PRELIMINARY REPORT

Serum Lipoprotein(a) Levels Before and After Subtotal Thyroidectomy in Subjects With Hyperthyroidism

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Lipoprotein(a) [Lp(a)], a lipoprotein that structurally resembles low-density lipoprotein (LDL), contains apolipoprotein(a) [apo(a)] and apolipoprotein B-100 (apo B). There exists a close inverse correlation between serum concentrations of LDL or apo B and concentrations of thyroid hormone in patients with thyroid disease, probably due to a change in LDL receptor activity. To clarify the relations between thyroid hormone and Lp(a), we measured serum Lp(a) levels in 13 hyperthyroid subjects before treatment (stage H), during the euthyroid stage induced immediately before performing a subtotal thyroidectomy (stage E), and during the hypothyroid stage observed transiently after the operation (stage L). The mean serum concentration of Lp(a) increased significantly ($P = .01$) from 9.4 mg/dL in stage H to 26.8 in stage L through the level of 15.5 mg/dL in stage E. There was no significant difference between the mean serum concentration of Lp(a) in these patients in stage E and healthy controls (14.2 mg/dL). There was a low but statistically significant negative correlation between the Lp(a) level and the serum free thyroxine (fT_4) concentration ($r = .31$, $P < .05$). The results suggest that thyroid hormone is a potent modulator of Lp(a) metabolism.

THE PRESENCE OF a high serum level of lipoprotein(a) [Lp(a)] is an independent risk factor for arteriosclerosis.[1-3] Recent structural analysis of Lp(a) showed a marked homology to plasminogen, which suggests that it has some relation to fibrinolysis.[4,5] Patients with thyroid disease reportedly demonstrate changes in the metabolism of lipoproteins, including intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL), both of which contain apolipoprotein (apo) B-100, also a risk factor for arteriosclerosis.[6,7]

Arteriosclerotic lesions are commonly observed in hypothyroid patients. Increases in serum LDL and intermediate-density lipoprotein in such patients are assumed to be contributory factors. Lp(a), a lipoprotein structurally similar to LDL, contains apo(a) and apo B-100.[8] There has been only one study on Lp(a) levels in patients with thyroid diseases. It showed that treatment of hypothyroidism reduced the serum level of LDL, but not of Lp(a). Those investigators concluded that thyroid hormones have little effect on Lp(a).[9] We performed a subtotal thyroidectomy on hyperthyroid patients. The serum Lp(a) level was determined in each patient in the hyperthyroid stage before treatment (stage H), the euthyroid stage induced immediately before surgery (stage E), and the transient hypothyroid stage 1 or 2 months after surgery (stage L).

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SUBJECTS AND METHODS

Subjects

The subjects were 13 Japanese patients (three men and 10 women; mean age, 25.5 ± 6.3 years) who were clinically diagnosed with hyperthyroidism. They were treated with methimazole (30 mg/d), and when the thyroid function became normal they received a subtotal thyroidectomy. None of the patients showed clinical or biochemical evidence of malignant neoplasms, renal or liver diseases, diabetes mellitus, familial hypercholesterolemia, or endocrinological disease other than hyperthyroidism. No patient was taking oral contraceptives, estrogens, diuretics, hypolipidemic drugs, or β-blockers.

The control group consisted of 418 apparently healthy Japanese (249 men and 169 women; mean age, 27 years) as verified by clinical and laboratory studies. Informed consent was obtained from each subject before the study.

Method

At each of the three stages (H, E, and L), venous blood was drawn after an overnight fast and analyzed for serum concentrations of Lp(a), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol (HDL-C), LDL cholesterol (LDL-C), and apo B. The concentrations of free triiodothyronine ([fT_3] normal range, 2.7 to 5.9 pg/mL), free thyroxine ([fT_4] normal range, 0.7 to 1.8 ng/dL), and thyrotropin ([TSH] normal range, 0.1 to 4 μU/mL) were measured by radioimmunoassay. Lp(a) levels were determined with the Tint Elize Kit (Biopool, Stockholm, Sweden). The standard curve for this assay was linear to 60 mg/dL Lp(a). Interassay and intraassay variances were in the same range as previously reported.[10] Enzymatic methods were used to determine serum TC and TG concentrations. The dextran sulfate–Mg^{2+} sedimentation method was used to measure the HDL-C concentration. Serum apo B was determined by an immunoturbidometric assay.[11]

LDL-C levels and the Atherogenic Index (A · I) were calculated as follows: LDL-C = (TC − HDL-C − TG)/5, and A · I = (TC − HDL-C)/HDL-C.

Table 1. Serum Levels of fT_3, fT_4, and TSH and Relative Body Weight in 13 Hyperthyroid Patients During Stage H, Stage E, and Stage L

Parameter	Stage		
	H	E	L
fT_3 (pg/mL)	20.0 ± 4.8 (9.5 ~ 25.5)	4.4 ± 1.8 (2.3 ~ 5.9)*	2.1 ± 0.9 (0.3 ~ 2.7)*†
fT_4 (ng/dL)	6.2 ± 1.9 (3.0 ~ 10.7)	1.3 ± 0.6 (0.7 ~ 1.8)*	0.4 ± 0.2 (0.1 ~ 0.7)*†
TSH (μU/mL)	0.077 ± 0.066 (0.02 ~ 0.09)		36.4 ± 39.1 (9.5 ~ 111.0)*
Relative body weight (%)	91.4 ± 8.2	98.0 ± 10.1	99.9 ± 9.6

NOTE. Values are the mean ± SD (range). Scheffe's test was used to determine whether the change during treatment was statistically significant. The relative body weight is the percentage of mean body weight corrected for age, sex, and height obtained from actuarial tables.[29]

*P = .001 *v* stage H.

†P = .001 *v* stage E.

Statistical Method

Data are reported as the mean ± SD. The statistical analysis used a nonparametric multiple comparison test (Scheffe's test for variable:rank) for comparison of the means.[12] Correlations were determined by Spearman's analysis. A level of P less than .05 was accepted as statistically significant.

RESULTS

Table 1 shows the mean values for body weight and serum fT_3, fT_4, and TSH. The data confirmed that all patients were in fact in the hyperthyroid, euthyroid, and hypothyroid stages at points H, E, and L, respectively.

Table 2 shows the changes in serum TC, TG, HDL-C, LDL-C, apo B, and Lp(a). TC, LDL-C, and apo B increased significantly from H to E and from E to L. As compared with H, HDL-C increased markedly at stages E and L.

As shown in Table 2 and Fig 1, all patients showed a marked increase in both the absolute value and the change in Lp(a) concentration during the course of treatment. Lp(a) was increased significantly in stage L as compared with H. Lp(a) was increased 2.6- and 4.9-fold, respectively, at stages E and L as compared with H. Even in the other 12 subjects, except for one case who showed an extraordinarily high level of Lp(a) before therapy, there was a significant increase of Lp(a) at stages E and L as compared with H. The mean Lp(a) concentration in normal controls (14.2 ± 10.1 mg/dL) was very close to the mean Lp(a) level at stage E in the subjects with hyperthyroidism. Table 3 shows that the concentration of Lp(a) was not correlated with those of other lipids or apolipoproteins. There was a significant ($P < .05$) negative correlation between the Lp(a) level and the change in thyroid hormone concentration.

DISCUSSION

We were able to evaluate the longitudinal change in serum levels of lipid and Lp(a) in the same patient from stages H to E to L. The lipid changes at each stage were consistent with previously published data.[13-15] Both LDL-C and apo B were below normal levels in the stage H, but returned to the normal range after administration of an antihyperthyroid agent. LDL-C and apo B increased significantly after subtotal thyroidectomy as compared with stages E or H.

We found serum Lp(a) to vary inversely with the change in thyroid hormone concentration. This is the first report to show a strong correlation between Lp(a) and thyroid hormone concentrations. A previous study by Klausen et al[9] failed to show a relationship between Lp(a) and thyroid hormone concentrations during the treatment of hypothyroid subjects by L-thyroxine substitution, probably because of small changes in thyroid hormone or Lp(a) levels in their subjects as compared with our studies.

Lp(a), a lipoprotein similar to LDL, possesses one apo

Table 2. Serum Concentrations of TC, TG, HDL-C, LDL-C, Apo B, and Lp(a) (mg/dL) in 13 Hyperthyroid Patients During Stage H, Stage E, and Stage L

Parameter	Stage		
	H	E	L
TC	118.3 ± 16.4 (95-152)	168.2 ± 35.5 (121-214)‡	223.8 ± 50.0 (159-282)‡§
TG	126.3 ± 16.4 (70-196)	185.4 ± 35.5 (113-316)	178.0 ± 123.6 (96-421)
HDL-C	36.8 ± 5.5 (31-46)	45.5 ± 8.0 (38-58)*	49.5 ± 11.7 (36-74)†
LDL-C	55.9 ± 11.9 (37-82)	82.5 ± 24.6 (47-132)†	137.1 ± 40.0 (85-202)‡§
Apo B	63.1 ± 15.8 (49-79)	106.4 ± 30.0 (86-186)‡	125.6 ± 39.7 (80-222)‡
Lp(a)	9.4 ± 13.9 (5.9 ± 6.3)	15.5 ± 16.4 (11.7 ± 9.8)*	26.8 ± 31.2 (18.8 ± 12.4)†‡
	1.0-51.0 (1.0-18.1)	3.0-60.0 (3.0-35.2)	7.0-123.0 (7.0-48.3)

NOTE. Values are the mean ± SD. Scheffe's test was used to determine whether the change during treatment was statistically significant. For Lp(a), the value in parentheses indicates the mean ± SD or range of Lp(a) in the other 12 cases except one case that shows an extraordinarily high level of serum Lp(a). See Fig 1.

*P = .05 *v* stage H.

†P = .01 *v* stage H.

‡P = .001 *v* stage H.

§P = .01 *v* stage E.

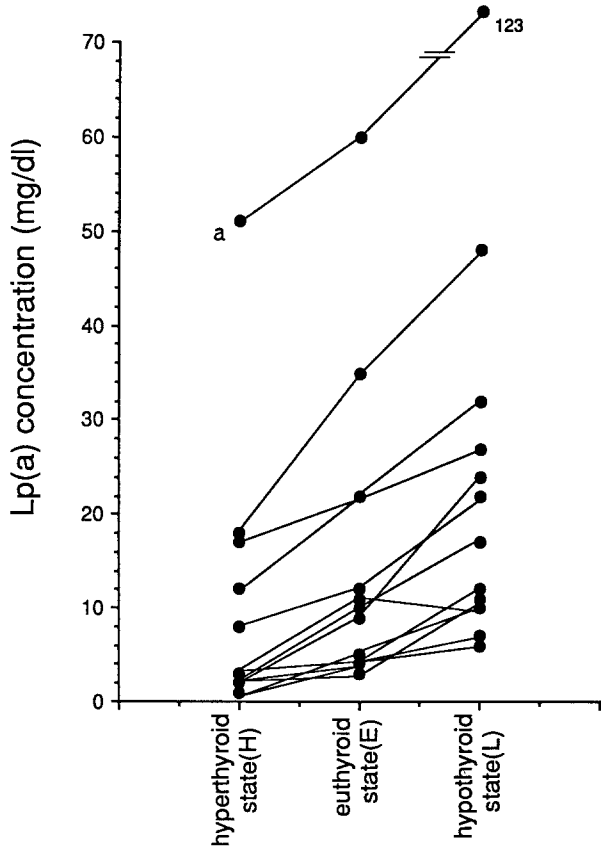

Fig 1. Changes in serum lp(a) concentration in 13 hyperthyroid patients in stage H, stage E, and stage L. (a) This case shows an extraordinarily high level of serum Lp(a). Means of Lp(a) levels with or without this case were calculated in Table 2.

B-100 molecule. Extensive studies of the effects of thyroid hormone on LDL metabolism showed that thyroid hormone regulates serum levels of LDL through an effect on LDL catabolism rather than on its biosynthesis. In patients with hyperthyroidism, low levels of LDL result from rapid catabolism of LDL despite an enhanced biosynthesis of cholesterol.[16,17] In hypothyroidism, a decrease in LDL receptor activity[18] retards clearance of LDL from the circulation.

It is puzzling that the results of studies in euthyroid subjects suggest that LDL receptors make only a small contribution to Lp(a) catabolism. In vitro studies of the interaction of Lp(a) with LDL receptors, using isolated bovine adrenal cortex and human fibroblasts,[19] and clinical studies using hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitor, which increases LDL receptor activity,[20] support these findings.

Table 3. Correlation Coefficients Between Serum Lp(a) Levels and Parameters Relating to Serum Lipid and Apolipoproteins After Subtotal Thyroidectomy in Hyperthyroid Subjects

Parameter	Correlation Coefficient	Probability
fT_4	−.33	.03
fT_3	−.31	.05
LDL-C	.27	.11
Apo B	.23	.17
TC	.18	.27
TSH	.16	.45
HDL-C	−.05	.75
TG	.01	.99

NOTE. Correlations between variables were analyzed by Spearman's method.

Serum Lp(a) remains remarkably constant over time,[21] being unaffected by diet and most drugs. Only nicotinic acid,[22] neomycin,[23] or a combination of pravastatin and ursodeoxycholic acid[24] may decrease Lp(a). LDL apheresis using a dextran sulfate column decreases both LDL and Lp(a).[25] In the present study, we observed no statistical change in body weight during the treatment of hyperthyroidism. A previous study by Kostner et al[26] failed to find any correlation between the serum Lp(a) level and body weight or nutritional state.

Finally, three cases among 12, except for one case of extraordinarily high pretreatment Lp(a), showed high Lp(a) levels over 25 mg/dL in stage L during the course of treatment of hyperthyroidism.

Since a serum Lp(a) level exceeding approximately 25 mg/dL is considered a risk factor for arteriosclerosis and myocardial infarction,[2,27,28] an elevated Lp(a) level and the increase of LDL that occurs in these cases of hypothyroidism may accelerate the progression of arteriosclerotic lesions either additively or synergistically. The results of the present study strongly suggest that thyroid hormone is a potent modulator of Lp(a) metabolism.

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