Cholesterol metabolism in hypothyroidism and hyperthyroidism in man

Jeffrey J. Abrams and Scott M. Grundy

Department of Medicine, Veterans Administration Medical Center and University of California, San Diego, CA 92161

Abstract Studies were carried out on cholesterol metabolism in 11 nonobese patients and 16 obese patients with hypothyroidism and 13 with hyperthyroidism. The patients underwent several investigations under metabolic ward conditions. Hypothyroid patients usually had an increase in low density lipoprotein (LDL)-cholesterol. Several mechanisms may have combined to cause a high LDL. For instance, the obese hypothyroid patients had an increase in cholesterol synthesis. Absorption of cholesterol also was increased frequently. However, other mechanisms not explored in this study probably contributed to most of the fall in LDL-cholesterol. Treatment of hypothyroid patients produced the expected fall in LDL. One possible mechanism could be that thyroid hormones enhance the conversion of cholesterol into bile acids; this mechanism has been suggested by other workers from animal studies. However, no evidence was obtained in either hypothyroid or hyperthyroid patients that thyroid hormones alter synthesis of bile acids. On the other hand, the hormones appeared to increase the synthesis of cholesterol. Patients with hypothyroidism frequently had supersaturated bile. The cause was mostly an enhanced secretion of biliary cholesterol associated with a tendency to obesity and increased synthesis of cholesterol. In contrast, the usually thin hyperthyroid patients did not have supersaturated bile. The studies show that thyroid hormones *a*) influence LDL-cholesterol by an action on the catabolism of LDL-independent of alterations in synthesis, catabolism, absorption, or excretion: b) stimulate synthesis of cholesterol; and c) affect biliary lipid metabolism in large part by influencing energy balance and cholesterol synthesis. — **Abrams, J. J., and S. M. Grundy.** Cholesterol metabolism in hypothyroidism and hyperthyroidism in man. *J. Lipid Res.* 1981. **22:** 323–338.

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The hypercholesterolemia of hypothyroidism and hypocholesterolemia of hyperthyroidism are long-recognized and well-accepted clinical findings (1–4). The mechanisms of hypercholesterolemia in hypothyroidism have been ascribed variously to decreased clearance of cholesterol from plasma (5–8), reduced conversion of cholesterol to bile acids in the liver (9–12), and delayed removal of low density lipoprotein from the plasma (13). The reverse actions have been suggested as being responsible for the low cholesterol concentrations in hyperthyroidism.

Because of these conflicting reports, we initiated a series of studies to examine further the actions of thyroid hormones on the metabolism of cholesterol and bile acids in man. These investigations were carried out to ascertain whether lowering of plasma cholesterol by thyroid hormones can be explained by alterations in synthesis, excretion, or absorption of sterols. At the same time, these same processes were examined for their relation to biliary lipids to determine whether thyroid dysfunction might modify saturation of bile with cholesterol.

METHODS

Patients

Studies on metabolism of cholesterol and bile acids were performed in most of the patients with hypo- and hyperthyroidism described in the accompanying paper (14), and in this paper the same numbers are used to designate each patient. The patients were divided into three groups, nonobese and obese hypothyroid patients, and hyperthyroid patients. In the following text, the numbers of patients in each study, along with their particular characteristics, will be delineated in more detail. These investigations were carried out on the Special Diagnostic and Treatment Unit, Veterans Administration Medical Center, San Diego, CA. All patients gave informed consent for their studies.

The results from the present subjects are compared to those obtained in normal subjects who were studied previously in our laboratory. Under each procedure outlined below, the characteristics of the control subjects are described.

Abbreviations: TG, triglyceride; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; GLC, gas–liquid chromatography; IW, ideal weight.

Experimental design

A total of 40 patients with thyroid disease was studied. Some of the patients were admitted to the hospital for only short periods (mostly for studies of triglyceride metabolism) and, except for measurements of plasma lipoproteins, they did not undergo detailed investigation of cholesterol metabolism. In particular, several hyperthyroid patients were too symptomatic from their disease to complete prolonged cholesterol balance. The status of each patient with regard to the period of hospitalization is given in Tables 1–3 of the companion paper (14).

Long-term patients, after a brief period of stabilization in the hospital, were started on an isocaloric diet and the intake of calories was adjusted so that body weights were maintained constant throughout the study. During the first month (Period I) the patients were maintained in their abnormal state (hypothyroid or hyperthyroid). In addition to the tests done on triglyceride metabolism described in the companion paper (14), the following measurements were made: *a*) plasma lipids twice weekly; *b*) cholesterol in the different lipoprotein fractions at the end of each period; *c*) neutral and acidic steroids from stool samples collected daily; *d*) lipid composition of gallbladder bile (determined weekly); and *e*) hepatic secretion of biliary lipids and pool sizes of bile acids.

After appropriate treatment of their disease state, and return to euthyroidism, each patient was restudied for another month (Period II). To keep patients at their pretreatment weight, it was usually necessary to alter the caloric intake as compared to Period I. Otherwise, Period II was identical to Period I, and the same measurements were made.

Methodology

Plasma lipids and lipoproteins. Total plasma cholesterol and TG were determined on a Technicon Auto-Analyzer (Model II, Technicon Instruments Corp., Tarrytown, NY (15, 16)). Concentrations of cholesterol in very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL) were estimated as described in the Lipid Research Clinics Manual of Laboratory Operations (17).

Cholesterol balance studies. Patients who underwent cholesterol balance studies were fed a diet of mixed solid food and liquid formula containing 40% of calories as fat. This diet was very low in cholesterol to facilitate measurements of sterol balance; it also contained a fat content and composition similar to the normal U.S. diet. Each day the patients were given three meals of liquid formula and one with solid food. Formulas were given at 8:30 AM, 4 PM, and 7 PM; they contained 15% of calories as milk protein, 45% as dextrose, and 40% as fat, mostly in the form of lard. Formulas were prepared by Hospital Diet Products Corp., Buena Park, CA. One solid meal was given at 11 AM and it contained dry cereal (corn flakes), nonfat bread, skim milk, added lard, and sugar for coffee. This diet provided for a low intake of cholesterol to facilitate estimation of cholesterol balance. Vitamin and mineral supplements were given daily. Each patient was weighed daily and caloric intake was adjusted to maintain weight at a constant level throughout the study.

Estimations of cholesterol balance were made as described earlier (18–21). Stools were collected throughout both dietary periods and usually were combined into 4–day pools. Fecal neutral and acidic steroids were isolated separately, and their masses were determined by gas–liquid chromatography (GLC) (18, 19). GLC analysis of neutral steroids distinguished between cholesterol and plant sterols and their steroid conversion products. Analyses were carried out entirely by chemical procedures. To correct for losses of neutral steroids, beta-sitosterol was given as capsules (225 mg twice daily) (20), and excretions of acidic steroids were corrected for variations in fecal flow by use of chromic oxide (21).

For control, 14 normal male subjects were studied on the same dietary regimen and by the same analytic techniques. Ages of controls ranged from 29 to 63 years (mean 51 years); their weights were 95–115% of ideal.

The data on cholesterol balance are expressed in three ways: *a*) as absolute values (mg/day), *b*) in relation to total body weight (mg/day per kg), and *c*) in relation to ideal body weight (mg/day per kg IW). We suggest that normalization of results to ideal weight may in some cases provide a better comparison between groups than absolute values or those corrected to total body weight. One advantage of expressing data in relation to ideal body weight is that it is possible to compare groups that differ in body size and degree of adiposity. For example, in obese patients, if balance data are based on actual rather than ideal weight, results will be distorted towards inordinately low values; in other words, dividing outputs by a large mass of adipose tissue may obscure real differences in absolute production rates. This issue will be considered in more detail in the Discussion section.

Lipid composition of gallbladder bile. Samples of fasting gallbladder bile were obtained three times during each of the two study periods. Samples were analyzed for cholesterol, bile acids, and phospholipids. Samples were aspirated from a single lumen tube positioned by X-ray guidance in the second portion of the

duodenum. Gallbladder contraction was stimulated by intraduodenal injection of an emulsion of safflower oil, which was free of cholesterol and phospholipids. Duodenal fluid rich in gallbladder bile was then collected by slow suction over a period of 20 min. The collected bile (30–50 ml) was thoroughly mixed and a 10-ml sample was retained for analysis; the remainder was returned to the patient via the tube. Samples were added immediately to 30 ml of chloroform-methanol 2:1. Methods for separation of lipid components were the same as used before in our laboratory (22). Cholesterol was measured on GLC as the trimethylsilyl ether (19). Phospholipids were estimated by the method of Rouser, Sidney, and Akira (23), and bile acids were determined by a standard enzymatic procedure (24, 25). Bile lipid composition was expressed as molar % for each lipid component according to Admirand and Small (25). Percent saturation was calculated by the criteria of Carey and Small (26); these workers found that saturation of bile is a function of total solids present. For calculation of percent saturation, we have assumed that gallbladder bile contained 10% solids (25, 26). For control, 14 subjects used for cholesterol balance also were employed as control for gallbladder bile composition. An average of three samples was obtained from each patient.

Outputs of biliary lipids. Hourly outputs of biliary cholesterol, bile acids, and phospholipids during constant feeding of a formula diet were determined by the marker-dilution technique of Grundy and Metzger (27). After an overnight fast, a three-lumen tube was positioned in the duodenum with the two most proximal outlets adjacent to the ampulla of Vater and the third outlet 10 cm distally. The tube was placed in the correct position with X-ray guidance. The same liquid formula as used throughout the study was infused continuously through one proximal lumen; β-sitosterol was also infused as a dilution marker. After allowing 4 hr for gallbladder contraction and for stabilization of hepatic bile secretion, hourly samples were obtained for 6 hr from the second proximal and distal outlets by slow and continuous aspiration. Less than 5% of intestinal contents passing these ports was aspirated through the tubes. Since the inputs of β-sitosterol and exogenous cholesterol were known with precision, the rate of hepatic cholesterol secretion could be estimated from the ratio of cholesterol to β-sitosterol at the distal outlet. These data combined with measurements of concentrations of bile acids and phospholipids relative to cholesterol at the proximal outlet permitted calculation of the hourly output of bile acids and phospholipids. Equations used in these calculations have been presented previously along with corrections for cholesterol contents of formula diets (27). In calculation of the percent saturation of hepatic bile, we have assumed that hepatic bile contains 3% solids (25, 26).

The pool size of bile acids was measured simultaneously with hepatic secretion rates as described before (22). Briefly, 5 μCi of [24-^{14}C]cholic acid (New England Nuclear, Boston, MA) was given intraduodenally at the beginning of the formula infusion. After 4 hr which allowed for equilibration, the ratio of isotope to total bile acids ("specific activity") became constant (22). A mean specific activity was determined on hourly samples over the next 6 hr, and the total pool of bile acids was determined by dividing the dose of radioactivity given by the mean specific activity.

For control, eight normal men were studied by the same methods; their ages ranged from 29 to 60 years (mean 47), and weights were 95–115% of ideal.

Cholesterol absorption. Net absorption of cholesterol was measured as recently described (28). The basic equation for determining cholesterol absorption is as follows:

$$\text{Mass absorbed} = (\text{daily biliary secretion} + \text{exogenous intake} - \text{daily fecal excretion})$$

Daily secretion rates of cholesterol were estimated by multiplying hourly secretion rates during continuous liquid formula infusion by 24; this conversion is based on our recent finding that hourly secretion of biliary cholesterol × 24 closely approximates duodenal outputs through a 24-hr period measured in patients given three equal meals at 8 AM, 1 PM, and 6 PM (28).

When estimating cholesterol absorption by this method, the value obtained is the net absorption of cholesterol between the upper duodenum and the anus. If the intestine contributes cholesterol to the lumen during the measurement, the net absorption will be reduced correspondingly. However, as we have shown (28), values for percentage cholesterol absorption are as high or higher than those obtained previously by other methods; this should not have occurred if intestinal secretion of cholesterol had been of consequence.

RESULTS

Plasma lipids and lipoprotein-cholesterol

Data for plasma lipids in nonobese, hypothyroid patients before and during therapy with T_4 are presented in **Table 1.** Before treatment, total plasma cholesterol averaged 289 ± 18 mg/dl and, in most patients, levels were reduced by T_4 therapy (mean

TABLE 1. Plasma lipids (nonobese hypothyroid patients)

Patient	Period[a]	Total Cholesterol[b]	Total Triglycerides[c]	LDL Cholesterol[d]	HDL Cholesterol[d]
		mg/dl ± SD	*mg/dl*	*mg/dl*	*mg/dl*
1	I	332 ± 44	234	308	59
	II	197 ± 33	139	144	55
2	I	226 ± 184	114	123	64
	II	255 ± 24	117	143	82
3	I	152 ± 13	87	104	40
	II	148 ± 5	96	112	38
4	I	159 ± 20	104	95	36
	II	134 ± 21	106	71	41
5	I	302 ± 12	150		
	II	273	92	142	47
6	I	250 ± 16	145	189	56
	II	216 ± 24	110	163	55
7	I	242 ± 38	131	200	38
	II	291	118	168	84
8	I	251 ± 22	139	199	56
	II	254 ± 4	152	188	40
9	I	303 ± 28	178	210	24
	II	263 ± 27	162	177	26
10	I	207 ± 17	196	123	49
	II	144 ± 7	130	89	35
40[e]	I	318 ± 59	535	159	42
	II	225 ± 24	349	109	30
Mean ± SEM	I	289 ± 18	183 ± 37	171 ± 20	46 ± 4
	II	221 ± 17[f]	141 ± 22	136 ± 13[f]	49 ± 6[g]

[a] Period I, hypothyroid period; II, treated period (euthyroid).
[b] Mean ± SD for six determinations in last 3 weeks of each period; exceptions are Patients 6 and 8 who had only one measurement in Period II.
[c] Mean value for plasma TG of each period; for variation, see Table 4, Ref 11.
[d] Value for one measurement at the end of each period.
[e] Patient 40 was not included in the companion study (14); he was 59 yr old and weighed 63 kg (100% of IW); his admission TSH was >100 units and T_4 was zero; the uric acid was 10.2 mg/dl.
[f] Difference between Period I and II was significantly different at $P < 0.05$ by paired *t*-test.
[g] Difference between Period I and II not statistically significant.

= 221 ± 17 mg/dl). Half of the patients had an initial LDL-cholesterol of greater than 185 mg/dl and, in all patients except one (No. 3), this fraction was decreased after return to the euthyroid state. The effects on HDL-cholesterol were variable. Some patients had an increase and others had a reduction, with the net effect being no change in the mean.

Similar results were observed for obese, hypothyroid patients (**Table 2**). Their degree of hypercholesterolemia was about the same as for the nonobese group. All patients except one had a reduction in total cholesterol with treatment and, in most patients, LDL-cholesterol was decreased as well. However, in those with initial hypertriglyceridemia, treatment with T_4 usually caused no change or an increase in LDL-cholesterol simultaneous with a reduction in TG. In these obese patients, HDL-cholesterol was relatively low, as has been reported generally for obese subjects (29). Treatment with T_4 did not cause a rise in HDL-cholesterol in this group.

As expected, patients with hyperthyroidism usually had a low plasma cholesterol (**Table 3**). Eleven of 13 had a concentration below 200 mg/dl. LDL-cholesterol concentrations likewise were low, and both total- and LDL-cholesterol increased with return to the euthyroid state. Several hyperthyroid patients also had relatively low HDL-cholesterol and, on the mean, this fraction increased significantly after therapy.

Cholesterol balance

Cholesterol balance data for the three groups of patients are shown in Tables 4, 6, and 8; based on the assumption that these patients were in the metabolic steady state, their balance data were converted into

TABLE 2. Plasma lipids (obese hypothyroid patients)

Patient	Period[a]	Total Cholesterol[b]	Total Triglycerides[c]	LDL Cholesterol[d]	HDL Cholesterol[d]
		mg/dl ± SD	*mg/dl*	*mg/dl*	*mg/dl*
11	I	221 ± 23	409	104	28
	II	186 ± 21	403	68	23
12	I	297	260	199	46
	II	215	40	140	67
13	I	370 ± 39	174	257	56
	II	370 ± 17	195	208	50
14	I	256	200	158	60
	II	218	190	125	55
15	I	296 ± 31	179		
	II	213 ± 25	167		
16	I	305 ± 25	557	174	32
	II	264 ± 29	294	175	39
17	I	261 ± 26	137	149	61
	II	179 ± 16	108	103	41
18	I	242 ± 15	136		
	II	139 ± 30	105		
19	I	541 ± 103	1806	49	19
	II	455 ± 55	1177	56	18
20	I	292 ± 21	292	176	23
	II	177 ± 51	179	55	21
21	I	377 ± 78	870	92	34
	II	211 ± 13	381	98	31
22	I	225	60	178	35
	II	214	40	166	40
23	I	387 ± 66	487	229	34
	II	274 ± 27	336	166	34
24	I	329 ± 32	178		
	II	228 ± 18	158		
25	I	263 ± 22	224	160	46
	II	239 ± 10	214	179	32
26	I	256 ± 23	179	181	48
	II	187 ± 42	111	155	35
Mean ± SEM	I	307 ± 20	384 ± 108	162 ± 15	40 ± 4
	II	236 ± 20[e]	256 ± 67[e]	130 ± 14[e]	37 ± 4[f]

[a] Period I, hypothyroid period; II, treated period (euthyroid).
[b] Mean ± SD for six determinations; exceptions are Patients 13, 15, and 23 who had only one measurement in each period.
[c] Mean value for plasma TG of each period; for variation, see Table 5, Ref 14.
[d] Value for one measurement at the end of each period.
[e] Difference significant at $P < 0.025$.
[f] Not significant.

values for synthesis of cholesterol and bile acids in Tables 5, 7, and 9. Also, values for production of cholesterol and bile acids are presented for 14 normal subjects in Table 5.

Data for five nonobese, hypothyroid patients are shown in **Tables 4** and **5.** Before therapy, cholesterol synthesis was somewhat lower in the hypothyroid state than in euthyroid controls (7.9 versus 9.6 mg/kg per day; Table 5). In contrast, production of bile acids was essentially normal before treatment. After therapy, four of five patients had an increase in outputs of neutral steroids. While this increase was not statistically significant for the group, total synthesis of cholesterol was increased significantly following

TABLE 3. Plasma lipids (hyperthyroid patients)

Patients	Period[a]	Total Cholesterol[b]	Total Triglyceride[c]	LDL Cholesterol[d]	HDL Cholesterol[d]
		mg/dl ± SD	*mg/dl*	*mg/dl*	*mg/dl*
27	I	114 ± 19	64	74	43
	II	156 ± 12	62	89	61
28	I	151 ± 25	116	86	46
	II	207 ± 21	104	152	46
29	I	117 ± 21	108	69	21
	II	194 ± 24	101		
30	I	100 ± 28	55	40	29
	II	179 ± 21	98	119	48
31	I	183 ± 70	103	94	45
	II	177 ± 14	83	116	56
32	I	179 ± 10	131	121	33
	II	255 ± 53	171	235	42
33	I	138 ± 17	123	82	37
	II	163 ± 13	117	111	47
34	I	206 ± 27	124	156	40
	II	262 ± 14	130	194	41
35	I	201 ± 22	186	129	34
	II	309 ± 25	231	210	51
36	I	165	66	88	66
	II	241	72	149	80
37	I	115 ± 29	70		
	II	209 ± 48	89	117	97
38	I	117 ± 12	118	115	37
	II	162	130	118	42
39	I	172 ± 23	110	118	43
	II	228 ± 18	158		
Mean ± SEM	I	155 ± 10	106 ± 10	99 ± 10	41 ± 3
	II	211 ± 13[e]	119 ± 13[f]	149 ± 15[f]	51 ± 4[f]

[a] Period I, hyperthyroid period; II, treated period (euthyroid).
[b] Mean ± SD for six determinations; exceptions are Patient 41 who had only one measurement in each period and Patient 38 who had one in Period II.
[c] Mean value for plasma TG of each period; for variation see Table 5, Ref 14.
[d] Value for one measurement at the end of each period.
[e] Differences between Periods I and II not significant.
[f] Differences significant at $P < 0.01$.

return to the euthyroid state. Despite the rise in cholesterol synthesis, production of bile acids was not altered by T_4 therapy.

Results for seven obese, hypothyroid patients are presented in **Tables 6** and **7.** When data were normalized to total body weight, cholesterol synthesis per kg was only slightly increased; but when normalized to ideal weight, which is a better reflection of actual production, synthesis rates for cholesterol were much greater than normal even before treatment (Table 7). The same was true for bile acids. Following treatment with T_4, fecal neutral steroids were significantly higher, as were total steroids and cholesterol balance (Table 6). Bile acid excretion was unchanged. Thus, as with nonobese patients, T_4 therapy caused a significant rise in cholesterol synthesis, but bile acid synthesis was not altered (Table 7). Thus, while treatment with T_4 caused a significant increase in synthesis of cholesterol, these patients were overproducing cholesterol and bile acids even before treatment.

When the data from a total of 12 nonobese and obese patients with hypothyroidism were combined, neutral steroid excretion was significantly lower by paired analysis before treatment (437 ± 51 mg/day) than after (621 ± 58 mg/day) ($P < 0.05$). Also, cholesterol balance (synthesis) before treatment (848 ± 117 mg/day) was less than following therapy (1071 ± 153 mg/day) ($P < 0.05$). On the other hand, combining

TABLE 4. Cholesterol balance data (nonobese hypothyroid patients)

Patient	Period[a]	Days:No. Determ.[b]	Cholesterol Intake	Fecal Steroid Excretions: Neutral Steroids	Acidic Steroids	Total Steroids	Cholesterol Balance
			mg/day	*mg/day ± SD*			
1	I	34:5	92	200 ± 29	143 ± 50	343 ± 66	251 ± 66
	II	34:6	92	452 ± 203	190 ± 71	642 ± 232	551 ± 232
4	I	34:5	148	576 ± 113	495 ± 86	1071 ± 180	923 ± 140
	II	51:6	118	676 ± 86	519 ± 134	1195 ± 66	1084 ± 64
6	I	29:5	135	330 ± 142	206 ± 72	536 ± 194	401 ± 194
	II	34:6	135	459 ± 68	393 ± 81	852 ± 78	718 ± 78
9	I	40:5	105	554 ± 54	275 ± 16	820 ± 36	715 ± 36
	II	32:6	105	471 ± 89	236 ± 23	708 ± 88	603 ± 88
10	I	24:6	99	291 ± 86	279 ± 128	570 ± 193	471 ± 193
	II	24:4	99	308 ± 51	389 ± 148	696 ± 183	597 ± 183
Mean ± SEM	I		116 ± 11	390 ± 74	335 ± 81	668 ± 126	552 ± 119
	II		110 ± 8[c]	473 ± 59[c]	345 ± 59[c]	819 ± 100[c]	711 ± 97[c]

[a] Period I, hypothyroid; Period II, euthyroid.
[b] Duration of balance period (days) and number of successive stool pools analyzed; the ratio of the two figures gives the average number of days in each pool.
[c] Difference between Periods I and II not statistically significant.

the bile acid data failed to produce a significant difference between the two periods.

Data for hyperthyroid patients are presented in **Tables 8** and **9.** For the small number of patients who were able to complete the balance studies, the results were variable. Two patients (Nos. 33 and 34) had a distinct elevation in synthesis of both cholesterol and bile acids. In the one of these, who was not obese (No. 33; 113% IW), production rates of cholesterol and bile acids were 15.9 and 10.1 mg/kg IW/day, respectively. In the other patient, who was obese (No. 39; 144% IW), synthesis rates were respectively 21.5 and 6.5 mg/kg IW/day. Two other hyperthyroid patients of normal weight had normal rates of syn-

TABLE 5. Steroid synthesis data (nonobese hypothyroid patients)

Patient	Period[a]	Cholesterol Synthesis		Bile Acid Synthesis	
		mg/kg/day	*mg/kg-IW/day*	*mg/kg/day*	*mg/kg-IW/day*
1	I	4.7	4.5	2.7	2.5
	II	10.2	9.8	3.5	3.4
4	I	14.1	14.8	7.6	7.9
	II	16.6	17.4	7.9	8.3
6	I	5.2	5.7	2.7	3.0
	II	9.3	10.3	5.1	5.6
9	I	8.1	9.6	3.1	3.7
	II	6.9	8.1	2.7	3.2
10	I	7.2	7.4	4.3	4.4
	II	9.2	9.3	6.0	6.1
Mean ± SEM	I	7.9 ± 1.7	8.4 ± 1.8	4.1 ± 0.9	4.3 ± 1.0
	II	10.4 ± 1.6[b]	11.0 ± 1.6[b]	5.0 ± 0.9[c]	5.3 ± 0.9[c]
Normal (14 subjects) Mean ± SEM		9.6 ± 0.6	10.1 ± 0.6	4.9 ± 0.5	5.1 ± 0.5

[a] Period I, hypothyroid period; II, euthyroid period.
[b] Difference between Periods I and II significant at $P < 0.05$ by paired t tests.
[c] Difference not significant.

TABLE 6. Cholesterol balance data (obese hypothyroid patients)

Patient	Period[a]	Days:No. Determ.[b]	Cholesterol Intake	Fecal Steroid Excretions: Neutral Steroids	Acidic Steroids	Total Steroids	Cholesterol Balance
			mg/day	*mg/day ± SD*			
11	I	24:6	215	583 ± 175	347 ± 174	929 ± 201	714 ± 199
	II	62:12	135	545 ± 261	608 ± 272	1153 ± 381	1018 ± 380
17	I	23:6	147	389 ± 53	904 ± 310	1293 ± 278	1146 ± 277
	II	26:6	147	534 ± 116	850 ± 483	1384 ± 559	1237 ± 559
19	I	25:5	109	413 ± 44	509 ± 149	922 ± 180	813 ± 180
	II	34:6	109	686 ± 198	483 ± 123	1169 ± 296	1060 ± 296
21	I	24:6	110	500 ± 32	652 ± 27	1152 ± 33	1041 ± 31
	II	37:6	114	938 ± 191	660 ± 90	1598 ± 184	1484 ± 184
23	I	33:5	145	862 ± 368	1085 ± 288	1947 ± 498	1802 ± 492
	II	35:6	160	956 ± 274	1644 ± 364	2600 ± 486	2440 ± 486
24	I	34:6	168	588 ± 95	456 ± 74	1044 ± 145	899 ± 145
	II	35:6	145	600 ± 161	293 ± 87	984 ± 176	749 ± 176
26	I	31:6	110	552 ± 77	568 ± 55	1120 ± 58	1010 ± 58
	II	29:6	110	827 ± 54	600 ± 30	1427 ± 63	1317 ± 63
Mean ± SEM	I		143 ± 15	555 ± 59	646 ± 99	1201 ± 134	1061 ± 135
	II		131 ± 8[c]	727 ± 68[d]	734 ± 165[c]	1474 ± 203[d]	1329 ± 205[d]

[a] Period I, hypothyroid; Period II, euthyroid.
[b] Duration of balance period (days) and number of successive stool pools analyzed; the ratio of the two figures gives the average number of days in each pool.
[c] Difference between Periods I and II not statistically significant.
[d] Difference between Periods I and II significant at $P < 0.025$.

thesis for both cholesterol and bile acids. Treatment of three patients with hyperthyroidism produced no change in the synthesis of either sterol.

Biliary lipid metabolism

Data for hourly output of biliary lipids and pool sizes of bile acids are presented for the three groups in Tables 10–12. **Table 10** compares data for four nonobese, hypothyroid patients with eight nonobese, euthyroid subjects. The results for the two groups were very similar for all variables. Also, in the hypothyroid patients, lipid composition and percent saturation of stimulated hepatic bile were unaltered by therapy. On the other hand, hepatic secretion of cholesterol was greater after therapy, which is in accord with a corresponding increase in fecal neutral steroids. The pool sizes of bile acids, which were in the normal range in the untreated state, were not changed by treatment.

In the eight obese patients with hypothyroidism (**Table 11**), the saturation of hepatic bile was greater than in nonobese patients with and without hypothyroidism (Table 10); this was due to a greater secretion of cholesterol in the obese group. Treatment with T_4 produced no consistent differences in either outputs of cholesterol, bile acids, and phospholipids or saturation of stimulated hepatic bile.

Complete studies of biliary lipid outputs were possible in only two patients with hyperthyroidism (**Table 12**). These patients had a relatively low saturation of stimulated hepatic bile, but otherwise their values were unremarkable. Furthermore, treatment produced no significant changes in any of the variables.

Finally, results for lipid composition of gallbladder bile are presented in Tables 13–15. The gallbladder bile of nonobese, hypothyroid patients was somewhat higher than that of comparable control subjects, but treatment of the former did not cause a significant reduction in bile saturation (**Table 13**). The gallbladder bile was much more saturated in obese, hypothyroid patients which is characteristic of obese patients in general (**Table 14**). In these patients, the molar percentages of the three biliary lipids were essentially unaffected by T_4 treatment, except that two obese patients (Nos. 20 and 21) had a distinct increase in bile saturation after return to the euthyroid state. By way of contrast, in the only two patients with hyperthyroidism in whom the study could be completed, molar % cholesterol and saturation were both lower before treatment, but they showed little change in either after return to the euthyroid state (**Table 15**).

Cholesterol absorption

Values for cholesterol absorption in eight patients with hypothyroidism are presented along with results in nine normal subjects in **Table 16.** During their

TABLE 7. Steroid synthesis data (obese hypothyroid patients)

Patient	Period[a]	Cholesterol Synthesis		Bile Acid Synthesis	
		mg/kg/day	*mg/kg-IW/day*	*mg/kg/day*	*mg/kg-IW/day*
11	I	8.6	10.2	4.2	5.0
	II	12.3	14.6	7.3	8.7
17	I	13.8	18.1	10.9	14.3
	II	14.9	19.5	10.2	13.4
19	I	9.0	12.0	5.7	7.5
	II	11.8	15.7	5.4	7.1
21	I	10.7	15.8	6.7	9.9
	II	15.3	22.5	6.8	10.0
23	I	14.3	22.5	8.6	13.6
	II	19.3	30.5	13.0	20.6
24	I	8.3	13.2	4.2	6.7
	II	6.9	11.0	2.7	4.3
26	I	8.0	20.2	4.5	11.4
	II	10.5	26.3	4.8	12.0
Mean ± SEM	I	10.4 ± 1.0	16.0 ± 1.7	6.4 ± 1.0	9.8 ± 1.3
	II	13.0 ± 1.5[b]	20.0 ± 2.6[b]	7.2 ± 1.3[c]	10.9 ± 2.0[c]

[a] Period I, hypothyroid period; II, euthyroid period.
[b] Difference between Periods I and II significant at $P < 0.05$ by paired t-test.
[c] Difference not significant.

hypothyroid period the patients did not have reduced absorption of cholesterol (66 ± 3% versus 63 ± 5% for normals). In fact, their percentage absorption was lower after treatment with T_4. Theoretically, this could have been due either to a greater flux of cholesterol into the intestine or to a more rapid transit. Although biliary input was somewhat increased by T_4, it is likely that the hormone also stimulates intestinal transit.

In the one hyperthyroid patient (No. 34) who was studied, the results are in accord. In the untreated period, cholesterol input was 852 mg/day; his fecal neutral steroids averaged 318 mg/day leaving an absorption of 534 mg/day (63%). Following therapy, his influx was greater, 1033 mg/day, but despite this his fecal neutral steroids dropped to 255 mg/day. Therefore, both absolute and percentage absorption (778 mg/day and 75%) were greater after return to the

TABLE 8. Cholesterol balance data (hyperthyroid patients)

Patient	Period[a]	Days:No. Determ.[b]	Cholesterol Intake	Fecal Excretions			Cholesterol Balance
				Neutral Steroids	Acidic Steroids	Total Steroids	
			mg/day	*mg/day ± SD*			
33	I	28:6	105	518 ± 111	724 ± 125	1242 ± 103	1137 ± 103
34	I	33:7	108	318 ± 51	282 ± 64	600 ± 109	492 ± 109
	II	33:6	97	155 ± 66	235 ± 84	490 ± 122	393 ± 122
35	I	35:6	94	473 ± 134	230 ± 68	703 ± 115	609 ± 115
	II	25:5	85	380 ± 139	259 ± 95	639 ± 224	554 ± 224
39	I	33:5	145	1183 ± 386	440 ± 43	1623 ± 413	1461 ± 413
	II	35:6	145	600 ± 161	293 ± 87	894 ± 176	749 ± 176
Mean ± SEM	I (4)		113 ± 11	623 ± 192	419 ± 111	1042 ± 239	925 ± 227
	I (3)		116 ± 15	658 ± 266	304 ± 50	975 ± 325	854 ± 305
	II (3)		109 ± 18[c]	378 ± 128[c]	262 ± 18[c]	674 ± 118[c]	565 ± 103[c]

[a] Period I, hyperthyroid; Period II, euthyroid.
[b] Duration of balance period (days) and number of successive stool pools analyzed; the ratio of the two figures gives the average number of days in each pool.
[c] Difference between Periods I and II not statistically significant.

TABLE 9. Steroid synthesis data (hyperthyroid patients)

Patient	Period[a]	Cholesterol Synthesis		Bile Acid Synthesis	
		mg/kg/day	*mg/kg-IW/day*	*mg/kg/day*	*mg/kg-IW/day*
33	I	14.1	15.9	9.0	10.1
34	I	6.6	7.5	3.8	4.3
	II	5.2	6.0	3.1	3.6
35	I	9.0	10.5	3.4	4.0
	II	8.2	9.5	3.8	4.5
39	I	14.9	21.5	4.5	6.5
	II	7.6	11.0	3.0	4.3
Mean ± SEM	I (3)	10.2 ± 2.5	13.2 ± 4.3	3.9 ± 0.3	4.9 ± 0.8
	II (3)	7.0 ± 0.9[b]	8.8 ± 1.5[b]	3.3 ± 0.3[b]	4.1 ± 0.3[b]

[a] Period I, hyperthyroid period; II, euthyroid period.
[b] Difference between Periods I and II not significant.

euthyroid state. Again, it seems likely that the more rapid intestinal transit associated with hyperthyroidism had reduced cholesterol absorption.

DISCUSSION

The hypocholesterolemic action of thyroid hormones is well known, and hypothyroid patients commonly have elevated plasma cholesterol while those with hyperthyroidism have the reverse. The present study was designed to ascertain the consequences of hypothyroidism and hyperthyroidism on the metabolism of cholesterol and bile acids and to determine whether abnormalities might be detected that correlate with variations in plasma cholesterol concentrations. At the same time, possible modifications in biliary lipids, which might be secondary to altered metabolism of cholesterol and bile acids, were explored.

Plasma lipoproteins

The present work discloses that thyroid dysfunction can affect cholesterol concentrations in each of

TABLE 10. Hourly outputs of biliary lipids and pool sizes of bile acids (nonobese, hypothyroid patients)

Patient	Period	Lipid Composition			Biliary Lipid Output			Bile Saturation (3% solids)	Bile Acid Pool Size
		Cholesterol	Bile Acids	Phospholipids	Cholesterol	Bile Acids	Phospholipids		
		molar % ± SD[a]			*mg/hr ± SD*[a]			*%*	*mg*
1	I				33 ± 8				1928
	II	4.1 ± 0.7	78.0 ± 2.0	17.6 ± 1.5	37 ± 4	940 ± 204	326 ± 41	85.2	2370
4	I	6.2 ± 0.8	76.7 ± 0.8	17.2 ± 1.1	45 ± 8	710 ± 116	249 ± 48	129.3	2142
	II	4.7 ± 1.4	76.5 ± 7.5	18.8 ± 6.2	60 ± 11	1382 ± 482	484 ± 100	92.9	2240
6	I	4.1 ± 0.7	78.1 ± 2.3	17.7 ± 1.6	41 ± 5	1029 ± 159	361 ± 43	85.0	2138
	II	4.9 ± 0.6	75.5 ± 1.1	19.6 ± 0.8	51 ± 5	1033 ± 110	418 ± 49	93.8	2099
7	I	4.1 ± 0.6	78.5 ± 1.1	17.3 ± 0.8	48 ± 4	1213 ± 249	415 ± 75	86.4	4161
8	I	3.6 ± 0.5	81.2 ± 1.3	15.0 ± 0.8	38 ± 5	1131 ± 215	324 ± 54	84.1	4789
	II	4.0 ± 0.3	79.0 ± 2.2	17.0 ± 2.0	53 ± 18	1365 ± 548	450 ± 175	85.5	5461
9	I	5.1 ± 0.7	74.6 ± 1.6	20.2 ± 1.4	53 ± 7	986 ± 176	416 ± 52	95.3	1620
	II	6.1 ± 0.4	75.3 ± 1.0	18.5 ± 1.0	58 ± 6	940 ± 150	358 ± 48	120.5	1796
Mean ± SEM	I (4)	4.8 ± 0.6	77.7 ± 1.4	17.5 ± 1.1	44 ± 3	964 ± 90	338 ± 35	98.4 ± 10.6	2672 ± 716
	II (4)	4.9 ± 0.4[b]	76.6 ± 0.8[b]	18.5 ± 0.5[b]	56 ± 2[c]	1180 ± 113[b]	428 ± 27[b]	98.2 ± 7.7[b]	2899 ± 859[b]
Normal 8 patients		4.7 ± 0.4	79.6 ± 1.0	15.6 ± 2.1	47 ± 0.7	1139 ± 180	340 ± 46	106.3 ± 3.2	2921 ± 434

[a] The data include means ± SD for six hourly samples during the steady state period of formula infusion.
[b] Difference not statistically significant between Periods I and II.
[c] Difference significant at $P < 0.025$.

TABLE 11. Hourly outputs of biliary lipids and pool sizes of bile acids (obese, hypothyroid patients)

Patient	Period	Lipid Composition			Biliary Lipid Output			Bile Saturation (3% solids)	Bile Acid Pool Size
		Cholesterol	Bile Acids	Phospholipids	Cholesterol	Bile Acids	Phospholipids		
		molar % ± SD[a]			*mg/hr ± SD*[a]			%	*mg*
15	I	5.1 ± 0.6	77.5 ± 1.5	17.2 ± 1.2	52 ± 11	976 ± 213	335 ± 90	107.0	3663
	II	7.1 ± 0.9	70.7 ± 2.5	22.0 ± 2.6	78 ± 12	1002 ± 199	515 ± 106	123.0	2560
16	I	4.8 ± 0.6	81.1 ± 4.7	14.0 ± 4.5	63 ± 20	1992 ± 707	600 ± 307	116.7	2959
	II	5.9 ± 0.9	70.5 ± 4.9	23.4 ± 5.4	42 ± 7	663 ± 135	348 ± 124	99.0	2569
17	I	5.1 ± 1.0	78.9 ± 1.5	15.9 ± 1.1	58 ± 5	1190 ± 189	363 ± 51	113.3	4670
	II	6.1 ± 1.0	73.8 ± 3.5	20.0 ± 2.6	74 ± 8	1238 ± 188	501 ± 57	113.9	5755
19	I	3.7 ± 0.3	72.9 ± 1.8	23.3 ± 1.5	43 ± 8	1089 ± 226	544 ± 103	63.2	4826
	II	5.4 ± 0.5	73.1 ± 1.9	21.4 ± 1.5	58 ± 5	1017 ± 188	463 ± 49	96.6	3453
20	I	5.8 ± 1.7	78.1 ± 3.3	16.0 ± 2.1	16 ± 9	320 ± 169	105 ± 65	127.6	2073
	II	4.8 ± 0.5	77.4 ± 1.5	17.5 ± 1.2	40 ± 7	815 ± 112	290 ± 45	99.6	1861
21	I	8.4 ± 1.6	73.6 ± 3.3	17.9 ± 3.0	71 ± 15	844 ± 254	315 ± 85	167.0	4329
	II	4.5 ± 1.0	74.9 ± 1.6	20.5 ± 1.2	72 ± 4	1686 ± 417	716 ± 170	83.6	3824
23	I	8.0 ± 0.6	74.0 ± 1.4	17.9 ± 0.9	86 ± 4	1030 ± 113	384 ± 25	159.5	3461
	II	9.8 ± 1.6	72.9 ± 3.1	17.0 ± 1.7	78 ± 20	775 ± 274	297 ± 68	199.7	2064
26	I	8.6 ± 1.5	72.1 ± 1.5	19.3 ± 1.0	77 ± 6	862 ± 146	360 ± 66	161.7	2591
	II	7.5 ± 0.5	74.1 ± 0.9	18.3 ± 0.7	75 ± 13	971 ± 223	373 ± 83	147.8	1413
Mean ± SEM	I	6.2 ± 0.7	76.0 ± 1.2	17.7 ± 1.0	58 ± 8	1038 ± 165	376 ± 53	127.0 ± 12.4	3572 ± 353
	II	6.4 ± 0.6[b]	73.4 ± 0.8[b]	20.0 ± 0.8[b]	65 ± 6[b]	1021 ± 114[b]	438 ± 50[b]	122.1 ± 13.9[b]	3085 ± 446[c]

[a] The data include means ± SD for six hourly samples during the steady state period of formula infusion.
[b] Difference not statistically significant between Periods I and II.
[c] Difference significant at $P < 0.025$.

the different lipoprotein fractions. The major alteration occurred in the LDL fraction. In both nonobese and obese patients with hypothyroidism, LDL-cholesterol was relatively high and treatment with T_4 produced a 20% reduction in both groups. Conversely, return to the euthyroid state in patients with hyperthyroidism evoked a mean rise in this fraction of 51%.

The influence of thyroid dysfunction on HDL-cholesterol seems more complex. Our hyperthyroid patients had lower levels before treatment than after. Thus, excess circulating thyroid hormone apparently lowers HDL as it does LDL. A similar result has been reported beforehand by Sachs, Wolfman, and Murthy (30), and more recently by Scottolini et al. (31).

Of interest, several of our hypothyroid patients also had relatively low values of HDL-cholesterol before treatment. However, decreased values were mostly present in the obese group and several nonobese patients actually had relatively high levels, as also was reported by Scottolini et al. (31). Both Sachs et al. (30) and Scottolini et al. (31) treated hypothyroid patients with thyroid hormone and noted a depression in HDL-cholesterol. This response was not reproduced

TABLE 12. Hourly outputs of biliary lipids and pool sizes of bile acids (hyperthyroid patients)

Patient	Period	Lipid Composition			Biliary Lipid Output			Bile saturation (3% solids)	Bile Acid Pool Size
		Cholesterol	Bile Acids	Phospholipids	Cholesterol	Bile Acids	Phospholipids		
		molar %[a]			*mg/hr ± SD*[a]			%	*mg*
33	I	3.4 ± 0.6	75.7 ± 5.0	20.7 ± 4.8	64 ± 12	1804 ± 270	774 ± 215	63.2	2832
	II	5.0 ± 0.6	73.5 ± 2.3	21.4 ± 1.8	51 ± 11	966 ± 207	435 ± 84	89.7	5516
34	I	3.6 ± 0.6	79.1 ± 2.9	17.2 ± 2.9	31 ± 4	902 ± 190	307 ± 85	76.4	2167
	II	4.6 ± 0.9	77.4 ± 1.6	17.9 ± 1.1	39 ± 11	998 ± 394	357 ± 140	94.2	2037
Mean ± SEM	I	3.5 ± 0.1	77.4 ± 1.7	19.0 ± 1.8	48 ± 17	907 ± 897	541 ± 234	69.8 ± 6.6	2500 ± 333
	II	4.8 ± 0.2[b]	75.5 ± 1.9[b]	19.7 ± 1.8[b]	45 ± 6[b]	982 ± 16[b]	396 ± 39[b]	92.0 ± 2.2[b]	3777 ± 1740[b]

[a] The data include means ± SD for six hourly samples during the steady state period of formula infusion.
[b] Difference not statistically significant between Periods I and II.

TABLE 13. Lipid composition of gallbladder bile and saturation indices (nonobese hypothyroid patients)

Patient	Period	Lipid Composition[a]			% Saturation (10% solids)
		Cholesterol	Bile Acids	Phospholipids	
			mole %		%
1	I	7.6	71.4	21.0	109
4	I	12.3	71.0	16.7	198
	II	9.5	69.0	22.0	131
6	I	7.7	71.8	20.4	112
	II	6.9	75.3	17.6	111
8	I	10.4	74.3	19.6	157
9	I	8.2	72.2	19.6	122
	II	11.2	66.1	22.5	150
Mean ± SEM	I (5)	9.2 ± 0.4	72.1 ± 0.3	19.5 ± 0.3	139 ± 8
	I (3)	10.1 ± 0.8	71.7 ± 0.2	18.9 ± 0.6	144 ± 16
	II (3)	9.2 ± 0.7[b]	70.1 ± 1.6[b]	20.7 ± 0.3[b]	131 ± 7[b]
Normal-14 subjects Mean ± SEM		7.7 ± 0.4	74.8 ± 0.9	18.6 ± 0.6	120 ± 4

[a] Values represent mean of three to four determinations in each period.
[b] Differences between Periods I and II not statistically significant.

in our patients, perhaps because of their relatively low levels before therapy. At least two factors may have been responsible for low HDL in our obese, hypothyroid patients. First, obesity itself is accompanied by reduced HDL (20), and second, many of these patients had hypertriglyceridemia which is known to be associated with a decreased HDL-cholesterol (32). Furthermore, with therapy, the HDL-lowering action of T_4 may have been offset to some extent by a fall in plasma TG.

Cholesterol balance

The decline of LDL-cholesterol induced by thyroid hormones might be explained by modification of the metabolism of cholesterol or bile acids. Two processes have been proposed by other workers (9–12, 33): thyroid hormones may *a*) stimulate conversion of cholesterol into bile acids or *b*) accentuate outputs of neutral steroids. Conceivably, as suggested by the current study, cholesterol absorption may also be depressed

TABLE 14. Lipid composition of gallbladder bile and saturation indices (obese hypothyroid patients)

Patient	Period	Lipid Composition[a]			% Saturation (10% solids)
		Cholesterol	Bile Acids	Phospholipids	
			mole %		%
15	I	11.7	69.3	18.9	174
	II	12.4	66.6	20.9	172
18	I	6.9	75.0	18.6	108
	II	6.1	73.8	10.0	91
19	I	7.7	67.7	24.6	100
	II	9.2	69.0	21.6	128
20	I	7.8	73.5	18.8	120
	II	12.6	66.1	21.2	173
21	I	8.1	71.0	20.8	116
	II	21.4	65.5	13.0	378
23	I	13.2	72.2	14.5	232
	II	12.8	72.8	14.3	228
Mean ± SEM	I	9.2 ± 1.0	71.5 ± 1.1	19.4 ± 1.3	142 ± 21
	II	12.4 ± 2.1	69.0 ± 1.5	16.8 ± 2.1	194 ± 41

[a] Values represent mean of three to four determinations in each period.

TABLE 15. Lipid composition of gallbladder bile and saturation indices (hyperthyroid patients)

Patient	Period	Lipid Composition			% Saturation (10% solids)
		Cholesterol	Bile Acids	Phospholipids	
			mole %		%
33	I	3.4	75.7	20.7	50
	II	5.0	73.5	21.4	72
34	I	3.6	79.1	17.2	60
	II	4.6	77.4	17.9	75
Mean ± SEM	I	3.5 ± 0.1	77.4 ± 1.7	19.0 ± 1.8	55 ± 5
	II	4.8 ± 0.2	75.5 ± 1.9	19.7 ± 1.8	73 ± 1

to some extent by the hormones. The results of our research corroborate prior reports that thyroid hormones increase outputs of neutral steroids. In our hypothyroid patients, these outputs were greater after T_4 therapy than before. Those with hyperthyroidism had the reverse; their neutral steroid excretion was higher before treatment than after. By way of contrast, outputs of acidic steroids were not modified by treatment in either group. This implies that thyroid hormones do not augment conversion of cholesterol to bile acids in man.

Although the excretion of neutral steroids is seemingly enhanced by the thyroid hormones, this action need not be the cause of plasma cholesterol lowering. Raised steroid outputs could result either from mobilization of cholesterol from existing pools (as plasma) or from promotion of cholesterol synthesis. The former should cause a temporary rise in steroid outputs, the latter a sustained increment. Examination of individual data favored the latter, i.e., a sustained elevation. Therefore, thyroid hormones probably stimulate cholesterol synthesis, and it seems unlikely that this action is related to their facility to lower LDL.

Several preceding workers have reported that cholesterol synthesis is suppressed in hypothyroidism

TABLE 16. Cholesterol absorption (hypothyroid patients)

Patient	Period	Cholesterol Input		Cholesterol Output	Cholesterol Absorption	
		Dietary	Biliary			
		mg/day	*mg/day*	*mg/day*	*mg/day*	%
1	I	92	792	200	684	77
	II	92	888	452	528	54
4	I	148	1080	576	652	53
	II	118	1440	676	882	57
6	I	135	984	330	789	71
	II	135	1224	459	900	66
9	I	105	1272	554	823	60
	II	105	1392	471	1026	69
19	I	109	1032	413	728	64
	II	109	1392	686	815	54
21	I	110	1704	500	1314	72
	II	114	1728	938	904	49
23	I	145	2064	862	1347	61
	II	160	1872	956	1076	53
26	I	110	1848	552	1406	72
	II	110	1800	827	1087	57
Mean ± SEM	I	119 ± 7	1347 ± 164	484 ± 70	967 ± 116	66 ± 3
	II	118 ± 7	1473 ± 118	683 ± 74	902 ± 64	57 ± 3
Normal-8 subjects Mean ± SEM		96 ± 7	1063 ± 97	403 ± 39	757 ± 58	65 ± 5

and increased in hyperthyroidism (5, 34–41). Our data are in agreement with these reports in a relative but not in an absolute sense. The net effect of treatment of hypothyroid patients with T_4 was to augment significantly the balance of cholesterol, and hence to stimulate synthesis. From these findings we must conclude that a lack of T_4 slackens production of cholesterol. Nonetheless, obese, hypothyroid subjects regularly had elevated synthetic rates. This phenomenon probably was due in part to an excessive intake of calories required to maintain their obesity; the overproduction of cholesterol in obese patients is well-recognized (42). An additional factor that may have contributed to excessive synthesis of cholesterol in these patients is a diminished oxidation of caloric substrate. As Keyes and Heimberg (43) observed for other lipids, the hypothyroid state may divert 2-carbon fragments away from oxidation to cholesterol synthesis. Thus, in our obese patients, the mean production of cholesterol in the hypothyroid state was greater than normal (16.0 ± 1.7 mg/day/kg IW versus 10.1 mg/day/kg IW for normals). Nevertheless, it was enhanced even more after treatment (to 20.0 ± 2.6 mg/day/kg IW). This finding again reveals that T_4 can increase synthesis. Nonetheless, we conclude that the caloric balance, as reflected by obesity or normal weight, is more important for controlling the level of cholesterol synthesis in hypothyroidism than are concentrations of circulating T_4. This conclusion also is supported by the four balance studies done in hyperthyroid patients (Table 9).

To summarize, alterations in synthesis, catabolism, absorption, or excretion of cholesterol cannot explain fully the changes in LDL-cholesterol found in patients with thyroid dysfunction. They nevertheless could play a supporting role. For example, in the untreated, hypothyroid state, many patients have an increase in synthesis of cholesterol and secretion of VLDL. Both could contribute to elevated LDL-cholesterol. Furthermore, absorption was relatively high in hypothyroid subjects which should bolster an elevated LDL. However, these factors probably are not crucial. More likely, LDL-cholesterol is influenced to a greater extent by an independent action of thyroid hormones on the catabolism of LDL. For example, Walton et al. (13) have reported a diminished removal of ^{131}I-labeled LDL in hypothyroid patients and accentuated clearance in those with hyperthyroidism. A stimulation of LDL catabolism by thyroid hormones also is supported by the preliminary report of Chait, Albers, and Bierman (44); they observed that T_4 enhances both binding and degradation of LDL in cultured human fibroblasts.

Biliary lipid metabolism

The influence of hypo- and hyperthyroidism on biliary lipid metabolism also was explored in this study. Preceding work in rats indicated that cholesterol concentrations in bile fall after these animals are made hypothyroid and rise when they are hyperthyroid (10, 45, 46). These findings were not confirmed in our studies in man. Two hyperthyroid patients did not have increased cholesterol secretion, and several patients with hypothyroidism did. An increased biliary cholesterol in obese, hypothyroid patients is in accord with our previous findings in obese, euthyroid subjects (42). This high secretion of biliary cholesterol in our hypothyroid patients evidently was the cause of the supersaturation of gallbladder bile often found in these patients. Furthermore, the failure to correct this abnormality completely by treatment with T_4 substantiates the concept that the state of nutrition (i.e., obesity or nonobesity) was the crucial determinant of bile saturation. Thus, the effects of thyroid hormones on biliary lipids must be due in large part to their influence on caloric balance.

Obesity and hypothyroidism

The division of our hypothyroid patients into nonobese and obese patients has been revealing. The nonobese patients clearly had hypercholesterolemia that could not be explained by overproduction of cholesterol or decreased synthesis of bile acids. This strongly suggests that other factors, such as decreased catabolism of LDL, are mainly responsible for elevated LDL-cholesterol. On the other hand, a majority of our patients with hypothyroidism were obese, and weight gain has been reported to be a presenting feature in 50 to 75% of patients with hypothyroidism (47–49). Presumably, the increase in weight is due to a reduction in oxidative utilization of calories. Once obesity is established and maintained, it can become an independent factor regulating lipid metabolism. Thus, despite their hypothyroidism, our obese patients exhibited an abnormally high synthesis of cholesterol that may have contributed in part to hypercholesterolemia. On the other hand, by keeping body weight constant in our obese subjects, we were able to show that thyroid hormone, independent of body weight, can stimulate the synthesis of cholesterol.

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