

Cholesterol absorption efficiency and sterol metabolism in obesity

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Abstract

Role of enterohepatic cholesterol metabolism in obesity-induced increase of cholesterol synthesis was studied in healthy lean (BMI < 24) and overweight (BMI > 31) subjects by measuring serum lipids (including plant sterols, cholestanol and cholesterol precursors), cholesterol absorption % (double-label method), sterol balance and biliary lipids. New aspects of sterol metabolism in obesity were as follows: low efficiency of cholesterol absorption, reduced ratios to cholesterol of serum and biliary plant sterols and cholestanol (5 α -derivative of cholesterol), and a marked increase of serum and biliary cholesterol precursor sterols. Percent of cholesterol absorption was positively related to serum cholestanol and plant sterols, and negatively to cholesterol synthesis, measured by the sterol balance technique or cholesterol precursor sterols in serum or bile. Total and endogenous cholesterol fluxes into the intestine were increased, but owing to low absorption percent, mass of cholesterol absorption was within control limits in the obese subjects. Thus, per gram of their large liver tissue the entry of intestinal cholesterol may even be subnormal. Percent of cholesterol absorption was insignificantly negatively ($r = -0.256$) related to intestinal cholesterol pool, but significantly to biliary concentrations of cholesterol ($r = -0.581$), bile acids ($r = -0.513$) and phospholipids ($r = -0.469$). Thus, dilution of labeled dietary cholesterol by expanded intestinal cholesterol pool could have contributed to subnormal efficiency of cholesterol absorption, or transfer of labeled dietary cholesterol from intestinal oil phase to micellar phase may be competitively inhibited by expanded biliary secretion, resulting in reduced absorption of dietary cholesterol. These mechanisms could have contributed to changes in metabolism of non-cholesterol sterols, especially of cholestanol and plant sterols. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Obesity; Cholesterol absorption; Cholesterol synthesis; Biliary sterols; Lathosterol; Sitosterol; Cholestanol

1. Introduction

Overweight frequently results in dyslipidemia and predisposes development of atherosclerosis [1,2]. Cholesterol synthesis [3,4] and turnover [5] are markedly enhanced in patients with obesity. It is quite clear that cholesterol synthesis in excessively enlarged adipose tissue covers insufficiently the markedly enhanced overall cholesterol formation in obesity [6–8]. This appears to be true even when the large, slowly turning-over squalene pool of adipocytes is considered [9]. Thus, the obesity-induced increase in cholesterol synthesis is believed to be enhanced in the liver partly in association with increased hepatic fatty acid influx

and high VLDL production [10]. In addition, LDL apoprotein (apo) B turnover is enhanced [11], suggesting that hepatic LDL apo B receptor activity is upregulated, possibly as a result of lack of hepatocellular cholesterol. As a matter of fact, the rate-limiting enzyme activity in cholesterol synthesis, hydroxymethyl glutaryl CoA-reductase (HMG-CoA), has been shown to be increased in the liver of obese subjects [12]. However, the mechanism by which hepatic cholesterol synthesis is activated is unknown, even though increased fatty acid flow to the liver may be important [10]. Since an earlier study involving a random male population suggested that obesity might reduce dietary cholesterol absorption [13] it seemed worth while to study the question more closely. To this end, cholesterol absorption studies were performed under normal dietary conditions at home in lean and obese subjects. In addition, cholesterol synthesis was studied by the

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Table 1
Data on lean and overweight subjects

| Case | Weight, kg | Height, cm | BMI, kg/m ² | Cholesterol intake, mg/day | Cholesterol absorption, % | Fecal steroids, mg/day | | Cholesterol synthesis, mg/day | |
|-------------|---------------|---------------|---------------------------|-------------------------------|------------------------------|---------------------------|-----------------|----------------------------------|-------------|
| | | | | | | Bile acids | Neutral sterols | Total sterols | |
| 1 | 65 | 170 | 22.5 | 486 | 48.7 | 212 | 850 | 1062 | 576 |
| 2 | 67 | 176 | 21.7 | 426 | 46.5 | 361 | 642 | 1003 | 577 |
| 3 | 72 | 179 | 22.3 | 461 | 47.8 | 202 | 750 | 952 | 491 |
| 4 | 85 | 191 | 23.3 | 492 | 61.9 | 428 | 467 | 895 | 403 |
| 5 | 72 | 178 | 22.9 | 365 | 52.7 | 469 | 652 | 1121 | 756 |
| 6 | 54 | 173 | 18.0 | 803 | 68.4 | 235 | 500 | 735 | -68 |
| 7 | 68 | 174 | 22.5 | 648 | 50.0 | 222 | 593 | 815 | 167 |
| 8 | 68 | 171 | 23.2 | 378 | 52.1 | 380 | 599 | 979 | 601 |
| 9 | 68 | 171 | 23.4 | 348 | 43.8 | 438 | 858 | 1296 | 948 |
| 10 | 78 | 183 | 23.3 | 725 | 42.7 | 326 | 861 | 1187 | 462 |
| Mean ± S.E. | 70 ± 3 | 177 ± 2 | 22.3 ± 0.5 | 513 ± 50 | 51.5 ± 2.5 | 327 ± 32 | 677 ± 46 | 1004 ± 54 | 491 ± 90 |
| 11 | 96 | 176 | 31.1 | 764 | 44.9 | 664 | 1139 | 1803 | 1039 |
| 12 | 107 | 174 | 35.2 | 341 | 55.7 | 937 | 1334 | 2271 | 1930 |
| 13 | 92 | 170 | 31.9 | 544 | 63.0 | 306 | 717 | 1023 | 479 |
| 14 | 97 | 176 | 31.4 | 455 | 48.9 | 590 | 999 | 1589 | 1134 |
| 15 | 108 | 179 | 33.8 | 612 | 35.5 | 489 | 1329 | 1818 | 1206 |
| 16 | 90 | 169 | 31.7 | 415 | 35.8 | 324 | 1192 | 1516 | 1101 |
| 17 | 97 | 174 | 31.9 | 606 | 35.8 | 623 | 1547 | 2170 | 1564 |
| 18 | 94 | 175 | 30.7 | 694 | 42.7 | 568 | 958 | 1526 | 832 |
| 19 | 111 | 178 | 34.9 | 667 | 32.3 | 790 | 1241 | 2031 | 1364 |
| 20 | 127 | 171 | 43.4 | 606 | 28.1 | 385 | 1492 | 1877 | 1271 |
| Mean ± S.E. | 102 ± 4* | 174 ± 1 | 33.6 ± 1.2* | 570 ± 42 | 42.3 ± 3.5* | 567 ± 64* | 1195 ± 80* | 1762 ± 116* | 1192 ± 124* |

* $P < 0.05$ from lean subjects.

sterol balance technique and by quantitation of serum non-cholesterol sterols. The latter have been shown to depend closely on cholesterol absorption and synthesis in normal population [14].

2. Materials and methods

2.1. Study population

Populations with clear overweight, i.e. body mass index (BMI) > 31 kg/m², and with normal weight, BMI < 24 kg/m², were selected for the study from a healthy volunteer male population. The age ranges were identical (49–51 years) in the lean ($n = 10$) and overweight ($n = 10$) subjects, and the heights were also similar (see Table 1). The study protocol was accepted by Ethical Committee and only those subjects who volunteered were accepted for the study.

2.2. Study design

The subjects were studied under home conditions for cholesterol absorption [15] and fecal steroid outputs. For this purpose, they were advised to consume their normal home diet and were placed on capsules three times a day (one capsule with each of three major meals), each capsule containing 0.14 μ Ci of ¹⁴C-cholesterol, 0.18 μ Ci of ³H-sitosterol and 200 mg of Cr₂O₃. A 3-day fecal collection was made at the end of the 7–10-day treatment period and the dietary composition was also recorded for the last 7 days. Biliary samples were obtained by duodenal intubation at the end of this time period.

2.3. Methods

Serum lipoproteins were separated by ultracentrifugation at the end of the 3 day stool collection using the methods recorded in Lipid Clinics Research Program [16]. In this procedure serum total, VLDL, LDL and HDL were recorded for cholesterol and triglycerides. In addition, HDL₂ and HDL₃ cholesterol and triglycerides were quantitated. Also, serum total cholestanol, desmosterol, lathosterol, campesterol and sitosterol contents were quantitated from non-saponifiable lipid material [17,18]. Biliary cholesterol, bile acids, phospholipids and non-cholesterol sterols were also quantitated. Since cholesterol precursors are concentrated in bile, as compared to serum, methyl sterols could also be determined directly from non-saponifiable biliary lipids [17,18]. Fecal fat [19], and steroids, including bile acids, neutral and plant sterols, and cholestanol contents, were quantitated [20]. Dietary intake of cholesterol and fat was calculated from the 7 days' dietary recalls [21].

2.4. Calculations

Cholesterol synthesis was obtained as the difference between fecal sterols of cholesterol origin and dietary cholesterol. Total intestinal cholesterol influx = fecal sterols of cholesterol origin/(1 — fractional cholesterol absorption). Endogenous influx of cholesterol = total intestinal cholesterol flux — dietary cholesterol. Total daily biliary lipid secretions, e.g. bile acids and non-cholesterol sterols = endogenous influx of cholesterol \times other biliary components/cholesterol ratios. Previous studies have indicated that this indirect quantitation of biliary lipids actually gives similar results with those obtained with direct measurement with intestinal intubation [22]. Fractional bile acid absorption = 1 — (fecal bile acid excretion/biliary bile acid secretion).

Statistical analyses of data were performed using Biomedical Data Processing Program [23]. Statistical significancies were tested with two-sided Student's *t*-test. Correlation coefficients were calculated using the least square method. Since the serum non-cholesterol sterols are carried in serum in lipoproteins, mainly in LDL similarly to cholesterol, they are standardized and expressed as ratios to cholesterol ($10^2 \times$ mmol/mol of cholesterol).

3. Results

3.1. Serum lipids and sterols

Serum total and lipoprotein cholesterol were not different between the obese and non-obese groups (Table 2). However, total and VLDL triglycerides were higher in obese versus lean subjects. In addition, the

Table 2
Serum lipids of lean and obese subjects^a

| Lipid | Lean | Obese |
|------------------|-----------------|------------------|
| Cholesterol | 6.27 \pm 0.23 | 6.37 \pm 0.45 |
| VLDL | 0.32 \pm 0.09 | 0.73 \pm 0.32 |
| LDL | 4.49 \pm 0.20 | 4.28 \pm 0.38 |
| HDL | 1.44 \pm 0.09 | 1.31 \pm 0.11 |
| HDL ₂ | 0.50 \pm 0.07 | 0.45 \pm 0.09 |
| HDL ₃ | 0.95 \pm 0.05 | 0.87 \pm 0.05 |
| Triglycerides | 1.13 \pm 0.16 | 2.19 \pm 0.62* |
| VLDL | 0.44 \pm 0.09 | 1.29 \pm 0.54* |
| Cholestanol | 88 \pm 8 | 64 \pm 7* |
| Desmosterol | 55 \pm 4 | 64 \pm 3 |
| Lathosterol | 117 \pm 15 | 167 \pm 18* |
| Campesterol | 195 \pm 18 | 114 \pm 11* |
| Sitosterol | 129 \pm 14 | 72 \pm 7* |

^a Cholesterol and triglycerides mmol/l; non-cholesterol sterols $10^2 \times$ mmol/mol of cholesterol. * $P < 0.05$ from lean subjects (triglycerides calculated on log scale). Mean \pm S.E.

Table 3
Fecal steroids, cholesterol synthesis, and dietary and fecal fat in lean and obese subjects^a

| Sterols | Lean | Obese |
|-------------------------------------------|--------------|---------------|
| Total steroids, mg/kg per day | 14.48 ± 0.74 | 17.28 ± 1.02* |
| Bile acids, mg/kg per day | 4.68 ± 0.41 | 5.58 ± 0.60 |
| Neutral sterols, mg/kg per day | 9.80 ± 0.68 | 11.70 ± 0.68 |
| Plant sterols, mg/kg per day ^b | 3.54 ± 0.31 | 2.88 ± 0.33 |
| Cholestanol, mg/kg per day | 0.18 ± 0.01 | 0.16 ± 0.02 |
| Cholesterol synthesis, mg/kg per day | 6.93 ± 1.35 | 11.64 ± 1.13* |
| Dietary fat, g/day | 109 ± 11 | 115 ± 9 |
| Fecal fat, g/day | 3.8 ± 0.4 | 5.0 ± 0.5 |

^a **P* < 0.05 from lean subjects. Mean ± S.E.

^b Fecal plant sterols; are identical with dietary plant sterol intake.

ratios of serum cholestanol, campesterol and sitosterol were significantly lower and that of lathosterol higher in the obese than in the lean subjects.

3.2. Fecal data

Fecal bile acid and neutral sterol outputs and, consequently, cholesterol synthesis were significantly higher in the obese than lean subjects (Table 1). These differences were significant also on the bases of mg/kg for fecal total steroids and cholesterol synthesis (Table 3). On the other hand, fecal plant sterols and cholestanol were similar in the two groups and no differences were found in dietary and fecal fat (Table 3). However, despite unaltered fat absorption, cholesterol absorption efficiency was significantly reduced in the obese group compared with the lean one (Table 1). Further calculations showed that in terms of mg/day the intestinal total and endogenous (mostly biliary) cholesterol fluxes were enhanced by obesity (Table 4). Accordingly, the amounts of total and especially of endogenous cholesterol fluxes were higher in the overweight (+ 693 mg/day for total and + 776 mg/day for endogenous) than in the lean subjects. However, owing to the low absorption efficiency, the amounts of

Table 4
Intestinal flux and absorption of cholesterol in lean and obese subjects

| Sterol | Total flux | | Total absorption | |
|------------|---------------|----------------|------------------|----------------|
| | Lean (mg/day) | Obese (mg/day) | Lean (mg/day) | Obese (mg/day) |
| Total | 1395 ± 54 | 2088 ± 120* | 717 ± 47 | 893 ± 107 |
| Diet | 513 ± 50 | 570 ± 42 | 268 ± 36 | 236 ± 22 |
| Endogenous | 881 ± 64 | 1517 ± 145* | 449 ± 52 | 657 ± 100 |
| | mg/kg per day | | | |
| Total | 20.4 ± 1.4 | 20.6 ± 1.2 | 10.6 ± 1.1 | 8.9 ± 1.1 |
| Diet | 7.5 ± 1.0 | 5.6 ± 0.4 | 4.0 ± 0.7 | 2.4 ± 0.3* |
| Endogenous | 12.8 ± 1.1 | 15.0 ± 1.4 | 6.6 ± 0.6 | 6.5 ± 1.0 |

* *P* < 0.05 from lean subjects. Mean ± S.E.

cholesterol absorbed were similar in the two groups and in terms of mg/kg per day tended even to be higher, significant for dietary cholesterol, in the lean than in the obese group.

3.3. Correlations

Correlations in Table 5 show that cholesterol absorption and serum plant sterols are interrelated and they are positively associated with HDL cholesterol and serum cholestanol to cholesterol ratio, and negatively with fecal elimination of cholesterol (mainly as neutral sterols) and cholesterol synthesis (shown by balance data and serum lathosterol ratio). Fecal plant sterols, which correspond to dietary plant sterol intake, were positively related to serum plant sterols and negatively to cholesterol absorption efficiency. Correlations with cholesterol synthesis and serum lathosterol ratio were opposite to those obtained with absorption. Serum cholestanol and plant sterol ratios run in parallel and exhibit negative correlations with serum lathosterol ratio. Cholesterol absorption percent showed an inverse relation to total intestinal cholesterol flux (mg/day) in combined (*r* = − 0.256; NS) groups, the respective correlations being significantly negative with biliary concentrations of cholesterol (*r* = − 0.581, *P* < 0.01), bile acids (*r* = − 0.513, *P* < 0.05) and phospholipids (*r* = − 0.469, *P* < 0.05).

3.4. Biliary lipids

Biliary lipid contents (Table 6) revealed no differences in mol% of cholesterol or in percent of distribution of bile acids. However, in terms of mmol/mol of cholesterol, biliary desmosterol, lathosterol, Δ⁸-lathosterol and total methylsterols, including methostenol, Δ⁸-methylsterols and lanosterol, were significantly increased, while those of campesterol and sitosterol were decreased in obesity. In terms of mmol/day, biliary secretion of cholesterol was clearly increased, while those of bile acids and phospholipids only tended to be elevated (Table 7). Reabsorption of bile acids were similar, 95.7% in the lean and 95.0% in obese subjects. From among the non-cholesterol sterols, biliary secretion of methylsterols, desmosterol and lathosterol were increased but those of cholestanol and plant sterols were unchanged; in terms of μmol/kg, secretion of cholesterol precursors was increased and that of plant sterols decreased.

4. Discussion

The present findings show the following four new aspects of sterol metabolism in obese patients: first, low cholesterol absorption efficiency, second, a decrease in serum and biliary plant sterols, third, a decrease in serum cholestanol, and fourth, a marked increase in

Table 5
Correlation of cholesterol absorption and synthesis, and serum lathosterol and campesterol to cholesterol ratios with lipoprotein cholesterol, serum non-cholesterol sterol ratios and fecal steroids in combined lean and obese groups ($n = 20$)

| Sterol | Absorption, % | Synthesis, mg/day | Lathosterol | | Campesterol | |
|-----------------------|---------------|-------------------|-------------------------|--|-------------------------|--|
| | | | mmol/mol of cholesterol | | mmol/mol of cholesterol | |
| VLDL cholesterol | -0.264 | 0.325 | 0.300 | | -0.286 | |
| LDL cholesterol | 0.249 | 0.072 | -0.463* | | 0.103 | |
| HDL cholesterol | 0.728* | -0.210 | -0.552* | | 0.338 | |
| Cholestanol | 0.444* | -0.449* | -0.743* | | 0.687* | |
| Lathosterol | -0.750* | 0.522* | 1.000 | | -0.454* | |
| Campesterol | 0.487* | -0.605* | -0.454* | | 1.000 | |
| Sitosterol | 0.461* | -0.620* | -0.453* | | 0.965* | |
| Fecal bile acids | -0.236 | 0.633* | 0.182 | | -0.383 | |
| Fecal neutral sterols | -0.751* | 0.686* | 0.662* | | -0.710* | |
| Cholesterol synthesis | -0.575* | 1.000 | 0.552* | | -0.605* | |
| Fecal plant sterols | -0.478* | 0.181 | 0.519* | | 0.584* | |

* $P < 0.05$.

serum and biliary cholesterol precursors. The major detectable factor is the reduced cholesterol absorption efficiency which apparently reflects dilution of dietary cholesterol in large intestinal pool of obese subjects, or prevention of dietary cholesterol incorporation into micellar phase by expanded biliary cholesterol secretion.

The question then arises what is responsible for this decreased cholesterol absorption in obesity. The present methodology quantitates accurately absorption efficiency, elimination and synthesis of cholesterol, and dietary intake and serum and biliary levels of plant sterols, but only indirectly dietary cholesterol, and biliary daily secretion and absolute absorption of sterols. Indirect and direct measurement of biliary cholesterol secretion revealed in our studies similar values, however [22]. Intestinal transit time [24,25], apo E polymorphism [26], and dietary plant sterols [27] can modify cholesterol absorption under basal conditions. No clear information is available on the actual cholesterol transit time in obesity. Apo E 2 phenotype is associated with low absorption [26], but in this population apo E 2 was not linked with obesity. However, large doses of dietary plant sterols [27] fed as supplement to a normal diet, interfere with cholesterol absorption in normal subjects [13] and in patients with intestinal exclusion [28]. In fact, the negative correlation between total fecal plant sterols (corresponds dietary intakes) and cholesterol absorption efficiency (Table 5) suggests that dietary plant sterols contribute to low absorption efficiency. However, even though the plant sterol intakes were similar in the two groups, the highest intake values in the obese group could have slightly contributed to absorption efficiency. Adjustment of daily plant sterol intake did not change absorption percentage, though. Markedly high association between HDL cholesterol and absorption efficiency suggests that increased

cholesterol absorption enhances HDL cholesterol level. Even though the respective correlation was not quite significant for absorbed mass of cholesterol, increased absorption increases HDL cholesterol, e.g. during cholesterol feeding [29].

The findings in Table 4 actually indicate that, despite low cholesterol absorption efficiency, the entry of cholesterol to the liver from the intestine was within normal limits as a result of large intestinal biliary flux of cholesterol. This observation actually raises the question of whether each hepatocyte of the enlarged liver receives a subnormal amount of intestinal cholesterol and whether resulting cholesterol depletion stimulates the liver to overproduce cholesterol. In fact, this situa-

Table 6
Biliary lipids in lean and obese subjects^a

| Lipid | Lean | Obese |
|-----------------------------------|------------|-------------|
| Cholesterol, M % | 9.3 ± 1.1 | 9.8 ± 0.8 |
| Phospholipids, M % | 22.5 ± 0.6 | 24.6 ± 2.0 |
| Bile acids, M % | 68.1 ± 1.1 | 65.5 ± 2.3 |
| Cholic (%) | 47.9 ± 3.2 | 43.1 ± 2.2 |
| Deoxy (%) | 8.5 ± 2.2 | 16.3 ± 3.5 |
| Cheno (%) | 40.1 ± 2.9 | 36.8 ± 2.8 |
| Cholestanol | 331 ± 61 | 311 ± 54 |
| Desmosterol | 58 ± 9 | 78 ± 9 |
| Lathosterol | 618 ± 67 | 982 ± 160* |
| Δ ⁸ -lathosterol | 68 ± 10 | 140 ± 23* |
| Methylsterols | 1090 ± 122 | 1595 ± 199* |
| Methostenol | 191 ± 30 | 307 ± 45* |
| Δ ⁸ -methostenol | 159 ± 18 | 264 ± 53 |
| Δ ⁸ -dimethylsterol | 66 ± 9 | 116 ± 21* |
| Δ ^{8,24} -dimethylsterol | 285 ± 31 | 330 ± 37 |
| Lanosterol | 389 ± 59 | 576 ± 64* |
| Campesterol | 549 ± 65 | 332 ± 41* |
| Sitosterol | 550 ± 66 | 317 ± 34* |

^a Non-cholesterol sterols in terms of $10^2 \times$ mmol/mol of cholesterol. * $P < 0.05$ or less from lean subjects. Mean ± S.E.

Table 7
Biliary lipid secretion in lean and obese subjects^a

| Steroid | Lean | Obese |
|-----------------------------|------------|-------------|
| Cholesterol | 236 ± 17 | 407 ± 39* |
| Phospholipids | 571 ± 134 | 1022 ± 163 |
| Bile acids | 1950 ± 253 | 3001 ± 520 |
| Cholestanol | 7.5 ± 1.4 | 13.1 ± 3.1 |
| Desmosterol | 1.4 ± 0.2 | 3.1 ± 0.4* |
| Lathosterol | 15.4 ± 2.6 | 37.3 ± 6.2* |
| Δ ⁸ -lathosterol | 1.7 ± 0.4 | 5.4 ± 0.9* |
| Methylsterols | 25.7 ± 2.8 | 64.9 ± 6.6* |
| Campesterol | 12.4 ± 1.4 | 13.2 ± 1.7 |
| Sitosterol | 12.3 ± 1.2 | 12.6 ± 1.3 |

^a Three first values in 10² × mmol/day, others in μmol/day. Methylsterols: sum of the five methylsterols in Table 6. **P* < 0.05 from lean subjects. Mean ± S.E.

tion resembles very much coeliac disease where cholesterol absorption efficiency is markedly reduced, but owing to clearly enhanced biliary cholesterol secretion the total cholesterol absorption is frequently within the normal levels and hepatic cholesterol synthesis is increased [30]. Hepatic synthesis of cholesterol per g of tissue seems to be similar in obese and non-obese subjects, but the large liver increased total hepatic cholesterol synthesis [12,31,32]. An additional, perhaps even more important reason may be obesity-associated increase in fatty acid flow and VLDL production to and from the liver [10,33]. However, LDL apo B removal is also increased [11,33] suggesting that LDL apo B receptors are upregulated. Activation of receptors and synthesis can be caused, e.g. by enhanced cholesterol secretion in bile [34] or VLDL secretion [10,33].

Cholesterol absorption efficiency can be reduced by expanded intestinal flux of biliary cholesterol in obesity through intestinal dilution of labeled cholesterol. However, the absorption efficiency was not related to intestinal cholesterol flux in a normal male population [13], in normoglycemic men with mild abdominal obesity and increasing insulin resistance [35], or during cholesterol feeding [36]; in these occasions the higher the intestinal cholesterol pool the higher was the amount of absorbed cholesterol. Our cholesterol feeding experiments caused a reduction in absorption efficiency of cholesterol in a normal male population [29], a finding in contrast to a recent paper, in which modification of fat and cholesterol intakes had virtually no effect on cholesterol absorption efficiency [37]. Absorption efficiency of cholesterol was reduced in mice by cholesterol feeding and transgene-induced overexpression of the scavenger receptor BI, because biliary cholesterol secretion was increased; biliary cholesterol concentration was negatively related to absorption efficiency suggesting that it competed with dietary cholesterol from micellar solubilization [38]. In the present obese population, mass of absorbed cholesterol was within control limits, chole-

sterol absorption efficiency was decreased and it was only insignificantly inversely related to intestinal cholesterol pool, but significantly to biliary concentrations of cholesterol, bile acids and phospholipids. Expanded cholesterol pool may have diluted labeled cholesterol contributing to reduced absorption efficiency, or increased biliary lipids prevented entry of labeled dietary cholesterol from oil phase to micellar phase, reducing absorption of labeled cholesterol of obese subjects. Insulin resistance could be an additional factor [35].

It is interesting to note that hypertriglyceridemic obese patients tended to increase their cholesterol absorption efficiency when put on a slightly hypocaloric diet [39]. Weight-reducing treatment actually lowers markedly cholesterol synthesis [40]. Our preliminary studies in obese type 2 diabetes subjects also showed that after a moderate weight reduction cholesterol absorption significantly improved on an isocaloric diet [41]. Reduced cholesterol absorption efficiency may actually be a way of nature to avoid extra cholesterol in obesity.

Plant sterols, cholestanol and cholesterol precursors behaved as shown earlier in normal population [14]. Thus, in obesity low sterol absorption efficiency appears to be responsible for low plant sterol and cholestanol absorption and serum levels. It should be borne in mind, however, that dietary plant sterols are markedly diluted by large intestinal cholesterol pool of these obese subjects, a factor that might lower their absorption. Calculation of plant sterol absorption from the present biliary secretion and fecal plant sterol data revealed that it was 3.8% for the lean and 3.4% for the obese subjects, respectively. Cholestanol, the 5α-saturated cholesterol derivative, behaves like plant sterols; even though its dietary intake is < 1 mg/day [42], some of it is produced by intestinal bacteria [43] and biliary secretion was 25 and 30% of fecal output in the lean and obese subjects, respectively. Obviously some of cholestanol was formed in the intestine.

Enhanced cholesterol synthesis increased serum ratios of precursor sterols and enhanced their biliary secretion. Serum methylated precursor sterols and squalene have been shown to be frequently elevated in obesity [40,44,45]. The present observation of increased serum precursors in terms of μmol/mol of biliary cholesterol or in μmol/day actually suggests that cholesterol was synthesized in enhanced amounts in the liver. A close correlation of hepatic HMG-CoA reductase activity and serum precursor sterols actually indicates the close association between the two parameters [46].

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