The lipid-lowering effect of ezetimibe in pure vegetarians

Jacob J. Clarenbach, Michael Reber, Dieter Lütjohann, Klaus von Bergmann, and Thomas Sudhop

Abstract Results of previous studies have shown that ezetimibe (10 mg/day) reduces LDL cholesterol in patients with mild hypercholesterolemia on a normal-cholesterol diet (dietary intake of 200–500 mg/day) by 16–22%. However, the LDL cholesterol-lowering effect of ezetimibe in subjects with an extremely low dietary cholesterol intake (vegetarians) has not been studied. We conducted a randomized, double-blind, placebo-controlled, two-phase crossover study in 18 healthy pure vegetarians to assess the effect of ezetimibe (10 mg/day) on plasma lipids, cholesterol absorption, and its synthesis. Treatment periods lasted 2 weeks each, with an intervening 2 week washout period. Fractional cholesterol absorption was determined using the continuous dual stable isotope feeding method. Mean dietary cholesterol intake in the pure vegetarians was extremely low and averaged 29.4 ± 16.8 and 31.4 ± 14.4 mg/day during the placebo and ezetimibe administration phases, respectively. Fractional cholesterol absorption during the placebo phase was 48.2 ± 8.2% and was decreased by 58% during ezetimibe treatment to 20.2 ± 6.2% (P < 0.001). This change in intestinal cholesterol absorption was followed by a significant reduction in LDL cholesterol of 17.3%. In individuals with extremely low dietary cholesterol intake, treatment with ezetimibe (10 mg/day) leads to a significant reduction of cholesterol absorption and a clinically relevant decrease of plasma LDL cholesterol, comparable to that of subjects with a normal dietary cholesterol intake. Thus, the lipid-lowering effect of ezetimibe is mediated mainly through a reduction of the absorption of endogenous (biliary) cholesterol. — Clarenbach, J. J., M. Reber, D. Lütjohann, K. von Bergmann, and T. Sudhop. The lipid-lowering effect of ezetimibe in pure vegetarians. J. Lipid Res. 2006. 47: 2820–2824.

Supplementary key words cholesterol absorption • cholesterol synthesis • campesterol • sitosterol • lathosterol

Decreasing serum cholesterol with HMG-CoA reductase inhibitors (statins) for the primary and secondary prevention of cardiovascular events has been demonstrated to be a very effective approach in many large-scale clinical trials (1, 2). Recently, the introduction of ezetimibe has given an additional treatment option for those patients who either do not achieve recommended treatment goals with statins alone or do not tolerate treatment with statins or other lipid-lowering drugs. In several clinical trials, it has been shown that ezetimibe (10 mg/day) decreases LDL cholesterol on average by 16–22% (3–5). Ezetimibe acts by reducing the absorption of cholesterol from the intestinal tract. This effect is thought to be mediated by blocking the sterol transporter Niemann-Pick C1-Like 1, located at the brush border membrane of the small intestine (6, 7). However, several other proteins are also involved in the intestinal uptake and transport of cholesterol and might also play a role in the mechanism of action of ezetimibe (8, 9).

We have previously demonstrated that ezetimibe reduces the fractional absorption of dietary cholesterol on average by 54% in subjects with mild to moderate hypercholesterolemia (10). Compared with baseline levels, reduction in total and LDL cholesterol averaged 15.1% and 20.4%, respectively. The subjects enrolled in that study had a dietary cholesterol intake between 200 and 500 mg/day. The concomitant measurements of fecal excretion of neutral sterols indicated that >600 mg/day of neutral sterols in feces during ezetimibe treatment must be of endogenous origin. These results suggest that the reduction of endogenous (biliary) cholesterol absorption by ezetimibe plays a major role in the decrease of total and LDL cholesterol.

To prove this hypothesis, we investigated the effect of ezetimibe on serum lipids, cholesterol absorption, and fecal excretion of neutral and acidic sterols in pure vegetarians with an extremely low dietary cholesterol intake.

METHODS

Study design

This was a randomized, double-blind, placebo-controlled, two-period crossover trial in 18 healthy vegetarians. Eligible subjects underwent a 2 week single-blind placebo run-in period to assess their compliance with a strict vegetarian diet. Upon successful completion of this run-in period, subjects were randomly assigned to one of two treatment sequences: either ezetimibe (10 mg/day) in period 1 and matching placebo in period 2, or...
placebo treatment in period 1 followed by ezetimibe in period 2. Each treatment period lasted 2 weeks, with an intervening 2 week washout period on single-blind placebo treatment.

The primary study end point was the treatment-induced change in intestinal cholesterol absorption. Changes in plasma LDL cholesterol and in indices of endogenous cholesterol and bile acid synthesis were secondary end points. The trial was conducted in full accordance with the Declaration of Helsinki. The trial protocol was approved by the local independent ethics committee. All subjects were informed of the nature and scope of the trial by a physician and gave informed consent before participation.

Subjects

Subjects who reported to be vegetarians for at least 6 months before study enrollment and whose dietary cholesterol intake was <70 mg/day, as assessed by 7 day food records obtained during the single-blind placebo run-in period, were eligible for study participation. Other inclusion criteria were age between 18 and 65 years, body mass index between 17.5 and 29 kg/m², plasma LDL cholesterol < 180 mg/dl, and plasma triglycerides < 250 mg/dl. Female volunteers of child-bearing potential were required to strictly adhere to safe contraceptive methods throughout the entire study. Subjects were excluded who reported a dietary intake of meat and/or eggs within 6 months before the study began. Subjects were also excluded who were on any lipid-lowering medications or who consumed dietary supplements containing fibrin or margarines enriched with phytosterols/phytostanols within 6 months before the study. Other exclusion criteria were a history of endocrine or metabolic disease known to affect plasma lipids or lipoproteins; a history of cardiovascular disease (coronary artery disease, peripheral or cerebral vascular disease, congestive heart failure or cardiac arrhythmias, clinically significant echocardiographic abnormalities including QT intervals > 440 ms); arterial hypertension, defined as systolic or diastolic blood pressure > 160 or 100 mm Hg, respectively; renal malfunction (plasma creatinine > 1.4 mg/dl, nephrotic syndrome, or other renal disease); fasting plasma glucose levels > 126 mg/dl or history of diabetes; a history of intestinal diseases (malabsorption, disorders of gastrointestinal motility, intestinal bypass or resection surgery, or any other abdominal surgery within 6 months before the study); liver transaminase levels greater than twice the upper limit of normal; acute or chronic infection with human immunodeficiency virus or hepatitis B or C virus; and poor mental function or unstable psychiatric disorders. Female subjects were excluded who were pregnant, in whom a pregnancy could not be excluded at the time of enrollment, or who were actively breast-feeding. Subjects were also excluded if they confessed to substance or drug abuse or if they did not pass a urinary drug screening test and/or alcohol breath test at the time of enrollment.

Eighteen healthy vegetarian subjects (14 women and 4 men) were recruited for this trial. The mean age was 26 years (range, 21–33 years), with mean body weight and body mass index averaging 63.3 kg and 21.7 kg/m², respectively. Throughout the study, subjects underwent repeated counseling by an experienced study nurse to ensure their constant compliance with the study medication and the vegetarian diet.

Cholesterol absorption measurement

Fractional cholesterol absorption was assessed during the second week of each treatment period using the continuous dual stable isotope feeding method (11). For this purpose, subjects ingested tracer capsules containing 3 mg of [2H₄]cholesterol and 3 mg of [2H₄]sitostanol three times daily for 7 days during the second week of each treatment period (days 8–14 and days 30–42, respectively). During the final 3 days of each treatment period, stool samples were collected and measurement of intestinal cholesterol absorption was performed by GC-MS from these samples as described previously (11).

Synthesis of cholesterol and bile acids

From the same fecal samples, the fecal excretion of neutral and acidic sterols was calculated with [2H₄]sitostanol as a fecal flow marker. Measurements were carried out by gas-liquid chromatography as described previously (12). Daily fecal excretion rates were calculated from the ratios of neutral and acidic sterols to the deuterium-labeled sitostanol in fecal samples, multiplied by the daily intake of deuterium-labeled sitostanol. Net cholesterol synthesis was then calculated as the sum of daily excretion of neutral and acidic sterols minus the mean dietary intake of cholesterol. Daily sterol intake was assessed from the last 7 days of the placebo run-in period and each of the treatment periods based on daily food diaries. A nutrition database program (Prodi 4.5; WVG) was used to calculate the mean daily cholesterol intake.

Plasma lipids

Blood samples for plasma lipid and lipoprotein analysis were drawn after an overnight fast at the beginning and end of each treatment period. Total cholesterol and triglycerides in plasma were measured by standard enzymatic methods. HDL cholesterol was determined from the supernatant after precipitation of apolipoprotein B-containing lipoproteins. LDL cholesterol was calculated by the Friedewald formula (13).

Noncholesterol sterols

Lathosterol, campesterol, and sitosterol were measured from the same fasting blood samples used for lipid analysis using GC-MS with epicothanol as the internal standard, as described previously (14).

Statistical analysis

Means and standard deviations were assessed using SPSS statistical software. Differences between the two treatment periods were evaluated for significance and carryover effects using modified t-tests appropriate for two-way crossover trials.

RESULTS

All volunteers completed the study and demonstrated excellent compliance with the study procedures based on pill counts and food diaries.

Absorption and synthesis of cholesterol

In all subjects, treatment with ezetimibe led to a reduction of fractional intestinal cholesterol absorption (Fig. 1). During the placebo and ezetimibe treatment phases, cholesterol absorption ranged from 32.1% to 65.8% (48.2 ± 8.2%, mean ± SD) and from 5.8% to 29.7% (20.2 ± 6.2%), respectively. Thus, treatment with ezetimibe resulted in a mean reduction of intestinal cholesterol absorption by 58.0 ± 14.3% (range, 29.7–85.1%).

The results for dietary cholesterol intake, fecal excretion of neutral and acidic sterols, and total endogenous cholesterol synthesis are summarized in Table 1. Mean dietary cholesterol intakes during the placebo and ezetimibe treat-
ment phases were 29 and 31 mg/day, respectively, with no significant difference between the two treatment phases. No subject exceeded a cholesterol intake of >70 mg/day during any of the two double-blind treatment phases.

Compared with placebo, fecal output of total neutral sterols increased by 81% during treatment with ezetimibe ($P < 0.001$). An increase of 35% in fecal excretion of acidic sterols was also observed, although this effect missed the level of statistical significance ($P = 0.052$). Total endogenous cholesterol synthesis increased by 72% on ezetimibe compared with placebo ($P < 0.001$). No significant carryover effects were observed with respect to sequence or period.

Plasma lipoproteins

Plasma lipoproteins are summarized in Table 2. Mean baseline LDL cholesterol averaged 94.2 mg/dl. The mean percentage changes from baseline to end point after 2 weeks of treatment were +13.1% ($P = 0.017$) on placebo and −6.3% ($P = 0.296$) on ezetimibe, resulting in a −17.3% treatment difference ($P < 0.001$). Similar results were obtained for total cholesterol, with a mean baseline value of 182.1 mg/dl. The mean percentage changes from baseline to end point were +4.6% ($P = 0.174$) on placebo and −5.7% ($P = 0.129$) on ezetimibe, resulting in a total difference of −9.9% ($P < 0.001$) on ezetimibe compared with placebo.

We did not detect any correlation between percentage change in cholesterol absorption and reduction in total and LDL cholesterol.

Changes in triglycerides and HDL cholesterol levels were not significantly different between treatment with ezetimibe and placebo. There was, however, a statistically significant 10% decrease in HDL cholesterol during treatment with ezetimibe compared with baseline values. A similar decrease in HDL cholesterol, although not significant, was observed during the placebo treatment period compared with baseline levels.

Plasma noncholesterol sterols

Results are presented in Table 3. The mean plasma concentration of lathosterol increased by 39%, and the ratio of lathosterol to cholesterol, a marker of hepatic HMG-CoA reductase activity (15) and total body cholesterol synthesis (16, 17), increased by 55% on ezetimibe compared with placebo ($P < 0.001$ for both). Treatment with ezetimibe reduced the plasma concentrations of the two plant sterols campesterol and sitosterol by 46% and 39%, respectively ($P < 0.001$ for both). Similar results were obtained for their ratios to cholesterol, with the mean decrease being 41% for the campesterol-to-cholesterol ratio and 33% for the sitosterol-to-cholesterol ratio ($P < 0.001$ for both).

Safety

Treatment with ezetimibe was well tolerated, and there were neither serious adverse events nor clinically relevant increases of laboratory parameters (including no aspartate or alanine aminotransferase increases >3-fold the upper limit of normal and no creatinine phosphokinase increases >2-fold the upper limit of normal).

**DISCUSSION**

Here, we demonstrate that the lipid-lowering effect of ezetimibe in pure vegetarians can be attributed almost exclusively to the inhibition of intestinal absorption of cholesterol that originates from biliary secretion.

In a previous trial conducted in volunteers on a typical Western diet with a daily cholesterol intake between 200 and 500 mg, Sudhop et al. had identified a 54% reduction in intestinal cholesterol absorption by ezetimibe (10 mg/day) compared with placebo treatment (10). In contrast, in the current trial in vegetarians, the mean daily cholesterol intake was considerably lower at only ~30 mg/day (Table 1). However, the mean percentage reduction of intestinal cholesterol absorption by ezetimibe was virtually identical at 58%, indicating that dietary cholesterol load has no influence on the relative inhibition of sterol absorption by ezetimibe. Further studies are needed to determine whether the inhibition of intestinal cholesterol absorption remains constant over longer periods of treatment.

There are typically two sources of cholesterol entering the intestinal tract. Food intake contributes to intestinal cholesterol with amounts ranging from <50 mg/day (in

---

**TABLE 1.** Fractional absorption of cholesterol, excretion of neutral and acidic sterols, and endogenous synthesis of cholesterol after 2 weeks of treatment with ezetimibe (10 mg/day) and placebo in 18 healthy vegetarians

| Parameter                          | Placebo    | Ezetimibe | $P$  |
|------------------------------------|------------|-----------|------|
| Cholesterol intake (mg/day)        | 29.4 ± 16.8| 31.4 ± 14.4| 0.600|
| Fractional cholesterol absorption (%) | 48.2 ± 8.2 | 20.2 ± 6.2 | <0.001|
| Cholesterol synthesis (mg/day)     | 595 ± 154  | 1,022 ± 285| <0.001|
| Neutral sterol excretion (mg/day)  | 461 ± 157  | 834 ± 211  | <0.001|
| Acidic sterol excretion (mg/day)   | 163 ± 74   | 220 ± 122  | 0.052|
reductions of 16–22% in subjects with a nonrestricted cho-
excretion by ezetimibe, it is not surprising that a signifi-
cantly low lipid levels, further reductions were achieved
during treatment with placebo. Despite these
this trial exhibited relatively low levels of total and LDL
the absorption of biliary cholesterol from the intestine.
must be of biliary origin, which demonstrates that, in vege-
table cholesterol had been affected by
increase that would have been observed if only the ab-
tration led to a mean increase in the fecal excretion of neu-
terol disposal (19). However, the role of this pathway in
existence of an important, alternative route for choles-
tine upon activation of the liver X receptor, indicating
As expected, the vegetarian subjects participating in
inability of the body to synthesize plant sterols (27).
finding is attributable to the different absorption rates
more pronounced than the effect on cholesterol. This
led to a significant reduction of plasma plant sterol levels
compared with placebo treatment. We were not able to detect any se-
sequence or carryover effects between the two treatment
periods. Therefore, the significant difference of total and
ldl cholesterol between the two treatment periods as
presented in Table 2 probably reflects the true drug effect.
There were no significant changes in the plasma levels of triglycerides and HDL cholesterol between the two treat-
ment periods. Although it has been reported that beneficial changes can occur (21, 22), they are generally small, and
this study was not powered to detect such small effects.
We observed a significant increase in endogenous cholesterol synthesis during treatment with ezetimibe (Table 1). Similarly, plasma lathosterol and the lathosterol-
to-cholesterol ratio exhibited marked increases (Table 3). These parameters are indicators of hepatic HMG-CoA re-
ductase activity (15) and total endogenous cholesterol synthesis (16, 17). Increases in endogenous cholesterol syn-
thesis have been reported in subjects treated with ezetimibe (10), and they most likely reflect a physiologic response to compensate for the extensive fecal loss of neutral sterols.
As described previously (7, 10, 23), ezetimibe treatment led to a significant reduction of plasma plant sterol levels compared with placebo treatment. In fact, this effect was more pronounced than the effect on cholesterol. This finding is attributable to the different absorption rates of campesterol and sitosterol compared with cholesterol (11, 24), their faster biliary elimination (25, 26), and the inability of the body to synthesize plant sterols (27).
Although it would have been desirable to limit the study population to subjects not ingesting any cholesterol at all

**TABLE 2. Plasma lipoproteins at baseline and after 2 weeks of treatment with ezetimibe (10 mg/day) and placebo in 18 healthy vegetarians**

| Parameter               | Treatment | Baseline Mean | Change from Baseline | Difference between Ezetimibe and Placebo |
|-------------------------|-----------|---------------|----------------------|----------------------------------------|
|                         |           | Mean          | %                    | P                                      | %                     |
| Total cholesterol (mg/dl)| Ezetimibe | 182.1         | 171.7                | −5.7                                   | 0.129                 | −9.9 0.001               |
|                         | Placebo   | 182.1         | 190.5                | 4.6                                    | 0.174                 | −17.3 0.001              |
| LDL cholesterol (mg/dl) | Ezetimibe | 94.2          | 88.3                 | −6.3                                   | 0.296                 | −10.0 0.017              |
|                         | Placebo   | 94.2          | 106.6                | 13.1                                   | 0.017                 | −2.3 0.49                |
| HDL cholesterol (mg/dl) | Ezetimibe | 66.4          | 59.8                 | −10.0                                  | 0.017                 | −7.9 0.053               |
|                         | Placebo   | 66.4          | 61.2                 | 5.2                                    | 0.001                 | −0.2 0.99                |
| Triglycerides (mg/dl)   | Ezetimibe | 107.6         | 118.2                | 9.9                                    | 0.304                 | −0.2 0.99                |
|                         | Placebo   | 107.6         | 118.4                | 10.1                                   | 0.207                 | −0.2 0.99                |

**TABLE 3. Lathosterol, campesterol, and sitosterol and their ratios to cholesterol in plasma after 2 weeks of treatment with ezetimibe (10 mg/day) and placebo in 18 healthy vegetarians**

| Sterol               | Placebo | Ezetimibe | P    |
|----------------------|---------|-----------|------|
| Lathosterol (mg/dl)  | 0.236 ± 0.124 | 0.327 ± 0.160 | <0.001 |
| Campesterol (mg/dl)  | 0.351 ± 0.134 | 0.180 ± 0.074 | <0.001 |
| Sitosterol (mg/dl)   | 0.249 ± 0.089 | 0.153 ± 0.052 | <0.001 |
| Ratio of lathosterol to cholesterol (µg/mg) | 1.212 ± 0.488 | 1.879 ± 0.773 | <0.001 |
| Ratio of campesterol to cholesterol (µg/mg) | 1.874 ± 0.733 | 1.097 ± 0.368 | <0.001 |
| Ratio of sitosterol to cholesterol (µg/mg) | 1.324 ± 0.456 | 0.885 ± 0.251 | <0.001 |
(e.g., pure vegans), we believe that the data presented here provide compelling evidence that the cholesterol-lowering effect of ezetimibe is mediated largely through the inhibition of biliary cholesterol absorption. Further investigations are necessary to define more clearly the influence of dietary cholesterol on the lipid-lowering effects of ezetimibe.

This study was funded in part by a grant of the Clinical Research, Endocrinology and Metabolism Merck Research Laboratories, Medical School Grant Committee for Ezetimibe.

REFERENCES

1. Expert Panel. 2001. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). J. Am. Med. Assoc. 285: 2486–2497.

2. Grundy, S. M., J. I. Cleeman, C. N. Merz, H. B. Brewer, Jr., L. T. Clark, D. B. Hunninghake, R. C. Pasternak, S. C. Smith, Jr., and N. J. Stone. 2004. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 110: 227–239.

3. Bays, H. E., P. B. Moore, M. A. Drehobl, S. Rosenblatt, P. D. Toth, C. A. Dujovne, R. H. Knopp, L. J. Lipka, A. P. LeBeaut, B. Yang, et al. 2001. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin. Ther. 23: 1290–1290.

4. Dujovne, C. A., M. P. Etinger, J. F. McNeer, L. J. Lipka, A. P. LeBeaut, R. Suresh, B. Yang, and E. P. Veltri. 2002. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am. J. Cardiol. 90: 1092–1097.

5. Knopp, R. H., H. Gitter, T. Truitt, H. Bays, C. V. Manion, L. J. Lipka, A. P. LeBeaut, R. Suresh, B. Yang, and E. P. Veltri. 2003. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur. Heart J. 24: 729–741.

6. Altman, S. W., H. R. Davis, Jr., L. J. Zhu, X. Yao, L. M. Hoos, G. Tetzloff, S. P. Iyer, M. Maguire, A. Golovko, M. Zeng, et al. 2004. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science. 305: 1261–1264.

7. Davis, H. R., Jr., L. J. Zhu, L. M. Hoos, G. Tetzloff, M. Maguire, J. Liu, X. Yao, S. P. Iyer, M. H. Lam, E. G. Lund, et al. 2004. Niemann-Pick C1 Like 1 (NPC1LI) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. J. Biol. Chem. 279: 33586–33592.

8. Smart, E. J., R. A. De Rose, and S. A. Farber. 2004. Annexin 2-caveolin 1 complex is a target of ezetimibe and regulates intestinal cholesterol transport. Proc. Natl. Acad. Sci. USA. 101: 3450–3455.

9. Kramer, W., F. Gribig, D. Corsiero, A. Pfenninger, W. Frick, G. Jahne, M. Rhein, W. Wendler, F. Lottspeich, E. O. Hochleitner, et al. 2005. Aminoepipside N (CD13) is a molecular target of the cholesterol absorption inhibitor ezetimibe in the enterocyte brush border membrane. J. Biol. Chem. 280: 1306–1320.

10. Sudhop, T., D. Lütjohann, A. Kodal, M. Igel, D. L. Tribble, S. Shah, I. Perevzvskaya, and K. von Bergmann. 2002. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 106: 1943–1948.

11. Lütjohann, D., C. O. Meese, J. R. Crouse, 3rd, and K. von Bergmann. 1993. Evaluation of deuterated cholesterol and deuterated sitostanol for measurement of cholesterol absorption in humans. J. Lipid Res. 34: 1039–1046.

12. Czubayko, F., B. Beumers, S. Lammensfuss, D. Lütjohann, and K. von Bergmann. 1991. A simplified micro-method for quantification of fecal excretion of neutral and acidic sterols for outpatient studies in humans. J. Lipid Res. 32: 1861–1867.

13. Friedewald, W. T., R. I. Levy, and D. S. Fredrickson. 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 18: 499–502.

14. Lütjohann, D., A. Brzezinka, E. Barth, D. Abramowski, M. Staufenbiel, K. von Bergmann, K. Beyerreuther, G. Muhlhauser, and T. A. Bayer. 2002. Profile of cholesterol-related sterols in aged amyloid precursor protein transgenic mouse brain. J. Lipid Res. 43: 1078–1085.

15. Björkhem, I., T. Miettinen, E. Reihner, S. Ewerth, B. Angelin, and K. Einarsso. 1987. Correlation between serum levels of some cholesterol precursors and activity of HMG-CoA reductase in human liver. J. Lipid Res. 28: 1137–1143.

16. Kempen, H. J., J. F. Galz, J. A. Gevers Leuven, H. A. van der Voort, and M. B. Katan. 1988. Serum lathosterol concentration is an indicator of whole-body cholesterol synthesis in humans. J. Lipid Res. 29: 1149–1153.

17. Miettinen, T. À., R. S. Tilvis, and Y. A. Kesaniemi. 1990. Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population. Am. J. Epidemiol. 131: 20–31.

18. Mok, H. Y., K. von Bergmann, and S. M. Grundy. 1979. Effects of continuous and intermittent feeding on biliary lipid outputs in man: application for measurements of intestinal absorption of cholesterol and bile acids. J. Lipid Res. 20: 389–398.

19. Kruit, J. K., T. Plosch, R. Havinga, R. Boerhof, P. H. Groth, A. K. Groen, and F. Kuipers. 2005. Increased fecal neutral sterol loss upon liver X receptor activation is independent of biliary sterol secretion in mice. Gastroenterology. 128: 147–156.

20. Ezzet, F., D. Wexler, P. Stakkevich, T. Kosoglu, J. Patrick, L. Lipka, L. Mellars, E. Veltri, and V. Batra. 2001. The plasma concentration and LDL-C relationship in patients receiving ezetimibe. J. Clin. Pharmacol. 41: 943–949.

21. Knopp, R. H., C. A. Dujovne, A. LeBeaut, L. J. Lipka, R. Suresh, and E. P. Veltri. 2003. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolemia: a pooled analysis from two controlled phase III clinical studies. Int. J. Clin. Pract. 57: 363–368.

22. Cruz-Fernandez, J. M., G. V. Bedarida, J. Adgye, C. Allen, A. O. Johnson-Levonas, and R. Massaad. 2005. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. Int. J. Clin. Pract. 59: 619–627.

23. Salen, G., K. von Bergmann, D. Lütjohann, P. Kwaitovich, J. Kane, S. B. Patel, T. Musliner, P. Stein, and B. Musser. 2004. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. Circulation. 109: 966–971.

24. Heinemann, T., G. Axmim, and K. von Bergmann. 1993. Comparison of intestinal absorption of cholesterol with different plant sterols in man. Eur. J. Clin. Invest. 23: 827–831.

25. Sudhop, T., Y. Sahin, B. Lindenthal, C. Hahn, C. Luers, H. K. Berthold, and K. von Bergmann. 2002. Comparison of the hepatic clearances of campesterol, sitosterol, and cholesterol in healthy subjects suggests that efflux transporters controlling intestinal sterol absorption also regulate biliary secretion. Gut. 51: 860–863.

26. Igel, M., U. Giesa, D. Lütjohann, and K. von Bergmann. 2003. Comparison of the intestinal uptake of cholesterol, plant sterols, and stanols in mice. J. Lipid Res. 44: 533–538.

27. Boberg, K. M., K. Einarsso, and I. Björkhem. 1990. Apparent lack of conversion of sitosterol into C24-bile acids in humans. J. Lipid Res. 31: 1083–1088.