Efficiency of intestinal cholesterol absorption in humans is not related to apoE phenotype

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Abstract The present study investigated the role of apolipoprotein E (apoE) phenotype on intestinal cholesterol absorption and cholesterol synthesis. Studies were carried out in eight subjects homozygous for the apoE4 and 12 subjects homozygous for the E2 allele (six normocholesterolemic volunteers and six patients with type III hyperlipoproteinemia). Cholesterol absorption did not differ between the three groups of subjects and averaged 38 ± 2% (mean ± SEM) in normolipemic E2/2, 37 ± 4% in type III hyperlipemic E2/2, and 41 ± 3% in E4/4 subjects, respectively. Dietary intake of fat and cholesterol had no influence on cholesterol absorption efficiency. A positive correlation between efficiency of cholesterol absorption and the ratio of campesterol to cholesterol in plasma, an indirect marker for cholesterol absorption, was observed after combining the results of the three groups (r = 0.504; P < 0.02). Bile acid and total cholesterol synthesis were also not affected by the different apoE alleles, but the well-known relationship between body weight and cholesterol synthesis was noticed (r = 0.574; P < 0.01). Thus, the present study provides evidence that the efficiency of intestinal absorption and synthesis of cholesterol in humans are not related to the apoE phenotype.

Materials and methods

Experimental design and subjects

This study was carried out with volunteers and patients attending the outpatient clinics of the Department of Internal Medicine, University of Marburg, and the Department of Clinical Pharmacology, University of Bonn, Germany. The primary aim was to compare the cholesterol absorption of subjects with

Supplementary key words biliary acid synthesis • cholesterol synthesis • apolipoprotein E • campesterol

The polymorphism of the human apolipoprotein E (apoE) is determined by three common alleles, E2, E3, and E4, resulting in six phenotypes (1). ApoE alleles strongly affect total cholesterol, LDL-cholesterol, apoB, and apoE concentrations in the population (2–6). The influence of different isoforms of apoE on plasma cholesterol concentrations has been explained by several mechanisms: A) receptor-binding affinities of the different apoE containing lipoproteins (7), B) dietary fat clearance (8), C) difference in the clearance of LDL apoB (9), and D) efficiency of intestinal cholesterol absorption (10–12). A higher intestinal cholesterol absorption efficiency was shown in subjects with at least one E4 allele as compared with subjects homozygous for E3 allele. The apoE3/3 subjects had higher cholesterol absorption than those homo- or heterozygous for the E2 allele (10). However, only four patients with the apoE2 isofrom (one homozygous for the E2 allele), and only one subject homozygous for the E4 allele were studied. In another study, Miettinen et al. (12) found a significant higher absorption in subjects with apoE3 and apoE4 compared with those with apoE2 alleles. This difference disappeared on a low fat low cholesterol diet. Again, only two subjects were homozygous for the Eapoe2 and Eapoe4 allele, respectively. Thus, the role of apoE phenotype on cholesterol absorption efficiency has not been studied systematically. We therefore measured cholesterol absorption efficiency together with cholesterol and bile acid synthesis in subjects homozygous for the e4 and e2 alleles. The latter group was divided into subjects with normal plasma cholesterol and triglycerides, and those patients with familial type III hyperlipoproteinemia. Concomitantly, we measured the plant sterol campesterol in plasma of all subjects. Intestinal absorption of dietary campesterol is directly related to cholesterol absorption (13) and the ratio of plasma campesterol to cholesterol is an indirect marker of the rate of cholesterol absorption (14).
apoE2/2 with the absorption of apoE4/4 carriers. Six normolipemic volunteers (E2/2), six patients with type III hyperlipoproteinemia (E2/2), and eight subjects (E4/4) (six had hypercholesterolemia) participated in the study. None of the subjects received lipid-lowering drugs for at least 6 weeks prior to the study and none had a history of excessive alcohol intake, diabetes, or other endocrine disorders, renal disease, or diseases of the liver or gastrointestinal tract. During the 1-week study, cholesterol absorption and fecal excretion of neutral and acidic sterols were measured. After an overnight fast, blood samples were collected for analysis of plasma lipids. Analysis of noncholesterol sterols was carried out overnight fast, blood samples were collected for analysis of plasma lipids. Analysis of noncholesterol sterols was carried out at the beginning and the end of this week. The study was in accordance with the Helsinki Declaration for Human Studies and the appearance of cholesterol during the passage through the small intestine compared with sitostanol, which served as non-absorbable marker by the following formula:

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\text{Percentage of cholesterol absorption} = \frac{\text{Fecal ratio of deuterium-labeled cholesterol and its bacterial degradation products coprostanol, coprostanone, and deuterium-labeled sitostanol, and from the ratio of deuterium-labeled cholesterol and sitostanol in the tracer capsules by gas liquid chromatography-mass spectrometry (GLC-MS), as previously described (16). The percentage of cholesterol absorption was calculated from the disappearance of cholesterol during the passage through the small intestine compared with sitostanol, which served as non-absorbable flow marker by the following formula:}
\]

### TABLE 1. Clinical characteristics and plasma lipid concentrations of normolipemic and hyperlipemic E2/E2 and E4/E4 carriers

| Subject | Apolipoprotein E2/2 (normolipemic, n = 6) | Apolipoprotein E2/2 (hyperlipemic, n = 6) | Apolipoprotein E4/4 (n = 8) |
|---------|------------------------------------------|------------------------------------------|---------------------------|
|         | Age (years)                              | Weight (kg)                              | BMI (kg/m²)               |
|         | 32.3 ± 3.5                               | 77.7 ± 6.0                               | 24.7 ± 1.2                |
|         | Cholesterol (enzymatic) (mg/dl)           | 155 ± 15                                 | 463 ± 70                  |
|         | Cholesterol (glc) (mg/dl)                 | 149 ± 11                                 | 273 ± 27                  |

Values are mean ± SEM.

*BMI, body mass index, [weight (kg)/height² (m)].

**Significantly different from normolipemic E2/2 carriers (P < 0.05).**

*Significantly different from normolipemic E2/2 carriers (P < 0.005).

**Significantly different from E4/4 carriers (P < 0.05).**

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### Analysis of plasma cholesterol and noncholesterol sterols

Concentrations of cholesterol and noncholesterol sterols (cholestanol, lathosterol, and campesterol) in plasma were measured by a modified gas liquid chromatographic method as previously described (13). Briefly, to 0.1 ml of plasma, 50 μg of 5α-cholestanol (Serva Feinbiochemica, Heidelberg, Germany) was added as internal standard. After alkaline hydrolysis, extraction with cyclohexane, and derivatisation to their trimethylsilyl-ethers, the sterols were separated on a 15 m dimethyl crosslinked column (Hewlett Packard HP, Böblingen, Germany).

### Cholesterol absorption

Cholesterol absorption was measured using the continuous isotope feeding method. For this purpose, subjects received stomach soluble capsules containing 3 mg of [26,26,26,27,27,27-H₃]cholesterol and 3 mg of [5,6,22,23-2H₄]sitostanol (Medical Isotopes Inc.) tid for 7 days, and fecal samples were collected on days 5, 6, and 7. The samples were stored at -20°C until analysis. Fractional cholesterol absorption was then calculated from the fecal ratio of deuterium-labeled cholesterol and its bacterial degradation products coprostanol, coprostanone, and deuterium-labeled sitostanol, and from the ratio of deuterium-labeled cholesterol and sitostanol in the tracer capsules by gas liquid chromatography-mass spectrometry (GLC-MS), as previously described (16). The percentage of cholesterol absorption was calculated from the disappearance of cholesterol during the passage through the small intestine compared with sitostanol, which served as non-absorbable flow marker by the following formula:

\[
\text{Cholesterol Absorption} = \frac{\text{Fecal ratio of deuterium-labeled cholesterol and its bacterial degradation products coprostanol, coprostanone, and deuterium-labeled sitostanol, and from the ratio of deuterium-labeled cholesterol and sitostanol in the tracer capsules by gas liquid chromatography-mass spectrometry (GLC-MS), as previously described (16). The percentage of cholesterol absorption was calculated from the disappearance of cholesterol during the passage through the small intestine compared with sitostanol, which served as non-absorbable flow marker by the following formula:}}
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### TABLE 2. Cholesterol absorption in normolipemic and hyperlipemic E2/E2, and E4/E4 carriers

| Subject | Apolipoprotein E2/2 (Normolipemic, n = 6) | Apolipoprotein E2/2 (Hyperlipemic, n = 6) | Apolipoprotein E4/4 (n = 8) |
|---------|------------------------------------------|------------------------------------------|---------------------------|
| 1       | 39.3 ± 2.0                               | 32.3 ± 0.6                               | 38.4 ± 2.5                |
| 2       | 40.3 ± 3.1                               | 43.1 ± 1.3                               | 48.9 ± 2.6                |
| 3       | 45.4 ± 2.1                               | 29.8 ± 2.4                               | 27.3 ± 4.2                |
| 4       | 31.2 ± 2.1                               | 33.2 ± 3.8                               | 33.2 ± 4.6                |
| 5       | 32.1 ± 3.2                               | 32.5 ± 2.2                               | 32.3 ± 4.0                |
| 6       | 38.5 ± 1.2                               | 32.5 ± 5.3                               | 49.8 ± 4.0                |
| 7       |                                           | 52.1 ± 3.3                               | 43.3 ± 2.4                |
| 8       |                                           | 43.3 ± 2.4                               | 40.8 ± 3.3                |

*Mean ± SEM

*Values are the mean ± SEM of 3 consecutive days.
ApoE Type | Energy | Protein | Fat | Carbohydrates | Fiber | Protein | Fat | Carbohydrates
--- | --- | --- | --- | --- | --- | --- | --- | ---
Normolipemic apoE2/2 (n = 6) | 2488 ± 658 | 82 ± 15 | 101 ± 30 | 259 ± 65 | 27 ± 6 | 14.2 ± 1.8 | 37.5 ± 8.3 | 43.7 ± 5.9
Hyperlipemic apoE2/2 (n = 6) | 1968 ± 662 | 82 ± 18 | 76 ± 36 | 205 ± 58 | 41 ± 6 | 17.8 ± 2.8 | 34.2 ± 5.8 | 44.0 ± 6.2
apoE4/4 (n = 8) | 2006 ± 440 | 83 ± 20 | 82 ± 18 | 195 ± 53 | 37 ± 7 | 17.1 ± 2.4 | 38.0 ± 6.7 | 40.1 ± 4.7

Values are mean ± SD (from one week dietary protocol).
*Significantly different from normolipemic E2/2 carriers (P < 0.05).

Cholesterol absorption [%] =

$$\frac{100 \times}{1 - \left( \frac{[\Delta H]_{\text{cholesterol}}^{\text{feco}} + [\Delta H]_{\text{coprostanol}}^{\text{feco}} + [\Delta H]_{\text{sitostanol}}^{\text{feco}}}{[\Delta H]_{\text{sitostanol}}^{\text{feco}}/\text{sitostanol}_{\text{capsule}} - [\Delta H]_{\text{sitostanol}}^{\text{feco}}/\text{sitostanol}_{\text{capsule}} \right)}$$

The cholesterol absorption rates were derived from the mean of day 5, 6, and 7.

**Fecal excretion of neutral and acidic sterols, and cholesterol synthesis**

Fecal excretion of neutral and acidic sterols was measured from the same fecal samples (days 5 to 7) collected for cholesterol absorption. For this purpose, each subject received sitostanol (30 mg tid) as a fecal recovery marker together with the stable isotope markers from day 1 to 7. Measurement of fecal neutral and acidic sterols together with sitostanol was performed by GLC (17). Daily fecal excretion rates of neutral and acidic sterols were then calculated as ratios to sitostanol in stools multiplied by the daily intake of sitostanol by the following formula:

1. Neutral sterol excretion (mg/d) =

$$\frac{(\text{cholesterol} + \text{coprostanol} + \text{coprostanone})(\text{mg/sample})}{\text{sitostanol}(\text{mg/sample})} \times \text{sitostanol intake (mg/d)}$$

2. Acidic sterol excretion (mg/d) =

$$\text{bile acids (mg/sample)} \times \text{sitostanol intake (mg/d)}$$

The net cholesterol balance was calculated as the sum of daily excretion of fecal neutral plus acidic sterols minus the mean of dietary cholesterol intake during this week.

**Dietary intake of cholesterol**

The subjects were trained by an experienced dietician to keep a food diary in which the kind, art of preparation, and amount of the food ingested was entered. All food and beverages were recorded. From the food diaries, the dietary cholesterol, protein, fat, carbohydrates, and fiber intakes were calculated with the computer program (18).

**Statistical analysis**

Results are given as mean ± SEM. The difference in percentage cholesterol absorption, dietary cholesterol intake, fecal excretion neutral and acidic sterols, cholesterol synthesis, plasma lipoproteins and plasma noncholesterol sterols were analyzed using unpaired Student’s t-test. Correlations were calculated by linear regression and stepwise regression analysis. P < 0.05 was considered significant. Data management and statistical analysis were performed using the statistical software SPSS/Windows (SPSS Inc.).

**RESULTS**

The clinical characteristics and plasma concentrations of cholesterol and triglycerides of the subjects included in the study are presented in Table 1. Patients with type III hyperlipoproteinemia had a higher body weight compared with the two other groups, but only the body mass indexes were significantly different. By definition, plasma cholesterol and triglycerides in patients with type III hyperlipoproteinemia were higher compared with normolipemic subjects homozygous for ε2 alleles. They also had higher total cholesterol and triglycerides compared with homozygous ε4 carriers. The latter subjects had significantly higher plasma cholesterol concentrations than normolipemic volunteers homozygous for apoE2. Results of total cholesterol measured either enzymatically or by GLC were identical.

Individual results on cholesterol absorption in the three different groups of subjects are presented in Table 2. Cholesterol absorption ranged from 27% to 53%. In all apoE2/2 carriers the cholesterol absorption averaged 38% and was not significantly different from the absorption in subjects with apoE4/4 (41%). Furthermore, cholesterol absorption in normolipemic apoE2/2 volunteers was not different from the rates in patients with type III hyperlipopro-

**TABLE 3. Dietary intake in normolipemic and hyperlipemic E2/E2, and E4/E4 carriers**

| ApoE Type | Energy | Protein | Fat | Carbohydrates | Fiber | Protein | Fat | Carbohydrates |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Normolipemic apoE2/2 (n = 6) | 2488 ± 658 | 82 ± 15 | 101 ± 30 | 259 ± 65 | 27 ± 6 | 14.2 ± 1.8 | 37.5 ± 8.3 | 43.7 ± 5.9 |
| Hyperlipemic apoE2/2 (n = 6) | 1968 ± 662 | 82 ± 18 | 76 ± 36 | 205 ± 58 | 41 ± 6 | 17.8 ± 2.8 | 34.2 ± 5.8 | 44.0 ± 6.2 |
| apoE4/4 (n = 8) | 2006 ± 440 | 83 ± 20 | 82 ± 18 | 195 ± 53 | 37 ± 7 | 17.1 ± 2.4 | 38.0 ± 6.7 | 40.1 ± 4.7 |

Values are mean ± SD (from one week dietary protocol).
*Significantly different from normolipemic E2/2 carriers.

**TABLE 4. Cholesterol balance in normolipemic and hyperlipemic apolipoprotein E2/E2 and E4/E4 carriers**

| Apolipoprotein | Dietary Cholesterol Intake | Neutral Sterols | Acidic Sterols | Cholesterol Synthesis |
| --- | --- | --- | --- | --- |
| mg/day |
| Normolipemic apoE2/2 (n = 6) | 294 ± 35 | 989 ± 148 | 681 ± 94 | 1376 ± 161 |
| Hyperlipemic apoE2/2 (n = 6) | 188 ± 29 | 902 ± 79 | 644 ± 75 | 1357 ± 136 |
| apoE4/4 (n = 8) | 179 ± 14 | 990 ± 79 | 658 ± 70 | 1469 ± 90 |

Values are the mean ± SEM.
*Significantly different from normolipemic E2/2 carriers.
teinemia. The normolipemic E2/2 subjects had a higher energy intake (~20%) compared with hyperlipidemic E2/2 and E4/4 carriers, the difference was not significant (Table 3). They also had lower fiber (g/d) (ns) and protein intake in percentage of total calories (P < 0.05). However, the efficiency of intestinal cholesterol absorption was independent from the dietary habits, including dietary fat, fiber, and cholesterol intake, as well as age and body weight, although dietary intake of cholesterol was significantly higher in normolipemic E2/2 volunteers compared with the two other groups.

Bile acid and total cholesterol synthesis did not differ between the groups (Table 4). In all subjects, there was a positive correlation between BMI and cholesterol synthesis (r = 0.626; P < 0.005) and between body weight and cholesterol synthesis (r = 0.574; P < 0.01) (Fig. 1).

Plasma concentrations of cholestanol, lathosterol, campesterol, and their ratios to cholesterol are summarized in Table 5. Patients with type III hyperlipoproteinemia had significantly higher concentrations of all noncholesterol sterols compared with normolipemic apoE2/2 carriers. Plasma concentrations of lathosterol in patients with type III hyperlipoproteinemia were also higher compared with subjects with apoE4/4 alleles. In subjects homozygous for e4, all noncholesterolemic plasma sterols were higher than in normolipemic E2/2 volunteers, but these differences were not statistically significant. However, the ratios of cholestanol, lathosterol, and campesterol to cholesterol did not differ between the three different subject groups. A significant correlation between the efficiency of cholesterol absorption and the ratio of campesterol to cholesterol in plasma was found in all subjects (r = 0.504; P < 0.02) (Fig. 1).

### DISCUSSION

Dietary cholesterol absorption in humans shows a wide variation (10, 16, 19–24). The reasons for this have not yet been elucidated in detail, although apoE isoforms have been implicated for some of these differences (10–12). However, no studies so far have systematically evaluated the role of apoE on cholesterol absorption efficiency. Therefore, the primary aim of the present study was to evaluate the role of the apoE on cholesterol absorption in humans. Participants of the present study were homozygous either for the e2 or the e4 allele. Furthermore, the apoE2 homozygous group consisted of six normocholesterolemic and six patients with familial type III hyperlipoproteinemia. We also compared bile acid and total cholesterol synthesis, as well as noncholesterol sterols in plasma. Thus, this is the first study where cholesterol absorption was compared in subjects homozygous for the apoE2 or the e4 allele. Therefore, the present results are more likely to estimate the role of apoE on cholesterol absorption than previous studies.

The cholesterol absorption efficiency in the subjects of the present study ranged from 27% to 53%. This finding is in line with previous studies with healthy volunteers and patients with hypercholesterolemia using the identical continuous isotope feeding method with deuterium (16, 24) or radioactive isotopes labeled markers (11, 21). Repeated measurements of cholesterol absorption in the same individuals revealed constant absorption efficiency (16, 24), confirming not only the reproducibility of the method, but also the intraindividual consistency of dietary cholesterol absorption. The reason for interindividual differences have never been defined, although it has been postulated that apoE could account for some of them (10–12). In the present study, the absorption efficiency between subjects homozygous for apoE2 or E4 did not differ, neither did the ratio of campesterol to cholesterol. However, the ratio of campesterol to cholesterol in plasma was related to the efficiency of intestinal cholesterol absorption, thus confirming previous observations from Miettinen et al. (14).

It may be speculated that the absorption efficiency of higher amounts of dietary cholesterol that enter the intesti-

### TABLE 5. Serum cholestanol, lathosterol, and campesterol and their ratios to cholesterol in normolipemic and hyperlipemic E2/E2, and E4/E4 carriers

| Apolipoprotein | Cholesterol | Lathosterol | Campesterol | Cholesterol/Cholesterol | Lathosterol/Cholesterol | Campesterol/Cholesterol |
|----------------|-------------|-------------|-------------|-------------------------|-------------------------|------------------------|
| Normal lipemic apoE2/2 (n = 6) | 0.46 ± 0.20 | 0.34 ± 0.07 | 0.37 ± 0.04 | 2.74 ± 0.93 | 2.39 ± 0.58 | 2.41 ± 0.18 |
| Hyperlipemic apoE2/2 (N = 6) | 1.12 ± 0.27 | 1.00 ± 0.36 | 0.74 ± 0.11 | 2.72 ± 0.40 | 2.03 ± 0.40 | 1.92 ± 0.21 |
| apoE4/4 (n = 8) | 0.75 ± 0.21 | 0.44 ± 0.07 | 0.54 ± 0.09 | 2.88 ± 0.80 | 1.64 ± 0.21 | 1.97 ± 0.29 |

Values are mean ± SEM.

* Significantly different from normolipemic E2/2 (P < 0.05).

* Significantly different from E4/4 carriers (P < 0.05).
nal tract is regulated by apoE alleles. Indeed, in humans the absorption efficiency declines during higher cholesterol intake (25). Thus, the apparent difference between the present results and those obtained by Kesäniemi et al. (10) may be attributed to the amount of dietary cholesterol intake. The dietary intake of cholesterol in patients investigated by Kesäniemi et al. (10) was, on average, more than twice as high (~400 mg/day) as during the present study (~200 mg/day). On the other hand, Miettinen et al. (12) demonstrated that reducing the amount of dietary intake of fat by ~57% and of cholesterol by ~64%, the relationship between efficiency of cholesterol absorption and the apoE phenotype was lost. In contrast, Sehayek et al. (23) found no relationship between different apoE phenotypes and cholest erol absorption in a small number of subjects with a low (~200 mg/day) and high (~600 mg/day) cholesterol diet.

In the present study, no relationship between percentage of cholesterol absorption and dietary cholesterol was observed, although cholesterol intake ranged from 62 mg/day to 409 mg/day. Furthermore, we found no relationship between the dietary intake of different nutrients and cholesterol absorption. This lack of relationship might be due to the small numbers of subjects studied. Total cholesterol and bile acid synthesis during the present study also did not differ between individuals with the apoE2 and apoE4 alleles. This is in line with the results of Kesäniemi et al. (10) and others (26, 27). The ratio of la-tholesterol to cholesterol, an indirect marker of hepatic and total cholesterol synthesis, was also not different between the different groups of subjects, confirming that cholesterol synthesis was not different between the groups.

In conclusion, the present study provides definitive evidence that the apoE locus is not involved in cholesterol absorption, at least during a dietary cholesterol intake in the range between 60 to 400 mg/day. This evidence is supplied directly by measurement of cholesterol absorption, and indirectly by the ratio of campesterol to cholesterol in plasma.

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