associated with a reduction of cardiovascular events in patients without coronary heart disease [29].

Some safety concerns have been raised about supplementation with phytosterols, since sitosterolemia, a rare genetic disorder characterized by high plasma levels of phytosterols, is associated with a high risk of cardiovascular events. However, plasma phytosterols levels in sitosterolemia are several orders of magnitude higher than the levels seen with supplementation with phytosterols [30].

The absorption of beta-carotene is slightly reduced by phytosterols. The absorption of other lipid-soluble

vitamins, such as alpha-carotene, lycopene, vitamin E, vitamin D and the level of vitamin K dependent clotting factors are unaffected by phytosterols supplementation [31].

Summary

A high level of plasma cholesterol is a significant risk factor for cardiovascular diseases. Reduction of LDL cholesterol with statins reduces morbidity and mortality. In patients who fail to achieve their LDL cholesterol target levels despite maximally tolerated statin therapy, and in patients at low risk for cardiovascular diseases, supplementation with phytosterols may help to reduce LDL cholesterol levels. The *AHA/ACC* secondary prevention guidelines for patients with coronary and other atherosclerotic vascular disease recommend the consumption of up to 2 grams per day of phytosterols, as part of a heart-healthy diet, to help reduce LDL cholesterol levels by 6–15% [32].

Conflict of interest: None declared

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation. 2012;125:e2-e220.
2. Catapano AL, Reiner Z, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217:3-46.
3. Brucker E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients — the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–414.
4. Turley SD, Dietschy JM. Sterol absorption by the small intestine. Curr Opin Lipidol. 2003;14:233–240.
5. Bosner MS, Lange LG, Stenson WF, Ostlund RE. Percent cholesterol absorption in normal women and men quantified with dual stable isotopic tracers and negative ion mass spectrometry. J Lipid Res. 1999;40:302–308.
6. Altmann SW, Davis HR, Zhu L, et al. Nieman-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. Science. 2004;303:1201-1204.
7. Davis HR, Zhu L, Hoos LM, et al. Nieman-Pick C1 like 1 (NPC1L1) is the intestinal phytosterols and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. J Biol Chem. 2004;279:33586-33592.
8. Lammert F, Wang DQ. New insights into the genetic regulation of intestinal cholesterol absorption. Gastroenterology. 2005; 129:718-34.
9. Yu L, Hammer RE, Li-Hawkins J, et al. Disruption of ABCG5 and ABCG8 in mice reveals their crucial role in biliary cholesterol secretion. Proc Natl Acad Sci USA. 2002;99:16237-16242.
10. von Bergmann K, Sudhop T, Lütjohann D. Cholesterol and plant sterol absorption: recent insights. Am J Cardiol. 2005;96(suppl):10D-14D.
11. Kris-Etherton PM, Hecker KD, Andrea Bonanome A, et al. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am J Med. 2002;113:71S–88S.
12. Grundy SM. Stanol esters as a component of maximal dietary therapy in the National Cholesterol Education Program Adult Treatment Panel III report. Am J Cardiol. 2005;96(suppl):47D–50D.
13. Pollak OJ. Reduction of blood cholesterol in man. Circulation. 1953;7:702–706.
14. Law M. Plant sterol and stanol margarines and health. BMJ. 2000;320;861–864.
15. Blair SN, Capuzzi DM, Gottlieb SO, et al. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. Am J Cardiol. 2000;86:46-52.
16. Neil HA, Meijer GW, Roe LS. Randomised controlled trial of use by hypercholesterolaemic patients of a vegetable oil sterol-enriched fat spread. Atherosclerosis. 2001;156:329-327.
17. Simons LA. Additive effect of plant sterol-ester margarine and cerivastatin in lowering low-density lipoprotein cholesterol in primary hypercholesterolemia. Am J Cardiol. 2002;90:737-740.
18. O'Neill FH, Brynes A, Mandeno R, et al. Comparison of the effects of dietary plant sterol and stanol esters on lipid metabolism. Nutr Metab Cardiovasc Dis. 2004;14:133–142.
19. Hansel B, Nicolle C, Lalanne F, et al. Effect of low-fat, fermented milk enriched with plant sterols on serum lipid profile and oxidative stress in moderate hypercholesterolemia. Am J Clin Nutr. 2007;86:790-6.
20. Thompson GR. Additive effects of plant sterol and stanol esters to statin therapy. Am J Cardiol. 2005;96(suppl):37D-39D.
21. Plana N, Nicolle C, Ferre R, et al. Plant sterol-enriched fermented milk enhances the attainment of LDL cholesterol goal in hypercholesterolemic subjects. Eur J Nutr. 2008;47:32-9.
22. Lau VWY, Journoud M, Jones PJH. Plant sterols are efficacious in lowering plasma LDL and non-HDL cholesterol in hypercholesterolemic type 2 diabetic and nondiabetic persons. Am J Clin Nutr. 2005;81:1351-8.
23. Jenkins DJA, Kendall CWC, Marchie A, et al. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. Am J Clin Nutr. 2005;81:380–7.
24. Calpe-Berdiel L, Escolà-Gil JC, Blanco-Vaca F. New insights into the molecular actions of plant sterols and stanols in cholesterol metabolism. Atherosclerosis. 2009;203:18–31.
25. Mannarino E, Pirro M, Cortese C, et al. Effects of a phytosterol-enriched dairy product on lipids, sterols and 8-isoprostane in hypercholesterolemic patients: a multicenter Italian study. Nutr Metab Cardiovasc Dis. 2009;19:84-90.

26. Cater NB, Garcia-Garcia AB, Lena Vega G, Grundy SM. Responsiveness of plasma lipids and lipoproteins to plant stanol esters. Am J Cardiol. 2005;96(suppl):23D–28D.
27. Plat J, Beugels I, Gijbels MJ, et al. Plant sterol or stanol esters retard lesion formation in LDL receptor-deficient mice independent of changes in serum plant sterols. J Lipid Res. 2006;47:2762-71.
28. Buchwald H, Varco RL, Boen JR, et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias. Arch Intern Med. 1998;158:1253-61.
29. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in incidence of coronary heart disease. JAMA. 1984;251:351-364.
30. Plat J, Mensink RP. Plant stanol and sterol esters in the control of blood cholesterol levels: mechanism and safety aspects. Am J Cardiol. 2005;96(suppl):15D-22D.
31. Katan MB, Grundy SM, Jones P, et al. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc. 2003;78(8):965-978.
32. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006;113:2363-72.