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Potential harmful correlation between homocysteine and low-density lipoprotein cholesterol in patients with hypothyroidism

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Abstract

Objective: Hypothyroidism (HO) can induce metabolic dysfunctions related to insulin resistance and dyslipidemia. Our previous studies showed that homocysteine (Hcy) impaired the coronary endothelial function and that Hcy can promote chemokine expression and insulin resistance (IR) by inducing endoplasmic reticulum stress in human adipose tissue and hypothyroid patients. The aim of this study was to investigate the potential harmful correlation between plasma Hcy and low-density lipoprotein cholesterol (LDL-C) in patients with HO.

Methods: A total of 286 subjects were enrolled. All subjects were divided into the following 3 groups: HO group, subclinical hypothyroidism (SHO) group, and control group. Statistical analyses were carried out to evaluate the correlation between the plasma levels of Hcy and LDL-C in HO patients. The changes in the plasma Hcy levels and other metabolic parameters were measured before and after levothyroxine (L-T4) treatment. The relationship between the changes in the plasma Hcy level and the LDL-C level was also evaluated after L-T4 treatment.

Results: In the patients with HO, both the plasma Hcy and LDL-C levels were significantly higher than those of the controls. The plasma levels of Hcy were positively correlated with the LDL-C level in the HO group. L-T4 treatment resulted in a significant decrease in the BMI, total cholesterol (TC), LDL-C, triglycerides (TG), apolipoprotein B (ApoB), and Hcy levels. Moreover, the decrease in Hcy (ΔHcy) was positively correlated with decreased LDL-C (ΔLDL-C) levels after L-T4 treatment in HO patients.

Conclusion: Our results suggest that the increased Hcy level was positively correlated with the LDL-C in the HO group. A potential harmful interaction may exist between Hcy and LDL-C under the HO condition. In addition to reducing the plasma levels of Hcy, L-T4 treatment exerts beneficial effects on patients with HO by improving dyslipidemia, including a decrease in the LDL-C level.

Abbreviations: ApoB = apolipoprotein B, BMI = body mass index, CAD = coronary artery disease, eNOS = endothelial nitric oxide synthase, FT3 = free triiodothyronine, FT4 = free unboundthyroxine, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, HHcy = hyperhomocysteinemia, HO = hypothyroidism, LDL = low-density lipoprotein, LDL-C = LDL-cholesterol, L-T4 = levothyroxine, SHO = subclinical hypothyroidism, TC = total cholesterol, TG = triglycerides, TSH = thyroid stimulating hormone.

Keywords: correlation, hyperhomocysteinemia, hypothyroidism, low-density lipoprotein cholesterol

1. Introduction

Hypothyroidism (HO) is a clinical syndrome caused by thyroid hormone deficiency that is characterized by a decreased metabolic rate.[1] Subclinical hypothyroidism (SHO) is defined as an elevated thyroid stimulating hormone (TSH) level with normal free unboundthyroxine (FT4) and free triiodothyronine (FT3) levels.[2] HO and SHO, the 2 most common endocrine disorders, are associated with an increased risk for atherosclerosis and a cluster of metabolic disorders.[3,4] Dyslipidemia is a common metabolic abnormality in patients with HO and SHO, which may be partially responsible for the high risk of cardiovascular disease.[5] Some scholars have suggested that HO leads to a decreased level of low-density lipoprotein (LDL) receptor expression on fibroblasts and hepatocytes, decreased LDL-cholesterol (LDL-C) uptake, and a consequent increase in the serum LDL-C levels.[6,7] Many studies have demonstrated that the association of thyroid disease with atherosclerotic cardiovascular disease may be partly explained by the regulation of lipid metabolism by thyroid hormone.[8]

Homocysteine (Hcy), a type of amino acid that is naturally found in blood plasma, is not harmful at normal levels, but when its levels are too high, it can result in health problems. Recent studies have shown that hyperhomocysteinemia (HHcy) is an independent risk factor for cardiovascular disease and accelerated atherosclerosis.[9,10] Elevated serum Hcy concentrations are

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common in patients with HO.[5] HHcy, together with hypercholesterolemia, may explain the accelerated atherosclerosis in HO. Our previous study demonstrated that there was significantly higher secretion of the chemokine monocyte chemoattractant protein-1 from monocytes in response to lipopolysaccharide in patients with HHcy.[10] Our studies also showed that HHcy could impair the coronary artery endothelial function in hyperhomocysteinemic patients.[11,12] Studies of humans and animals have shown that LDL-C causes vascular endothelial dysfunction that leads to coronary artery disease (CAD) mainly by increasing oxidative stress, impairing endothelial nitric oxide synthase (NOS) activity, and attenuating the bioavailability of NO.[13,14] In the present work, we performed a cross-sectional study to investigate the potential harmful interaction between Hcy and LDL-C in HO patients. Furthermore, we investigated the effects of levothyroxine (L-T4) on the changes in the Hcy and LDL-C level in HO patients.

2. Materials and methods

2.1. Subjects

A total of 286 participants were recruited from the Endocrinology Department of the Beijing Chao-yang Hospital during the period from January 2013 to December 2013. SHO is characterized by a serum TSH above the upper reference limit in combination with a normal FT4. This designation is only applicable when the thyroid function has been stable for weeks or more and the hypothalamic–pituitary–thyroid axis is normal. An elevated TSH level, usually above 10 mIU/L, in combination with a subnormal FT4 level, characterizes overt HO.[15] Patients were excluded from the study if they had a history of diabetes mellitus or impaired glucose tolerance, hypertension, acute or chronic hepatic and renal diseases, severe anemia, acute myocardial infarction or stoke. Seventy-three patients were excluded. The final study cohort included 177 patients of those initially enrolled, which included 75 patients with HO and 102 patients with SHO. The control group included 109 age- and sex-matched health subjects who were recruited from the Endocrinology Department of the Beijing Chao-yang Hospital during the same period. No participants were undergoing treatment. HO patients received an appropriate dose of L-T4 based on the drug label. The study protocol was designed according to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Beijing Chao-yang Hospital. All subjects gave their written informed consent.

2.2. Sample collection

All subjects underwent a screening assessment for basic demographic information (i.e., age, sex, body height and weight). The body mass index (BMI) was calculated as the height (kg)/weight^2 (m^2). After an overnight fast, blood sample was collected from the peripheral vein of subjects. A routine analysis consisting of FT3, FT4, TSH, Hcy, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C, triglycerides (TG), and apolipoprotein B (ApoB) were determined. Hcy was determined by enzymatic cycling assay-based quantification using the corresponding kits from Baiding Biotech (Beijing, China), and normal reference value was $<15\,\mu$mol/L.[16] FPG, TC, HDL-C, LDL-C, and TG were determined by Dade-Behring Dimension RXL Autoanalyzer (Dade Behring Diagnostics, Marburg, Germany). The reference intervals were 3.62 to 5.7 mmol/L (TC), 1.03 to 1.55 mmol/L (HDL-C), 1.81 to 3.36 mmol/L (LDL-C), and 0.56 to 2.26 mmol/L (TG), respectively.

FT3, FT4, and TSH were examined by electrochemiluminescence immunoassay (ECLIA) of Abbott Architect i2000 (Abbott Diagnostics, Abbott Park, IL). The reference intervals were 1.71 to 3.71 pg/mL (FT3), 0.7 to 1.48 ng/dL (FT4), and 0.35 to 4.94 μIU/mL (TSH). The subjects with HO were divided into 2 groups based on the Hcy value: normal Hcy ($\leq 15\,\mu$mol/L) and HHcy ($>15\,\mu$mol/L). We compared the changes in the LDL-C under different Hcy conditions. Furthermore, we compared the changes in the Hcy level under different LDL-C conditions (≤ 3.36 or >3.36 mmol/L).

2.3. Statistical analyses

The data were analyzed using the SPSS 21.0 software program (SPSS, Inc., Chicago, IL) to identify significant effects between the patient groups and corresponding controls. Continuous data, such as the age, BMI, TC, LDL-C, HDL-C, FPG, Hcy, and ApoB, were expressed as the means $\pm$ standard deviation (SD). Nonnormally distributed variables, such as the TG, were expressed as medians (25th and 75th percentiles). The differences between groups were analyzed by ANOVA. Normally distributed data were analyzed by Student t test and a paired-sample T test. Nonnormally distributed data were analyzed by the Mann–-Whitney U test and the Wilcoxon test. Pearson rank correlation was used to assess the relationship between the decrease in Hcy and the decrease in LDL-C. Spearman rank correlation was used to assess the relationship between Hcy and the LDL-C index. Comparisons between groups at baseline and after L-T4 treatment were performed with independent sample t tests. All tests were 2 tailed, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the HO and SHO patients and healthy controls

The baseline characteristics of the subjects are listed in Table 1. The age, BMI, and FPG were similar among the 3 groups. The HO group had significant higher levels of TC, HDL-C, LDL-C, and TG than SHO and control groups. But between the SHO and control groups, the difference of plasma lipid was not significant. The Hcy levels were also significantly higher in the HO group than other 2 groups ($17.93 \pm 6.86\,\mu$mol/L vs $14.81 \pm 4.57\,\mu$mol/L vs $13.51 \pm 3.75\,\mu$mol/L, all $P < 0.05$) (Fig. 1). In the HO group, with the Hcy increasing (Hcy $>15\,\mu$mol/L), the prevalence of dyslipidemia (LDL-C >3.36 mmol/L) increased ($P < 0.01$). Similarly, the LDL-C was also increased (LDL-C >3.36 mmol/L) in HHcy (Hcy $>15\,\mu$mol/L) patients (Figs. 2 and 3).

3.2. The changes in metabolic parameters after L-T4 treatment

The values obtained after treatment with L-T4 are shown in Table 2. After the exclusion of 30 patients who were lost to follow-up, 45 of the HO patients experienced a significant decrease in the BMI, TC, HDL-C, LDL-C, TG, Hcy, and ApoB. The changes in the Hcy and LDL-C are summarized in Figs. 4 and 5. The level of Hcy was significantly decreased (15.85 ± 5.35 vs 13.65 ± 3.91, $P < 0.01$), while the LDL-C recovered (3.62 ± 1.17 vs 2.77 ± 0.74, $P < 0.001$) after L-T4 treatment.

Table 1

Baseline characteristics of HO, SHO patients, and healthy controls.

	Control (n = 109)	SHO (n = 102)	HO (n = 75)	P
Sex (M/F)	26/83	11/91	7/68	0.003
Age, y	44.98 ± 12.78	45.60 ± 13.91	42.00 ± 14.08	0.188
BMI, kg/m^2	23.81 ± 3.43	24.41 ± 3.43	24.70 ± 3.52	0.232
TC, mmol/L	4.81 ± 0.91	5.08 ± 1.21	6.13 ± 1.76*,†	0.000
LDL-C, mmol/L	2.78 ± 0.81	2.99 ± 0.92	3.49 ± 1.17*,‡	0.000
HDL-C, mmol/L	1.60 ± 0.34	1.52 ± 0.34	1.68 ± 0.68‡	0.028
TG, mmol/L	0.94 (0.70, 1.47)	1.19 (0.80, 1.74)$^{||}$	1.44 (0.92, 2.42)*,§	0.000
FPG, mmol/L	5.02 ± 0.45	5.16 ± 0.66	5.06 ± 0.70	0.257
Hcy, μmol/L	13.51 ± 3.75	14.81 ± 4.57	17.93 ± 6.86*,†	0.000
ApoB, g/L	0.84 ± 0.25	0.86 ± 0.33	1.07 ± 0.36*,†	0.000

Summary of the clinical characteristic of the research in 75 HO patients, 102 SHO patients, and 109 age- and sex-matched nonhypothyroid controls before the treatment.
HO patients had a significantly higher TC, HDL-C, LDL-C, TG, Hcy, and ApoB compared with SHO and control groups.
Age, BMI, TC, LDL-C, HDL-C, FPG, Hcy, and ApoB were expressed as the mean ± SD. TG was expressed as median (IQR).
$P < 0.05$ was considered statistically significant.
ApoB = apolipoprotein B, BMI = body mass index, FPG = fasting plasma glucose, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, HO = hypothyroidism, LDL-C = low-density lipoprotein cholesterol, SHO = subclinical hypothyroidism, TC = total cholesterol, TG = triglyceride.
* $P < 0.001$ significantly different compared with control group.
† $P < 0.001$ significantly different compared with SHO group.
‡ $P < 0.01$ significantly different compared with SHO group.
§ $P < 0.05$ significantly different compared with SHO group.
$^{||}$ $P < 0.05$ significantly different compared with control group.

3.3. Correlation between the changes in the Hcy level and the improvement in the LDL-C level before and after L-T4 treatment

After adjusting for sex, BMI, FT4, and FBG, a significant positive correlation was observed between the Hcy and LDL-C levels in the HO group ($r = 0.632$, $P < 0.001$) (Fig. 6). However, there was no significant correlation observed in the SHO group ($r = 0.095$, $P = 0.32$). We found that a decrease in the Hcy (ΔHcy) was positively correlated with a decreased in the LDL-C (ΔLDL-C, $r = 0.412$, $P < 0.05$). The results are shown in Fig. 7.

4. Discussion

In the present study, we found that TC, HDL-C, LDL-C, and TG values in the HO group were significantly higher than those in the SHO and control groups. The plasma Hcy levels were also significantly higher in the HO group than in the SHO group and controls. After adjusting for sex, BMI, FT4, and FBG, a significant positive correlation was observed between the Hcy and LDL-C levels in the HO group. We found that a decrease in the Hcy was positively correlated with a decreased in the LDL-C.

In patients with HO, increased Hcy levels may result from 2 mechanisms; increased Hcy formation or decreased renal Hcy clearance due to the direct effects of thyroid hormones on the Hcy metabolism in the liver and clearance by the kidney.[17] Many studies have proven that the plasma Hcy level is an independent risk factor for CAD because it induces endothelial injury, oxidative stress, smooth muscle hypertrophy, and oxidation of LDL-C.[18,19] Our previous study also demonstrated that Hcy might act as an atherogenic factor by promoting the production of chemokines, reactive oxygen species, and oxidized LDL-C, thus enhancing the progression of cardiovascular disease.[20] In HO patients, the plasma Hcy levels were 17.93 ± 6.86 μmol/L. We have previously shown that coronary flow velocity reserve were impaired when Hcy > 15 μmol/L.[21] A population-based

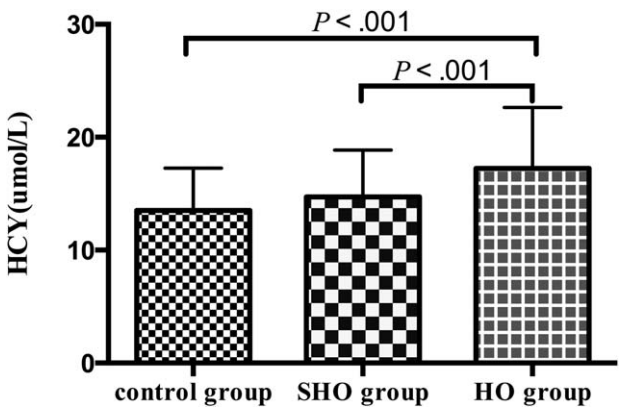

Figure 1. Plasma levels of Hcy in study subjects, n = 102 in control group, n = 109 in SHO group and n = 75 in HO group. Values were expressed as the means ± SD. $P < 0.05$ was considered statistically significant. Hcy = homocysteine.

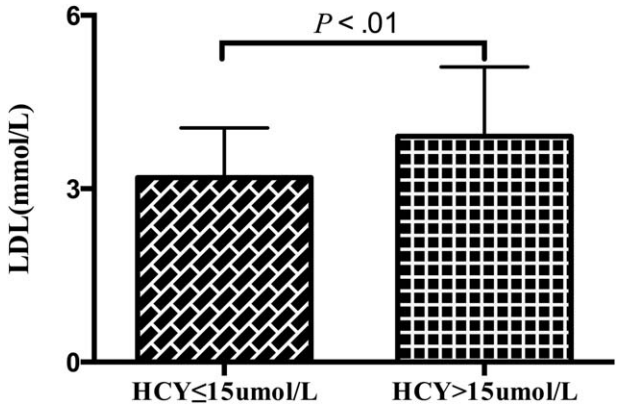

Figure 2. Normal Hcy (≤15 μmol/L) and HHcy group (>15μmol/L) in HO patients (n = 75). The changes of LDL-C under different Hcy status. Values were expressed as the means ± SD. $P < 0.05$ was considered statistically significant. Hcy = homocysteine, LDL-C = low-density lipoprotein cholesterol.

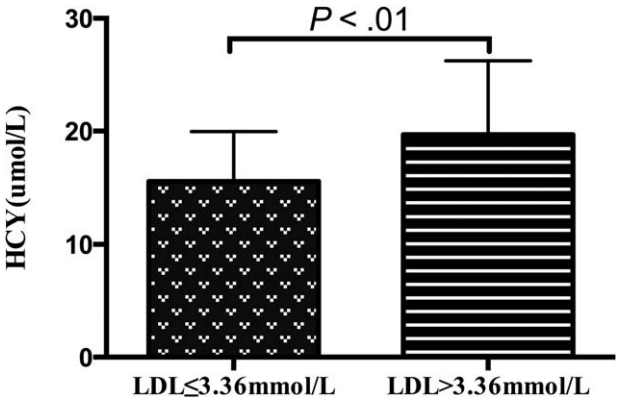

Figure 3. The changes of Hcy under different LDL-C (≤3.36 or >3.36 mmol/L) status in HO patients (n = 75). Values were expressed as the means ± SD. $P < 0.05$ was considered statistically significant. Hcy = homocysteine, LDL-C = low-density lipoprotein cholesterol.

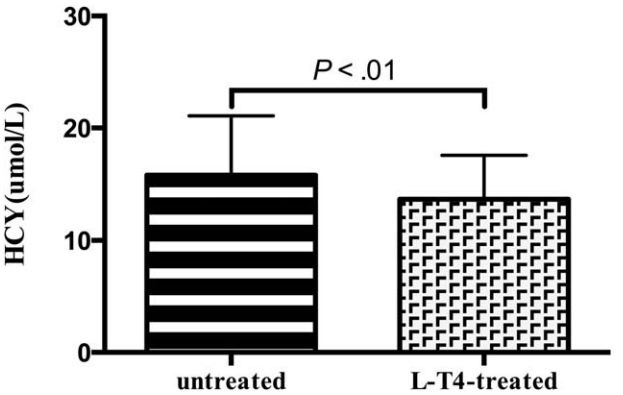

Figure 4. Hcy values of HO subjects (n = 45) before and after levothyroxine (L-T4) treatment. Values were expressed as means ± SD, and $P < 0.05$ was considered statistically significant.

prospective cohort study (mean follow-up, 5.3 years) was conducted by Nurk et al,[22] which showed that Hcy was a strong predictor of cardiovascular disease (CVD) in elderly individuals. The study also demonstrated that at baseline, participants with preexisting had higher mean Hcy values than individuals without CVD. Furthermore, multiple risk factor-adjusted CVD hospitalization rate ratios in 5 Hcy categories (<9, 9–11.9, 12–14.9, 15–19.9, and ≥20 μmol/L) were as follows: 1 (reference level), 1.00, 1.34, 1.67, and 1.94, respectively ($P < 0.001$). The study by Nakano et al suggested that an elevated plasma Hcy level might promote LDL-C nitration and increased scavenger receptor uptake, providing a molecular mechanism that may contribute to CAD.[7] Elevated LDL-C levels may be partly responsible for the high risk of cardiovascular disease associated with HO. This suggests that the total serum Hcy levels might be correlated with the LDL-C level in patients with HO. In this study, we provide data showing a positive correlation between Hcy and LDL-C in patients with HO.

In the present study, the serum TC, HDL-C, LDL-C, and TG levels were significantly higher in patients with HO compared with the SHO and control groups (Table 1, $P < 0.05$). In our observations, the subjects in the HO group had higher Hcy and LDL-C levels than the subjects in the SHO and control groups. Our results were consistent with the findings of previous studies,[23–26] but were not in agreement with those reported by Orzechowska-Pawilojc et al,[27] who observed that the Hcy levels were nonsignificantly higher in patients with HO compared to healthy subjects. In HO patients, we found that the Hcy levels were positively correlated with the LDL-C level after adjustment for sex, BMI, FT4, and FBG. We observed a higher prevalence of dyslipidemia in HHcy patients. These data are consistent with previous studies that have reported that the enhanced atherosclerosis in hyperhomocysteinemic patients might be partly attributable to Hcy-related LDL-C atherogenicity.[28] We acknowledged the statistical limitations of the study due to the small sample size. All HO should be treated. After the exclusion of 30 patients who were lost to follow-up, 45 of the HO patients experienced L-T4 treatment. L-T4 treatment significantly reduced the BMI, TC, HDL-C, LDL-C, TG, Hcy, and ApoB in our patients. In accordance with our results, Orzechowska-Pawilojc et al[27] also reported a significant decrease in the Hcy levels following L-T4 treatment in women with HO. Thyroid hormone replacement is a routine and conventional clinical practice for patients with HO and has been shown to ameliorate

Table 2

Clinical characteristics and Hcy levels before and after levothyroxine (L-T4) treatment.

	Untreated (n = 45)	L-T4 treated (n = 45)	P
BMI, kg/m^2	25.2 ± 3.9	24.0 ± 3.9	0.000*
TC, mmol/L	6.27 ± 1.79	4.79 ± 1.10	0.000*
LDL-C, mmol/L	3.62 ± 1.17	2.77 ± 0.74	0.000*
HDL-C, mmol/L	1.70 ± 0.70	1.40 ± 0.35	0.000*
TG, mmol/L	1.23 (0.96, 1.88)	1.08 (0.75, 1.34)	0.004#
FPG, mmol/L	4.99 ± 0.73	4.99 ± 0.55	0.962
Hcy, μmol/L	15.85 ± 5.35	13.65 ± 3.91	0.009#
ApoB, g/L	1.13 ± 0.37	0.88 ± 0.30	0.002#

Summary of the clinical characteristics of 45 HO patients before and after treatment. Age, BMI, TC, LDL-C, HDL-C, FPG, Hcy, and ApoB were expressed as the mean ± SD. TG was expressed as median (IQR).

ApoB = apolipoprotein B, BMI = body mass index, FPG = fasting plasma glucose, Hcy = homocysteine, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

$P < 0.05$ was considered statistically significant.

* $P < 0.001$, BMI, TC, LDL-C, and HDL-C was significantly decreased after L-T4 treatment.

# $P < 0.01$, Hcy, TG, and ApoB was significantly decreased.

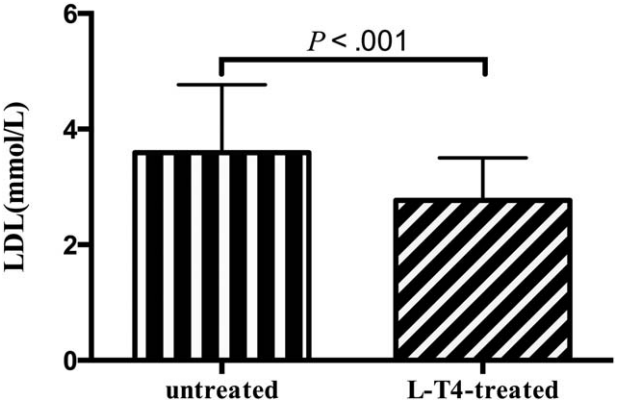

Figure 5. LDL-C values of HO subjects (n = 45) before and after levothyroxine (L-T4) treatment. Values were expressed as means ± SD, and $P < 0.05$ was considered statistically significant.

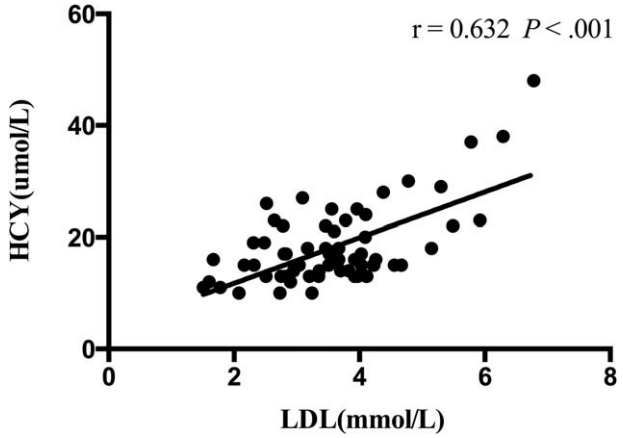

Figure 6. Correlation between the Hcy and LDL-C in the HO groups. In 75 HO patients, after adjustment for sex, BMI, FT4, and FBG, the Hcy was correlated with the LDL-C ($r = 0.632$, $P < 0.001$).

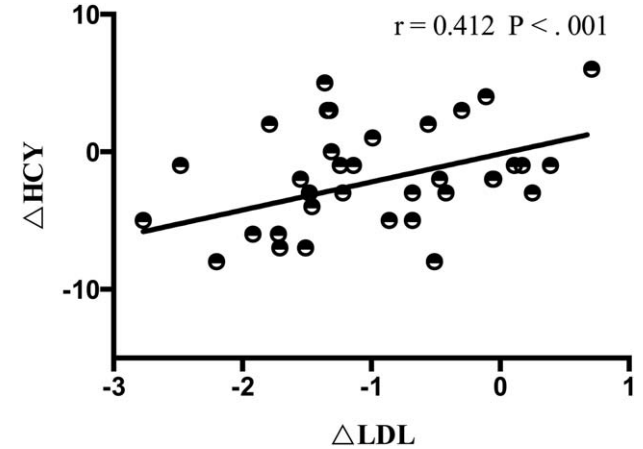

Figure 7. Correlation between the decreased Hcy (ΔHcy) and the decreased LDL-C (ΔLDL) after treatment with L-T4. In 45 HO patients, the decreased Hcy (ΔHcy) was correlated with the decreased LDL-C (ΔLDL) after treatment with L-T4 ($r = 0.412$, $P < 0.05$).

the lipid profiles in patients with atherosclerosis.[29,30] In addition, we found that the decreased Hcy levels positively correlated with decreased LDL-C. The significant improvements in the Hcy and LDL-C levels might be due to the presence of positive mutual interactions.

Dyslipidemia, consisting of high levels of total and LDL cholesterol, is a common finding in patients with HO and SHO.[5] Hcy stimulates the production and secretion of cholesterol by hepatic cells; this may contribute to the association between cholesterol and Hcy observed in the present study.[31] Elevated Hcy levels promote the synthesis of several proinflammatory cytokines in the arterial walls and circulating cells. Our previous studies indicated that the coronary artery endothelial function might be impaired in essential hypertensive patients with HHcy; furthermore, chronic HHcy might contribute to CAD by inducing dysfunction of the coronary artery endothelium.[32] The uncoupling of endothelial nitric oxide synthase (eNOS) induced by HHcy might at least partly explain this adverse effect.[33] Our previous studies also found that the LDL-C level inversely correlated with the coronary flow velocity reserve in patients with Type 2 diabetes.[34] In agreement with the observations made by Engin et al,[33] HO was associated with both systemic oxidative stress and with specific morphological changes in endothelial cells, which are believed to represent very early stages of atherosclerosis.

Our present results showed a positive correlation between the LDL-C and Hcy levels in HO patients, which was not significant in the SHO patients and controls. This is consistent with a previous study by Saleh[35] that documented a strong relationship between the serum Hcy levels and lipid concentrations especially the concentrations of cholesterol in hypothyroid rats. Conversely, several other investigations demonstrated that Hcy was nonsignificantly correlated with the TC level in overt hypothyroid patients ($r = 0.288$, $P = 0.12$).[36] However, HHcy and LDL-C were both associated with endothelial dysfunction and cardiovascular disease. In our study, elevated plasma levels of Hcy promoted LDL-C, and the LDL-C level was also increased in HHcy patients. The discovery of aggregation of LDL-C by Hcy thiolactone and production of foam cells from cultured human macrophages helped to clarify the connection between Hcy and the cholesterol of LDL-C.[37] In the view of Ravnskov, cholesterol participates in atherogenesis by binding to the lipid constituents of microorganisms, forming aggregates. Hcy exacerbates the process of trapping of LDL-C aggregates by narrowing of arterial lumens by causing endothelial dysfunction, further facilitating aggregation of LDL-C by forming homocysteinyl groups attached to LDL-C, and by antibody formation to homocysteinylated LDL-C and to oxidized LDL-C (oxLDL-C), impeding the passage of LDL aggregates.[38]

HHcy may contribute to cardiovascular risk by increasing the LDL-C level and promoting LDL-C recruitment into atherosclerotic plaques. In addition to reducing the plasma levels of Hcy, L-T4 treatment exerts beneficial effects on patients with HO by improving dyslipidemia, such as by decreasing the LDL-C level. On the contrary, studies of subjects with cerebrovascular disease in the Vitamin Intervention for Stroke Prevention (VISP) trial,[39] cardiovascular disease in the Norwegian Vitamin Trial (NORVIT) and Heart Outcomes Prevention Evaluation (HOPE2) trials,[40,41] and vascular disease from chronic renal failure in the HOST trial[42] showed no reduction in stroke or heart attack or improvement in mortality from B vitamin intervention.

5. Conclusion

Our results suggest that an increased Hcy level is positively correlated with the LDL-C level in HO patients. A potential harmful correlation may exist between Hcy and LDL-C under the condition of HO. In addition to reducing the plasma levels of Hcy, L-T4 treatment exerts beneficial effects on patients with HO by improving dyslipidemia, such as by decreasing the LDL-C level.

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