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BRIEF REPORT

Effect of Levo-Thyroxine Replacement on Non-High-Density Lipoprotein Cholesterol in Hypothyroid Patients

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Context: Recently, non-high-density lipoprotein cholesterol (non-HDL-C), a measure of total cholesterol minus HDL-C, has emerged as a predictor of cardiovascular disease.

Objective: We evaluated the effect of L-T_4 replacement on non-HDL-C levels in patients with primary hypothyroidism.

Methods: Thirteen patients with overt hypothyroidism and 26 patients with subclinical hypothyroidism participated in the study. The lipid profiles, including non-HDL-C, were measured in patients with hypothyroidism before and 3 months after L-T_4 replacement was started.

Results: After L-T_4 replacement, the serum concentrations of all lipoproteins, exclusive of lipoprotein (a) [Lp(a)], were significantly decreased in patients with overt hypothyroidism. In patients with subclinical hypothyroidism, the serum concentrations of total cholesterol, non-HDL-C, remnant-like particle cholesterol, and apolipoprotein B (Apo B) were significantly decreased, whereas no significant changes in the serum concentrations of low-density lipoprotein cholesterol, HDL-C, triglycerides, apolipoprotein A-I, and Lp(a) were observed. In all 39 patients, the reduction in the non-HDL-C levels correlated with the reduction in the low-density lipoprotein cholesterol, remnant-like particle cholesterol, and Apo B levels. However, the reduction in the non-HDL-C levels did not correlate with the reduction in the HDL-C, Lp(a), and apolipoprotein A-I levels.

Conclusions: This study is the first to show that L-T_4 replacement may reduce serum concentrations of non-HDL-C in patients with hypothyroidism. The study also suggests that such altered serum concentrations of non-HDL-C in hypothyroidism may be related to the disturbed metabolism of low-density lipoprotein, remnant lipoprotein, and Apo B. **(*J Clin Endocrinol Metab* 92: 608–611, 2007)**

ELEVATED LEVELS OF low-density lipoprotein cholesterol (LDL-C) have been consistently associated with an increased risk for development of cardiovascular disease (1). Therefore, LDL-C is a major therapeutic target in the treatment of dyslipidemia (2). However, the use of the non-high-density lipoprotein cholesterol (non-HDL-C) level has been suggested as a better tool for risk and treatment assessments than the LDL-C level (3). The non-HDL-C level is defined as the difference between the total cholesterol (TC) and HDL-C levels. The reason this recommendation has been made is that non-HDL-C includes all cholesterol present in lipoprotein particles considered to be atherogenic, including LDL, lipoprotein (a) (Lp[a]), intermediate-density lipoprotein, and very low-density lipoprotein remnants. Non-HDL-C has been shown in a variety of studies to be predictive of cardiovascular disease (4).

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Abbreviations: Apo A-I, Apolipoprotein A-I; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); OH, overt hypothyroidism; RLP-C, remnant-like particle cholesterol; SH, subclinical hypothyroidism; TC, total cholesterol; TG, triglyceride.

Hypothyroidism is associated with an atherogenic lipid profile, including greater serum concentrations of LDL-C (5) or Lp(a) (6). We reported the disturbed metabolism of remnant lipoprotein in overt hypothyroidism (OH) (7) and subclinical hypothyroidism (SH) (8).

In the present study, we measured the serum concentrations of non-HDL-C in patients with OH and SH before and after free T_4 replacement to investigate the effect of thyroid hormone replacement on non-HDL-C in patients with hypothyroidism.

Patients and Methods

Patients

We recruited 13 patients with OH (mean ± SD, age, 53 ± 17 yr; mean body mass index, 23.9 ± 3.4 kg/m^2) and 26 patients with SH (age, 55 ± 17 yr; mean body mass index, 22.4 ± 3.3 kg/m^2) who had been referred to Kuma Hospital in Kobe, Japan. OH was diagnosed on the basis of elevated serum TSH levels and lowered free T_4 levels. SH was diagnosed on the basis of elevated serum TSH levels (≥6 mU/liter) and free thyroid hormone levels (free T_4 and free T_3) within the normal range. The condition of hypothyroidism in each patient was stable because patients with OH had to have been in a documented hypothyroid state for at least 1 month and patients with SH for at least 3 months before enrollment. The causes of OH included Hashimoto thyroiditis (n = 7) and radioiodine therapy (3 to 16 yr previously; n = 6) for hyperthyroidism. The causes of SH included Hashimoto thyroiditis (n = 14) and thyroid

surgery (2 to 15 yr previously; n = 5) or radioiodine therapy (3 to 10 yr previously; n = 7) for hyperthyroidism. None of the patients had a history of coronary heart disease, acute illness, pregnancy, or disorders that affect lipid metabolism (*e.g.* diabetes mellitus, renal failure, nephrotic syndrome, or pancreatitis). None of the patients were on a thyroid hormone therapy or lipid-lowering agent at study entry. All patients gave their informed consent for the study, which was approved by the Institutional Ethics Committee.

Study protocol

After both the patients with OH and SH fasted overnight, blood samples at the baseline were drawn to determine the serum lipid concentrations and thyroid function tests. L-T_4 replacement was then initiated (25 or 50 μg/d) in the patients. All patients were advised to maintain their dietary habits during the study period. To normalize the serum TSH levels, the L-T_4 dosage was adjusted according to the serum TSH concentrations measured at 4-wk intervals after L-T_4 replacement was initiated. The mean final dose of L-T_4 required to normalize the serum TSH levels was 83 ± 31 μg/d in the patients with OH and 47 ± 18 μg/d in the patients with SH. The lipid profiles were evaluated 3 months after treatment was started.

Laboratory determinations

The levels of TC, HDL-C, and triglycerides (TG) were measured by enzyme assays. The non-HDL-C levels were calculated as TC − HDL-C. The LDL-C levels were calculated by the Friedewald formula. None of our patients had high serum concentrations of TG greater than 4.52 mmol/liter that would have limited the calculation of LDL. The serum Lp(a) concentration was measured using a latex agglutination assay (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). Apolipoprotein B (Apo B) and apolipoprotein A-I (Apo A-I) were measured by immunoturbidimetry. The remnant-like particle cholesterol (RLP-C) was prepared using an immunoseparation technique (Japan Immunoresearch Laboratories, Takasaki, Japan) (9). Serum concentrations of free T_4 (reference range, 9.0–20.6 pmol/liter), free T_3 (2.6–5.7 pmol/liter), and TSH (0.3–5.0 mU/liter) were measured by enzyme immunoassays (Dainabot Co., Tokyo, Japan).

Statistical analysis

Grouped data were expressed as means ± SD. Treatment effects (pre- *vs.* post-T_4 replacement) were analyzed by the paired *t* test in case of normal distribution and by the Wilcoxon signed rank test in case of nonparametric distribution. Significance was defined as a corresponding *P* value of less than 0.05 (two-sided). Spearman's rank correlation was used to assess the correlation between the reduction of non-HDL-C and the reduction of associated lipoproteins and apolipoproteins.

Results

The characteristics and lipid profiles of patients with OH and SH before and after L-T_4 replacement are listed in Table 1. Before correction of the hypothyroid state, the mean TSH level was 72.5 ± 27.7 mU/liter in patients with OH and 9.46 ± 3.48 mU/liter in patients with SH. After L-T_4 replacement, the serum levels of TSH and free T_4 were within the normal range in all patients. Body mass indices were unchanged in both OH and SH.

In the patients with OH, the levels of serum TC, non-HDL-C, LDL-C, Apo B, and RLP-C were remarkably decreased after L-T_4 replacement ($P < 0.0005$). The serum levels of HDL-C, TG, and Apo A-I were significantly decreased by L-T_4 replacement, although not remarkably decreased ($P < 0.05$). The serum Lp(a) levels were unchanged. In patients with SH, the serum levels of TC, non-HDL-C, RLP-C, and Apo B decreased significantly after L-T_4 replacement. However, the serum LDL-C levels decreased, but these lower levels were not significantly different from the pretreatment levels ($P = 0.09$). The serum levels of TG, HDL-C, Apo A-I, and Lp(a) did not change significantly.

Table 2 presents the Spearman correlation coefficients between the reduction of non-HDL-C and the reduction of associated lipoproteins and apolipoproteins. As expected in view of the way in which non-HDL-C has been calculated, the reduction in the non-HDL-C levels correlated strongly with the reduction in the LDL-C ($r = 0.96$). The reduction in the non-HDL-C levels also correlated strongly with the reduction in the Apo B levels ($r = 0.95$). In addition, the reduction in the non-HDL-C levels correlated with the reduction in the RLP-C ($r = 0.56$). However, the reduction in the non-HDL-C levels did not correlate with the reduction in the HDL-C ($r = 0.26$), Lp(a) ($r = 0.16$), and Apo A-I levels ($r = 0.37$).

Discussion

The most common abnormalities of lipoprotein metabolism associated with hypothyroidism are elevated levels of TC and LDL-C. These changes are accounted for by the effect of thyroid hormone on lipoprotein lipase activity (10) and the

TABLE 1. The characteristics and lipid profiles in patients with OH and SH before and after L-T_4 replacement therapy

	OH (n = 13)		SH (n = 26)	
	Before	After	Before	After
Body mass index (kg/m^2)	23.9 ± 3.4	23.4 ± 3.4	22.4 ± 3.3	22.2 ± 3.2[a]
TSH (mU/liter)	72.45 ± 27.68	2.23 ± 2.58[a,b]	9.46 ± 3.48	1.81 ± 1.31[b]
Free T_4 (pmol/liter)	4.25 ± 2.23	17.19 ± 3.16[b]	12.1 ± 2.57	15.96 ± 3.6[b]
Free T_3 (pmol/liter)			3.93 ± 0.54	4.24 ± 0.72[b]
TC (mmol/liter)	8.03 ± 1.45	5.47 ± 1.05[b]	5.82 ± 0.88	5.55 ± 1.02[b]
TG (mmol/liter)	1.04 ± 0.46	0.75 ± 0.38[b]	1.2 ± 0.45	1.16 ± 0.56
HDL-C (mmol/liter)	2.21 ± 0.81	1.82 ± 0.6[b]	1.6 ± 0.47	1.59 ± 0.46
LDL-C (mmol/liter)	5.3 ± 1.61	3.08 ± 0.79[b]	3.67 ± 0.84	3.47 ± 0.9
Apo A-I (mg/dl)	184 ± 51	164 ± 38[b]	142 ± 22	141 ± 21[a]
Apo B (mg/dl)	147 ± 36	96 ± 25[b]	102 ± 17	94 ± 17[a,b]
Lp(a) (mg/dl)	20 ± 10	18 ± 13	18 ± 15	16 ± 15
RLP-C (mmol/liter)	0.14 ± 0.03	0.09 ± 0.03[b]	0.13 ± 0.05	0.11 ± 0.05[b]
Non-HDL-C (mmol/liter)	5.82 ± 1.52	3.65 ± 0.95[b]	4.22 ± 0.91	3.96 ± 0.98[b]

Values are expressed as the mean ± SD. Replacement effects of L-T_4 were analyzed by paired *t* test and [a] by Wilcoxon signed rank test for nonparametric distribution.

[b] $P < 0.05$ *vs.* before L-T_4 replacement therapy.

TABLE 2. Correlation between the reduction of non-HDL-C and the reduction of associated lipoproteins and apolipoproteins

Variable	Correlation (r)
Lipoprotein	
LDL-C	0.96
HDL-C	0.26
RLP-C	0.56
Lp(a)	0.16
Apolipoprotein	
Apo A-1	0.37
Apo B	0.95

Spearman correlation coefficients were used.

expression of the LDL receptor (11) and probably play an important role in atherogenesis in untreated hypothyroidism. In the present study, although we observed significant changes of the LDL-C levels in patients with OH, we did not find these changes in SH. A meta-analysis of the effect of L-T_4 replacement on lipoproteins in SH demonstrated a mean decrease of 0.20 mmol/liter in the TC level and 0.26 mmol/liter in the LDL-C level (12). We may not have observed a significant effect of L-T_4 replacement on the LDL-C levels because of our relatively small sample or the short-term (3 month) treatment period. However, because of the majority of the non-HDL-C being accounted for by LDL-C and a strong correlation between non-HDL-C and LDL-C regarding the reduction, the changes in the non-HDL-C levels in hypothyroidism may be mainly related to changes in the LDL-C levels rather than the other way around.

Although LDL is widely accepted as the major atherogenic lipoprotein, TG-rich lipoproteins such as chylomicron remnants and very low-density lipoprotein remnants still play an important role in atherogenesis. These remnants are taken up by macrophages in the arterial walls to produce foam cells and thus may be a risk factor for atherosclerosis (13). The Adult Treatment Panel III report of the National Institutes of Health placed more emphasis on TG-rich lipoprotein and HDL as secondary targets for lipid-lowering drugs than the Adult Treatment Panel II report, and non-HDL-C has been identified as a secondary target in patients with higher TG levels such as diabetes (14). Our data showed that L-T_4 replacement caused a significant reduction in the remnant lipoprotein levels in patients with OH and SH. In addition, the correlation in changes between remnant lipoprotein and non-HDL-C levels suggested that the changes of not only LDL-C, but also remnant lipoprotein, contribute to the changes of the non-HDL-C levels in hypothyroidism.

As in the previous studies (6, 15), we observed significant changes in the Apo B levels after L-T_4 replacement in patients with OH and SH. The total Apo B concentration is a marker of the atherogenic particles in serum and reflects the number of very low-density lipoprotein and intermediate-density lipoprotein particles as well as the number of LDL particles (16). A previous study demonstrated that Apo B is a more powerful predictor of coronary heart disease than LDL-C (17). Because of the high correlation between non-HDL-C and Apo B in recent studies (14), non-HDL-C is considered a good surrogate marker for Apo B. Our data suggest that non-HDL-C may be an alternative to Apo B in patients with hypothyroidism because of the good correlation.

OH, with its accompanying hypercholesterolemia, is widely recognized as a risk factor for cardiovascular disease (18). On the other hand, although SH is highly prevalent, it is controversial whether SH is a risk factor for cardiovascular disease. A recent study (19) suggested that SH indicated a risk for cardiovascular disease, but the other study suggested that it did not (20). Whether there is an association between non-HDL-C levels and cardiovascular disease in patients with OH and SH remains to be determined.

There were some possible limitations in the present study. The study's sample size was relatively small, and its design was not placebo-controlled. In addition, with only 3 months of treatment and a starting dose of only 25 to 50 μg, patients with OH were likely still hypothyroid over a portion of this time and so the effectiveness of the treatment would be likely underestimated. Properly controlled studies are needed to demonstrate whether T_4 replacement therapy alters non-HDL-C levels in patients with hypothyroidism.

In summary, the present study has demonstrated, probably for the first time, that T_4 replacement therapy induces reduction of the non-HDL-C levels, a novel atherogenic indicator, in both OH and SH. Such determination of serum non-HDL-C levels in addition to the already known LDL-C or Apo B may provide relevant information on the cardiovascular risk in hypothyroidism.

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