



Case Report

Effects of Phytosterol Supplements on Hyperlipidemia: Case Series and Review of the Literature

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Citation: Pulipati VP, Benes LB, Horan MK, Davidson MH (2020) Effects of Phytosterol Supplements on Hyperlipidemia: Case Series and Review of the Literature. Ann Case Report 06: 573. DOI: 10.29011/2574-7754.100573

Received Date: 01 December, 2020; **Accepted Date:** 28 December, 2020; **Published Date:** 31 December, 2020

Abstract

Hyperlipidemia is a well-recognized modifiable risk factor for globally prevalent cardiovascular diseases. Statin therapy with lifestyle changes continues to be the preferred primary intervention for the treatment of atherogenic dyslipidemias and cardiovascular disease risk reduction. In patients with statin-associated side-effects and/or suboptimal lipid control, non-statin therapies and nutraceuticals are used as supplemental therapies with maximally tolerated statins. Phytosterols are bioactive sterols of plant origin that have been increasingly available as nutraceuticals, dietary supplements, and functional foods. They competitively inhibit the absorption of dietary cholesterol from intestinal micelles leading to a decrease in serum cholesterol. Various organizations and committees have acknowledged phytosterols as an adjunct to lipid-lowering therapies with good tolerability and safety. Their utility is most recognized in patients who do not qualify for pharmacotherapy, decline pharmacotherapy, have statin and/or non-statin associated side-effects. Herein, we highlight a single-center experience with phytosterol use in six patients with uncontrolled hyperlipidemia.

Keywords: Cardiovascular diseases; Dietary supplements; Hyperlipidemia; Phytosterols; Nutraceuticals

Abbreviations: ABCG: ATP-binding cassette subfamily G member gene; APOE: Apolipoprotein E; ASCVD: Atherosclerotic cardiovascular disease; CAC: Coronary artery calcification; CK: Serum creatine kinase; CVD: Cardiovascular diseases; DM: Diabetes Mellitus; GRAS: Generally Recognized as Safe; HDL-C: Serum high-density lipoprotein cholesterol; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C: Serum low-density lipoprotein cholesterol; Lp(a): Serum lipoprotein (a); MI: Myocardial infarction; NPC1L1: Niemann-Pick C1-Like 1 protein; OTC: Over-the-counter; PCSK9: Proprotein convertase subtilisin/Kexin type 9; SASE: Statin-associated side effects; TC: Total cholesterol; TG: Serum triglycerides; U.S. FDA: The United States Food and Drug Administration

Introduction

Hyperlipidemia is a well-recognized modifiable risk factor for globally ubiquitous CVD that is the leading cause of morbidity and mortality [1,2]. The growing epidemics of unhealthy lifestyle, metabolic syndrome, DM, and obesity that are associated with adverse lipid alterations prompts an urgent need for interventions

to prevent the worsening of the world-wide CVD burden. Prevalent atherogenic lipid abnormalities include an increase in serum LDL-C, serum TG, serum Lp(a), and a decrease in serum HDL-C [3]. The discovery of statins (HMG-CoA reductase inhibitors) was a remarkable milestone in lipid-lowering pharmacology. To the present day, statins in addition to a healthy lifestyle continue to be the cornerstone for the treatment of atherogenic dyslipidemias and CVD risk reduction. Despite good tolerability and safety profile, statins are sometimes associated with side-effects of variable severity which can lead to suboptimal therapy and poor cholesterol control. Non-statins (ezetimibe, PCSK9 inhibitors, bempedoic acid) and in select cases, nutraceuticals (phytosterols) have been used as a supplement and/or alternative therapy when the maximal dose of statin monotherapy or the maximally tolerated statins are unable to reach the patient-specific optimal LDL-C.

Phytosterols are bioactive sterols of plant origin that are functionally similar to the animal-derived cholesterol with a structural difference in the side chain [4]. The most abundant types of phytosterols are beta-sitosterol, campesterol, and stigmasterol [5]. Dietary sources rich in phytosterols include vegetable oil, vegetable-fat spreads, nuts, seeds, and cereal with an estimated average daily intake of 150 to 450 mg in a typical Western diet [6].

Phytosterols have been demonstrated to competitively inhibit the absorption of dietary cholesterol from intestinal micelles, subsequently leading to a decrease in serum cholesterol levels [7]. Due to favorable lipid-lowering ability, phytosterols have been increasingly available in various forms such as nutraceuticals, dietary supplements, and functional foods [8]. However, despite the promising potential for assisting with hyperlipidemia control, concerns have been raised regarding long-term safety and the overall impact on cardiovascular outcomes. Herein, we highlight a single-center experience with phytosterol use in six patients with uncontrolled hyperlipidemia.

Case 1: A 72-year-old African-American female was referred for management of hyperlipidemia. Past medical history includes mitral valve prolapse and essential hypertension. The patient is a never smoker with no personal or family history of premature CVD. She was initially diagnosed with hyperlipidemia (LDL-C 157 mg/dL, Ref <100 mg/dL) with a 10-year ASCVD risk score of 14% (intermediate risk) at age 61 during routine preventive work-up. She was advised lifestyle changes and moderate-intensity statin. Despite detailed and frequent counseling patient declined statins for the next 10 years due to personal preference. At the time of our evaluation, the patient was asymptomatic and mentioned compliance with a healthy lifestyle. Physical exam revealed a BMI 23 kg/m² with no evidence of xanthoma, xanthelasma, or corneal arcus. Further evaluation for secondary etiologies of hyperlipidemia was unremarkable. The CAC score was zero Agatston. Her repeat estimated 10-year ASCVD risk score was 19% suggestive of intermediate to near-high risk. Despite reassuring CAC score, in the setting of hyperlipidemia and intermediate to high ASCVD risk score she was deemed as a candidate for lipid-lowering therapy. After the patient-clinician discussion, she was offered low to moderate-intensity statin with a target LDL-C <100 mg/dL. She continued to decline statin but expressed interest in trying phytosterols. She was started on monotherapy with chewable plant sterol esters 1.14 grams twice daily with meals. Pre and post-phytosterol lipid profile after 28 weeks of therapy is shown in (Table 1) with a net 26% decrease in LDL-C.

Laboratory data	Pre-phytosterol (no lipid-lowering therapy)	Post-phytosterol (on plant sterol esters# for 28 weeks)
Serum Total Cholesterol Ref: <200 mg/dL	226	204
Serum Low-density lipoprotein Cholesterol Ref: <100 mg/dL	164	122
Serum High-density lipoprotein Cholesterol Ref: >60 mg/dL	68	68
Serum Triglycerides Ref: <150 mg/dL	71	68
# plant sterol esters: 1.14 g per serving twice daily with meals (daily total plant sterol ester intake 2.28 g/day).		

Table 1: Laboratory data for patient 1.

Case 2: A 30-year-old Caucasian female was referred for management of hyperlipidemia. Past medical history includes migraine and acne vulgaris. The patient is a never smoker with no personal history of CVD. Family history of MI in the father at age 40, dyslipidemia in the mother. She was initially diagnosed with hyperlipidemia (LDL-C 187 mg/dL) at age 12 and was advised lifestyle changes. At age 23, she was noted to have persistent hyperlipidemia (LDL-C 163 mg/dL) hence was started on statins. She tried multiple statins over the next few years including the lowest dose of an alternate statin but experienced severe muscle side-effects leading to statin discontinuation. At age 29, she declined re-trial with low dose statin and started taking OTC lipid-lowering supplements (red yeast rice, L-methyl folate, krill oil) with no significant change in LDL-C. At the time of our evaluation, the patient was asymptomatic, mentioned compliance with OTC supplements, and a healthy lifestyle. The physical exam revealed a BMI of 26 kg/m² with no evidence of xanthoma, xanthelasma, or corneal arcus. Further evaluation for secondary etiologies of hyperlipidemia revealed a new diagnosis of pre-diabetes (A1C 5.9%, Ref <5.7%), the rest of the workup was unremarkable. In the setting of hyperlipidemia and family history of premature CVD, she was deemed as a candidate for lipid-lowering therapy. After patient-clinician discussion, due to the history of SASE, she was offered non-statin therapy with target LDL-C <100 mg/dL. Patient expressed interest in trying phytosterols. She was started on chewable plant sterol esters 1.14 grams twice daily with meals. Pre and post-phytosterol lipid profile after 24 weeks of therapy is shown in (Table 2) with a net 32% decrease in LDL-C.

Laboratory data	Pre-phytosterol (on OTC*)	Post-phytosterol (OTC* + plant sterol esters# for 24 weeks)
Serum Total Cholesterol Ref: <200 mg/dL	265	204
Serum Low-density lipoprotein Cholesterol Ref: <100 mg/dL	193	132
Serum High-density lipoprotein Cholesterol Ref: >60 mg/dL	42	44
Serum Triglycerides Ref: <150 mg/dL	292	289
*OTC, Over-the-counter supplements - red yeast rice, L-methyl folate, krill oil # plant sterol esters: 1.14 g per serving twice daily with meals (daily total plant sterol ester intake 2.28 g/day)		

Table 2: Laboratory data for patient 2.

Case 3: A 64-year-old Asian male was referred for management of hyperlipidemia. The patient had no other medical co-morbidities, is a never smoker with no personal or family history of premature CVD. He was initially noted to have hyperlipidemia (LDL-C 210 mg/dL) at age 53 during routine preventive work-up, prompting lifestyle counseling and initiation of statin therapy. The patient tried multiple statins over the next few years including a lowest dose, alternate day dose and non-statin ezetimibe but experienced severe muscle side-effects with a significant elevation in CK levels. At the time of our evaluation, the patient was asymptomatic and mentioned compliance with a healthy lifestyle. Physical exam revealed a BMI of 21 kg/m² with no evidence of xanthoma, xanthelasma, or corneal arcus. Further evaluation for secondary etiologies of hyperlipidemia was unremarkable. The CAC score was 172 Agatston (representing 80th percentile for the patient’s age, race, and gender). In the setting of hyperlipidemia and significant preclinical atherosclerosis, he was deemed as a candidate for lipid-lowering therapy. After the patient-clinician discussion, due to intolerable side effects with statins and ezetimibe, he was advised to start PCSK9 inhibitors with a target LDL-C <100 mg/dL. Per patient preference, he was initially started on red yeast rice two capsules twice a day with a modest response (LDL-C decreased from 150 to 133 mg/dL) but he experienced muscle cramps hence he self-titrated to one capsule a day. After the re-discussion of benefits, risks, and the need for better LDL-C control, he agreed to try PCSK9 inhibitors. He tolerated three doses of subcutaneous Alirocumab 75mg every 2 weeks with good LDL-C response (LDL-C decreased from 158 to 80 mg/dL). Due to insurance preference, medication was changed to subcutaneous Evolocumab 140mg every 2 weeks. He experienced non-specific intolerable muscular symptoms with Evolocumab. While working on insurance approval for Alirocumab he was started on chewable plant sterol esters 1.14 grams twice daily with meals. After 6 weeks of therapy, his LDL-C decreased from 203 (while on one capsule red yeast rice per day) to 153 mg/dL (while on low dose red yeast rice + plant sterol) with a net 25% decrease in LDL-C.

Case 4: A 66-year-old female was referred for management of hyperlipidemia. The patient had no other significant past medical history. She was a former smoker with 7 pack-year history, quit smoking at age 33. Family history of MI in father at age 44, brother at age 36, when both were active smokers. The patient was initially diagnosed with hyperlipidemia (LDL-C 214 mg/dL) during routine preventive blood work, she was advised lifestyle changes and statin. She tried multiple statins over the next few years including the lowest dose of an alternate statin but experienced severe muscle side-effects leading to statin discontinuation. She was later started on non-statin ezetimibe 10mg daily with a reasonable LDL-C response (while on ezetimibe, LDL-C was 135 mg/dL). At the time of our evaluation, the patient was asymptomatic, mentioned compliance with a healthy lifestyle, and ezetimibe 10mg daily. The physical exam revealed a BMI of 25 kg/m² with no evidence of xanthoma, xanthelasma, or corneal arcus. Further evaluation for secondary etiologies of hyperlipidemia was unremarkable. The CAC score was 43 Agatston (representing the 70th percentile for the patient’s age, race, and gender). In the setting of hyperlipidemia, preclinical atherosclerosis, and family history of premature CVD she was advised to continue ezetimibe 10mg daily, and was suggested re-trial with low dose statin to target LDL-C <100 mg/dL. The patient declined statin re-trial due to prior experience with severe SASE and expressed interest in trying phytosterols. After patient-clinician discussion, she was started on chewable plant sterol esters 1.14 grams twice daily with meals. Pre and post-phytosterol lipid profile after 30 weeks of therapy is shown in (Table 3) with a net 12% decrease in LDL-C.

Laboratory data	Pre-phytosterol (Ezetimibe 10mg daily)	Post-phytosterol (Ezetimibe 10 mg daily + plant sterol esters# for 30 weeks)
Serum Total Cholesterol Ref: <200 mg/dL	200	201
Serum Low-density lipoprotein Cholesterol Ref: <100 mg/dL	135	119
Serum High-density lipoprotein Cholesterol Ref: >60 mg/dL	50	60
Serum Triglycerides Ref: <150 mg/dL	84	114
# plant sterol esters: 1.14 g per serving twice daily with meals (daily total plant sterol ester intake 2.28 g/day)		

Table 3: Laboratory data for patient 4.

Case 5: A 48-year-old Asian male was referred for management of hyperlipidemia. No other significant past medical co-morbidities. The patient is a never smoker with no personal history of CVD. A family history of MI in the mother, age, and smoking status when the event occurred is unclear. The patient was initially diagnosed with hyperlipidemia (LDL-C 150 mg/dL) at age 46 during routine preventive blood work, he was advised lifestyle changes and statin. He tried multiple statins including the lowest dose of an alternate statin but experienced non-specific muscular side-effects and cognitive impairment leading to statin discontinuation. At the time of our evaluation, the patient was asymptomatic, mentioned compliance with a healthy lifestyle. The physical exam revealed a BMI of 31 kg/m² with no evidence of xanthoma, xanthelasma, or corneal arcus. Further evaluation for secondary etiologies of hyperlipidemia was unremarkable. The CAC score was 89 Agatston (representing between 75 and 90 percentiles for the patient’s age and gender). After patient-clinician discussion, in the setting of hyperlipidemia, preclinical atherosclerosis, and family history of CVD he was advised to initiate low dose rosuvastatin 5mg daily, ezetimibe 10mg daily, and chewable plant sterol esters 1.14 grams twice daily with meals with target LDL-C <100 mg/dL. Pre and post-phytosterol lipid profile after 16 weeks of therapy is shown in (Table 4) with a net 71% decrease in LDL-C.

Laboratory data	Pre-phytosterol (no lipid-lowering therapy)	Post-phytosterol (rosuvastatin 5mg daily + ezetimibe 10mg daily + plant sterol esters# for 16 weeks)
Serum Total Cholesterol Ref: <200 mg/dL	248	131
Serum Low-density lipoprotein Cholesterol Ref: <100 mg/dL	182	53
Serum High-density lipoprotein Cholesterol Ref: >60 mg/dL	58	59
Serum Triglycerides Ref: <150 mg/dL	93	95
# plant sterol esters: 1.14 g per serving twice daily with meals (daily total plant sterol ester intake 2.28 g/day)		

Table 4: Laboratory data for patient 5.

Case 6: A 64-year-old Caucasian female was referred for management of hyperlipidemia. Medical history includes moderate aortic stenosis and essential hypertension. The patient is a never smoker with no personal or family history of premature CVD. The patient was initially diagnosed with hyperlipidemia (LDL-C 156 mg/dL) during routine preventive blood work, she was advised lifestyle changes and statin. She tried multiple statins including the lowest dose of an alternate statin but experienced severe muscular side-effects leading to statin discontinuation. At the time of our evaluation, the patient was asymptomatic, mentioned compliance with a healthy lifestyle. The physical exam revealed a BMI of 36.8 kg/m² with no evidence of xanthoma, xanthelasma, or corneal arcus. Further evaluation for secondary etiologies of hyperlipidemia revealed a new diagnosis of pre-diabetes (A1C 6.1%), the rest of the workup was unremarkable. The CAC score was 4 Agatston (representing 43th percentile for the patient’s age and gender). Her estimated 10-

year ASCVD risk score was 9.8% suggestive of intermediate risk. In the setting of hyperlipidemia, preclinical atherosclerosis and intermediate ASCVD risk score she was deemed as a candidate for lipid-lowering therapy. After the patient-clinician discussion, due to prior severe SASE, she was offered non-statin therapy with a target LDL-C <100 mg/dL. She expressed interest in trying phytosterols. She was started on monotherapy with chewable plant sterol esters 1.14 grams twice daily with meals. After 72 weeks of therapy, her LDL-C decreased from 156 to 122 mg/dL (while on plant sterol monotherapy) with a net 22% decrease in LDL-C.

Discussion

As discussed in our case series, common clinical indications for phytosterol therapy include patients with low to moderate ASCVD risk who do not qualify for pharmacotherapy, patients who decline pharmacotherapy, as an adjunct therapy in patients with high CVD risk with suboptimal LDL-C control on maximally tolerated lipid-lowering therapy especially in situations of statin and/or non-statin associated side-effects. In our center, we prescribe plant sterols as three chewable pieces per serving (plant sterol esters 1.14 g per serving) twice daily with meals (daily total plant sterol ester intake 2.28 g/day) manufactured by Piper Biosciences, Los Altos, California. All six patients tolerated plant sterols well without any side effects.

The mechanism of action of phytosterols is not completely understood but has been attributed to the displacement of dietary cholesterol from intestinal micelles, modulation of the expression of lipid regulatory genes through liver X receptor activation, interaction with NPC1L1, ABCG5, ABCG8, and APOE [7]. There have been mixed reports regarding the effect of phytosterols on inflammatory markers and limited evaluation of their effects on endothelial health [9]. Phytosterols are hydrophobic with low water solubility and poor bioavailability, hence esterification with dietary fatty acids has been utilized to facilitate improved incorporation of phytosterols into micelles for lipid-lowering efficacy [10]. The optimal effects were observed when phytosterols were consumed with the main meal and twice daily [10]. The lipid-lowering effect of phytosterol is dose-dependent and plateaus at doses above 3 grams per day due to the saturation of the cholesterol uptake process with an overall LDL-C lowering effect of about 5-15% [6,11,12]. Genetic variations such as CYP7A1 and APOE polymorphisms have been reported to cause inter-individual variability in LDL-C response to phytosterol [13].

Since patients with APOE4 homozygosity tend to have higher dietary cholesterol absorption, they show a prominent reduction in serum cholesterol with phytosterols [14]. Per U.S. FDA approved claims, plant sterol esters of 1.3 grams or more per day have been associated with reduced risk of CVD [15]. The addition of phytosterols to other lipid-lowering therapies have shown

synergistic effects. In a prospective randomized study involving 86 patients to evaluate the effects of the addition of phytosterols to lipid-lowering therapies, the addition of phytosterols 2 grams daily for 4 weeks to atorvastatin 40 mg daily reduced LDL-C by 6.5% and addition to combination therapy (atorvastatin 40mg + ezetimibe 10mg daily) reduced LDL-C by 4% ($p < 0.05$ for all) without additional effects on markers of cholesterol absorption or synthesis [16]. In addition to response equivalent to doubling the dose of statin, phytosterol has been reported to lower TG by 6 to 9% at a dose of 2 grams per day in hypertriglyceridemic patients [9]. Plant stanols are saturated or hydrogenated plant sterols with a relatively poor intestinal absorption compared to plant sterols (0.02-0.3% vs 0.4-5%) [14]. Per U.S. FDA approved claims, plant stanol esters of 3.4 grams or more per day have been associated with reduced risk of CVD [15]. Comparison of plant sterols and stanols at doses less than 3 grams per day showed no significant difference in lipid-lowering efficacy [17].

Per U.S. FDA, phytosterol esters have GRAS status [18]. Common side effects include mild bloating, diarrhea, or constipation. Sitosterolemia, a rare autosomal recessive disorder of ABCG5/ABCG8, causing impaired elimination and substantial accumulation of plant sterols/stanols with subsequent hemolytic abnormalities, xanthomas, and premature atherosclerosis has raised curiosity if phytosterols could be harmful [19]. In sitosterolemia, the serum phytosterol levels are often 20 to 45 times the typical values [20]. Among patients with more commonly occurring heterozygous phytosterolemia (1 in 500 people), the phytosterol challenge did not influence circulating cholesterol levels [21]. The effects of phytosterols on cardiovascular morbidity and mortality have not been well established. In a systemic review and meta-analysis of 17 studies involving 11,182 participants, there was no evidence of an association between serum plant sterol levels and the risk of CVD [22]. The evaluation of the effects of phytosterols on fat-soluble vitamin absorption showed a significant reduction in serum carotene but no effects on vitamin D, vitamin A and vitamin K [20]. In conclusion, over the last few decades, phytosterols have been established to provide a convenient, safe, and modestly efficacious adjunct to lipid-lowering therapies with reproducible effects. The evolving understanding of phytosterol function, metabolism, and interaction with patient-specific factors such as genetics has led to increased awareness and utility of this therapeutic option in clinical practice. Further research on the effects of phytosterols on cardiovascular outcomes is warranted.

Acknowledgment

V.P.P., L.B.B., M.K.H., M.H.D. designed the study; V.P.P. analyzed data; V.P.P., L.B.B., M.H.D. wrote the paper and V.P.P., L.B.B., M.K.H., M.H.D had primary responsibility for final content. All authors read and approved the final manuscript.

Conflicts of Interest

Vishnu Priya Pulipati, MD: No conflicts of interest

Lane B. Benes, MD, FACC: No conflicts of interest

Mary K. Horan, RN, BSN, MS: No conflicts of interest

Michael H. Davidson, MD, FACC, FNLA: Consultant and Speaker for Amgen, Esperion, New Amsterdam, Novo Nordisk, Piper Biosciences, Regeneron, Sanofi

Funding Support

Piper Biosciences, Los Altos, California (Funding limited to publication expenses only)

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