Cholesterol Production in Obesity

By Tatu A. Miettinen, M.D.

SUMMARY
Sterol-balance studies were performed in 10 control subjects, 10 normolipidemic obese patients, and 10 hypertriglyceridemic (type IV, mostly obese) patients on a low-cholesterol solid-food diet. Fecal elimination of cholesterol was markedly elevated in the overweight patients and tended to be high in the hypertriglyceridemic subjects also. A significant correlation was found between body weight and fecal excretion of neutral, acidic, and total steroids, indicating that the greater the body weight the higher was the rate of cholesterol synthesis. Sterol-balance data in obese subjects showed that excess daily cholesterol production roughly amounted to 20 mg/kg of adipose tissue. The control subjects produced only 12 mg/kg of body weight daily. Thus, obesity is associated with an increased rate of cholesterol synthesis in man. However, the correlation between serum cholesterol concentration and cholesterol production was low, suggesting that the overall rate of cholesterol synthesis was not the only factor determining the serum cholesterol level. That enhanced cholesterol production is not an irreversible phenomenon in obese subjects was indicated by the normalization of sterol-balance values in three overweight patients after their weights had been reduced by total fast followed by a low-calorie diet.

Additional Indexing Words:
Hypercholesterolemia  Hypertriglyceridemia  Fecal steroids  Bile acids  Sterol balance

Hypercholesterolemia is frequently found in patients with obesity, so that the average serum cholesterol level is significantly higher in overweight subjects than in lean ones, and usually a significant correlation exists between serum cholesterol and obesity.1,2 It should be borne in mind, however, that a great many obese patients have normal serum lipid concentrations.3 Hypercholesterolemia4,5 and obesity6 are known to be associated with the development of ischemic heart disease, although the association is relatively weak in the case of obesity, according to recent studies.7 It therefore seemed worthwhile to study the cholesterol metabolism of obese patients in greater detail, the sterol-balance technique being used for determination of cholesterol synthesis. Kinetic analysis of serum cholesterol after administration of radioactive cholesterol has disclosed a positive correlation between cholesterol production and excess body weight.8 Results of the preliminary studies9,10 and those reported here clearly demonstrate that obesity enhances cholesterol synthesis very potently and that reduction of weight effectively normalizes cholesterol production.

Material and Methods
Sterol balance was measured in three groups of patients, for whom clinical data are presented in table 1. The control group consisted partly of volunteers from among the laboratory personnel and partly of hospital patients with no detectable metabolic or other active disease. The obese group consisted of 10 markedly overweight patients, most of whom were hospitalized for reduction of weight. Although at the time of admission to the hospital some of the patients had
Table 1

**Clinical and Laboratory Data of Subjects**

<table>
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<tr>
<th>No.</th>
<th>Clinical findings</th>
<th>Diabetes, glucose tolerance</th>
<th>Age (yr)</th>
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<th>Relative weight</th>
<th>Serum lipids (mg/100 ml)</th>
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<td></td>
<td></td>
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<td>Cholesterol</td>
</tr>
</tbody>
</table>

**Control subjects**

1–10 Mean ± se

11 Gallstones I Diabetes 63 F 95 1.76 295 155 244 131
12 — Normal 24 M 120 1.65 254 111 233 85
13 — Normal 47 M 90 1.32 240 110 210 140
14 CHD Diabetic 47 M 112 1.58 328 201 200 170
15 Spondylarthr (inact) Normal 25 M 87 1.21 180 85 154 70
16 — Diabetic 47 M 110 1.72 193 126 175 136
17 Gallstones Normal 29 F 83 1.48 245 156 191 123
18 HCD Diabetes 54 F 138 2.42 319 225 280 150
19 CHD; previous CVA Diabetic 58 M 152 2.08 275 213 201 139
20 — Diabetic 26 F 105 1.72 219 145 187 —

11–20 Mean ± se

109 ± 7 1.69 ± 0.11 255 ± 16 153 ± 17 208 ± 12 127 ± 10

**Obese subjects**

**Hypertriglyceridemic subjects**

21 Xanthelasmata; duodenal ulcer Normal 34 M 75 1.21 412 2120 340 500
22 Xanthelasmata Diabetic 51 M 112 1.60 416 590 324 676
23 Cutaneous xanthomatosis; CHD Diabetic 43 M 71 1.09 700 1190 456 490
24 Arth rhum (inact) Diabetic 40 M 91 1.38 — — 267 251
25 CHD Normal 36 M 86 1.39 359 428 341 349
26 CHD; previous CVA Normal 50 M 61 0.98 298 297 223 203
27 CHD Diabetic 57 M 75 1.12 359 296 281 318
28 — Diabetic 57 F 66 1.25 500 2080 314 1120
29 Cutaneous xanthomatosis; CHD Diabetic 55 M 86 1.28 581 2157 347 930
30 — Diabetic 36 M 101 1.44 556 661 348 310

21–30 Mean ± se

82 ± 5 1.27 ± 0.06 465 ± 43 1091 ± 272 330 ± 21 544 ± 103

*At the start of the low-cholesterol diet.

Abbreviations: CHD = coronary heart disease; CVA = cerebrovascular accident; HCD = hypertensive cardiovascular disease.
slightly elevated serum cholesterol and/or triglycerides, the serum lipid values were within normal limits during the period of fecal collections. In this group excess body weight (calculated as the difference between the actual and ideal weights) ranged from 15 to 80 kg and relative weight (absolute weight/ideal weight) from 1.21 to 2.42. Diabetes (controlled by diet) or diabetic glucose tolerance was found in six of the patients, two of whom had gallstones and two had clinical and electrocardiographic signs of coronary heart disease; one patient (no. 19) of the latter group had heart failure, which required relatively large doses of digitalis and diuretics for compensation. The third group contained 10 patients in whom hypertriglyceridemia was conspicuous and whose lipoprotein pattern was consistent with type IV hyperlipoproteinemia according to the classification of Fredrickson et al., although in some of them hypercholesterolemia and β-lipoprotein bands in lipoprotein electrophoresis were also relatively marked. The excess body weight in this group ranged from −1 to 42 kg and the relative body weight from 0.98 to 1.60. Two of the patients had cutaneous xanthomatosis, six had clinical and electrocardiographic signs of ischemic heart disease but no heart failure, and seven exhibited diabetic glucose tolerance.

All of the subjects were placed on a low-cholesterol solid-food diet, and chemic oxide (Cr₂O₃) and β-sitosterol were given so that the respective corrections for fecal flow and degradation of cholesterol during intestinal transit could be made. From one to three 3-day stool collections were made for each subject after 5–10 days on the diet, Cr₂O₃, and β-sitosterol. Analysis of the diet showed that the average cholesterol content was 120 mg/2400 kcal. In patients 12, 14, and 19 the study was repeated after the weights had fallen, in response to total fast followed by a low-calorie diet, by 38, 13, and 68 kg, respectively. In view of the times for which the new stable weights had been maintained (12, 1, and 6 months after weight reduction had been achieved), it was assumed that a new metabolic steady state had already been attained.

Serum cholesterol was measured according to the method of Pearson and associates and triglycerides by the method of Carlson. Dietary sterols and fecal acidic and neutral steroids were measured by the thin-layer chromatographic gas-liquid chromatographic method. In one case, recovery of administered and dietary β-sitosterol in the feces was only 70%, and neutral steroid excretion was therefore corrected for the recovery of β-sitosterol. In the others, the values for recovery ranged from 94 to 108%, suggesting that no sterol degradation had occurred. Therefore, in these cases the results were expressed in relation to Cr₂O₃, which was determined according to Bolin and associates.

Sterol balance, which in the steady state is equal to cholesterol synthesis, was obtained as the difference between fecal steroids derived from cholesterol and dietary cholesterol. Because weight reduction with a low-calorie diet was found to lead to decreased fecal steroid excretion in obese subjects, the amount of calories was rigidly adjusted to maintain the body weight constant. None of the subjects studied actually showed any significant change in weight during the experimental period of 14–19 days, at the end of which the fecal collections were performed. This indicates that a steady state with respect to calories had been achieved.

Cholesterol intake varied little during the study, ranging, according to analyses, from 98 to 136 mg/2400 kcal; serum cholesterol was constant during the experimental period; and fecal steroid analyses of 2–3 consecutive collections in each subject (for one control and one hypertriglyceridemic patient only a single collection was available) showed constant excretion. The latter was indicated by the finding that the difference between the total fecal steroids of the first and third (or second) collection did not differ significantly from zero (± 21 ± 30 mg/day). The same was true of acidic and neutral steroids, indicating that cholesterol elimination from the body as bile acids and as cholesterol itself was stable. It is therefore reasonable to infer that the subjects of the three groups were in a comparable metabolic steady state.

On the assumption that their ideal body weights the obese and hypertriglyceridemic patients would synthesize cholesterol at the rate observed in the controls, their theoretical, ideal sterol balance was calculated by multiplying the ideal weight by the average sterol-balance value of the controls, expressed as milligrams per day per kilogram of body weight. Excess sterol balance, corresponding to excess cholesterol synthesis, was the difference between the actual and ideal values for sterol balance.

**Results**

Table 2 shows that in the obese patients fecal excretion of acidic, neutral, and total steroids (derived from cholesterol) is markedly higher than in the controls or even in the hypertriglyceridemic patients. The differences between the two latter groups were insignificant, although the actual (but not ideal) body weights were markedly higher in the hypertriglyceridemic group than in the controls. The sterol-balance values indicate that in the obese...
## Table 2

**Sterol Balance in Control Subjects and in Patients with Obesity and Hypertriglyceridemia**

<table>
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<tr>
<th>No.</th>
<th>Sex</th>
<th>Number of analyses</th>
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<th>Fecal steroids (mg/day)</th>
<th>Fecal steroids (mg/day/kg)</th>
<th>Sterol balance (mg/day)</th>
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<td>Neutral</td>
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</table>

**Control subjects**

**Females** Mean ± se 154 ± 16 489 ± 83 642 ± 91 3.1 ± 0.3 9.6 ± 1.4 12.7 ± 1.5 -571 ± 91 -11.3 ± 1.5

**Males** Mean ± se 317 ± 32* 780 ± 121 1097 ± 109* 4.4 ± 0.3* 10.8 ± 1.5 15.2 ± 1.2 -985 ± 104* -13.6 ± 1.2

**Obese subjects**

**1-10** Mean ± se 235 ± 32 634 ± 85 869 ± 101 3.7 ± 0.3 10.2 ± 1.0 13.9 ± 1.0 -777 ± 95 -12.4 ± 1.0

**Females** Mean ± se 376 ± 30† 1338 ± 118† 1714 ± 145† 3.7 ± 0.3 13.0 ± 1.3 16.6 ± 1.6 -1607 ± 141† -15.6 ± 1.6

**Males** Mean ± se 488 ± 110 1216 ± 102† 1704 ± 110† 4.2 ± 0.7 11.3 ± 1.2 15.5 ± 1.0 -1582 ± 108† -14.4 ± 1.0

**Hypertriglyceridemiac subjects**

**11-20** Mean ± se 443 ± 67† 1263 ± 76† 1706 ± 83† 4.0 ± 0.4 12.0 ± 0.9 15.9 ± 0.8 -1592 ± 81† -14.9 ± 0.8

*Statistically significant difference (P < 0.05) from females; †from controls; and ‡from hypertriglyceridemic subjects. Daily intake of dietary cholesterol was 92 ± 8 mg in controls; 114 ± 4 mg in obese patients; and 102 ± 6 mg in hypertriglyceridemic patients.
group cholesterol synthesis was twice as high, and in the hypertriglyceridemic subjects 1.3 times as high, as in the controls. Since the average relative weights of the three groups were 1.69, 1.27, and 0.96, and since their ideal weights were the same, it can be concluded that obesity, particularly without hyperlipidemia, effectively stimulates cholesterol synthesis in man.

Figure 1 shows the positive correlations between body weight and the fecal excretion of neutral, acidic, and total steroids. The controls exhibited a significant correlation for all parameters, the lighter females having lower acidic- and total-steroid values, and less-negative sterol-balance values than the heavier males. However, the sex difference, which was not seen in the obese patients because of the similar weight of the two sexes, disappeared when fecal-steroid values were expressed per kilogram of body weight, although even then the bile acid output was slightly lower in the women than in the men (table 2). The association between fecal steroids and body weight tended to be less significant in the hypertriglyceridemic than in the obese subjects, because, particularly in one markedly obese and hypertriglyceridemic patient, cholesterol elimination, both as bile acids and as neutral steroids, happened to be relatively low. Sterol balance, when expressed per kilogram of body weight, was no longer significantly higher in the obese (−14.9 ± 0.8 mg) than in the hypertriglyceridemic (−13.0 ± 1.1 mg) or control subjects (−12.4 ± 1.0 mg). The positive correlation (r = 0.64) between excess body weight and excess sterol balance (fig. 2) indicates that cholesterol synthesis is enhanced over a wide range of obesity. The average increment of cholesterol synthesis per kilogram of adipose tissue was calculated for the obese subjects by dividing the excess sterol balance by the excess body weight. It was found to be 20 ± 2 mg/kg/day, which again demonstrates the effectiveness of adipose tissue in enhancing cholesterol production in man, cholesterol synthesis in the control subjects being only 12 mg/kg/day. However, the correlation between serum cholesterol and sterol balance or excess balance (fig. 3) did not reach a significant level in this small series, which indicates that the serum cholesterol concentration is not determined solely by the overall rate of cholesterol synthesis. Neither body weight, excess weight, nor relative weight of the obese group was correlated significantly with the serum cholesterol concentration.

From table 3 it is seen that in three excessively obese subjects reduction of weight to near-normal values led to a marked decrease in the elimination of fecal cholesterol from the body. This indicates that the
abnormally high cholesterol synthesis occurring in obese subjects can be normalized by effective weight reduction.

Discussion

The results of the present study show that cholesterol synthesis is normally proportional to body size, obesity being especially potent in stimulating this process. Thus, the marked difference in cholesterol synthesis found between the male and female control subjects disappeared when the values were expressed per kilogram of body weight. No sex difference was seen in the obese patients, among whom the body weight happened to be similar in males and females (Fig. 1). The fact that in our earlier series21 no difference (expressed in relation to total body weight) was found between men and women turned out, on retrospective study, to be due to the similar body weights in the two groups.

Only a few sterol-balance studies made with accurate methods on human subjects have

![Figure 2](http://circ.ahajournals.org/)

**Figure 2**

Relationship between excess body weight and excess sterol balance in patients with obesity (○) and hypertriglyceridemia (●).

<p>| Table 3 |</p>
<table>
<thead>
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<th>Patient no. 12</th>
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<th>Patient no. 14</th>
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<th>Patient no. 19</th>
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*Three determinations of dietary cholesterol in each body weight showed that the average intake had fallen significantly between the two studies in cases 12 and 19 (31 and 49 mg/day, respectively) and insignificantly (14 mg/day) in case 14.
been reported so far. Effects of dietary fats on fecal steroid excretion were studied by Connor and associates in six normocholesterolemic prisoners. The mean sterol-balance values for two control periods on a cholesterol-free liquid-formula diet (fat consisted of cocoa butter), one before and the other after a corn-oil diet, were −783 and −682 mg/day (neutral steroids corrected for losses of β-sitosterol), respectively. Despite marked differences in the diet, the figures are in good agreement with the control value of the present study (−777 mg/day). The data did not appear to be correlated with body weight. Grundy and Ahrens reported sterol-balance data on formula diets varying in cholesterol, plant sterol, and fat composition, for 15 hypercholesterolemic (type II, types as described by Fredrickson and associates), one normocholesterolemic, and four hypertriglyceridemic (three type V and one type IV) subjects. The sterol balance ranged from −374 to −749 mg/day for hypercholesterolemic subjects and from −726 to −1833 mg/day for hyperglyceridemic subjects on a formula diet containing saturated fat; the data appeared to bear some relationship to body weight. In 43 patients with familial hypercholesterolemia, sterol balance, fecal neutral steroids, and bile acids were found to be correlated with body weight. As in the present investigation, some but not all of the hyperglyceridemic patients exhibited a high bile acid production in the studies by Grundy and Ahrens and by Kottke. In the latter series bile acid metabolism was measured isotopically, and a marked interindividual heterogeneity in bile acid production was observed.

Monkey adipose tissue synthesizes cholesterol in vitro at a rate that would account for the increment revealed by sterol-balance data in the obese subjects studied here. However, more recent studies have indicated that human and rat adipocytes are not able to convert labeled glucose or acetate into cholesterol, and that adipose tissue is only a cholesterol-storage organ that receives its cholesterol from circulating lipoproteins or chylomicron. The liver and intestinal mucosa, on the other hand, have been shown to be the sites where serum cholesterol is primarily synthesized, which suggests that these organs are responsible for the augmented production of cholesterol in obesity. Studies with a labeled acetate-mevalonate mixture also indicated that synthesis was markedly enhanced in obese patients and that this stimulation took place between acetate and mevalonate. Furthermore, the rapid appearance of newly synthesized radioactive cholesterol in the serum suggested that it originated from a rapidly equilibrating cholesterol pool, supposedly situated primarily in the liver and intestinal wall. Hypertriglyceridemic (type IV) subjects, who are usually obese and whose cholesterol synthesis in the present study was only moderately increased, have been shown by Salen et al. to have a high rate of intestinal cholesterol synthesis. The latter was minimal in hypercholesterolemic (type II) patients, but it was markedly stimulated by interruption of the enterohepatic circulation of bile acids with cholestyramine; clofibrate inhibited synthesis in the cholestyramine-treated hypercholesterolemic patients and in a case with hypertriglyceridemia.

The cholesterol ester turnover is also higher in obese subjects than in lean ones and is significantly correlated not only with body weight but also with serum cholesterol and triglyceride concentrations. Nestel et al., using the two-pool model for calculation of cholesterol metabolism, showed that cholesterol production, which bears no correlation to serum cholesterol, is increased by 22 mg/day/kg of excess body weight. This is in good agreement with the value of 20 mg/day/kg obtained in the present study by direct measurement of the fecal end products of cholesterol metabolism.

Primarily enhanced elimination of cholesterol from the body, resulting, for instance, from treatment with cholestyramine or from an ileal bypass operation is almost always accompanied by a reduced level of serum cholesterol. The magnitude of the latter is not correlated with the increment of fecal
elimination, owing to a compensatory increase in the synthesis and possibly in the mobilization of tissue cholesterol.\textsuperscript{31, 32} On the other hand, primarily enhanced synthesis, such as obviously occurs in obesity, can be assumed to increase the serum cholesterol level in almost every case, although the magnitude of the increase is not necessarily correlated with the enhancement of synthesis, because simultaneous stimulation of cholesterol elimination prevents this augmentation to an extent which differs from one subject to another. This compensatory increase of elimination is enough to keep the serum cholesterol level low in some obese patients, while in others elimination may be more or less defective, so that hypercholesterolemia results. Thus, the latter may accompany both reduced and enhanced synthesis; in familial hypercholesterolemia the primary disorder appears to be defective elimination of cholesterol, this being secondarily associated with a compensatory decrease in cholesterol synthesis;\textsuperscript{9, 10, 21} in obesity it is synthesis that is primarily enhanced, but in some cases augmentation of elimination is not proportionate and hypercholesterolemia results.

The variable response of elimination to enhanced cholesterol synthesis in obesity may explain why the serum cholesterol level usually shows only a weak correlation with body weight or body fatness.\textsuperscript{1, 2} However, since obesity is frequent in modern society, it may, as a potent factor enhancing cholesterol synthesis, be a very important etiologic factor in hypercholesterolemia and hence in ischemic heart disease, even though, according to the more recent epidemiologic studies,\textsuperscript{7} the association between the latter and obesity is relatively weak. Weight reduction was accompanied with a marked decrease in cholesterol synthesis in the limited number of subjects studied. This therapeutic measure, so commonly recommended for prevention and treatment of hypercholesterolemia and ischemic heart disease, seems to be a very effective procedure as far as reduction of cholesterol synthesis is concerned. Weight reduction has actually been reported to decrease the serum cholesterol level in obese subjects,\textsuperscript{34} although in the new steady state initial values may be resumed.\textsuperscript{35}

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