Combined Effects of Ezetimibe and Phytosterols on Cholesterol Metabolism
A Randomized, Controlled Feeding Study in Humans

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**Background**—Both ezetimibe and phytosterols inhibit cholesterol absorption. We tested the hypothesis that the combination of ezetimibe and phytosterols is more effective than ezetimibe alone in altering cholesterol metabolism.

**Methods and Results**—Twenty-one mildly hypercholesterolemic subjects completed a randomized, double-blind, placebo-controlled, triple-crossover study. Each subject received a phytosterol-controlled diet plus (1) ezetimibe placebo + phytosterol placebo, (2) 10 mg/d ezetimibe + phytosterol placebo, and (3) 10 mg/d ezetimibe + 2.5 g phytosterols for 3 weeks each. All meals were prepared in a metabolic kitchen. Primary outcomes were intestinal cholesterol absorption, fecal cholesterol excretion, and low-density lipoprotein cholesterol levels. The combined treatment resulted in significantly lower intestinal cholesterol absorption (598 mg/d; 95% confidence interval [CI], 368 to 828) relative to control (2161 mg/d; 95% CI, 1112 to 3209) and ezetimibe alone (1054 mg/d; 95% CI, 546 to 1561; both P<0.0001). Fecal cholesterol excretion was significantly greater (P<0.0001) with combined treatment (962 mg/d; 95% CI, 757 to 1168) relative to control (505 mg/d; 95% CI, 386 to 625) and ezetimibe alone (794 mg/d; 95% CI, 615 to 973). Plasma low-density lipoprotein cholesterol values during treatment with control, ezetimibe alone, and ezetimibe + phytosterols averaged 129 mg/dL (95% CI, 116 to 142), 108 mg/dL (95% CI, 97 to 119), and 101 mg/dL (95% CI, 90 to 112; P<0.0001 relative to control).

**Conclusion**—The addition of phytosterols to ezetimibe significantly enhanced the effects of ezetimibe on whole-body cholesterol metabolism and plasma low-density lipoprotein cholesterol. The large cumulative action of combined dietary and pharmacological treatment on cholesterol metabolism emphasizes the potential importance of dietary phytosterols as adjunctive therapy for the treatment of hypercholesterolemia.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00863265.

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Key Words: intestinal absorption ■ diet ■ isotopes ■ mass spectrometry ■ randomized controlled trial

Inhibition of intestinal cholesterol absorption (both dietary and biliary cholesterol) represents an effective approach to reduce plasma low-density lipoprotein (LDL) cholesterol. Phytosterols, plant sterols that are structurally similar to cholesterol, reduce cholesterol absorption and LDL cholesterol in humans. Consumption of ≈2 g/d phytosterols reduces LDL cholesterol by 8.8%.1 It is believed that plant sterols reduce cholesterol absorption by competing with cholesterol for micelle formation, thus reducing the amount of cholesterol available for uptake.2 Because of the presence of the apical sterol transporters ABCG5/8, phytosterols themselves are not absorbed to a great extent, supporting an intraintestinal action of phytosterols in reducing cholesterol absorption.

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Ezetimibe is a potent pharmacological inhibitor of intestinal cholesterol absorption that reduces LDL cholesterol by 15% to 20% when given to subjects with primary hypercholesterolemia at a dose of 10 mg/d.3,4 Niemann-Pick Cl–like 1 (NPC1L1) is a key protein expressed in the apical membrane of enterocytes and is responsible for the uptake of both cholesterol and phytosterols into enterocytes.5,6 Ezetimibe blocks cholesterol uptake by inhibiting NPC1L1,7 a mechanism distinct from that of phytosterols.

Because of these different mechanisms of action, it is difficult to predict whether ezetimibe combined with phytosterols will have synergistic or antagonistic effects on cho-
lesterol absorption. By inhibiting the uptake of phytosterols and cholesterol into enterocytes, ezetimibe may increase the effective interactions between phytosterols and cholesterol in the lumen, the key site where phytosterols reduce cholesterol absorption.

In the present study, we tested the hypotheses that, compared with ezetimibe alone, ezetimibe combined with phytosterols will reduce cholesterol absorption, increase fecal cholesterol excretion, and decrease LDL cholesterol. A phytosterol-controlled diet was provided during each 3-week treatment period: (1) ezetimibe placebo+phytosterol placebo, (2) ezetimibe+phytosterol placebo, and (3) ezetimibe+phytosterol supplement.

Methods

Subjects

Healthy subjects with moderately elevated LDL cholesterol levels were recruited from the greater Cache County community of Utah. Eligible subjects were between 18 and 80 years of age with a body mass index between 20.0 and 35.0 kg/m². LDL cholesterol between 100 and 189 mg/dL (averaged from 2 screening visits on different days), and resting blood pressure <160/95 mm Hg; were free of chronic diseases; and were not taking prescription medications known to affect lipid metabolism. The study was approved by the Institutional Review Board at the University of Utah. All subjects were provided written informed consent. The study was conducted at the Center for Advanced Nutrition of Utah State University from April to September 2009. Recruitment was stopped when the anticipated number of subjects had completed it.

Study Design

Twenty-two eligible subjects were randomly assigned to 1 of 6 possible treatment sequences in a randomized, double-blind, placebo-controlled, triple-crossover design. The 3 treatments included (1) ezetimibe placebo+phytosterol placebo, (2) ezetimibe 10 mg/d+phytosterol placebo, and (3) ezetimibe 10 mg/d+phytosterol supplement 1.9 g/2000 kcal. Each treatment period lasted 3 weeks with 1 week between periods. Participants completed a 3- to 5-day run-in period to become familiar with the foods and study requirements. Subjects, clinical investigators, and staff at both universities were masked to the treatment condition. Blinding was done separately for ezetimibe and phytosterols. Ezetimibe and placebo were prepared by Merck, Inc and sent directly to the study site. Phytosterols were prepared at Washington University as soybean oil solutions and were labeled A, B, or C and then incorporated into the diet at Utah State University. Data and patient samples were analyzed at Washington University with the use of coded identifiers.

Phytosterol-Controlled Diet

To control the phytosterol content of the background diet, we used a phytosterol-controlled diet (0.12 g phytosterols/2000 kcal, 159±4.9 mg/d) adapted from a low-phytosterol diet that we previously designed. This enabled us to accurately quantify the effects of ezetimibe alone and ezetimibe plus phytosterol supplements. All foods and beverages were prepared in the Center for Advanced Nutrition metabolic kitchen. The average prescribed energy level (2643±65 kcal/d) for the 9-week feeding period was individualized on the basis of each subject’s estimated resting metabolic rate and physical activity level, with adjustments made if body weight changed. The composition of the diet was 57% carbohydrate, 15% protein, and 28% fat. Participants were required to eat breakfast and dinner at the feeding center during weekdays, with the rest of the meals taken out. Subjects were instructed to consume all provided foods; a limited choice of additional seasonings and beverages was permitted. A multivitamin/multimineral supplement (Equate Complete, Perrigo Co, Allegan, MI) was given daily at dinner.

Ezetimibe and Phytosterol Treatment

Ezetimibe (10 mg/d) or placebo was given once daily. The phytosterol supplement (2.5±0.1 g/d) or placebo was administered in 2 daily beverages, one consumed with breakfast and another with dinner. Each beverage contained Carnation Instant Breakfast, skim milk, vanilla-flavored extract, powdered fiber supplement (Benefiber, Novartis, Parsippany, NJ), and soybean oil, with or without added phytosterol esters.

Analyses

Efficiency of intestinal cholesterol absorption and fecal cholesterol excretion were determined by administering gelatin capsules containing 2 mg [3H]cholesterol (CDN Isotopes, Quebec, Canada) and 1 mg [4,4-D2]sitosterol (Medical Isotopes, Pelham, NH) dissolved in soybean oil twice daily for the last 5 days of each 21-day treatment period. Stool samples were collected on days 20 and 21, and aliquots were saponified, extracted, and analyzed for cholesterol, coprostanol, coprostanone, sitostanol, and bile acids with 5α-cholestan and hydoxycholeic acid as internal standards and using negative and positive ion chemical ionization gas chromatography/mass spectrometry. The results for days 20 and 21 were averaged. The calculations of percent cholesterol absorption, fecal cholesterol excretion, and excretion of cholesterol metabolites have been described previously.11 Fecal bile acids were hydrolyzed in base, extracted, converted to n-butanol esters and trimethylsilyl ethers, and analyzed by gas chromatography/mass spectrometry.12 Fasted blood was collected in the morning on 2 consecutive days at the end of each 3-week treatment period, after a minimum of a 10-hour fast and 48 hours without alcohol. Plasma cholestanol and lathosterol were measured as markers for cholesterol absorption and biosynthesis, respectively; these values were normalized by expressing them relative to plasma total cholesterol concentration.13 Total cholesterol and glycerol-blanked triglycerides were measured by commercial automated enzymatic kits. High-density lipoprotein (HDL) cholesterol was measured in serum after precipitation of apolipoprotein B-containing lipoproteins by dextran sulfate and magnesium14; LDL cholesterol was calculated with the Friedewald equation;15 non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. Plasma phytosterols were analyzed by gas chromatography/mass spectrometry.11

Compliance

Adherence to the controlled diet and phytosterol-supplemented beverages was monitored during meals consumed at the feeding center and by quantification of meals consumed outside the center. Volunteers completed an itemized daily checklist of all foods and beverages included in each of the study meals that were packed and eaten away from the feeding center and listed any nonstudy foods consumed on the same checklist. Uneaten foods or beverages were weighed to determine missed calories. Adherence to ezetimibe treatment was based on returned pill counts.

Statistical Analysis

Assuming an SD of 19.0 mg/dL for plasma LDL cholesterol and an SD of 14.7 mg/dL for the difference in LDL cholesterol between placebo and phytosterol-supplemented conditions,1 a sample size of 20 subjects gives 90% power to detect a 12.9-mg/dL difference between treatments with a significance level of 0.05. To allow for attrition, a balanced randomization scheme was designed by a Washington University statistician for 24 subjects using 6 balanced permutations of 3 treatments in blocks of 5 in which all subjects receive all treatments in random order. All data analysis was performed with SAS software (version 9.2, SAS Institute Inc, Cary, NC). Treatment effects were determined by ANOVA, including sequence, period, treatment-by-period interaction, and a random effect for participant nested within sequence. When the overall ANOVA treatment effect was significant (P<0.05), Tukey-adjusted P values for multiple treatment comparisons are reported. Data were log transformed when appropriate. Data are reported as mean±SE or mean with 95% confidence interval (CI).
Results
Twenty-two subjects (9 women, 13 men; 20 whites, 1 Asian, 1 Hispanic) were randomized. As shown in Figure 1, of the 175 adults assessed for eligibility, 153 were excluded: 75 individuals did not meet inclusion criteria (eg, body mass index or LDL cholesterol outside the inclusion parameters, unstable thyroid or hypertensive disease, exclusionary medications or dietary supplements, diabetes mellitus, elevated triglycerides), 39 declined participation (ie, inability to comply with either the study schedule or the diet, unwilling to take the study medication), and 39 were excluded for other reasons (ie, no response to e-mail or voice mail after initial contact). Of the 22 subjects enrolled, 1 female subject dropped out after 1 treatment period because of a family emergency. Twenty-one subjects completed all 3 treatment periods and were subjected to analysis. They were 47 ± 10 years of age (limits, 23 to 75 years) with a body mass index of 27.7 ± 0.9 kg/m² (limits, 21.5 to 34.7 kg/m²), blood pressure of 121/73 mm Hg, fasting glucose concentration of 87 ± 10 mg/dL, and alanine aminotransferase of 32.1 ± 1.6 U/L. No adverse events were observed. Plasma alanine aminotransferase level was 30.7 ± 2.7 U/L during placebo and rose significantly to 36.2 ± 2.5 U/L (P = 0.02 versus placebo) only during ezetimibe plus phytosterols. Plasma alanine aminotransferase level was not significantly different during ezetimibe alone (36.3 ± 3.6 U/L) compared with placebo (P = 0.06). Fasting plasma glucose (P = 0.20), insulin (P = 0.84), and high-sensitivity C-reactive protein (P = 0.36) were unchanged by the treatments.

Adherence to the diet was excellent, with only 3 of 1323 meals missed throughout the study. Compliance with ezetimibe and its placebo was 100%, and compliance with the phytosterol and placebo beverages was 99%. On average, body weight was stable within 0.7 kg (limits, −2.7 to 0.2 kg) during the 9 weeks of controlled feeding.

Percent cholesterol absorption was 34% lower with ezetimibe alone than with placebo (the Table and Figure 2A). A larger reduction of 53% relative to placebo was observed with the combination of ezetimibe plus phytosterols; this represents a 27% reduction relative to ezetimibe alone. Fecal cholesterol excretion was 64% higher with ezetimibe alone than with placebo (the Table and Figure 2B). The combination of ezetimibe and phytosterols caused a further increase in fecal cholesterol excretion that was 24% higher than with ezetimibe alone and 102% higher than with placebo. Consistent with a reduction in percent cholesterol absorption measured with stable isotopes and gas chromatography/mass spectrometry, the biomarker for cholesterol absorption, cholestanol, was highest with placebo and lowest in response to ezetimibe plus phytosterols (the Table). Moreover, the biomarker for cholesterol biosynthesis, lathosterol, was 52% higher with ezetimibe alone compared with placebo, 65% higher with ezetimibe plus phytosterols relative to placebo, and 9% higher in response to the combined treatment than with ezetimibe alone (the Table). Fecal bile acid excretion tended to be higher on ezetimibe alone compared with placebo (P = 0.04) and was significantly higher with combined treatment relative to placebo (P = 0.002).

Ezetimibe alone reduced plasma LDL cholesterol by 16% (the Table and Figure 2C). The addition of phytosterols to ezetimibe caused a further reduction in LDL cholesterol of 7% relative to ezetimibe alone and 22% relative to placebo. Similarly, ezetimibe alone reduced plasma total cholesterol and non-HDL cholesterol, and additional reductions were observed in response to the combination of ezetimibe and phytosterols. Both ezetimibe alone and ezetimibe plus phytos-
sterols reduced the ratio of LDL to HDL cholesterol compared with the placebo condition, although this ratio did not differ between the 2 ezetimibe conditions. Interestingly, the combined treatment of ezetimibe plus phytosterols reduced plasma triglycerides, whereas ezetimibe alone did not. On the other hand, ezetimibe alone caused a small but statistically significant increase in plasma HDL cholesterol, whereas the combination of ezetimibe and phytosterols did not (the Table).

The plasma concentrations of total phytosterols and all individual phytosterols (expressed relative to total cholesterol concentration) were lower in response to ezetimibe alone compared with placebo (the Table). The addition of phytosterols to ezetimibe caused an increase in total and all phytosterols.

![Figure 2. Effects of ezetimibe alone and in combination with phytosterol supplementation on (A) intestinal cholesterol absorption, (B) fecal cholesterol excretion, and (C) plasma low-density lipoprotein (LDL) cholesterol. Each subject received a phytosterol-controlled diet (159 ± 4.9 mg/d) plus (1) ezetimibe placebo + phytosterol placebo (double placebo), (2) 10 mg/d ezetimibe + phytosterol placebo, and (3) 10 mg/d ezetimibe + phytosterol supplement (2.5 ± 0.1 g/d) for 3 weeks each using a triple-crossover design. Values shown are individual results with means.](http://circ.ahajournals.org/figs/599)
individual phytosterols relative to ezetimibe alone and an increase in all individual phytosterols except sitosterol compared with placebo. Plasma total phytosterols did not differ between placebo and the combined treatment of ezetimibe plus phytosterols (P=0.06).

The treatment by period interaction was significant for the ratio of plasma stigmasterol to total cholesterol (P=0.02) and for plasma triglycerides (P=0.01). However, on multiple comparison testing with Tukey-adjusted P values, no between-period differences within treatment group were significant (P>0.05). The random effect for participant nested within sequence was examined and significant only for fecal excretion (P=0.02). At each treatment condition, excretion values were smaller for participants receiving treatments in the sequence of combination ezetimibe plus phytosterols, ezetimibe alone, and placebo compared with participants receiving treatments in sequences in which ezetimibe alone was directly preceded by the placebo condition. Assuredly, for all outcomes, the period effect was not significant (P>0.05).

Discussion

Intestinal cholesterol absorption is a multistep process that represents an attractive target for reducing LDL cholesterol; this mechanism is distinct from that of statin drugs, which inhibit cholesterol biosynthesis. Phytosterols and the drug ezetimibe each reduce the efficiency of cholesterol absorption by 25% to 54%, but by different mechanisms of action, raising the possibility that they may be therapeutically combined. In this study, we evaluated the combined effects of ezetimibe and phytosterols on cholesterol metabolism using sterol tracers labeled with stable isotopes and a phytosterol-controlled diet. The major finding was that phytosterols enhanced the effects of ezetimibe on reducing cholesterol absorption, increasing cholesterol excretion, and reducing plasma LDL cholesterol.

The ezetimibe dose of 10 mg/d used in our study, which is the standard clinical dose, gives a near-maximal response for reducing LDL cholesterol in dose-ranging trials; likewise, phytosterol supplementation of 2 g/d is also associated with near-peak responsiveness. Therefore, the enhancing effect of phytosterols on ezetimibe is likely to represent complementary mechanisms of action on cholesterol metabolism. Phytosterols act within the gut lumen to reduce the availability of micellar cholesterol, whereas ezetimibe acts in the enterocyte and the liver to inhibit the cholesterol transporter NPC1L1. This enhancing effect of phytosterols also suggests that the action of phytosterols might be independent of the ABCG5/8 transporters in humans, as demonstrated in mice. The small but significant additional reduction in LDL cholesterol observed with the combined treatment in our study differs from the results of a previous open-label trial in which phytosterol supplementation (2 g/d) did not have additional benefits on LDL cholesterol in ezetimibe-treated subjects. Ezetimibe treatment was not masked in that study and the diet was not controlled for phytosterol content.

The fundamental mechanism of action of both ezetimibe and phytosterols is to reduce cholesterol absorption. In our study, cholesterol absorption (measured with stable isotopes and estimated from plasma cholestanol) was reduced in response to ezetimibe alone and was reduced further when phytosterols were combined with ezetimibe treatment. Similarly, adding phytosterols to ezetimibe significantly increased fecal cholesterol excretion, providing further support that phytosterols enhance the effect of ezetimibe on whole-body cholesterol metabolism. The increase in cholesterol biosynthesis (estimated from plasma lathosterol) in response to the combined treatment suggests a compensatory response to relative cholesterol deficiency.

Plasma phytosterol levels were reduced by 40% with ezetimibe alone, even though dietary phytosterol intake was relatively low owing to the phytosterol-controlled diet. With the introduction of phytosterol supplements, the levels rose, but only to levels observed during the placebo condition. This result emphasizes the efficiency with which ezetimibe blocks systemic phytosterol absorption and shows that phytosterols can reduce cholesterol absorption despite being blocked from absorption by ezetimibe. This suggests that the mechanism by which phytosterols reduce cholesterol absorption is independent of that of ezetimibe.

The largest effect of combining ezetimibe and phytosterols was on cholesterol excretion. Whereas the reduction in circulating LDL ranged from 16% with ezetimibe alone to 22% with ezetimibe plus phytosterols and inhibition of cholesterol absorption was 34% (ezetimibe alone) and 53% (combined treatment), the increases in fecal cholesterol excretion were 64% with ezetimibe alone and 103% with ezetimibe plus phytosterols. Recently, the intestine has been demonstrated to play an important role in reverse cholesterol transport through a novel pathway referred to as transintestinal cholesterol excretion. It is possible that ezetimibe and the combined treatment increased cholesterol excretion through this newly discovered pathway. More work is needed to determine the clinical benefits of increasing fecal cholesterol excretion by combining ezetimibe and phytosterols.

Conclusions

The results of the present study clearly demonstrate enhanced effects on intestinal cholesterol absorption, fecal cholesterol excretion, and plasma LDL cholesterol when phytosterol supplementation was combined with the drug ezetimibe. Additional benefits of combining ezetimibe and phytosterols were observed for non-HDL cholesterol. These enhanced effects indicate that ezetimibe and phytosterols have different mechanisms of action on cholesterol metabolism. It is important to determine whether this combined treatment approach will provide better clinical outcomes.

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**Disclosures**

Washington University and Dr Ostlund have a financial interest in Lifeline Technologies, Inc, a startup company commercializing emulsified phytosterols. Emulsified phytosterols and Lifeline products were not used in this work. The other authors report no conflicts.

**References**


**CLINICAL PERSPECTIVE**

The US National Cholesterol Education Program recommends both supplemental phytosterols, categorized as a therapeutic lifestyle change, and drugs, including ezetimibe, for low-density lipoprotein cholesterol reduction. However, relatively little is known about cotreatment with phytosterols and ezetimibe. Is such a combination helpful because both reduce cholesterol absorption, or could differing mechanisms of action vitiate the effectiveness of each? Answering this question is not straightforward because it requires careful control of dietary phytosterols and concomitant measurement of cholesterol absorption and excretion, as well as low-density lipoprotein cholesterol. In this article, we have used a controlled feeding trial incorporating a baseline diet containing phytosterols in the lower range of current consumption and adding ezetimibe and phytosterols to it. The results show that phytosterols given with ezetimibe further reduce low-density lipoprotein cholesterol and result in a substantial increase in fecal cholesterol excretion and reduction in cholesterol absorption efficiency. The expected rise in plasma phytosterols is blunted by ezetimibe. These results show that phytosterols and ezetimibe can be used together without adverse interaction and that their fundamental effects on whole-body cholesterol metabolism complement one another.
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Phytosterol 식이는 Ezetimibe의 콜레스테롤 감소 효과를 증가시킨다: 약물 치료 중에도 식사 조절은 중요하다

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Summary

배경
Ezetimibe와 phytosterol은 둘 다 콜레스테롤 흡수를 억제한다. Ezetimibe 단독 투여보다는 phytosterol과의 병용 투여가 콜레스테롤 흡수를 더 강하게 억제하여 이상지질혈증 대사 개선에 도움이 될 것인가를 연구하였다.

방법 및 결과
21명의 고콜레스테롤혈증 환자를 대상으로 이중맹검, 대조군 비교, 삼중 교차연구를 시행하였다. 모든 환자들은 대사 조절된 phytosterol 제한 식이를 섭취하였다. 환자들은 각 단계마다 3주 동안 (1) ezetimibe placebo+phytosterol placebo, (2) 10mg/d ezetimibe + phytosterol placebo, (3) 10mg/d ezetimibe + 2.5g phytosterol을 섭취하였다. 연구의 일차목표점은 콜레스테롤 장 흡수, 콜레스테롤 대변 배설 그리고 저밀도지단백 콜레스테롤의 혈중 수치였다.

연구 결과, 장에서의 콜레스테롤 흡수의 경우, ezetimibe와 phytosterol 병용 투여(598mg/d)가 대조군(2,161mg/d)이나 ezetimibe 단독 투여(1,054mg/d)에 비해 유의하게 낮은 장 흡수를 보였다(P<0.0001). 대변으로의 콜레스테롤 배설의 경우 역시, ezetimibe와 phytosterol 병용 투여(962mg/d)가 대조군(505mg/d)이나 ezetimibe 단독 투여(794mg/d)에 비해 유의하게 높은 배설률을 보였다(P<0.0001). 혈중 저밀도지단백 콜레스테롤 수치의 경우, ezetimibe와 phytosterol 병용 투여(101mg/dL) 혹은 ezetimibe 단독 투여(108mg/dL)가 대조군(129mg/dL)에 비해 유의하게 낮은 수치를 보였다(P<0.0001).

결론
Ezetimibe에 phytosterol을 추가하여 병용 치료하는 것은 ezetimibe의 콜레스테롤 대사 조절 및 저밀도지단백 콜레스테롤 조절 가능성을 유의하게 개선한다. 이상지질혈증 조절에 있어서 식이 조절과 약물 치료의 병용 요법의 효과를 보면 약물 치료에 추가적인 식이 조절, 특히 phytosterol의 중요성을 알 수 있다.
이 연구에서 ezetimibe에 추가적으로 phytosterol을 투여함에 따라 소장의 콜레스테롤 흡수 감소와 간의 콜레스테롤 합성을 억제하는 두 가지의 효과가 동시에 나타났다. 콜레스테롤 흡수 감소의 경우, ezetimibe 단독 투여는 대조군에 비하여 34% 감소시켰으나, ezetimibe와 phytosterol 병용 투여는 53% 감소시켜서 투여량의 투여는 추가적으로 19% 흡수 감소 효과를 보였다. 콜레스테롤 합성의 경우, ezetimibe 단독 투여는 대조군에 비하여 52% 감소시켰고, ezetimibe와 phytosterol 병용 투여는 65% 감소시켜서 투여량의 투여는 추가적으로 13% 감소 효과를 보였다. 저밀도지단백 콜레스테롤 수치의 경우, ezetimibe 단독 투여는 대조군에 비하여 16% 감소시켰고, ezetimibe와 phytosterol 병용 투여는 22% 감소시켜서 투여량의 투여는 추가적으로 6% 감소 효과를 보였다. 콜레스테롤 흡수 감소와 함께 콜레스테롤을 촉매하는 저밀도지단백 콜레스테롤의 변화를 반영하였으며, 각 항목별 분모가 다르고 ABCG5/8에 의한 phytosterol 재배설이란 변수가 있기 때문에 직접적인 비교는 오직이 초래할 것이다.

Ezetimibe 10mg/d 투여가 저밀도지단백 콜레스테롤을 15-20% 감소시킨다고 알려져 있고, phytosterol 2g/d 투여가 저밀도지단백 콜레스테롤을 약 8.8% 감소시키며, 이는 최대 용량 효과라고 알려져 있기에, 이 연구는 병용 투여에 의해 부가적인 효과를 그대로 얻을 수 있음을 보여준다. Ezetimibe와 phytosterol 모두 콜레스테롤 합성을 억제하기에 병용 투여하였을 때 효과가 반감될 것이라는 데도 불구하고, 이러한 부가적인 효과가 나온 것은 두 제제의 작용기전이 다르기 때문이다. Ezetimibe는 콜레스테롤 흡수를 억제하는 Niemann-Pick C1-like 1(NPC1L1)을 억제하지만, phytosterol은 micelle 형성을 통해 흡수를 억제하여 경쟁적으로 콜레스테롤 흡수를 억제한다. 그럼기에 병용 투여는 유의하게 중성지방을 감소시킨 효과를 보인 것으로 생각된다.

한편으로, ezetimibe 효과에 의해 소장세포 표면에 흡수를 기다리는 콜레스테롤이 많아지면 phytosterol의 경쟁 효과가 감소하여 부가적인 효과를 감소할 것이란 우려도 있지만, 이 연구에서는 그렇지 않은 것을 보여 주었다. Ezetimibe 단독 투여에 비해 추가적인 저밀도지단백 콜레스테롤 감소가 6% 정도이고, LDL/HDL 콜레스테롤 비율에는 큰 변화가 없어서 평가에 비해 효과가 미미하다는 반론도 있다. 하지만, 식이 조절만으로 약물 투여에 추가적인 효과를 6-8% 보인다는 것은 매우 중요한 의미이며, 약물 치료 중인 모든 환자에서 식이 조절의 중요성을 다시 한번 보여 준다. 또한, 혈중 phytosterol의 미미한 증가 이외에는 별다른 부작용이 없다는 것도 phytosterol 식이요법의 중요점이다.

Reference
Combined Effects of Ezetimibe and Phytosterols on Cholesterol Metabolism
A Randomized, Controlled Feeding Study in Humans

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Background—Both ezetimibe and phytosterols inhibit cholesterol absorption. We tested the hypothesis that the combination of ezetimibe and phytosterols is more effective than ezetimibe alone in altering cholesterol metabolism.

Methods and Results—Twenty-one mildly hypercholesterolemic subjects completed a randomized, double-blind, placebo-controlled, triple-crossover study. Each subject received a phytosterol-controlled diet plus (1) ezetimibe placebo + phytosterol placebo, (2) 10 mg/d ezetimibe + phytosterol placebo, and (3) 10 mg/d ezetimibe + 2.5 g phytosterols for 3 weeks each. All meals were prepared in a metabolic kitchen. Primary outcomes were intestinal cholesterol absorption, fecal cholesterol excretion, and low-density lipoprotein cholesterol levels. The combined treatment resulted in significantly lower intestinal cholesterol absorption (598 mg/d; 95% confidence interval [CI], 368 to 828) relative to control (2161 mg/d; 95% CI, 1112 to 3209) and ezetimibe alone (1054 mg/d; 95% CI, 546 to 1561; both \( P < 0.0001 \)). Fecal cholesterol excretion was significantly greater (\( P < 0.0001 \)) with combined treatment (962 mg/d; 95% CI, 757 to 1168) relative to control (505 mg/d; 95% CI, 386 to 625) and ezetimibe alone (794 mg/d; 95% CI, 615 to 973). Plasma low-density lipoprotein cholesterol values during treatment with control, ezetimibe alone, and ezetimibe + phytosterols averaged 129 mg/dL (95% CI, 116 to 142), 108 mg/dL (95% CI, 97 to 119), and 101 mg/dL (95% CI, 90 to 112; \( P < 0.0001 \) relative to control).

Conclusion—The addition of phytosterols to ezetimibe significantly enhanced the effects of ezetimibe on whole-body cholesterol metabolism and plasma low-density lipoprotein cholesterol. The large cumulative action of combined dietary and pharmacological treatment on cholesterol metabolism emphasizes the potential importance of dietary phytosterols as adjunctive therapy for the treatment of hypercholesterolemia.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00863265.

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Key Words: intestinal absorption ■ diet ■ isotopes ■ mass spectrometry ■ randomized controlled trial

Inhibition of intestinal cholesterol absorption (both dietary and biliary cholesterol) represents an effective approach to reduce plasma low-density lipoprotein (LDL) cholesterol. Phytosterols, plant sterols that are structurally similar to cholesterol, reduce cholesterol absorption and LDL cholesterol in humans. Consumption of \( \approx 2 \) g/d phytosterols reduces LDL cholesterol by 8.8%. It is believed that plant sterols reduce cholesterol absorption by competing with cholesterol for micelle formation, thus reducing the amount of cholesterol available for uptake. Because of the presence of the apical sterol transporters ABCG5/8, phytosterols themselves are not absorbed to a great extent, supporting an intraintestinal action of phytosterols in reducing cholesterol absorption.

Clinical Perspective on p 175

Ezetimibe is a potent pharmacological inhibitor of intestinal cholesterol absorption that reduces LDL cholesterol by 15% to 20% when given to subjects with primary hypercholesterolemia at a dose of 10 mg/d. Niemann-Pick C1–like 1 (NPC1L1) is a key protein expressed in the apical membrane of enterocytes and is responsible for the uptake of both cholesterol and phytosterols into enterocytes. Ezetimibe blocks cholesterol uptake by inhibiting NPC1L1, a mechanism distinct from that of phytosterols. Because of these different mechanisms of action, it is difficult to predict whether ezetimibe combined with phytosterols will have synergistic or antagonistic effects on cho-
lesterol absorption. By inhibiting the uptake of phytosterols and cholesterol into enterocytes, ezetimibe may increase the effective interactions between phytosterols and cholesterol in the lumen, the key site where phytosterols reduce cholesterol absorption.

In the present study, we tested the hypotheses that, compared with ezetimibe alone, ezetimibe combined with phytosterols will reduce cholesterol absorption, increase fecal cholesterol excretion, and decrease LDL cholesterol. A phytosterol-controlled diet was provided during each 3-week treatment period: (1) ezetimibe placebo + phytosterol placebo, (2) ezetimibe + phytosterol placebo, and (3) ezetimibe + phytosterol supplement.

Methods

Subjects
Healthy subjects with moderately elevated LDL cholesterol levels were recruited from the greater Cache County community of Utah. Eligible subjects were between 18 and 80 years of age with a body mass index between 20.0 and 35.0 kg/m². LDL cholesterol between 100 and 189 mg/dL (averaged from 2 screening visits on different days), and resting blood pressure <160/95 mm Hg; were free of chronic diseases; and were not taking prescription medications permitted. A multivitamin/multimineral supplement (Equate Complete, Perrigo Co, Allegan, MI) was given daily at dinner.

Study Design
Twenty-two eligible subjects were randomly assigned to 1 of 6 possible treatment sequences in a randomized, double-blind, placebo-controlled, triple-crossover design. The 3 treatments included (1) ezetimibe placebo + phytosterol placebo, (2) ezetimibe 10 mg/d + phytosterol placebo, and (3) ezetimibe 10 mg/d + phytosterol supplement. 1.9 g/2000 kcal. Each treatment period lasted 3 weeks with 1 week between periods. Participants completed a 3- to 5-day run-in period to become familiar with the foods and study requirements. Subjects, clinical investigators, and staff at both universities were masked to the treatment condition. Blinding was done separately for ezetimibe and phytosterols. Ezetimibe and placebo were prepared by Merck, Inc and sent directly to the study site. Phytosterols were prepared at Washington University as soybean oil solutions and were labeled A, B, or C and then incorporated into the diet at Utah State University. Data and patient samples were analyzed at Washington University with the use of coded identifiers.

Phytosterol-Controlled Diet
To control the phytosterol content of the background diet, we used a phytosterol-controlled diet (0.12 g phytosterols/2000 kcal, 159±49 mg/d) adapted from a low-phytosterol diet that we previously designed. This enabled us to accurately quantify the effects of ezetimibe alone and ezetimibe plus phytosterol supplements. All foods and beverages were prepared in the Center for Advanced Nutrition metabolic kitchen. The average prescribed energy level (2643±65 kcal/d) for the 9-week feeding period was individualized on the basis of each subject’s estimated resting metabolic rate and physical activity level, with adjustments made if body weight changed. The composition of the diet was 57% carbohydrate, 15% protein, and 28% fat. Participants were required to eat breakfast and dinner at the feeding center during weekdays, with the rest of the meals eaten away from the feeding center and listed any nonstudy foods or beverages consumed outside the center. Volunteers completed an itemized daily checklist of all foods and beverages included in each of the study meals that were packed and eaten away from the feeding center and listed any nonstudy foods consumed on the same checklist. Unneat foods or beverages were weighed to determine missed calories. Adherence to ezetimibe treatment was based on returned pill counts.

Ezetimibe and Phytosterol Treatment
Ezetimibe (10 mg/d) or placebo was given once daily. The phytosterol supplement (2.5±0.1 g/d) or placebo was administered in 2 daily beverages, one consumed with breakfast and another with dinner. Each beverage contained Carnation Instant Breakfast, skim milk, vanilla-flavored extract, powdered fiber supplement (Benefiber, Novartis, Parsippany, NJ), and soybean oil, with or without added phytosterol esters.

Analyses
Efficiency of intestinal cholesterol absorption and fecal cholesterol excretion were determined by administering gelatin capsules containing 2 mg [H2]cholesterol (CDN Isotopes, Quebec, Canada) and 1 mg [H3]sitostanol (Medical Isotopes, Pelham, NH) dissolved in soybean oil twice daily for the last 5 days of each 21-day treatment period. Stool samples were collected on days 20 and 21, and aliquots were saponified, extracted, and analyzed for cholesterol, coprostanol, sitostanol, and bile acids with 5α-cholestanol and hyodeoxycholic acid as internal standards and using negative and positive ion chemical ionization gas chromatography/mass spectrometry. The results for days 20 and 21 were averaged. The calculations of percent cholesterol absorption, fecal cholesterol excretion, and excretion of cholesterol metabolites have been described previously. Fecal bile acids were hydrolyzed in base, extracted, converted to n-butanol esters and trimethylsilyl ethers, and analyzed by gas chromatography/mass spectrometry. Fasted blood was collected in the morning on 2 nonconsecutive days at the end of each 3-week treatment period, after a minimum of a 10-hour fast and 48 hours without alcohol. Plasma cholesterol and lathosterol were measured as markers for cholesterol absorption and biosynthesis, respectively; these values were normalized by expressing them relative to plasma total cholesterol concentration. Total cholesterol and glycerol-blended triglycerides were measured by commercial automated enzymatic kits. High-density lipoprotein (HDL) cholesterol was measured in serum after precipitation of apolipoprotein B-containing lipoproteins by dextran sulfate and magnesium chloride; LDL cholesterol was calculated with the Friedewald equation; non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. Plasma phytosterols were analyzed by gas chromatography/mass spectrometry.

Compliance
Adherence to the controlled diet and phytosterol-supplemented beverages was monitored during meals consumed at the feeding center and by quantification of meals consumed outside the center. Volunteers completed an itemized daily checklist of all foods and beverages included in each of the study meals that were packed and eaten away from the feeding center and listed any nonstudy foods consumed on the same checklist. Unneat foods or beverages were weighed to determine missed calories. Adherence to ezetimibe treatment was based on returned pill counts.

Statistical Analysis
Assuming an SD of 19.0 mg/dl for plasma LDL cholesterol and an SD of 14.7 mg/dl for the difference in LDL cholesterol between placebo and phytosterol-supplemented conditions, a sample size of 20 subjects gives 90% power to detect a 12.9-mg/dl difference between treatments with a significance level of 0.05. To allow for attrition, a balanced randomization scheme was designed by a Washington University statistician for 24 subjects using 6 balanced permutations of 3 treatments in blocks of 5 in which all subjects receive all treatments in random order. All data analysis was performed with SAS software (version 9.2, SAS Institute Inc, Cary, NC). Treatment effects were determined by ANOVA, including sequence, period, treatment-by-period interaction, and a random effect for participant nested within sequence. When the overall ANOVA treatment effect was significant (P<0.05), Tukey-adjusted P values for multiple treatment comparisons are reported. Data were log transformed when appropriate. Data are reported as mean±SE or mean with 95% confidence interval (CI).
Results

Twenty-two subjects (9 women, 13 men; 20 whites, 1 Asian, 1 Hispanic) were randomized. As shown in Figure 1, of the 175 adults assessed for eligibility, 153 were excluded: 75 individuals did not meet inclusion criteria (eg, body mass index or LDL cholesterol outside the inclusion parameters, unstable thyroid or hypertensive disease, exclusionary medications or dietary supplements, diabetes mellitus, elevated triglycerides), 39 declined participation (ie, inability to comply with either the study schedule or the diet, unwilling to take the study medication), and 39 were excluded for other reasons (ie, no response to e-mail or voice mail after initial contact). Of the 22 subjects enrolled, 1 female subject dropped out after 1 treatment period because of a family emergency. Twenty-one subjects completed all 3 treatment periods and were subjected to analysis. They were 47 ± 3 years of age (limits, 23 to 75 years) with a body mass index of 27.7 ± 0.9 kg/m² (limits, 21.5 to 34.7 kg/m²), blood pressure of 121 ± 1/73 ± 1 mm Hg, fasting glucose concentration of 87 ± 1 mg/dL, and alanine aminotransferase of 32.1 ± 1.6 U/L. No adverse events were observed. Plasma alanine aminotransferase level was 30.7 ± 2.7 U/L during placebo and rose significantly to 36.2 ± 2.5 U/L (P = 0.02 versus placebo) only during ezetimibe plus phytosterols. Plasma alanine aminotransferase level was not significantly different during ezetimibe alone (36.3 ± 3.6 U/L) compared with placebo (P = 0.06). Fasting plasma glucose (P = 0.20), insulin (P = 0.84), and high-sensitivity C-reactive protein (P = 0.36) were unchanged by the treatments.

Adherence to the diet was excellent, with only 3 of 1323 meals missed throughout the study. Compliance with ezetimibe and its placebo was 100%, and compliance with the phytosterol and placebo beverages was 99%. On average, body weight was stable within 0.7 kg (limits, −2.7 to 0.2 kg) during the 9 weeks of controlled feeding.

Ezetimibe alone reduced plasma LDL cholesterol by 16% (the Table and Figure 2C). The addition of phytosterols to ezetimibe caused a further reduction in LDL cholesterol of 7% relative to ezetimibe alone and 22% relative to placebo. Similarly, ezetimibe alone reduced plasma total cholesterol and non-HDL cholesterol, and additional reductions were observed in response to the combination of ezetimibe and phytosterols. Both ezetimibe alone and ezetimibe plus phyto-
sterols reduced the ratio of LDL to HDL cholesterol compared with the placebo condition, although this ratio did not differ between the 2 ezetimibe conditions. Interestingly, the combined treatment of ezetimibe plus phytosterols reduced plasma triglycerides, whereas ezetimibe alone did not. On the other hand, ezetimibe alone caused a small but statistically significant increase in plasma HDL cholesterol, whereas the combination of ezetimibe and phytosterols did not (the Table).

The plasma concentrations of total phytosterols and all individual phytosterols (expressed relative to total cholesterol concentration) were lower in response to ezetimibe alone compared with placebo (the Table). The addition of phytosterols to ezetimibe caused an increase in total and all

![Figure 2](image-url)
individual phytosterols relative to ezetimibe alone and an increase in all individual phytosterols except sitosterol compared with placebo. Plasma total phytosterols did not differ between placebo and the combined treatment of ezetimibe plus phytosterols (P = 0.06).

The treatment by period interaction was significant for the ratio of plasma stigmastanol to total cholesterol (P = 0.02) and for plasma triglycerides (P = 0.01). However, on multiple comparison testing with Tukey-adjusted P values, no between-period differences within treatment group were significant (P > 0.05). The random effect for participant nested within sequence was examined and significant only for fecal excretion (P = 0.02). At each treatment condition, excretion values were smaller for participants receiving treatments in the sequence of combination ezetimibe plus phytosterols, ezetimibe alone, and placebo compared with participants receiving treatments in sequences in which ezetimibe alone was directly preceded by the placebo condition. Assuredly, for all outcomes, the period effect was not significant (P > 0.05).

**Discussion**

Intestinal cholesterol absorption is a multistep process that represents an attractive target for reducing LDL cholesterol; this mechanism is distinct from that of statin drugs, which inhibit cholesterol biosynthesis. Phytosterols and the drug ezetimibe each reduce the efficiency of cholesterol absorption by 25% to 54%, but by different mechanisms of action, raising the possibility that they may be therapeutically combined. In this study, we evaluated the combined effects of ezetimibe and phytosterols on cholesterol metabolism using sterol tracers labeled with stable isotopes and a phytosterol-controlled diet. The major finding was that phytosterols enhanced the effects of ezetimibe on reducing cholesterol absorption, increasing cholesterol excretion, and reducing plasma LDL cholesterol.

The ezetimibe dose of 10 mg/d used in our study, which is the standard clinical dose, gives a near-maximal response for reducing LDL cholesterol in dose-ranging trials; likewise, phytosterol supplementation of 2 g/d is also associated with near-peak responsiveness. Therefore, the enhancing effect of phytosterols on ezetimibe is likely to represent complementary mechanisms of action on cholesterol metabolism. Phytosterols act within the gut lumen to reduce the availability of micellar cholesterol, whereas ezetimibe acts in the enterocyte and the liver to inhibit the cholesterol transporter NPC1L1. This enhancing effect of phytosterols also suggests that the action of phytosterols might be independent of the ABCG5/8 transporters in humans, as demonstrated in mice. The small but significant additional reduction in LDL cholesterol observed with the combined treatment in our study differs from the results of a previous open-label trial in which phytosterol supplementation (2 g/d) did not have additional benefits on LDL cholesterol in ezetimibe-treated subjects. Ezetimibe treatment was not masked in that study and the diet was not controlled for phytosterol content.

The fundamental mechanism of action of both ezetimibe and phytosterols is to reduce cholesterol absorption. In our study, cholesterol absorption (measured with stable isotopes and estimated from plasma cholestanol) was reduced in response to ezetimibe alone and was reduced further when phytosterols were combined with ezetimibe treatment. Similarly, adding phytosterols to ezetimibe significantly increased fecal cholesterol excretion, providing further support that phytosterols enhance the effect of ezetimibe on whole-body cholesterol metabolism. The increase in cholesterol biosynthesis (estimated from plasma lathosterol in response to the combined treatment suggests a compensatory response to relative cholesterol deficiency.

Plasma phytosterol levels were reduced by 40% with ezetimibe alone, even though dietary phytosterol intake was relatively low owing to the phytosterol-controlled diet. With the introduction of phytosterol supplements, the levels rose, but only to levels observed during the placebo condition. This result emphasizes the efficiency with which ezetimibe blocks systemic phytosterol absorption and shows that phytosterols can reduce cholesterol absorption despite being blocked from absorption by ezetimibe. This suggests that the mechanism by which phytosterols reduce cholesterol absorption is independent of that of ezetimibe.

The largest effect of combining ezetimibe and phytosterols was on cholesterol excretion. Whereas the reduction in circulating LDL cholesterol ranged from 16% with ezetimibe alone to 22% with ezetimibe plus phytosterols and inhibition of cholesterol absorption was 34% (ezetimibe alone) and 53% (combined treatment), the increases in fecal cholesterol excretion were 64% with ezetimibe alone and 103% with ezetimibe plus phytosterols. Recently, the intestine has been demonstrated to play an important role in reverse cholesterol transport through a novel pathway referred to as transintestinal cholesterol excretion. It is possible that ezetimibe and the combined treatment increased cholesterol excretion through this newly discovered pathway. More work is needed to determine the clinical benefits of increasing fecal cholesterol excretion by combining ezetimibe and phytosterols.

**Conclusions**

The results of the present study clearly demonstrate enhanced effects on intestinal cholesterol absorption, fecal cholesterol excretion, and plasma LDL cholesterol when phytosterol supplementation was combined with the drug ezetimibe. A additional benefits of combining ezetimibe and phytosterols were observed for non-HDL cholesterol. These enhanced effects indicate that ezetimibe and phytosterols have different mechanisms of action on cholesterol metabolism. It is important to determine whether this combined treatment approach will provide better clinical outcomes.

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CLINICAL PERSPECTIVE
The US National Cholesterol Education Program recommends both supplemental phytosterols, categorized as a therapeutic lifestyle change, and drugs, including ezetimibe, for low-density lipoprotein cholesterol reduction. However, relatively little is known about cotreatment with phytosterols and ezetimibe. Is such a combination helpful because both reduce cholesterol absorption, or could differing mechanisms of action vitiate the effectiveness of each? A nswering this question is not straightforward because it requires careful control of dietary phytosterols and concomitant measurement of cholesterol absorption and excretion, as well as low-density lipoprotein cholesterol. In this article, we have used a controlled feeding trial incorporating a baseline diet containing phytosterols in the lower range of current consumption and adding ezetimibe and phytosterols to it. The results show that phytosterols given with ezetimibe further reduce low-density lipoprotein cholesterol and result in a substantial increase in fecal cholesterol excretion and reduction in cholesterol absorption efficiency. The expected rise in plasma phytosterols is blunted by ezetimibe. These results show that phytosterols and ezetimibe can be used together without adverse interaction and that their fundamental effects on whole-body cholesterol metabolism complement one another.