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Effect of Thyroid Function on Concentrations of Lipoprotein(a)

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The effect of thyroid hormones on concentrations of lipoprotein(a) [Lp(a)] was analyzed in 60 patients with active thyroid dysfunction (hyperthyroidism 30 cases, hypothyroidism 32 cases, and 2 cases with opposite changes) and after normalization of the thyroid state. Treatment of hyperthyroidism increased the mean Lp(a) concentrations by 60% (from 73 to 102 mg/L, $P < 0.002$); at the same time, low-density lipoprotein cholesterol (LDL-C) increased by 53% (from 2.6 to 3.7 mmol/L, $P < 0.0001$) and apolipoprotein B (apo B) by 35% (from 0.91 to 1.17 g/L, $P < 0.0005$). In hypothyroidism, the opposite changes were observed: mean Lp(a) decreased from 136 to 114 mg/L (10%, $P < 0.02$), LDL-C from 4.6 to 3.9 mmol/L (13%, $P < 0.01$), and apo B from 1.51 to 1.20 g/L (14%, $P < 0.01$). Although the changes in Lp(a) concentrations did correlate with changes of LDL-C during treatment of hyperthyroidism ($r = 0.43$, $P < 0.05$), and with changes in apo B during thyroxine-substitution therapy for hypothyroidism ($r = 0.46$, $P < 0.05$), we observed no associations between Lp(a) and LDL-C or apo B in the euthyroid state. These data cannot rule out the possibility that the thyroid hormone-induced increase in LDL-C receptor activity was responsible for the decreased concentrations of Lp(a) in hyperthyroidism. Given that LDL-C is ~30% of the Lp(a) molecule but the changes in Lp(a) concentrations are comparable with those in LDL-C (60% vs 53%), and given that Lp(a) is metabolized by an LDL-C-receptor-independent pathway, the present data suggest a direct effect of thyroid hormones on Lp(a) synthesis.

Indexing Terms: *cholesterol · lipoproteins · apolipoproteins · hyperthyroidism · hypothyroidism · lipoprotein receptor*

Thyroid disorders are known to influence lipoprotein metabolism (*1–5*). The changes in plasma concentrations of cholesterol are primarily due to changes in the low-density lipoprotein (LDL) fraction.[2] In hyperthyroidism, an increase in mRNA for LDL receptors has been observed, inducing an increased number and activity of LDL receptors (*2, 4*) and thus leading to a decrease in concentrations of LDL and total cholesterol (*2*). The opposite changes are observed during hypothyroidism: The increase in apolipoprotein (apo) B and LDL concentrations is not due to increased secretion, but rather to decreased removal rates (*4*).

Conflicting results are reported with regard to lipoprotein(a) [Lp(a)] changes during thyroid dysfunction (*6, 7*). Lp(a), an LDL-like particle, consists of an LDL-molecule linked to apo(a), a glycoprotein structurally related to plasminogen, the zymogen of plasmin (*8*). In contrast to plasminogen, however, apo(a) cannot be converted to the proteolytic form. Therefore, Lp(a) can be expected to be a potentially thrombogenic and atherogenic agent. Because Lp(a) also shares the apo B antigen with LDL, perhaps Lp(a) is metabolized through the LDL cholesterol (LDL-C) receptor pathway. However, the data available so far favor an LDL-C-receptor-independent pathway (*9, 10*).

In the present study, we assessed the changes in Lp(a) concentrations during active thyroid dysfunction and in the euthyroid state.

Patients and Methods

Patients

Sixty patients were included in the study. We analyzed the lipid profile during 62 changes from acute thyroid dysfunction to the stable euthyroid state or to clearly improved conditions [euthyroid values for free thyroxine (FT_4) and triiodothyronine (T_3) with slightly abnormal values for thyrotropin (TSH)]. We evaluated 30 cases (26 female, 4 male) in the hyperthyroid state, 32 (25 female, 7 male) during hypothyroidism. In two cases, a follow-up of opposite changes was possible (hyperthyroidism, postpartum thyroiditis). The mean (± SD) observation periods were 186 ± 142 days (hyperthyroid group) and 171 ± 129 days (hypothyroid group).

Methods

Thyroid-function tests. TSH (TSH IRMAclon) and T_3 (RIAcid; both from Henning, Berlin, Germany) were measured with radioimmunometric assays: The TSH assay had an interassay imprecision (CV) of 17% at 0.5 mIU/L, 5% at 3.9 mIU/L; T_3 showed an interassay imprecision of 7.8% at 2.2 nmol/L. FT_4 values were determined with the Abbott IMx system (Abbott Labs., Abbott Park, IL); between-run imprecision was 7% at 9.0 μmol/L, 5.2% at 15.6 μmol/L.

Lipid analytes. Lp(a) was measured with the apo(a) RIA from Pharmacia (Uppsala, Sweden); between-run imprecision was 6.8% at 45 mg/L, 9.7% at 93 mg/L. Apo A-I and apo B were determined with an immunonephelometric assay system (BNA; Behringwerke, Marburg, Germany); between-run imprecision was 4.6% at 1.70 g/L for apo A-I, 3.3% at 1.22 g/L for apo B. Total cholesterol and triglyceride concentrations were measured by

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[2] Nonstandard abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); FT_4, free thyroxine; T_3, triiodothyronine; TSH, thyrotropin (thyroid-stimulating hormone); and apo, apolipoprotein.

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enzymatic methods with a Hitachi 717 (Boehringer Mannheim, Mannheim, Germany); high-density lipoprotein cholesterol was measured in the supernate after precipitation with phosphotungstate/Mg^{2+} (Boehringer Mannheim). LDL-C was calculated according to the Friedewald formula (*11*).

Statistics. The data are presented as mean ± SD. Because of the skewed distribution of the Lp(a) values, we performed a logarithmic transformation of the results and reported the mean of the transformed results (68% range of variance). Changes in thyroid or lipid markers during treatment of thyroid dysfunction were tested by the Wilcoxon paired rank test (*12*).

Results

The changes in thyroid and lipid markers are summarized in Table 1. Treatment of hyperthyroidism resulted in a clear decrease of FT_4 and T_3 values, concomitant with an increase in cholesterol, LDL-C, apo B, and Lp(a) concentrations. The mean increase in Lp(a) was 60% ($P < 0.002$ vs initial values). Opposite changes were observed during T_4 treatment of hypothyroidism: a marked increase in FT_4 and T_3, concomitant with a decrease in total cholesterol, LDL-C, and apo B. Again, the change in Lp(a) concentrations was significant, although this was only a decrease of 10% ($P < 0.02$ vs initial values). In contrast to the situation in hyperthyroidism, the Lp(a) response to treatment of hypothyroidism displayed an extensive variety: Some patients showed a marked decrease (e.g., see Figure 1), whereas in other cases almost no changes were observed, and in a few cases Lp(a) concentrations increased. The changes of apo B and LDL-C concentrations parallel those of Lp(a) (Figure 2). No significant correlations were obtained between Lp(a) and apo B or LDL-C concentrations in euthyroid subjects. However, we observed a significant association between changes in concentrations of Lp(a) and of LDL-C in the hyperthyroid group ($r = 0.43$, $P < 0.05$) and between changes of Lp(a) and of apo B in the hypothyroid group ($r = 0.46$, $P < 0.05$). Again, the changes during treatment of hyperthyroidism were more pronounced than those seen during treatment with T_4 substitution in hypothyroidism (Table 2).

In two patients we were able to monitor lipid parameters over a long period during several changes in thyroid function (Figure 1). One, a 76-year-old man with hyperthyroidism (supposedly Graves disease), was treated by radiotherapy with adjuvant therapy with methimazole. Consequently, he developed hypothyroidism; the methimazole was stopped, and he became hyperthyroid again, which led to the reinstitution of the methimazole therapy. Figure 1 (left) clearly indicates the opposite changes during the course of therapy in this patient.

Figure 1 (right) depicts FT_4 and Lp(a) concentrations in a 27-year-old woman with postpartum thyroiditis. During her pregnancy, she had consulted with clinical symptoms of hyperthyroidism, but thyroid-function tests indicated she was euthyroid. The pregnancy had to be terminated early by caesarean section due to the development of high liver-enzyme/low platelet syndrome, and the patient delivered a healthy boy. Six months later, the woman developed hypothyroidism (initial data shown in Figure 1). High concentrations of antibodies to thyroid peroxidase were measured and substitution therapy with low-dose T_4 was initiated. Subsequently, the patient developed hyperthyroidism, and therapy with propylthiouracil was started. Not only the anti-thyroid peroxidase antibodies, but also the TSH-receptor antibodies were slightly increased at this time. One year after delivery, the patient returned to an euthyroid state. Again, the course of Lp(a) was opposite that of FT_4 during the whole course of therapy.

Discussion

Thyroid hormones influence not only total cholesterol, LDL-C, and apo B concentrations (*3*), they also clearly show an effect on Lp(a) concentrations (*7*, and the present study). The effects in hyperthyroidism were more pronounced than those in hypothyroidism: mean increase of 60% during treatment of hyperthyroidism vs a decrease of 10% during T_4 substitution for hypothyroidism. Given the genetically determined great variations in individual Lp(a) values (*13*), the changes during

Table 1. Changes in Lipid Concentrations during Therapy for Thyroid Disfunction

	Hyperthyroidism (n = 30)		Hypothyroidism (n = 32)	
Analyte	Before therapy	During/after therapy	Before therapy	During T_4 substitution
TSH, mIU/L	0.05 ± 0.04	5.36 ± 11.2[a]	51.6 ± 51.5	5.5 ± 5.7[a]
FT_4, pmol/L	42.0 ± 12.2	16.4 ± 8.4[a]	7.6 ± 4.4	18.7 ± 5.7[a]
T_3, nmol/L	4.5 ± 2.0	2.1 ± 0.6[a]	1.3 ± 0.7	1.7 ± 0.5
Cholesterol, mmol/L	4.5 ± 1.0	5.9 ± 1.4[a]	6.8 ± 1.5	5.9 ± 1.4[c]
LDL-C, mmol/L	2.6 ± 0.8	3.7 ± 1.2[a]	4.6 ± 1.3	3.9 ± 1.2[d]
HDL-C, mmol/L	1.3 ± 0.3	1.4 ± 0.4[f]	1.4 ± 0.4	1.3 ± 0.3
Apo A-I, g/L	1.49 ± 0.25	1.66 ± 0.28[d]	1.60 ± 0.34	1.60 ± 0.29
Apo B, g/L	0.91 ± 0.27	1.17 ± 0.36[b]	1.51 ± 0.36	1.20 ± 0.24[d]
Lp(a), mg/L[g]	73 (46–117)	102 (62–168)[c]	136 (88–217)	114 (69–191)[e]

[a] $P < 0.0001$; [b] $P < 0.0005$; [c] $P < 0.002$; [d] $P < 0.01$; [e] $P < 0.02$; [f] $P < 0.05$. [g] Mean (and 68% range of variance). HDL-C, high-density lipoprotein cholesterol.

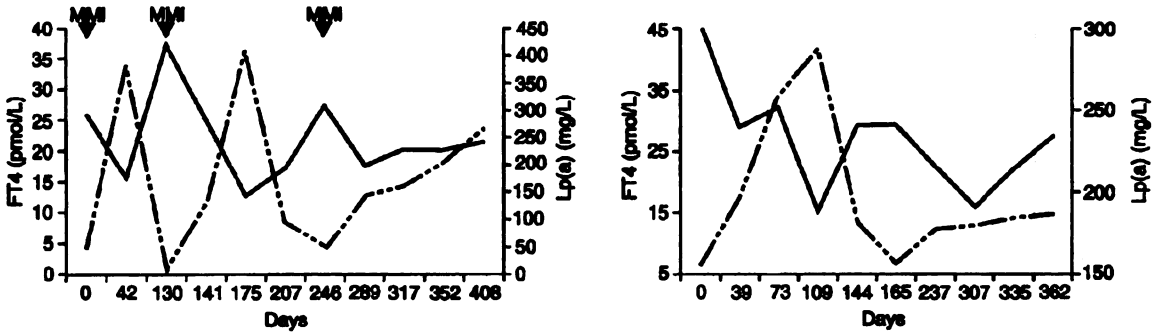

Fig. 1. Changes in Lp(a) (—) and FT_4 (- - -) concentrations (*left*) after radioiodine therapy for hyperthyroidism [to control hyperthyroidism, the patient received supportive therapy with methimazole (MMI)] and (*right*) in a patient with postpartum thyroiditis

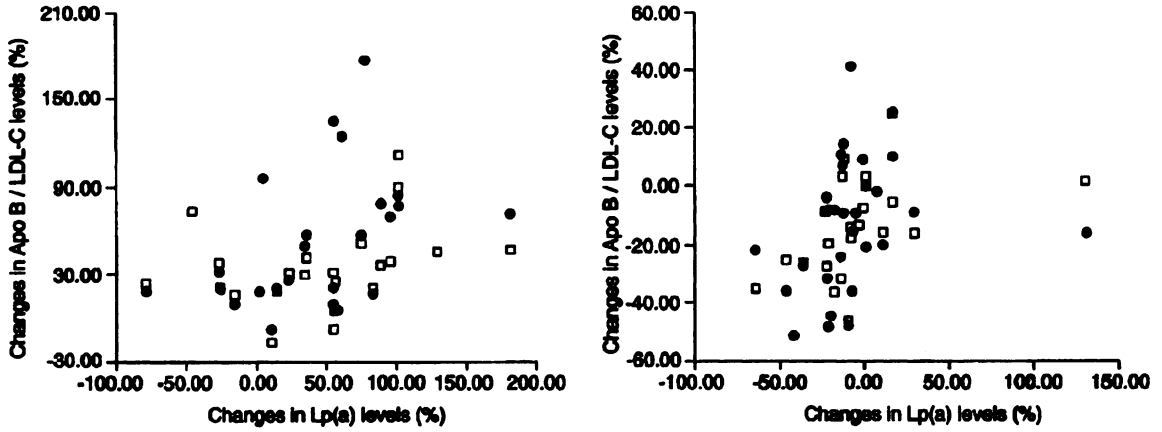

Fig. 2. Relative changes in Lp(a)-, apo B-, and LDL-C concentrations (*left*) during treatment of 30 patients for hyperthyroidism and (*right*) during T_4 substitution in 32 patients for hypothyroidism
Relative changes in apo B (□); relative changes in LDL-C (●)

Table 2. Relative Changes (%)[a] in Lp(a), Apo B, and LDL-C Concentrations during Treatment for Thyroid Dysfunction

	Hyperthyroidism (n = 30)	Hypothyroidism (n = 32)
Lp(a)	160 ± 92 (60% increase)	90 ± 34 (10% decrease)
Apo B	135 ± 29 (35% increase)	86 ± 17 (14% decrease)
LDL-C	153 ± 47 (53% increase)	87 ± 23 (13% decrease)

[a] Changes after therapy compared with initial values.

treatment of hypothyroidism may be masked. Klausen et al. (*6*) found no changes in Lp(a) concentrations during T_4 substitution therapy of hypothyroidism. In their study, the initial Lp(a) values were surprisingly low (166 mg/L), compared with those reported by de Bruin et al. (*7*) for patients in the hypothyroid state (255 mg/L). Our own data (136 mg/L in the hypothyroid state) were even lower. Because the patient group studied by Klausen et al. was small (13 patients vs 30 in the present study), and the hormonal effect on Lp(a) is only small (mean decrease of 10% in the present study), conceivably the former authors were unable to show the effect we found. A further problem is posed by the great genetically determined variability in Lp(a) concentrations within the normal population (*13, 14*). The behavior of Lp(a) as an acute-phase protein is another reason why it may be difficult to demonstrate the effect of thyroid hormones on Lp(a) during T_4 substitution therapy.

In contrast to the discrepant results for Lp(a), the changes in total cholesterol, LDL-C, and apo B are consistent in all three follow-up studies (*6, 7,* and present data) and confirm earlier findings (*3, 5, 15*): Hyperthyroidism leads to decreased total cholesterol, LDL-C, and apo B, whereas in hypothyroidism the opposite changes are observed. However, the changes were more pronounced during treatment of hyperthyroidism than of hypothyroidism (Table 1). These data suggest that the effect of thyroid hormones is directly in the realm of protein synthesis. The T_4-induced increase in concentrations of the mRNA for LDL-C receptors leads to an increase in LDL-receptor number and activity (*2, 4*) and thus to a decrease in LDL-C and total cholesterol. Therefore, the increase in LDL-C and total cholesterol during hypothyroidism is caused by a decreased clearance rather than increased production or secretion of LDL-C.

Another mechanism leading to decreases in LDL-C and possibly also Lp(a) is the synthesis of apo B. In the animal model, an effect of thyroid hormones on processing of apo B mRNA has been demonstrated. Whereas thyroid hormones apparently have no effect on total

concentrations of apo B mRNA, thyroid hormones modulate the editing of apo B mRNA, leading to a decrease in the abundance of apo B100 mRNA and an increase in apo B48 mRNA (*16*). Therefore, we postulate that thyroid hormones not only increase the clearance of LDL-C by increasing the activity of the LDL receptor, but suppress LDL-C synthesis through modulating the processing of apo B mRNA.

Little is known about how the concentration of Lp(a) is influenced by thyroid hormones. Given that Lp(a) is composed of apo(a) linked by disulfide bonds to apo B in the LDL-C particle, one could postulate that a decrease in synthesis of apo B100 would lead to a decrease in Lp(a) concentrations. However, no consistent relationships between Lp(a) and LDL-C with regard to concentrations of apo B have been observed in the normal populations (unpublished data). Although some large cohort studies demonstrated a weak association between Lp(a) and LDL-C concentrations, with correlation coefficients between 0.1 and 0.3 (*17, 18*), this correlation disappeared if corrected for the LDL-C content in the Lp(a) molecule (*19*). Furthermore, an increase in daily cholesterol intake led to a significant increase in LDL-C levels without changes in Lp(a) levels (*20*). Similarly, HMG-CoA reductase inhibitors have no effect on Lp(a) concentrations, despite their excellent reduction of LDL-C content (*21–23*). Apparently, the Lp(a) concentration depends on the amount of apo(a) available for binding to apo B and not vice versa. The apo(a) synthesis is under multigenic control (*24*). Therefore, thyroid hormones, which are known to affect biosynthesis at the transcriptional and (or) translational level, could reasonably also exert an effect on apo(a) biosynthesis. Studying patients with familial hypercholesterolemia, Utermann et al. (*24*) demonstrated that Lp(a) concentrations in plasma could be determined by variation at more than one gene locus.

The present data suggest that thyroid hormones have a direct suppressive effect on apo(a) synthesis. Until now no clear relationship could be demonstrated between apo(a) and apo B or LDL-C concentrations, even if corrected for apo(a) phenotypes (Engler, Riesen: unpublished observation). The possibility that the decrease in Lp(a) concentrations during hyperthyroidism could also be mediated by increased activity of the LDL-C receptor cannot be ruled out by the present data, but the studies so far favor an LDL-C-receptor-independent metabolism for Lp(a) (*9, 10, 25*). Furthermore, the LDL-C content in Lp(a), ~30% (*19*), cannot explain the Lp(a) reduction in hyperthyroidism either, because the 60% increase in Lp(a) during treatment for hypothyroidism is comparable with the changes observed for LDL-C concentrations (53%).

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