Metabolism of plasma triglycerides in hypothyroidism and hyperthyroidism in man

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Abstract Studies on plasma triglycerides (TG) were performed in 10 nonobese and 16 obese patients with hypothyroidism and in 13 with hyperthyroidism. Nonobese, hypothyroid patients generally had normal levels of TG, but obese patients often had hypertriglyceridemia. In most hypothyroid patients l-thyroxine treatment lowered plasma TG, and most hyperthyroid patients had low TG. One mechanism whereby thyroid hormones might decrease plasma TG could be to increase lipoprotein lipase (LPL). However, post-heparin LPL was not increased after therapy, nor was it increased in hyperthyroid patients. In contrast, hypothyroid patients had abnormally low levels of post-heparin hepatic triglyceride lipase. In hypothyroid patients without hypertriglyceridemia, clearance of chylomicrons was normal. A few obese, hypothyroid patients with fasting hypertriglyceridemia had low clearance of chylomicrons, which may have been due in part to competition for removal of excess endogenous TG. Thus, no evidence was obtained for a significant abnormality in chylomicron metabolism in hypothyroidism. Nonobese, hypothyroid patients had normal synthesis and clearance of very low density lipoprotein (VLDL)-TG. In contrast, VLDL-TG synthesis was increased in 8 obese, hypothyroid patients, and fractional clearance rates were relatively low compared to obese, euthyroid subjects. In striking contrast, hyperthyroid patients had remarkable facility in clearing VLDL-TG. Thus, TG metabolism is not grossly deranged in hypothyroidism, but thyroid hormones apparently can promote catabolism of VLDL.—**Abrams, J. J., S. M. Grundy, and H. Ginsberg.** Metabolism of plasma triglycerides in hypothyroidism and hyperthyroidism in man. *J. Lipid Res.* 1981. **22:** 307–322.

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The actions of thyroid hormones on plasma cholesterol concentrations are well-recognized. In contrast, there are conflicting reports about the influence of these hormones on the metabolism of plasma triglycerides. Several workers have reported that patients with hypothyroidism are prone to hypertriglyceridemia (1–8), possibly related to a decrease in lipoprotein lipase (3, 4, 9). However, elevated plasma TG has been observed less consistently than increased concentrations of cholesterol (6, 10). To understand better the effects of thyroid disease (hypo- and hyperthyroidism) on plasma TG metabolism, we have carried out a series of studies on turnover of chylomicrons and very low density lipoprotein-triglyceride (VLDL-TG) in one group of patients with hypothyroidism and in another with hyperthyroidism. Our findings indicate that thyroid hormones have multiple actions on TG metabolism that can influence their plasma concentrations. However, in spite of these actions, many patients in both categories of thyroid dysfunction are able to compensate so as to maintain plasma TG concentrations in the normal range.

METHODS

Patients

Thirty-nine patients with thyroid dysfunction were studied on the Special Diagnostic and Treatment Unit (metabolic unit), Veterans Administration Medical Center, San Diego, CA. Thyroid functional status was defined by T_4 and TSH measurements in all patients. Twenty-six patients had hypothyroidism, and 13 had hyperthyroidism. In the former group of the 26, 5 patients were women; in the latter group, all were men. All the patients gave informed consent for the investigation.

For hypothyroid patients, ages ranged from 31 to 70 years (mean 54 years). Their admission levels of T_4 were consistently low (mean 1.3 ± 0.22 μg/dl ± SEM[1]). On admission, plasma cholesterol averaged 300 ± 16 mg/dl, and triglycerides were 266 ± 37 mg/dl. Uric acid concentrations were occasionally elevated (mean 7.4 ± 0.36 mg/dl). Ten patients were less than 120% of ideal weight (IW), and they were designated nonobese, hypothyroid patients. Their clinical character-

Abbreviations: VLDL-TG, very low density lipoprotein triglyceride; IW, ideal weight; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase; LDL, low density lipoprotein; HDL, high density lipoprotein; FCR, fractional catabolic rate; FFA, free fatty acids.

[1] All results in this paper are listed as mean ± SEM unless otherwise indicated.

TABLE 1. Clinical data (non-obese hypothyroid patients)

Patient	Age	Sex	Height	Weight	Ideal Weight	T_4	TSH	Admission Lipids		Uric Acid
								Cholesterol	TG	
	yr		*cm*	*kg*	*%*	*mg/dl*	*Units*	*mg/dl*	*mg/dl*	*mg/dl*
1[a]	47	M	157	54	96	0	>100	365	283	5.8
2[b]	60	M	168	63	101	0	>100	250	114	6.4
3[b]	60	M	166	61	102	0.4	>100	158	97	5.9
4[a]	54	M	169	66	105	0	100	189	116	6.4
5[c]	54	M	166	65	107	2.0	90	294	210	6.8
6[a]	62	M	178	77	110	1.2	76	247	132	6.9
7[d]	54	M	178	77	110	5.0	55	253	151	5.7
8[a]	50	M	188	88	112	2.0	>100	284	131	6.2
9[a]	61	M	184	88	118	2.0	>100	304	151	10.2
10[a]	47	M	162	69	118	0.6	>100	219	273	4.0

[a] These patients were hospitalized for a prolonged period for detailed studies of cholesterol metabolism.
[b] Patients 2 and 3 were hospitalized for a prolonged period but did not undergo cholesterol balance studies.
[c] Patient 5 was studied as an outpatient and hospitalized only for tests.
[d] Patient 7 was hospitalized for 1 month in the hypothyroid state, but was treated as an outpatient.

istics and duration of hospitalization are shown in **Table 1.** The remaining 16 patients were greater than 120% IW, and clinical data for these obese, hypothyroid patients are given in **Table 2.** The division between nonobese and obese may be somewhat arbitrary because varying amounts of myxedematous fluid may be present in hypothyroid patients.

Among the 13 hyperthyroid patients, all had clinical evidence of their disease (**Table 3**). In only three was ideal weight greater than 120%. Plasma concentrations of T_4 were consistently increased (mean 21 ± 2 μg/dl), and TSH was always low (mean 2.6 ± 0.2 units). Their plasma cholesterol on admission averaged 158 ± 12 mg/dl, TG was 155 ± 13 mg/dl, and uric acid levels were 6.4 ± 0.4 mg/dl.

None of the patients in either group had clinical evidence of gastrointestinal disorders, and none were taking medication known to affect lipid or lipoprotein metabolism.

A series of euthyroid subjects previously studied in our laboratory has been used to describe normal values for each variable under consideration. Characteristics of these control subjects are described subsequently with the discussion of each variable.

Experimental design

Patients were admitted to the hospital for either brief or prolonged periods depending on whether they underwent detailed study of their cholesterol metabolism (see accompanying paper; Ref. 11). Those

TABLE 2. Clinical data (obese hypothyroid patients)

Patient	Age	Sex	Height	Weight	Ideal Weight	T_4	TSH	Admission Lipids		Uric Acid
								Cholesterol	TG	
	yr		*cm*	*kg*	*%*	*mg/dl*	*Units*	*mg/dl*	*mg/dl*	*mg/dl*
11[a]	55	M	178	86	121	2.9	27	203	238	8.2
12[b]	34	M	173	81	123	1.9	>100	297	194	6.2
13[c]	70	F	165	63	125	3.4	>100	437	158	11.2
14[b]	50	F	178	83	127	0.1	59	256	207	—
15[a]	60	M	176	89	130	0.8	>100	296	179	7.0
16[a]	45	M	182	96	131	2.0	60	350	830	8.8
17[a]	48	M	176	86	131	2.5	>100	265	150	—
18[b]	61	M	192	97	132	1.0	45	262	123	6.2
19[a]	64	M	175	90	133	0	>100	546	591	10.3
20[a]	31	M	164	81	136	0	70	385	590	6.7
21[a]	59	M	173	97	147	1.2	44	288	440	8.5
22[b]	44	M	198	126	150	2.2	>100	225	132	—
23[a]	57	M	180	113	158	0.9	88	419	405	4.2
24[a]	55	M	177	109	160	0.9	77	329	178	9.7
25[c]	57	F	168	92	176	1.6	>100	332	−52	7.5
26[a]	52	F	165	126	252	2.0	>100	258	200	7.8

[a] These patients were hospitalized for a prolonged period for detailed study of cholesterol metabolism.
[b] These patients were hospitalized only for tests.
[c] Patient 25 was hospitalized throughout the study but did not undergo cholesterol balance studies.

TABLE 3. Clinical data (hyperthyroid patients)

Patient	Age	Sex	Height	Weight	Ideal Weight	T_4	TSH	Admission Lipids		Uric Acid
								Cholesterol	TG	
	yr		*cm*	*kg*	*%*	*mg/dl*	*Units*	*mg/dl*	*mg/dl*	*mg/dl*
27[a]	24	M	165	51	85	32	1.4	91	51	6.3
28[b]	56	M	171	58	87	19	2.0	148	116	—
29[b]	59	M	178	67	95	26	4.0	134	106	5.8
30[b]	31	M	182	74	100	22	2.0	103	56	7.2
31[b]	42	M	178	73	103	17	3.0	147	82	5.0
32[b]	42	M	181	76	106	18	2.0	189	110	6.2
33[c]	39	M	179	81	113	14	2.0	134	108	5.8
34[c]	65	M	172	75	115	14	3.7	211	251	5.9
35[c]	63	M	162	68	117	27	4.3	225	187	8.0
36[d]	29	F	163	64	119	17	2.2	165	77	4.2
37[b]	34	M	180	92	128	42	3.0	94	70	4.6
38[b]	31	M	184	100	135	12	2.0	185	111	7.2
39[c]	55	M	177	98	144	15	3.4	172	110	7.9

[a] Patient 27 was hospitalized for full study but did not undergo cholesterol balance studies.
[b] Patients had abbreviated hospitalizations because of their hyperthyroidism and did not undergo cholesterol balance studies.
[c] These patients were hospitalized for a prolonged period for detailed studies of cholesterol metabolism.
[d] Patient 36 was hospitalized only for tests.

patients who were and were not in the hospital for prolonged periods are designated by footnotes in Tables 1–3. Patients undergoing long-term hospitalization were given a repetitive diet of mixed solid food and liquid formula, as described in the companion paper (11). Those admitted only for testing were on an ad lib diet at home but maintained their weights at constant levels throughout the study. The following describes the protocol of hospitalized patients. The same sequence of investigation was carried out on patients admitted only for tests except that some of the patients did not undergo all of the tests.

Period I. The first month was a control period. During this period, the following tests were carried out: *a*) thryoid function tests (T_4 and TSH) weekly; *b*) plasma cholesterol and TG twice weekly, and in the last week of hospitalization; *c*) clearance of chylomicrons; *d*) transport of VLDL-TG; *e*) plasma post-heparin lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL); and *f*) particle sizes of VLDL. In addition, several variables of cholesterol and bile acid metabolism were estimated as described in the accompanying paper (11).

Treatment phase. After Period I, hypothyroid patients were treated with l-thyroxine (Synthroid®) in small incremental doses with titration against their serum TSH levels. This phase usually lasted for about 2 weeks, and after the euthyroid state (normal TSH) was achieved, patients were allowed to stabilize on the maintenance dose for 2 more weeks before beginning the next period.

After their control period, hyperthyroid patients were treated with ^{131}I by the Nuclear Medicine Section of the Veterans Administration Medical Center. These patients were discharged to be followed once monthly as outpatients; when they reached euthyroid status, which usually required 2–3 months, they were readmitted for study.

Period II. During the second period of the study, the patients were restabilized at their pretreatment weight. Some changes in caloric intake usually were needed because of altered thyroid status. Otherwise, Period II was identical to Period I, and the same tests were carried out.

Methodology

Thyroid function tests. Thyroid function tests were done routinely on admission of all patients; these included plasma thyroxine (T_4), resin-T_3 uptake, T_3 (radioimmunoassay), thyroid stimulating hormone (TSH), free T_4 index, and thyroid antibodies. Also, each patient had an I^{131} uptake and technetium scan to define their thyroid size better; these data were used to calculate the I^{131} dose in the cases of hyperthyroidism. T_4 and TSH were repeated weekly during hospitalization in both hypo- and hyperthyroid patients; these tests were done to confirm stable thyroid function, and in the case of hypothyroid patients, to monitor incremental doses of l-thyroxine.

Plasma lipids. Total plasma cholesterol and TG were determined on a Technicon Auto Analyzer (Model II, Technicon Instruments Corp., Tarrytown, NY) (12, 13).

Post heparin LPL and HTGL activities. Post-heparin plasma was obtained from blood drawn 15 min after intravenous injection of 60 IU/kg sodium heparin (Riker Labs., Inc.) Subjects had been fasting for 14 hr prior to sampling. Samples were cooled immediately on ice and centrifuged at 4°C for 30 min at 480 *g*. The

plasma was removed and recentrifuged for 30 min at 750 *g* at 4°C. Samples were then immediately assayed or stored at −70°C up to 3 months before assay. LPL and HTGL activities were determined as described by Baginsky and Brown (14). For control, post-heparin lipase activities were carried out in 16 normal men (ages 20–50 years) and 21 normal women (ages 20–50 years).

Chylomicron clearance rates were determined according to Grundy and Mok (15). Briefly, subjects were intubated with a single-lumen tube which was positioned in the duodenum. Fat (safflower oil) was infused at a rate of 200 mg/kg per hr. Before infusion and after a 5-hr equilibrated period, 10 ml of blood was collected hourly for the next 5 hr. Plasma was separated and stored at 4°C. Chylomicrons were separated from other lipoproteins by preparative ultracentrifugation through a saline layer (1.6×10^6 g-min in a Beckman SW-41 rotor). The lower layer in the centrifuge tube was removed quantitatively through a pinhole in the bottom of the tube and was analyzed for TG and cholesterol. Chylomicron-TG was taken as the differences between pooled total TG and the concentration in the infranatant, the latter designated lipoprotein-TG, or nonchylomicron-TG. The latter term includes TG in VLDL, LDL, and HDL. For most patients fasting TG includes TG in these three lipoproteins with none in chylomicrons. In one patient (No. 19), fasting chylomicrons were present and a prespin was done to remove chylomicrons. In his case, the term "fasting TG" refers to the TG contained in the infranatant, again corresponding to TG in VLDL, LDL, and HDL.

After 5 hr of fat infusion, concentrations of total plasma TG and chylomicron-TG became constant and remained so throughout the study. Assuming that absorption of fat was complete, this finding indicates that influx and removal of chylomicron-TG were constant, i.e., 200 mg/kg per hr. From this value and the increment in chylomicron-TG, the residence time of TG in the chylomicron fraction could be calculated as the reciprocal of the fractional catabolic rate (FCR), where FCR = input of chylomicron-TG (200 mg/kg per hr) ÷ plasma pool of chylomicron-TG (mg). The residence time of chylomicron-TG will be expressed in units of minutes (min).

Rates of chylomicron clearance in hypothyroid and hyperthyroid patients were compared with those of 45 normal and hyperlipidemic subjects reported previously (15).

Transport of VLDL-TG was estimated by multicompartmental analysis using the method of Zech et al. (16). This technique involved analysis of plasma VLDL-TG radioactivity data conducted over a 48-hr interval after injection of [^{3}H]glycerol. Each patient was given a regimen of fat-free formula throughout the study. Feedings were given every 3 hr around the clock; they began 36 hr prior to injection of [^{3}H]glycerol and were continued for 48 hr following the injection. The diet contained 60% of the calories needed to maintain the patient's weight at a constant level. In other words, 40% of weight-maintenance calories in the form of fat was withheld. Of the remaining 60% given to the patient, 45% was in the form of carbohydrate, and 15% was protein (as casein). Removal of fat from the diet was required to prevent contamination of the VLDL-TG fraction with intestinal chylomicron-TG, and caloric intake was reduced to prevent carbohydrate-induced hypertriglyceridemia (17). On the other hand, maintenance of some caloric intake was needed to prevent a fall in VLDL-TG secondary to prolonged fasting (18). With the feeding schedule chosen, VLDL-TG concentrations were constant throughout the study.

At time of injection, 300 μCi of [2-^{3}H]glycerol (New England Nuclear Corporation, Boston, MA) were given intravenously, and blood samples were drawn at 15 min, 1.0, 1.5, 2.0, 2.5, 4, 5, 6, 7, 8, 11, 13, 15 hr and then every 3 hr up to 48 hr. Blood samples containing EDTA were immediately centrifuged at 3000 rpm for 20 min at 5°C. The plasma was stored at 4°C. VLDL was isolated by preparative ultracentrifugation and specific activities of VLDL-TG were estimated with VLDL-cholesterol, as recently described (16).

The specific activity curves of VLDL-TG following the injection of [^{3}H]glycerol have several components including a short delay period followed by a rapid upswing, a flatness at the top of the curve, a rapid, linear decay for several hours followed by a slow decay (or "tail") out to 48 hr. The complexity of this curve requires a multicompartmental model for analysis. The major features of our model include *a*) a delay pool at the synthetic site to explain the short retardation in upswing of the curve, *b*) a fast-synthetic compartment to account for the sharp upswing and decline in the specific activity curve, *c*) a slow-synthesis compartment to explain the tail of the curve, and *d*) a four-step delipidation chain in the plasma to describe the flatness at the top of the curve. In our previous report (16), evidence was provided to support our contention that the major portion of the "tail" of the specific activity is due to a slow-synthesis compartment. Other factors that could contribute to the tail are a slow-removal pathway in the plasma compartment and exchange of TG between VLDL and other lipoproteins. Although it seems likely that both factors do exist, the report of Zech et al. (16) describes our reasons for believing that their contribu-

tions to the slowly-decaying component of the curves are small.

The values calculated by multicompartmental analysis include transport (or synthesis) and fractional catabolic rates (FCR) of plasma VLDL-TG. The plasma mass of VLDL-TG was calculated from VLDL-TG concentration and the estimated plasma volume. The latter was calculated as previously reported (16) using the following equation: plasma volume (liters) = ideal weight × (0.045) + excess weight × (0.010). Ideal weight was calculated from Standard Metropolitan Life Insurance tables (19), assuming that all patients were of medium body frame.

Since patients of this study were of different heights and weights, it was necessary to normalize the results so that a meaningful comparison among the various groups could be made. A common method for normalizing VLDL-TG transport data is to express them as mg/hr per kg of total body weight. However, as recently shown by Grundy et al. (20), calculation of transport rates per kg total body weight may be misleading. In obese subjects, it decreases the calculated transport to inordinately low values, as compared to absolute transports. In other words, dividing transport by a large mass of adipose tissue can obscure real increases in production of VLDL-TG, a process presumably confined to the liver and intestine. To overcome this problem, Grundy et al. (20) proposed that transport rates be expressed as mg/hr per kg ideal weight. Their work showed a high correlation between rates expressed in this way and absolute transport rates across a wide range of transport rates for subjects of all degrees of obesity. For this reason, transport rates for VLDL-TG will be expressed as mg/hr per kg IW in the results section.

Particle sizing of VLDL was performed by electron microscopy as described by Groszek and Grundy (21). VLDL was isolated by preparative ultracentrifugation and, following negative staining with phosphotungstic acid, photographs were made on a Zeiss EM-10 electron microscope. Particle-size distributions were obtained from electron micrographs using a 48-channel Zeiss TGZ-3 particle analyzer.

RESULTS

Plasma lipids

Results for TG in plasma and VLDL are presented along with post-heparin lipase activities for nonobese and obese patients with hypothyroidism and hyperthyroid patients in **Tables 4–6,** respectively. In nonobese, hypothyroid patients, plasma total TG was almost always in the normal range (i.e., below 200 mg/dl). Likewise, 8 of 16 obese, hypothyroid patients had normal TG. Thus, hypothyroidism per se, especially in the absence of obesity, rarely induced clinical hypertriglyceridemia. On the other hand, 8 obese patients had elevated plasma TG, and in a few cases the increases were marked.

Treatment of hypothyroid patients with T_4 generally caused a reduction of plasma TG, and mean values for both groups were lower after return to euthyroidism. Thus, the hypothyroid state apparently caused a slight increase in TG, but usually not to abnormally high levels. In some of those with marked hypertriglyceridemia (i.e., Nos. 16, 19, 20), treatment caused a distinct reduction of TG. Nevertheless, most of those with striking elevations of TG did not normalize their lipids after treatment suggesting that they had an underlying primary hypertriglyceridemia perhaps accentuated by obesity.

As shown in Table 6, patients with hyperthyroidism almost always had normal plasma TG in the untreated state, and values were essentially unchanged by therapy.

Postheparin lipases

In both groups of hypothyroid patients (Tables 4 and 5), post-heparin LPL was in the normal range, and treatment did not produce a significant change. The same was true for hyperthyroid patients (Table 6). In contrast, HTGL appeared reduced in both groups of hypothyroidism; this conclusion is based on the following: *a*) these patients, who consisted mostly of men, had distinctly lower values than control men (see footnote *e*, Table 4); *b*) treatment with T_4 produced a highly significant increase in HTGL for both groups (and for the combined data of all hypothyroid patients); and *c*) hypothyroid patients had appreciably lower levels than untreated and treated with hyperthyroidism patients. In the latter group, values for HTGL were somewhat higher before than after treatment of hyperthyroidism, but the differences were not statistically significant.

Chylomicron clearance

Table 7 presents results for chylomicron clearance in 9 hypothyroid patients with normotriglyceridemia. The results for 21 euthyroid, normotriglyceridemic patients are shown for comparison. In control subjects, the rise in chylomicron-TG averaged 49 ± 6 mg/dl, and residence time was 6.5 ± 0.9 min. For the untreated hypothyroid patients, the increase in chylomicron-TG was similar (27 ± 3 mg/dl), as was residence time (3.4 ± 0.4 min). In these patients, therefore, their hypothyroidism did not delay chylomicron

TABLE 4. Plasma and VLDL triglycerides and lipases (non-obese hypothyroid patients)

Patient[a]	Period	Plasma TG	VLDL TG	Postheparin Lipolytic Activity	
				HTGL	LPL
		mg/dl ± SD (n)[b]	*mg/dl*	*μmol FA/hr/ml*	
1	I	234 ± 77	174	6.0	3.2
	II	139 ± 38	90	10.3	3.9
2	I	114 ± 2	68	3.8	10.6
	II	117 ± 24	71	14.2	25.3
3	I	87 ± 18	49	4.7	8.6
	II	76 ± 11	41	10.5	12.0
4	I	104 ± 26	59		
	II	106 ± 23	61		
5	I	150 ± 89 (3)	100	22.3	26.1
		92 (1)	52	32.4	22.0
6	I	145 ± 18	96	24.0	12.8
	II	110 ± 18	65	38.0	17.7
7	I	131 ± 30	83	16.9	6.7
	II	118 (1)	104	18.1	27.4
8	I	139 ± 32	90	24.7	16.3
	II	152 ± 28	102	28.1	10.6
9	I	178 ± 21	125	20.0	24.8
	II	162 ± 27	110	22.7	26.7
10	I	196 ± 54	140	11.6	18.0
	II	130 ± 53	82	19.8	14.4
Mean ± SEM	I	147 ± 14	98 ± 12	14.9 ± 2.8	14.1 ± 2.6
	II	118 ± 9[c]	78 ± 7[c]	21.6 ± 3.2[d]	17.8 ± 2.7[c]
Normal men (n = 15)[e]				25.7 ± 2.1	15.4 ± 1.3
Normal women (n = 21)[e]				14.0 ± 1.2	16.8 ± 1.0

[a] See footnotes in Table 1 as to whether patients were studied for brief or prolonged periods as inpatients.

[b] Unless otherwise indicated, the data for mean ± SD represent six values taken during the last 3 weeks of each period; if the patient was admitted only for tests, the number in parentheses gives how many measurements were made.

[c] Differences between Periods I (hypothyroid) and II (euthyroid) were not significant at $P < 0.05$ by paired analysis.

[d] Difference significant by paired analysis ($P < 0.05$).

[e] Ages for normal men and women ranged from 20 to 50 yrs.

clearance. In contrast, the increment in non-chylomicron (lipoprotein)-TG was greater in hypothyroid patients than in controls (70 ± 10 vs 20 ± 10 mg/dl); likewise, cholesterol concentrations tended to increase more in the hypothyroid patients. Treatment of hypothyroidism had little effect on overall clearance of chylomicron-TG which had been essentially normal before therapy.

Chylomicron clearance data for hypertriglyceridemic, hypothyroid patients are given in **Table 8;** the results are compared to those of 31 euthyroid subjects who also had elevated TG. All of this group of hypothyroid patients were obese. Their responses were variable. Two patients (Nos. 17 and 19) had a normal clearance of chylomicrons despite fasting hypertriglyceridemia. The remainder had prolonged residence times as was typical of many euthyroid, hypertriglyceridemic patients. A finding of some interest was that nonchylomicron-TG during duodenal infusion frequently increased markedly in contrast to only small increments in this same fraction of euthyroid subjects. Treatment with T_4 strikingly reduced residence times of chylomicron-TG as it lowered total fasting TG. On the other hand, the apparently abnormal rise in nonchylomicron-TG persisted after therapy in most of the patients.

Table 9 presents results for the hyperthyroid group. The residence time of chylomicron-TG was in

TABLE 5. Plasma and VLDL triglycerides and lipases (obese hypothyroid patients)

Patient[a]	Period	Plasma TG	VLDL TG	Postheparin Lipolytic Activity	
				HTGL	LPL
		mg/dl ± SD (n)[b]	*mg/dl*	*μmol FA/hr/ml*	
11	I	409 ± 125	328	13.4	9.3
	II	403 ± 88	323	20.4	9.4
12	I	260 (1)	197	10.3	10.1
	II	40 (1)	15	18.5	13.4
13	I	174 ± 29	102	18.7	17.2
	II	195 ± 24	118	28.7	20.7
14	I	200 (1)	122	14.8	19.2
	II	190 (1)	114	11.9	19.1
15	I	179 ± 30 (9)	125	17.5	4.8
	II	167 ± 31 (21)	115	50.8	6.0
16	I	557 ± 243	459	23.0	20.3
	II	294 ± 50	227	27.6	16.0
17	I	137 ± 13	88	13.1	7.3
	II	108 ± 21	63	15.0	5.0
18	I	136 ± 32 (5)	88	17.9	11.6
	II	105 (1)	51	28.8	11.1
19	I	1806 ± 372	1559	11.2	21.9
	II	1177 ± 611	1005		14.4
20	I	292 ± 48	225	20.0	7.0
	II	179 ± 34	125	60.8	8.1
21	I	870 ± 298	734	19.2	18.8
	II	381 ± 71	303	30.4	17.1
22	I	60 (1)	29	12.5	10.8
	II	40 (1)	15	20.1	15.5
23	I	487 ± 118	397	12.2	10.0
	II	336 ± 80	264	—	—
24	I	178 ± 37	125	4.5	14.1
	II	158 ± 27	107	11.7	17.1
25	I	224 ± 4	141	16.3	12.1
	II	214 ± 27	133	21.1	10.6
26	I	179 ± 36	106	12.9	11.1
	II	111 ± 49	52	16.6	9.3
Mean ± SEM	I	384 ± 108	302 ± 95	14.8 ± 1.1	12.9 ± 1.3
	II	226 ± 71[c]	199 ± 63[c]	24.2 ± 3.9[c]	12.9 ± 1.2[d]

[a] See footnotes in Table 2 as to whether patients were studied for brief or prolonged periods as inpatients.

[b] See footnote *b* of Table 4.

[c] Differences between Periods I (hypothyroid) and II (euthyroid) were significant at $P < 0.02$ by paired analysis.

[d] Differences not significant at $P < 0.05$.

the normal range during the hyperthyroid period, and no differences were noted after return to the euthyroid state.

VLDL-TG transport

Data for transport of VLDL-TG are shown for the three groups in **Tables 10, 11,** and **12.** For comparison, data also are given for 27 subjects with normal VLDL-TG and normal weight (Table 10) and for 10 euthyroid, obese patients (Table 11). Eight patients with hypothyroidism were nonobese (Table 10). Their values for concentrations, transport rates, and FCR of VLDL-TG were very similar to non-obese, euthyroid patients. Thus, despite their hypothyroidism,

TABLE 6. Plasma and VLDL triglycerides and lipases (hyperthyroid patients)

Patient[a]	Period	Plasma TG	VLDL TG	Postheparin Lipolytic Activity	
				HTGL	LPL
		mg/dl ± SD (n)[b]	*mg/dl*	*μmol FA/hr/ml*	
27	I	64 ± 14	24	9.2	5.6
	II	62 ± 18	23	11.4	5.2
28	I	116 ± 22 (4)	70	10.2	26.1
	II	104 ± 29 (4)	59	17.1	7.3
29	I	108 ± 31 (4)	62	32.0	10.7
	II	101 ± 24 (4)	57	11.7	6.0
30	I	55 (1)	26	28.4	10.7
	II	98 ± 20 (4)	56	40.8	17.1
31	I	103 ± 62 (3)	59	63.5	15.8
	II	83 ± 28 (2)	46	42.1	35.2
32	I	131 ± 21 (3)	83	66.8	10.1
	II	171 ± 9 (3)	118	22.6	17.6
33	I	123 ± 23	76	28.0	9.0
	II	117 ± 31	71	30.0	12.1
34	I	124 ± 26	77	20.4	12.4
	II	130 ± 22	82	20.8	15.9
35	I	186 ± 18	132	12.2	5.6
	II	231 ± 28	171	10.2	5.7
36	I	66 (1)	25	31.9	17.0
	II	72 (1)	29	19.6	17.1
37	I	70 ± 5 (4)	37	5.8	5.4
	II	89 ± 23 (6)	50	4.6	10.6
38	I	118 ± 10 (6)	72	32.4	14.1
	II	130 (1)	82	26.5	14.3
39	I	110 ± 30	65	16.3	8.5
	II	158 ± 27	107	11.7	17.6
Mean ± SEM	I	106 ± 10	62 ± 8	27.5 ± 5.3	11.6 ± 1.6
	II	119 ± 13[c]	73 ± 11[c]	20.7 ± 3.2[c]	14.0 ± 2.2[c]

[a] See footnotes in Table 3 as to whether patients were studied for brief or prolonged periods as inpatients.

[b] See footnote *b* of Table 4.

[c] Difference between Periods I (hypothyroid) and II (euthyroid) were not statistically significant at $P < 0.05$ by paired analysis.

these patients demonstrated no evidence of a removal defect for VLDL-TG.

Eight other hypothyroid patients were obese (>120% IW) (Table 11), and their results are compared to those of ten obese, euthyroid subjects with normal plasma TG. Both concentrations and transport rates of VLDL-TG were much greater than those of normal subjects and non-obese, hypothyroid patients. On the other hand, the transport rates in obese, hypothyroid patients were only slightly greater than in the obese, euthyroid subjects. However, the mean FCR in the former group was about half that of the latter, and consequently, the average VLDL-TG concentration of the hypothyroid group was much greater than that of euthyroid patients. In other words, obese, hypothyroid patients failed to enhance their clearance capacity, as did euthyroid patients, and thus they were unable to maintain their VLDL-TG levels in the normal range.

Table 12 shows results for ten hyperthyroid patients. Only two of these patients were obese, and their data will be considered with the others. The mean VLDL-TG concentration was relatively low (74 ± 11 mg/dl), and yet transport was frequently on the high side of normal (mean = 12.8 ± 1.8 mg/hr/kg IW). The low levels of VLDL-TG thus were the result of an unusually high FCR (0.441 ± 0.010 hr^{-}).

The effects of treatment on VLDL-TG transport

TABLE 7. Chylomicron clearance[a] (normotriglyceridemic, hypothyroid patients)

Patient	Wt	Period	Fasting Lipids		Fat Infusion Lipids			Δ	Residence Time
			Chol	TG	Chol	LP-TG	CM-TG	LP-TG	CM-TG
			mg/dl			*mg/dl*		*mg/dl*	*min*
Hypothyroid									
1	NOR	I	390	177	427	287	30	110	4.1
		II	162	191	173	104	15	−87	2.0
2	NOR	I	230	118	217	172	37	54	4.9
		II	200	119	226	169	118	50	15.8
4	NOR	I	135	36	163	164	37	128	4.8
		II	146	123	170	222	20	99	2.6
5	NOR	I	274	63	307	118	32	55	4.1
		II	237	74	255	147	48	73	6.1
6	NOR	I	250	104	275	167	21	59	2.6
		II	203	140	221	164	22	24	2.8
7	NOR	I	240	156	256	253	16	97	2.0
8	NOR	I	232	202	251	254	35	52	4.3
9	NOR	I	229	204	257	226	35	22	4.2
		II	221	123	255	200	29	77	3.5
10	NOR	I	235	113	250	193	16	80	1.9
24	OB	I	277	179	293	220	11	41	1.0
Mean ± SEM									
10 patients		I	249 ± 20	135 ± 18	270 ± 22	205 ± 16	27 ± 3	70 ± 10	3.4 ± 0.4
6 patients		I	251 ± 34	117 ± 26	274 ± 37	189 ± 24	32 ± 2	71 ± 16	4.1 ± 0.3
6 patients		II	195 ± 14	128 ± 15	217 ± 15	168 ± 17	25 ± 5	39 ± 27	5.5 ± 2.1
Euthyroid									
21 subjects			176 ± 9	114 ± 9	178 ± 11	133 ± 12	49 ± 6	20 ± 10	6.5 ± 0.9

[a] Abbreviations: Chol, cholesterol; TG, triglyceride; LP-TG, lipoprotein-TG; CM-TG, chylomicron-TG; NOR, normal; OB, obese.

in hypo- and hyperthyroid patients also are presented in Tables 10, 11, and 12. In five non-obese, hypothyroid patients, who were studied in both periods, VLDL-TG levels increased after treatment by 26% ($P < 0.05$) (Table 10). This increment was due to a significant increase in VLDL-TG synthesis; the FCR was not altered by treatment. Seven obese patients with hypothyroidism also were studied in the two periods. In contrast to the non-obese patients, T_4 treatment in obese subjects caused a significant reduction in VLDL-TG. In these obese patients, the reduction of VLDL-TG was due to a significantly decreased transport and not to a greater FCR. These data thus present the paradox that non-obese, hypothyroid patients accelerated their synthesis of VLDL-TG with T_4 treatment while the reverse occurred in the obese patients.

For eight hyperthyroid patients, VLDL-TG levels were increased only slightly after treatment (Table 12). Transport rates remained essentially the same as did the FCR. Thus, despite a return to the euthyroid state, the hyperthyroid patients maintained a rapid clearance for VLDL-TG.

VLDL particle sizes

The particle-size distributions of VLDL for hypothyroid and hyperthyroid patients are presented in **Table 13.** These results are compared to those of ten normal, euthyroid subjects and ten hyperlipidemic patients also studied in our laboratory (21). Patients with hypothyroidism were found to have a relatively large percentage of their VLDL particles in the small diameter ranges (i.e., 100–250 Å). Although it has been shown previously from this laboratory that the VLDL fraction can have significant proportions of its particles in this range (21), patients with hypothyroidism appeared to have a disproportionately high fraction of small VLDL. Those with hyperthyroidism, in contrast, generally had a typical distribution.

DISCUSSION

The most striking action of thyroid hormones on plasma lipids is to lower plasma cholesterol. The influence of these hormones on triglycerides has been defined less well, and the present study was under-

TABLE 8. Chylomicron clearance[a] (hypertriglyceridemic, hypothyroid patients)

Patient	Wt	Period	Fasting Lipids		Fat Infusion Lipids			Δ	Residence Time
			Chol	TG	Chol	LP-TG	CM-TG	LP-TG	CM-TG
			mg/dl			*mg/dl*		*mg/dl*	*min*
Hypothyroid									
11	OB	I	262	540	272	1235	179	695	21
		II	160	377	186	1347	205	970	24
16	OB	I	273	495	287	663	82	168	9
		II	260	229	278	508	16	279	2
18	OB	I	214	291	214	248	34	−43	4
		II	158	79	163	100	5	21	0.5
19[b]	OB	I	670	2910	538	2540	1072	−370	226
		II	350	1320	372	1676	279	356	30
20	OB	I	291	429	313	1064	614	635	66
		II	124	197	126	255	150	58	16
21	OB	I	428	950	455	1540	408	590	41
		II	188	377	207	606	58	229	6
Mean ± SEM		I	356 ± 69	936 ± 405	347 ± 50	1215 ± 323	398 ± 161	279 ± 176	61 ± 34
		II	207 ± 34	430 ± 184	222 ± 36	749 ± 256	119 ± 45	319 ± 140	13 ± 5
Hypertriglyceridemia (euthyroid) 31 patients			239 ± 8	375 ± 37	240 ± 8	414 ± 34	270 ± 33	39 ± 15	34 ± 4

[a] Abbreviations: Chol, cholesterol; TG, triglyceride; LP-TG, lipoprotein-TG; CM-TG, chylomicron-TG; NOR, normal; OB, obese.
[b] Values from patient 19 not included in calculation of the means.

taken to discover whether thyroid hormones significantly alter TG metabolism.

Elevations of plasma TG have been reported frequently in hypothyroidism. However, a review of the literature reveals that some patients with hypothyroidism have normal TG (10, 22); others have mild to moderate elevations (1, 3, 7, 22), and a few have marked hypertriglyceridemia (6, 10, 22). Our data are in accord. Not every patient with hypothyroidism had hypertriglyceridemia; however, a significant fraction of them did. In 7 of 26 patients, TG levels were greater than 250 mg/dl. Although a return to the euthyroid state rarely reduced TG by a striking degree, mean TG levels in most patients were lower after therapy, indicating that hypothyroidism must have some TG-elevating effect. Furthermore, hyperthyroid patients generally had lower TG levels than those with hypothyroidism. Thus we might examine possible mechanisms whereby thyroid hormone lowers TG or a deficiency of this hormone raises them.

One way in which thyroid hormone might lower TG would be to promote their clearance from plasma. If so, patients with hypothyroidism theoretically should have reduced clearance of either exogenous or endogenous TG. However, as noted by Nikkila and Kekki (4) and confirmed in this study, hypertriglyceridemia in hypothyroid patients usually is not of the "fat-induced" or exogenous type; that is, most patients do not have fasting chylomicronemia. Furthermore, in quantitative measurements of chylomicron turnover, hypothyroid patients without fasting hypertriglyceridemia were found to clear chylomicrons as well as did normal subjects. In some patients with hypertriglyceridemia, a delayed clearance of chylomicrons was noted; however, this same phenomenon was observed previously in euthyroid patients with fasting hypertriglyceridemia (15), and thus it is not unique for hypothyroidism. In hypothyroid patients with hypertriglyceridemia, treatment with T_4 appeared to improve chylomicron clearance, but this may have been due simply to a reduction in VLDL and decreased competition for removal sites. Therefore, the weight of our data indicate that *most* hypothyroid patients do not possess a clearance defect for chylomicrons.

These observations were surprising because several workers have reported that patients with hypothyroidism may have a deficiency of "lipoprotein lipase" as measured by post-heparin lipolytic activity (PHLA) (3, 4, 9). In the present study, we reexamined this possiblity by fractionating PHLA into two enzymes: LPL and HTGL. In our hypothyroid patients, heparin-releasable LPL was in the normal range and was not altered by treatment. Therefore,

we have not confirmed that hypothyroid patients have a deficiency of LPL; this is consistent with the finding that they have a normal clearance of chylomicrons.

In contrast to LPL, postheparin HTGL was low in the hypothyroid state. This decrease in HTGL was observed in both nonobese and obese patients with hypothyroidism. Furthermore, activities of HTGL returned to normal in both groups following T_4 therapy. Apparently, however, this enzyme does not play a significant role in lipolysis of chylomicrons, at least to the extent that a reduction in HTGL can affect chylomicron clearance in an adverse way. There is the possibility that low HTGL might have been responsible in part for the unusually high rise in nonchylomicron-TG during duodenal infusion of fat. Whether this increase in nonchylomicron-TG reflects a delayed removal of chylomicron remnants or more VLDL-sized, small chylomicrons was not determined.

Although chylomicron clearance in most hypothyroid subjects is not impaired, the possibility remains that thyroid hormone could influence catabolism of VLDL, the other TG-rich particle of plasma. Indeed, when plasma TG is elevated in hypothyroidism, the increase occurs mainly in VLDL. Mechanisms for endogenous hypertriglyceridemia in hypothyroid subjects have been examined previously by Nikkila and Kekki (4); they estimated turnover rates of plasma TG using single-exponential analysis of VLDL-TG specific-activity curves following injection of [^{3}H]glycerol. Although the validity of their method can be questioned (16, 20), their conclusions are of interest nevertheless. They suggest that synthesis of plasma TG in hypothyroidism is normal, but the fractional clearance (FCR) is markedly reduced.

In our patients with hypothyroidism, the majority had normal concentrations of VLDL-TG. This was almost invariably true for nonobese patients, but several of the obese also have normal TG. Among those without increased TG, fractional clearance rates of VLDL-TG were in the same range as those of euthyroid, normotriglyceridemic subjects. These observa-

TABLE 9. Chylomicron clearance (hyperthyroid patients)[a]

Patient	Period	Fasting Lipids		Fat Infusion Lipids			Δ	Residence Time
		Chol	TG	Chol	LP-TG	CM-TG	LP-TG	CM-TG
		mg/dl			*mg/dl*		*mg/dl*	*min*
27	I	83	34	94	53	15	19	2.0
	II	154	75	161	74	23	−1	3.1
28	I	97	67	125	154	22	58	2.9
	II	211	99	228	146	21	47	2.9
29	I	109	95	121	190	32	95	4.3
	II	174	75	167	245	52	170	7.0
30	I	101	30	117	84	22	54	2.9
	II	153	59	165	207	77	148	10.4
31	I	125	79	119	164	31	85	4.1
	II	175	72	186	170	53	98	7.0
33	I	103	61	113	74	19	13	2.3
34	I	196	142	209	232	53	90	6.4
	II	201	118	219	182	26	74	3.1
35	I	175	154	203	273	48	121	5.7
	II	229	229	237	330	32	101	3.8
37	I	92	53	92	61	3	8	0.3
	II	173	68	191	125	24	57	2.7
38	I	166	101	175	200	52	99	5.6
39	I	170	73	189	139	27	66	2.8
	II	162	78	176	57	71	79	7.3
Mean ± SEM								
11 patients	I	129 ± 12	81 ± 12	142 ± 13	148 ± 22	29 ± 5	64 ± 11	3.6 ± 0.6
9 patients	I	128 ± 14	81 ± 14	141 ± 15	150 ± 23	28 ± 5	66 ± 12	3.5 ± 0.6
9 patients	II	181 ± 9	97 ± 18	192 ± 10	180 ± 25	42 ± 7	86 ± 17	5.3 ± 0.9

[a] Abbreviations: Chol, cholesterol; TG, triglyceride, LP-TG, lipoprotein-TG; CM-TG, chylomicron-TG.

TABLE 10. VLDL-TG transport data (nonobese hypothyroid group)

Patient	Period	VLDL-TG	VLDL-TG Transport			FCR
		mg/dl	*mg/hr*	*mg/hr/kg*	*mg/hr/kg IW*	hr^{-1}
1	I	112	676	12.5	12.0	0.230
	II	114	976	18.1	17.3	0.326
2	I	72	362	5.8	5.8	0.173
	II	115	1004	15.9	16.1	0.300
4	I	34	43	7.1	7.4	0.456
	II	49	384	5.9	6.1	0.262
5	I	65	709	10.9	11.7	0.367
7	I	103	756	9.8	10.8	0.219
8	I	209	2039	23.3	26.1	0.265
9	I	138	777	8.9	10.5	0.153
	II	200	1215	13.9	16.4	0.165
10	I	132	680	9.9	11.7	0.167
	II	136	1065	15.5	18.3	0.254
Hypothyroid (mean ± SEM)						
8 patients	I	99 ± 25	755 ± 204	11.0 ± 2.4	12.0 ± 2.2	0.254 ± 0.038
5 patients	I	98 ± 20	508 ± 136	8.8 ± 1.2	9.5 ± 1.2	0.235 ± 0.056
5 patients	II	123 ± 24[a]	929 ± 142[b]	13.9 ± 2.1[b]	14.8 ± 2.2[b]	0.261 ± 0.027[a]
Euthyroid, nonobese (mean ± SEM)						
27 patients		136 ± 7	872 ± 71	11.4 ± 0.7	12.1 ± 0.8	0.207 ± 0.016

[a] The difference between Periods I and II was not statistically significant at $P < 0.05$ for the five patients studied in both periods.
[b] Difference between Periods I and II significant at $P < 0.05$ by paired analysis.

tions in hypothyroid patients without hypertriglyceridemia plainly indicate that many patients with hyperthyroidism do not have a clinically significant defect in removal of VLDL-TG.

Following treatment of our nonobese patients with T_4, their plasma concentrations of VLDL-TG actually showed a slight increase. This rise was the result of enhanced synthesis of VLDL-TG, and it is contrary to what might have been expected from the recent report of Keyes and Heimberg (23). These workers showed in isolated, perfused rat livers that the hypothyroid state caused a reduction in oxidation of fatty acids and a greater production of VLDL-TG. Although these observations undoubtedly are true, the in vivo situation may be different. Previous investigators (24–31) have found that in hypothyroidism the circulating levels of free fatty acids (FFA) are reduced that might curtail availability of FFA as a precursor for synthesis of VLDL-TG. With T_4 treatment, FFA flux should be increased which may account for the rise in synthetic rates of VLDL-TG in nonobese, hypothyroid patients.

In contrast to nonobese patients, those with both hypothyroidism and obesity commonly had elevated concentrations of VLDL-TG. Without doubt, their hypertriglyceridemia was due partly to overproduction of VLDL-TG and to increasing the load on the TG removal system. The data showed that obese, hypothyroid patients, like obese, euthyroid patients previously studied in our laboratory (20), have an excessive production of VLDL-TG. In euthyroid patients with obesity, elevated synthesis of VLDL presumably is due to enhanced fasting FFA and augmented intake of total calories; both should provide increased fatty acids and glucose for VLDL-TG synthesis. Increased caloric intake also may be a major factor in the elevated transport of VLDL-TG in our obese, hypothyroid patients. Despite their hypothyroidism, most of the obese subjects were found to require increased caloric intake to maintain constant body weight. Nonetheless, their synthesis of VLDL-TG may have been further accentuated by hypothyroidism. One mechanism could be that shown by Keyes and Heimberg (23), i.e., curtailed hepatic oxidation of FFA and diversion to TG synthesis. Also, if peripheral utilization of FFA and glucose is lessened by low thyroid hormone, as it unquestionably is, any unused calories of either type may be shunted to the liver for synthesis of VLDL-TG. Both mechanisms are compatible with the data ob-

tained after treatment of hypothyroidism in these patients. During treatment with T_4, caloric intake had to be raised somewhat to maintain constant body weight, but in spite of the greater ingestion of calories, secretion of VLDL-TG waned. Thus, augmented oxidation of FFA and glucose in both the periphery and liver may have diminished substrate availability for synthesis of VLDL-TG.

Although overproduction of VLDL-TG was a major factor in hypertriglyceridemia in our obese, hypothyroid patients, it should be noted that these patients did not synthesize more VLDL-TG than most obese, euthyroid patients without hypertriglyceridemia who were studied earlier in our laboratory (20). The latter patients seemingly had the capacity to amplify removal of VLDL-TG to compensate for their overproduction and thus to avoid development of hypertriglyceridemia. The obese patients with hypothyroidism evidently did not have the same facility to accelerate clearance in response to overproduction, and consequently they developed elevated TG. Thus, they can be said to have a relative defect in clearance of VLDL-TG. From a clinical viewpoint, the catabolic defect for VLDL-TG in hypothyroidism becomes evident only during the challenge of excess production of VLDL-TG and is not apparent when synthetic rates are in the normal range. Nevertheless, in most nonobese patients with hypothyroidism, the FCR increased with T_4 therapy despite a rise in synthetic rate (Table 10); this certainly suggests that T_4 increases the clearance of VLDL-TG. The concept that T_4 promotes VLDL-TG removal is supported by the results in hyperthyroid patients. In these patients, the FCR of VLDL-TG was twice that of normal. Despite the fact that many of these patients had synthetic rates of VLDL-TG in the high-normal range, which could have been due to heightened mobilization of FFA from adipose tissue, their concentrations usually were very low. This was due to their rapid clearance of VLDL-TG.

Of interest, abnormalities in VLDL-TG metabolism in hyperthyroid and obese, hypothyroid patients did not revert entirely to normal following therapy. Several obese patients maintained varying degrees of hypertriglyceridemia after T_4 therapy. This may have been due to slow return of catabolic mechanisms to normal, to persistent obesity, or possibly in some cases, to an underlying primary hypertriglyceridemia.

TABLE 11. VLDL-TG transport data (obese hypothyroid)

Patient	Period	VLDL-TG	VLDL-TG Transport			FCR
		mg/dl	*mg/hr*	*mg/hr/kg*	*mg/hr/kg IW*	hr^{-1}
11	I	261	1977	23.8	28.4	0.214
	II	200	1345	16.2	19.3	0.190
16	I	415	2376	24.7	26.5	0.145
	II	289	2191	22.8	24.4	0.192
17	I	103	1084	11.4	15.8	0.272
	II	76	612	6.4	8.9	0.209
19	I	450	1827	20.3	27.0	0.108
21	I	513	2756	28.4	41.8	0.135
	II	304	1984	20.5	30.1	0.163
24	I	82	1483	13.6	21.4	0.415
	II	80	669	6.1	9.6	0.192
25	I	307	1326	14.4	25.4	0.113
	II	249	1675	18.2	32.0	0.176
26	I	74	695	5.5	13.9	0.192
	II	52	410	3.3	8.2	0.161
Hypothyroid (mean ± SEM)						
8 patients	I	276 ± 62	1691 ± 241	17.8 ± 2.8	25.0 ± 3.1	0.199 ± 0.039
7 patients	I	251 ± 66	1671 ± 277	17.4 ± 3.1	24.7 ± 3.5	0.212 ± 0.094
7 patients	II	179 ± 41[a]	1269 ± 270[a]	13.4 ± 3.0[a]	18.9 ± 3.9[a]	0.183 ± 0.006[b]
Euthyroid (obese) (mean ± SEM)						
10 patients		127 ± 15	1414 ± 248	12.3 ± 2.1	19.9 ± 3.4	0.315 ± 0.049

[a] Period II significantly different from Period I by paired t test ($P < 0.05$).
[b] Period II not significantly different from Period I.

TABLE 12. VLDL-TG transport data (hyperthyroid group)

Patient	Period	VLDL-TG	VLDL-TG Transport			FCR
		mg/dl	*mg/hr*	*mg/hr/kg*	*mg/hr/kg IW*	hr^{-1}
27	I	27	344	6.7	5.7	0.502
	II	51	970	19.0	16.2	0.750
28	I	85	811	14.0	12.2	0.347
29	I	81	1401	20.9	19.9	0.569
	II	97	1045	15.6	14.8	0.355
30	I	22	428	5.8	5.8	0.601
	II	61	1125	15.3	15.3	0.569
31	I	116	1114	15.3	15.7	0.298
	II	95	1032	14.1	14.5	0.337
33	I	107	1500	18.6	21.0	0.404
34	I	80	47	6.4	7.3	0.175
	II	115	987	13.2	15.1	0.260
35	I	120	442	6.5	7.6	0.120
	II	154	775	11.4	13.3	0.163
37	I	37	1047	16.6	16.6	0.873
	II	39	510	8.1	8.1	0.404
39	I	60	1094	10.0	15.8	0.542
	II	80	669	6.1	9.6	0.405
Mean ± SEM						
10 patients	I	74 ± 11	822 ± 154	12.1 ± 1.8	12.8 ± 1.7	0.397 ± 0.119
8 patients	I	68 ± 13	738 ± 170	10.6 ± 2.0	11.8 ± 1.8	0.460 ± 0.088
8 patients	II	87 ± 13[a]	889 ± 76[a]	13.2 ± 1.3[a]	13.4 ± 0.9[a]	0.405 ± 0.085[a]

[a] Period II not significantly different from Period I by paired analysis.

TABLE 13. VLDL particle size distribution (by diameter)

Subjects	VLDL Particle Frequency (%)					Mean Å	SD	TG	Chol
	<100 Å	100–170 Å	170–250 Å	250–300 Å	<300 Å			*mg/dl*	*mg/dl*
Hypothyroid									
8	4	34	27	7	28	235	109	241	244
9	2	38	27	12	22	230	102	213	253
10	0	0	26	50	24	286	48	171	167
11	10	46	10	8	26	228	148	361	193
21	0	42	24	4	29	245	124	561	293
26	0	4	27	41	28	287	76	93	233
Mean ± SEM	3 ± 2	27 ± 9	24 ± 3	20 ± 9	26 ± 2	252 ± 12		273 ± 74	230 ± 20
Hyperthyroid									
28	0	2	15	42	41	302	63	104	104
29	0	0	32	35	33	284	64	118	93
30	0	28	19	19	34	261	108	51	96
32	0	0	11	37	51	332	78	179	131
34	0	0	9	34	58	325	70	150	186
39	2	1	12	35	50	318	75	90	48
Mean ± SEM	0 ± 0	5 ± 5	16 ± 4	34 ± 3	45 ± 5	304 ± 12		115 ± 20	110 ± 21
Euthyroid subjects (n = 10)									
Mean ± SEM	0 ± 0	10 ± 4	15 ± 4	24 ± 4	50 ± 6	308 ± 15		81 ± 16	192 ± 8
Euthyroid hyperlipidemia (n = 10)									
Mean ± SEM	3 ± 2	5 ± 2	17 ± 4	25 ± 3	50 ± 4	310 ± 10		347 ± 40	232 ± 13

Likewise, even after treatment of hyperthyroid patients and return to the euthyroid state, many of these patients still had an increased FCR of VLDL-TG. This phenomenon has been noted before by Nikkila and Kekki (4), and it presumably mirrored the continued activation of clearance pathways after removal of the stimulus of hyperthyroidism. Presumably this effect would dissipate over a longer period of time.

The mechanism by which thyroid hormone promotes clearance of VLDL-TG has not been elucidated by this study. Seemingly it is not entirely the consequence of stimulated synthesis of lipoprotein lipase (LDL). The quantities of this enzyme that could be released by heparin injection were not decreased in hypothyroid patients, nor were they greatly affected in hyperthyroid patients who had accelerated removal rates. Thus, other poorly-understood mechanisms must have been involved. An intriguing possibility is that thyroid hormones enhance removal of remnants of chylomicrons and VLDL. For example, we noted that nonchylomicron (lipoprotein)-TG and -cholesterol were frequently increased to an unusual degree during infusion of fat into the duodenum; this increase is compatible with a delayed removal of chylomicron remnants. Also of interest was our finding that the VLDL fraction in hypothyroid patients often contained many small particles (less than 250 Å). The portion of these small particles was much greater than found in normal or hyperthyroid patients. An excess of small VLDL conceivably could be an indication of a defective conversion of VLDL to LDL; this is consistent with the observation that hypothyroid patients may sometimes exhibit the pattern of Type III hyperlipoproteinemia (dysbetalipoproteinemia) (11, 32). The defect in this latter disorder is thought to be related to an abnormal catabolism of VLDL, possibly with accumulation of remnants (32). The possibility that the high proportion of small VLDL in hypothyroid patients is somehow linked to the consistently low levels of HTGL observed in our hypothyroid patients may be worthy of more exploration.

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