0270-9139/89/0906-0852$02.00/0
HEPATOLOGY

Vol. 9, No. 6, pp. 852-855, 1989
Printed in U.S.A.

Bile Acid Metabolism in Human Hyperthyroidism

JÜRGEN PAULETZKI, FRANS STELLAARD AND GUSTAV PAUMGARTNER
Department of Medicine II, Klinikum Grosshadern, University of Munich, Munich, Federal Republic of Germany

Decreased levels of serum cholesterol are a well-recognized finding in hyperthyroidism. Since the conversion to bile acids is an important pathway for the elimination of cholesterol, we studied primary bile acid kinetics in seven hyperthyroid patients before and after medical treatment. Pool sizes, fractional turnover and synthesis rates of cholic acid and chenodeoxycholic acid were determined after oral administration of 50 mg [^{13}C]cholic acid and 50 mg [^{13}C]chenodeoxycholic acid. ^{13}C/^{12}C isotope ratios in serum were measured by capillary gas chromatography/electron impact mass spectrometry.

Compared with the euthyroid state, serum cholesterol levels were distinctly lower in hyperthyroidism (150 ± 33 vs. 261 ± 51 mg per dl, $p < 0.01$). Thyroid hormone excess caused a 34% reduction in cholic acid synthesis (5.8 ± 2.8 vs. 7.9 ± 4.2 μmoles per kg per day, $p < 0.02$), which was associated with a 47% decrease in cholic acid pool size (11.7 ± 3.4 vs. 22.0 ± 5.2 μmoles per kg, $p < 0.01$). Chenodeoxycholic acid kinetics exhibited no apparent changes. Thus, total primary bile acid synthesis was diminished by 20% in hyperthyroidism. After normalization of thyroid function, the ratio of cholic acid/chenodeoxycholic acid pool size increased in all patients. This was paralleled by a rise in the ratio of concentrations of cholic acid/chenodeoxycholic acid in serum.

The depression of cholic acid synthesis in the presence of unaltered chenodeoxycholic acid synthesis found in hyperthyroid subjects is compatible with an inhibition of hepatic 12α-hydroxylation by thyroid hormone. Furthermore, evidence is provided that, in man, the low serum cholesterol levels found during hyperthyroidism are not caused by an increased conversion of cholesterol to bile acid.

Low levels of serum cholesterol are a frequent finding in hyperthyroidism (1). The effects of thyroid hormone on sterol metabolism, however, have not been sufficiently studied. Hepatic conversion of cholesterol to bile acids is an important pathway for the elimination of cholesterol (2). In rats, thyroid hormone increases the activity of cholesterol-7α-hydroxylase (3, 4), the rate-limiting enzyme of bile acid synthesis, but data on the conversion of cholesterol to cholic acid and chenodeoxycholic acid in human hyperthyroidism are still lacking. Such data are even more desirable as thyroid hormone stimulates cholesterol biosynthesis (5) and increases receptor-mediated low-density lipoprotein (LDL) uptake (6–8). Therefore, we studied primary bile acid kinetics in hyperthyroid patients before and after treatment.

PATIENTS AND METHODS

Seven patients (six females and one male; age 45 to 79 years) with hyperthyroidism were included in the study. Five patients suffered from Graves' disease, and two patients had multinodular toxic goiter. Initially, all patients showed clinical signs of overt hyperthyroidism with tachycardia, excessive sweating, nervousness and heat intolerance. There was no heart failure or diarrhea. All patients were successfully treated by thiamazole (Favistan®; Merck, Darmstadt, Federal Republic of Germany) as documented by normalization of clinical and laboratory status. They all had normal routine liver tests, which were not altered by thiamazole therapy. During the entire study period, the patients remained on their regular diet.

The kinetics of primary bile acids, postprandial serum bile acid concentrations and fasting serum lipid concentrations were determined in all patients in the hyperthyroid state and 3 months after stabilization of normal thyroid function following effective medical therapy. Informed consent was obtained from all patients. Measurements of bile acid kinetics with stable isotopes were approved by the ethical committee of the University Hospitals of the University of Munich.

The kinetics of cholic acid and chenodeoxycholic acid (pool size, fractional turnover rate and synthesis rate) were determined by an isotope dilution technique (9). The simultaneous oral administration of 50 mg [24-^{13}C]cholic acid and 50 mg [24-^{13}C]chenodeoxycholic acid (Merck, Sharp and Dohme, Montreal, Canada) was followed by blood sampling over 4 days. ^{13}C/^{12}C isotope ratios of cholic acid and chenodeoxycholic acid were measured in serum by capillary gas liquid chromatography/electron impact mass spectrometry (9). A 25 m x 0.32 mm fused silica capillary OV-1701 column (CP Sil 19 CB; Chrompack, Middleburg, The Netherlands) was directly inserted into a Finnigan 4000 mass spectrometer. The measured ^{13}C/^{12}C isotope ratios were converted into atom % excess. Pool size and fractional turnover rate were subsequently calculated from the ln atom % excess-time curve. Synthesis rate was determined by multiplying pool size and fractional turnover rate (9).

Postprandial (2 hr) serum concentration of cholic acid, chenodeoxycholic acid and deoxycholic acid were determined by capillary gas liquid chromatography (9). A 25 m x 0.32 mm fused silica capillary OV-1701 column was used in a Carlo Erba 4160 gas chromatograph.

Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels were measured enzymatically by means of commercial kits (Boehringer, Mannheim, Federal Republic of Germany). LDL-cholesterol was calculated according to Friedwald's formula (10).

Received January 18, 1988, accepted October 27, 1988.
Address reprint requests to: J. Pauletzki, M.D., Department of Medicine II, Klinikum Grosshadern, Marchioninistr. 15, D-8000 Munich 70, Federal Republic of Germany.

The data are expressed as mean ± S.D. Statistical significance ($p < 0.05$) was tested with the Wilcoxon test for paired samples (11).

RESULTS

Hyperthyroid patients revealed a low serum cholesterol, which rose distinctly after normalization of thyroid function in all patients (150 ± 33 vs. 261 ± 51 mg per dl, $p < 0.01$) (Table 1). This was paralleled by an increase in LDL-cholesterol and HDL-cholesterol. The triglyceride levels remained unchanged. There was no significant alteration of body weight while achieving euthyroidism (Table 1).

In hyperthyroidism, cholic acid pool size was reduced to 53% of the euthyroid value (11.7 ± 3.4 vs. 22.0 ± 5.2 μmoles per kg, $p < 0.01$) (Fig. 1). Despite a concomitant increase in fractional turnover rate of 56% (0.56 ± 0.37 vs. 0.36 ± 0.17 day^{-1}, $p < 0.02$), there was a 34% inhibition of cholic acid synthesis rate (5.8 ± 2.8 vs. 7.9 ± 4.2

TABLE 1. Patient characteristics before and after treatment of hyperthyroidism

	Before treatment	After treatment
Thyroxine (μg/dl)	19.4 ± 3.2[a]	7.1 ± 3.2[b]
Triiodothyronine (ng/ml)	3.6 ± 1.3	1.6 ± 0.6[b]
Cholesterol (mg/dl)	150 ± 33	261 ± 51[b]
HDL-cholesterol (mg/dl)	43 ± 13	81 ± 23[b]
LDL-cholesterol (mg/dl)	82 ± 23	155 ± 32[b]
Triglycerides (mg/dl)	127 ± 45	143 ± 48
Body weight (kg)	63.3 ± 13.9	66.5 ± 16.3
Body mass index (kg/m^2)	24.5 ± 4.2	25.6 ± 4.7

There were six females and one male, age 45 to 79 years.
[a] Mean ± S.D.
[b] Significantly different from pretreatment value ($p < 0.01$).

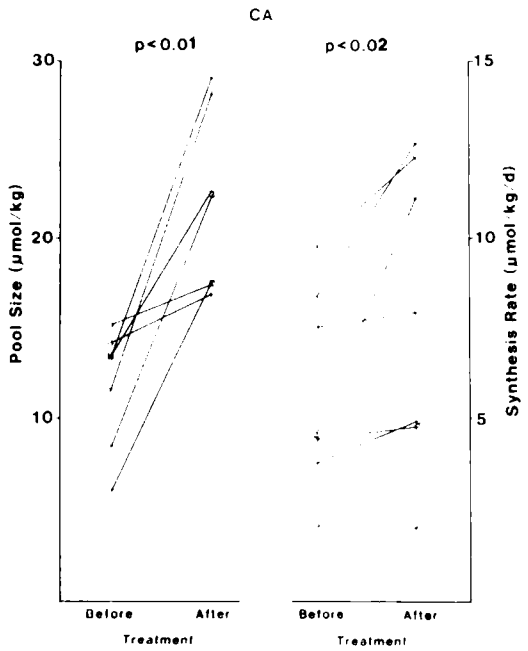

FIG. 1. Pool size and synthesis rate of cholic acid before and after treatment of hyperthyroidism.

TABLE 2. Primary bile acid kinetics in hyperthyroidism before and after treatment

	Before treatment	After treatment
Cholic acid		
Pool size (μmoles/kg)	11.7 ± 3.4[a]	22.0 ± 5.2[b]
Fractional turnover rate (day^{-1})	0.56 ± 0.37	0.36 ± 0.17[c]
Synthesis rate (μmoles/kg/day)	5.8 ± 2.8	7.9 ± 4.2[c]
Chenodeoxycholic acid		
Pool size (μmoles/kg)	20.6 ± 6.8	19.7 ± 6.7
Fractional turnover rate (day^{-1})	0.33 ± 0.19	0.36 ± 0.20
Synthesis rate (μmoles/kg/day)	5.9 ± 2.3	6.6 ± 3.7
Cholic acid/chenodeoxycholic acid		
Pool size	0.57 ± 0.13	1.19 ± 0.32[b]
Synthesis rate	0.96 ± 0.20	1.26 ± 0.61
Cholic acid + chenodeoxycholic acid		
Pool size (μmoles/kg)	32.3 ± 9.5	41.7 ± 10.6
Synthesis rate (μmoles/kg/day)	11.6 ± 5.0	14.6 ± 6.9[d]

[a] Mean ± S.D.
[b] Significantly different from pretreatment value ($p < 0.01$).
[c] Significantly different from pretreatment value ($p < 0.02$).
[d] Significantly different from pretreatment value ($p < 0.03$).

μmoles kg^{-1} day^{-1}, $p < 0.02$) (Fig. 1, Table 2). The reduction in cholic acid pool size and synthesis rate were also significant when these parameters were not related to body weight. Chenodeoxycholic acid pool size, fractional turnover rate and synthesis rate exhibited no apparent changes during treatment (Table 2).

Total synthesis rate of primary bile acids was diminished by 20% in hyperthyroidism (11.6 ± 5.0 vs. 14.6 ± 6.9 μmoles kg^{-1} day^{-1}, $p < 0.03$). In addition, a trend toward a smaller total pool size of primary bile acids was found during thyrotoxicosis (Table 2). The significant reduction in the ratio of cholic acid/chenodeoxycholic acid pool size during hyperthyroidism vanished after normalization of thyroid function. A similar change was noted in the ratio of cholic acid/chenodeoxycholic acid synthesis rate, but it did not reach statistical significance (Fig. 2, Table 2).

Hyperthyroidism altered postprandial serum concentrations of cholic acid, chenodeoxycholic acid and deoxycholic acid only to a minor extent. The fraction of cholic acid was 14% in the hyperthyroid state and 20% after normalization of thyroid function, whereas the total concentration of serum bile acids remained constant. The ratio of cholic acid/chenodeoxycholic acid serum concentrations was reduced in hyperthyroidism (Table 3).

DISCUSSION

The results of this study demonstrate that the decrease in serum cholesterol found in patients with hyperthyroidism is not mediated by an augmented conversion of cholesterol to bile acids. Although total serum cholesterol, LDL-cholesterol and HDL-cholesterol were lower in the hyperthyroid than in the euthyroid state, bile acid

synthesis was not increased. By contrast, thyroid hormone excess significantly decreased cholic acid synthesis, whereas chenodeoxycholic acid synthesis remained unchanged.

Hellström and Lindstedt (12) measured cholic acid pool size, turnover and half-life in hyperthyroid patients and found them not significantly different from a group of hypothyroid subjects. However, the kinetics of both primary bile acids, cholic acid and chenodeoxycholic acid, have not been studied previously in hyperthyroid patients before and after treatment. Furthermore, previous investigations of bile acid metabolism in hypothyroidism yielded conflicting results. In hypothyroid patients, therapy with *l*-thyroxine caused an increase in cholic acid pool size with a parallel rise in turnover, whereas cholic acid half-life remained unchanged (12). However, it could not be excluded that the decreased cholic acid pool size in hypothyroidism was merely the result of an increased intestinal conversion of cholic acid to deoxycholic acid related to hypothyroid constipation.

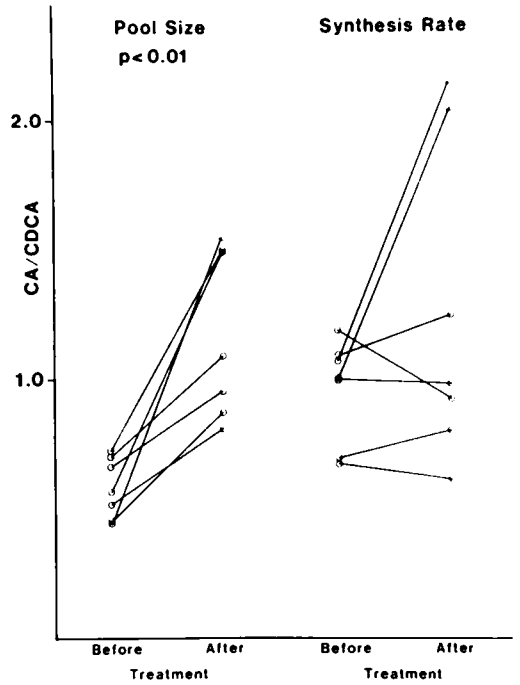

FIG. 2. Ratios of cholic acid (CA/chenodeoxycholic acid (CDCA) pool size and synthesis rate before and after treatment of hyperthyroidism.

TABLE 3. Postprandial (2 hr) serum concentration of cholic acid, chenodeoxycholic acid + deoxycholic acid and relative fractions of cholic acid, chenodeoxycholic acid and deoxycholic acid in hyperthyroidism before and after treatment

	Before treatment	After treatment
Cholic acid + chenodeoxycholic acid + deoxycholic acid (μmoles/liter)	8.57 ± 6.29[a]	9.97 ± 7.49
Cholic acid (%)	14.0 ± 5.2	20.4 ± 5.3[b]
Chenodeoxycholic acid (%)	53.3 ± 7.3	50.9 ± 8.0
Deoxycholic acid (%)	33.0 ± 9.3	29.0 ± 10.5
Cholic acid/chenodeoxycholic acid	0.26 ± 0.09	0.41 ± 0.13[b]

[a] Mean ± S.D.

[b] Significantly different from pretreatment value ($p < 0.02$).

During treatment of hypothyroid patients, Angelin et al. (13) reported a rise in chenodeoxycholic acid synthesis, whereas cholic acid and total primary bile acid synthesis were not significantly affected. No change was noted in pool size or fractional turnover rate of either cholic acid or chenodeoxycholic acid.

According to Abrams and Grundy (14), total bile acid excretion in feces is not altered by thyroid dysfunction, implying that thyroid hormone does not stimulate total bile acid synthesis in man to any major extent.

In rats, it has been shown that thyroid hormone inhibits 12α-hydroxylase (15) and stimulates 26-hydroxylase (16). Since the 26-hydroxylase probably has no regulatory importance in human liver (17), our results are compatible with the assumption of an inhibition of 12α-hydroxylase by thyroid hormone in man. There is some controversy whether different cholesterol precursor pools exist for the synthesis of cholic acid and chenodeoxycholic acid (18). Therefore, our data cannot exclude a different effect of thyroxine on separate precursor pools.

Thyroid hormone can accelerate intestinal transit (19). As our patients revealed an enhanced fractional turnover rate of cholic acid in the hyperthyroid state, a possible influence of alterations in the enterohepatic circulation ought to be considered. If excessive intestinal hypermotility causes a significant bile acid loss, a compensatory increase in bile acid synthesis should have occurred. But if, on the other hand, intestinal hypermotility leads to an increased hepatic flux of bile acids, bile acid synthesis could be reduced by inhibition of 7α-hydroxylase. Furthermore, the depression of microsomal 12α-hydroxylase in human liver after treatment with chenodeoxycholic acid (20) suggests an inhibitory effect of reabsorbed bile acids on this enzyme. Therefore, it is possible that the inhibition of 12α-hydroxylase by thyroid hormone could be partially related to moderately accelerated enterohepatic cycling with an increased portal concentration of bile acids.

Our results are compatible with the concept of 12α-hydroxylase inhibition by thyroid hormone, as previously described in rats (15). Furthermore, evidence is provided that cholesterol-7α-hydroxylase is not stimulated in human hyperthyroidism but rather seems to be inhibited, in contrast to data from animal experiments (3, 4). The reason for this obvious discrepancy is not sufficiently clear. Species differences may play a role, but it cannot be excluded that an enhanced bile acid loss due to excessive acceleration of intestinal transit in animals led to an increase in cholesterol-7α-hydroxylase activity.

HDL has been proposed as a major donor of precursor cholesterol for bile acid synthesis in man (21). Besides the fall in LDL-cholesterol, our patients also showed a comparable reduction in HDL-cholesterol during thyrotoxicosis. Thus, in hyperthyroidism, reduced levels of HDL-cholesterol might contribute to the diminished cholic acid synthesis rate. Nevertheless, in our study we did not find any significant correlation between HDL-

cholesterol and either the pool size or synthesis rate of the primary bile acids.

In conclusion, our data suggest that the low serum levels of cholesterol found in human hyperthyroidism are not caused by an augmented conversion of cholesterol to bile acids. A net loss of cholesterol also could be achieved by enhanced biliary cholesterol excretion. However, the few data available do not disclose any apparent effect of thyroid hormone on the output of cholesterol in bile (13, 14). Certainly, more quantitative studies on cholesterol balance relating LDL-receptor activity to enteral absorption, endogeneous synthesis and biliary excretion of cholesterol and to bile acid synthesis will be necessary to further elucidate the mechanism by which thyroid hormone decreases serum cholesterol levels in man.

Acknowledgments: The skillful technical assistance of E. König, R. Nuber and G. Dyck as well as the secretarial help of J. Steinberg are gratefully acknowledged.

REFERENCES

1. Peters JP, Man EB. The significance of serum cholesterol in thyroid disease. J Clin Invest 1950; 29:1–11.
2. Einarsson K, Angelin B. Hyperlipoproteinemia, hypolipidemic treatment and gallstone disease. In: Grundy SM, ed. Bile acids and atherosclerosis, Vol. 15. New York: Raven Press, 1986: 67–97.
3. Wada F, Hirata K, Nakao K, et al. Participation of the microsomal electron transport system involving cytochrome P-450 in 7α-hydroxylation of cholesterol. J Biochem 1969; 66:699–703.
4. Balasubramaniam S, Mitropoulos KA, Myant NB. Hormonal control of the activities of cholesterol-7α-hydroxylase and hydroxymethylglutaryl-CoA-reductase in rats. In: Matern S, Hackenschmidt J, Back P, et al. eds. Advances in bile acid research, Vol. III. Stuttgart: Schattauer Verlag, 1975: 61–67.
5. Lipsky SR, Bondy PK, Man EB, et al. The effects of triiodothyronine on the biosynthesis of plasma lipids from acetate-1-^{14}C in myxedematous subjects. J Clin Invest 1955; 34:950.
6. Chait A, Bierman EI, Albers JJ. Regulatory role of triiodothyronine in the degradation of low density lipoprotein by cultured human skin fibroblasts. J Clin Endocrinol Metab 1979; 48:887–889.
7. Walton UW, Scott PJ, Dykes PW, et al. The significance of alterations in serum lipids in thyroid dysfunction. II. Alterations of the metabolism and turnover of ^{131}I-low density lipoprotein in hypothyroidism and thyrotoxicosis. Clin Sci 1965; 29:217–238.
8. Thompson GR, Sontar AK, Spengel FA, et al. Defects of receptor-mediated low density lipoprotein catabolism in homozygous familial hypercholesterolemia and hypothyroidism in vivo. Proc Natl Acad Sci USA 1981; 78:2591–2595.
9. Stellaard F, Sackmann M, Sauerbruch T, et al. Simultaneous determination of cholic acid and chenodeoxycholic acid pool sizes and fractional turnover rates in human serum using ^{13}C-labeled bile acids. J Lipid Res 1984; 25:1313–1319.
10. Friedwald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502.
11. Snedecor GW, Cochran WG, eds. Statistical methods. Ames, Iowa: Iowa State University Press, 1980.
12. Hellström K, Lindstedt S. Cholic acid turnover and biliary bile acid composition in humans with abnormal thyroid function. J Lab Clin Med 1964; 63:666–679.
13. Angelin B, Einarsson K, Leijd B. Bile acid metabolism in hypothyroid subjects: response to substitution therapy. Eur J Clin Invest 1983; 13:99–106.
14. Abrams JJ, Grundy SM. Cholesterol metabolism in hypothyroidism and hyperthyroidism in man. J Lipid Res 1981; 22:323–338.
15. Mitropoulos KA, Suzuki M, Myant NB, et al. Effects of thyroidectomy and thyroxine treatment on the activity of 12α-hydroxylase and on some components of microsomal electron transfer chains in rat liver. FEBS Lett 1968; 1:13–15.
16. Björkhem I, Danielsson H, Gustafsson J. The effect of thyroid hormone on 26-hydroxylation of C_{27}-steroids in rat liver. FEBS Lett 1973; 31:20–22.
17. Björkhem I. Mechanism of bile acid biosynthesis in mammalian liver. In: Danielsson H, Sjövall J, eds. New comprehensive biochemistry: sterols and bile acids. Amsterdam: Elsevier, 1985: 231–279.
18. Einarsson K, Ahlberg J, Angelin B, et al. Evidence for the presence of different cholesterol precursors in man. In: Preisig R, Bircher J, eds. The liver. Quantitative aspects of structure and function. Aulendorf, Federal Republic of Germany: Editio Cantor, 1979: 233–238.
19. Thomas FB, Caldwell JH, Greenberger NJ. Steatorrhoea in thyrotoxicosis. Relation to hypermotility and excessive dietary fat. Ann Intern Med 1973; 78:669–675.
20. Ahlberg J, Angelin B, Björkhem I, et al. Effects of treatment with chenodeoxycholic acid on liver microsome metabolism of steroids in man. J Lab Clin Med 1980; 95:188–194.
21. Schwartz CC, Vlahcevic ZR, Halloran LG, et al. An in vivo evaluation in man of the transfer of esterified cholesterol between lipoproteins and into the liver and bile. Biochim Biophys Acta 1981; 663:143–162.