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Hypothyroidism, Hyperlipidemia and Hyperhomocysteinemia Cause Cardiovascular Diseases

Biochemistry

KEYWORDS : Hypothyroidism, High – Density Lipoprotein- Cholesterol (HDL-C), Apoprotein A1 (Apo-A1), Homocysteine

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ABSTRACT

Hypothyroidism is significantly impaired lipid metabolism and increase cardiovascular disease risk. The plasma levels of High Density Lipoprotein – Cholesterol (HDL-C) and Apolipoprotein – A1 (APO – A1) were altered in patients with hypothyroidism. This change was mediated by hyperhomocysteinemia. Hyperhomocysteinemia significantly induced insulin resistance and impaired coronary artery endothelial function in patients with hypothyroidism. Hyperhomocysteinemia is also an independent risk factor for condirac diseases.

Method: *A total of 800 subjects were enrolled, among them control group (n=744) and hypothyroidism (n=56). The Thyroid Stimulating Hormone (TSH) in hypothyroidism was found over 5.2 µIU/ml and in control group was below 5.2 µU/ml. The plasma levels of lipid indexes were measured. Statistical analysis were performed to evaluate the correlation between them. The plasma levels of lipid were significantly found higher in the hypothyroidism. The plasma homocysteine level of controls was found below 15 mmol/L and the plasma homocysteine level of hyptyroidism was found over 15 mmol/L. The plasma level of homocysteine was significantly higher in hypothyroidism.*

Results: *The Thyroid Stimulating Hormone (TSH) level was significantly higher in the hypothyroidism the controls ($p<0.05$) the plasma levels of High Density Lipoprotein – Cholesterol (HDL-C) and Apolipoprotein A1 (Apo-A1) were markedly increased compared to controls (Apo A1: $p<0.05$: HDL – C $p<0.01$). The plasma homocysteine level was correlated with level of Apo A1 in hypothyroidism $r = 0.32$ and control $r = 0.317$: all <0.01*

Conclusion:*Hypothyroidism significantly impaires lipid metabolism and increases cardiovascular disease risk. Homocysteine levels were significantly increased in patients with hypothyroidism. This increased homomcysteine levels impaire cardiovascular function via the inhibition of Apo-A1 expression and impairment of its antioxidants capacity.The present finding provide new era into the pathogenesis of hypothyroidism in induced metabolic disorders.*

Introduction:

Hypothyroidism (HO) the most common endocrine disorder can induce metabolic dysfunction [1] and increase the risk of cardiovascular disease [2, 3]. In patients with HO, dyslipidemia may account for the high risk of cardiovascular disease, including elevated levels of total cholesterol (CHOL), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) [4, 5]. The major role of high-density lipoprotein cholesterol (HDL-C) is reverse cholesterol transport, in which cholesterol from the peripheral tissue and vessel wall can be transported to the liver. HDL-C exerts anti-inflammatory, antioxidant, anticoagulant, and profibrinolytic activities that may further protect against cardiovascular disease [6]. The relationships between coronary artery disease and low levels of plasma HDL-C have been demonstrated in earlier studies [7, 8]. Apolipoprotein A1 (Apo A1) is the major protein component of HDL-C and exerts anti-atherogenic effects via several mechanisms, including reverse cholesterol transport [9, 10]. Reduced HDL-C and Apo A1 levels increase the risk of cardiovascular disease.

Homocysteine (Hcy) levels are increased in patients with HO [11, 12], and Hcy is associated with the severity of lipid metabolissm dysfunction. Hyperhomocysteinemia (Hcy) is an independent risk factor for atherosclerosis [13, 14]. It is demonstrated that Hcy induced insulin resistance in patients with HO [15] and impaired coronary artery endothelial function in patients with hypertension or hypertriglyceridemia [16, 17]. There is a negative association between levels of Hcy and Apo A1 and both cardiovascular events and atherosclerosis disease [18, 19, 20]. Thyroid hormones affect reverse cholesterol transport by increasing the activity of hepatic lipase and cholesteryl ester transfer protein (CETP), and these changes may result in HDL-C and Apo A1 being increased in HO. With increasing Hcy levels, however, some Hcy molecules are converted to homocysteine thiolactone (Hcy T), which forms an isopeptide bond with the lysine residues of proteins; this process is known as N-homocysteinylation [21]. A recent study found that N-homocysteinylation of Apo A1 impairs its antioxidant ability [22]. However, associations between Hcy and Apo A1 levels have not been well characterized. In this present study, we tested for potential associations between levels of Hcy and Apo A1 that could help explain the increased risk of arteriosclerotic coronary artery disease associated with hypothyroidism.

Methods:

A total of 800 subjects were enrolled for this study. Hypothyroidism is a thyroid hormone deficiency and can develop as a primary disease of the thyroid gland itself. An elevated thyrotropin is known also as thyroid stimulating hormone (TSH) level, usually above 5.2 µIU/ml, along with a subnormal free thyroxine (FT4) level, characterizes overt hypothyroidim [23]. Hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range and when serum FT4 and free triiodothyronine (FT3) concentrations are within the normal reference ranges [24, 25]. This designation is only applicable when thyroid function has been stable for several weeks, the hypothalamic–pituitary–thyroid axis is normal, and there is no recent or ongoing severe illness. Exclusion criteria were as follows: patients with cardiovascular disease. .

Hyperhomocystenemia was defined as a plasma Homocysteine level greater than 15 μmol/l [17]. Based on the presence of Hyperhomocysteinemia. The normal reference value of Homocysteine was less than 15 μmol/L. In the Hypothyroidism group, the patients with a plasma level of Homocysteine >15 μmol/l were termed the Hypothyroidism Hypohmocysteinemia group (n = 56).

Measurements of plasma levels of Hcy

Plasma Hcy concentrations were determined using an enzymatic cycling assay-based quantitative method using kits from Coba(USA) according to the manufacturer's instructions. The normal reference value was less than 15 μmol/l.

Measurements of blood lipid and thyroid function indexes

Levels of CHOL, HDL-C, LDL-C, TG, Apo A1, and Apo B were determined using a Cobas Dimension RXL Autoanalyser (Germany). Reference intervals for CHOL, HDL-C, LDL-C, TG, Apo A1 and Apo B were 3.62–5.70 mmol/l, 1.03–1.55 mmol/l, 1.81–3.36 mmol/l, 0.56–2.26 mmol/l, 1.00–1.70 g/l, and 0.40–1.20 g/l, respectively.Levels of FT3, FT4 and TSH were determined by an electrochemiluminescence immunoassay (ECLIA) using an Abbott Architect I2000 (Abbott Diagnostics, Abbott Park, IL, USA). Reference intervals for FT3, FT4, and TSH were 1.71–3.71 pg/ml, 0.7–1.48 ng/dl and 0.35–4.94 μIU/ml, respectively.

Results

The clinical characteristics and laboratory test findings of subjects are summarized in Table 1. The incidence of HO in females was significantly higher than that in males. The CHOL, HDL-C, LDL-C, Apo A1 and Apo B values in the HO group were significantly higher than those in the SHO and control groups; no differences were detected between HO and control groups [CHOL: 5.98 ± 1.67 vs. 5.09 ± 1.21 and 5.00 ± 1.00 mmol/l; HDL-C: 1.62 ± 0.40 vs. 1.47 ± 0.33 and 1.47 ± 0.30 mmol/l; LDL-C: 3.47± 1.21 vs. 3.03 ± 0.95 and 2.89 ± 0.81 mmol/l; Apo A1: 1.49 ± 0.38 vs. 1.34 ± 0.28 and 1.35 ± 0.27 g/l (Fig. 1); Apo B: 1.01 ± 0.34 vs. 0.92 ± 0.26 and 0.89 ± 0.24 g/l; respectively; all $p < 0.05$]. A significant increase in the Hcy levels was observed in patients with HO. l $p < 0.05$].

Table 1
Characteristics and laboratory test findings involved in this study

Variables	Control group (n = 744)	HO (n = 56)	p-value
Sex, M/F	10/84	8/65	0.973
Age, years	46.78 ± 11.22	43.07 ± 13.55	0.077
BMI, km/m²	24.15 ± 3.25	24.63 ± 3.19	0.990
CHOL, mmol/l	5.00 ± 1.00	5.98 ± 1.67†‡	<0.001**
HDL-C, mmol/l	1.47 ± 0.30	1.62 ± 0.40†‡	0.027*
LDL-C, mmol/l	2.89 ± 0.81	3.47 ± 1.21†‡	0.001**
TG, mmol/l	1.12 (0.79–1.69)	1.28 (0.88–1.76)	0.708
Apo A_1, g/l	1.35 ± 0.27	1.49 ± 0.38†‡	0.005**
Apo B, g/l	0.89 ± 0.24	1.01 ± 0.34†‡	0.007**
Hcy, μmol/l	13.00 (10.75–15.00)	15.00 (13.00–21.50)†‡	<0.001**
TSH, μIU/ml	5.2 (0.4-5.6)	10.5 (0.781-0.461)	<0.001**

Summary of the clinical characteristics and laboratory test results of the study controls, (744 patients with 56 patients with Hypothyroidism). The data are expressed as means ± SDs unless otherwise indicated. TG and Hcy levels are presented as medians (25th and 75th percentiles). BMI body mass index, CHOL total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TG triglycerides, Apo A1 apolipoprotein A1, Apo Bapolipoprotein B, Hcy homocysteine. Comparisons among groups were performed.

Table 2
Comparison of characteristics and the laboratory test findings are as follows.

Parameters	Control group	HO group
	N-control group (n = 744)	N-HO group(n = 56)
Sex, M/F	6/70	1/36
Age, years	46.42 ± 11.21	41.73 ± 10.48
BMI, km/m²	23.89 ± 3.09	23.96 ± 3.32
CHOL, mmol/l	4.99 ± 1.03	5.73 ± 1.15[cd]
HDL-C, mmol/l	1.48 ± 0.31	1.79 ± 0.34 [cd]
LDL-C, mmol/l	2.87 ± 0.82	3.36 ± 0.94 [cd]
TG, mmol/l	1.18 (0.78–1.72)	1.03 (0.83–1.63)
$ApoA_1$, g/l	1.38 ± 0.28	1.59 ± 0.38 [cd]
ApoB, g/l	0.88 ± 0.25	0.99 ± 0.29 [c]

Correlation between plasma levels of Hcy and both thyroid function and blood lipid indexes

Table 3 shows that Hcy was negatively correlated with the levels of FT3 and FT4 ($r = -0.543$ and -0.504, $p < 0.01$, respectively) in the HO group and positively correlated with TSH levels in the HO ($r = 0.461$, $p < 0.01$). The plasma Hcy levels were correlated with HDL-C in both the HO groups ($r = -0.375$ and -0.356, all $p < 0.01$, respectively). Additionally, the Hcy levels were negatively correlated with Apo A1 in the HO, and control groups ($r = -0.320$, -0.337 and -0.317; all $p < 0.01$, respectively).

Table 3
Correlations among plasma Hcy levels, thyroid function, and blood lipid indexes

	Control group (n = 744)		HO (n = 56)	
	r	p-value	r	p-value
Age, years	0.101	0.331	0.048	0.685
BMI, km/m²	0.139	0.180	0.121	0.309
FT_3, pg/ml	−0.178	0.087	−0.543	<0.001
FT_4, ng/dl	−0.102	0.327	−0.504	<0.001
TSH, μIU/ml	−0.029	0.781	0.461	<0.001
CHOL, mmol/l	0.097	0.352	0.128	0.282
HDL-C, mmol/l	−0.178	0.085	−0.375	0.001
LDL-C, mmol/l	0.082	0.434	0.046	0.697
TG, mmol/l	−0.041	0.693	0.103	0.387
Apo A_1, g/l	−0.317	0.002**	−0.320	0.006
Apo B, g/l	0.073	0.482	0.002	0.990

Discussion

HO associated with atherosclerosis [2, 3]. A major factor that contributes to this condition is dyslipidemia, which is observed in these patients [4, 5]. The relationship between coronary artery disease and low levels of plasma HDL-C has been demonstrated in earlier, prospective studies [7, 8]. Apo A1 is a major protein component of HDL-C and may exert anti-atherogenic effects through several mechanisms.

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Reduced levels HDL-C and Apo A1 increase the risk of cardiovascular disease. However, some studies and our present findings indicate that HDL-C and Apo A1 levels are increased in patients with HO show an effect on anti-atherosclerotic function. HHcy is an independent risk factor for cardiovascular disease [13, 14]. HHcy increases cardiovascular disease via various mechanisms, including endothelial dysfunction, oxidative stress, endoplasmic reticulum stress, smooth muscle cell proliferation and platelet aggregation [26, 27, 28, 29]. Our previous study demonstrated that HHcy induced insulin resistance in patients with HO [15] and impaired coronary artery endothelial function in patients with hypertension or hypertriglyceridemia [16, 17]. Some studies have shown that Hcy levels are increased in hypothyroid patients [11, 12]. Our previous study demonstrated that HHcy might contribute to atherogenesis by enhancing the responsiveness of monocytes to inflammatory stimuli and thereby promoting insulin resistance via the induction of endoplasmic reticulum stress in adipose tissue along with impairing coronary artery endothelial function [16, 17]. HHcy can inhibit reverse cholesterol transport by reducing circulating HDL via the inhibition of Apo A1 protein synthesis, resulting in an increased risk of atherosclerosis [30, 31]. Concurrently, other studies reported that HHcy impaired the antioxidant ability of Apo A1 and HDL-C [22]. In this present study, we provide for the first time evidence for a negative correlation between Hcy and Apo A1 in patients with HO

We observed that subjects in the control had lower levels of CHOL, HDL-C, LDL-C, Apo A1 and Apo B than individuals in the HO group. By altering lipid metabolism, HO accelerates the process of atherogenesis and increases cardiovascular risk. Overt HO is characterized by hypercholesterolemia and a marked increase in LDL-C and Apo B because of decreased fractional clearance of LDL-C, which is a consequence of fewer LDL-C receptors in the liver. Apo A1, a major protein component of HDL, is a major contributor to the anti-atherosclerotic effects. Levels of HDL-C are elevated in HO because of decreased CETP and hepatic lipase activity, which are both enzymes regulated by thyroid hormones [32]. Increased levels of CHOL, LDL-C and Apo B are linked to atherosclerosis. Hcy was significantly higher in the HO group. Our findings are consistent with those of previous studies [11, 12]. Hcy is a sulfur-containing amino acid that is formed during methionine metabolism. Intensive studies have identified HHcy as an independent risk factor for atherosclerosis [13, 14]. Our previous study demonstrated that HHcy may contribute to atherogenesis by enhancing the responsiveness of monocytes to inflammatory stimuli and promoting leukocyte recruitment into atherosclerotic plaques [33]. A portion of Hcy is converted to HcyT by methionyl-tRNA synthetase. Indeed, levels of plasma HcyT are increased in humans with HHcy caused by mutations in the cystathionine β-synthase or 5, 10-methylene-tetrahydrofolate reductase genes [21]. HcyT, a cyclic thioester, forms an isopeptide bond with lysine residues of proteins, which is known as N-homocysteinylation. The N-homocysteinylation of proteins can lead to the loss or modulation of protein function. In addition, N-homocysteinylated proteins may cause atherosclerosis via cell death, inflammation, and adaptive immune responses. N-homocysteinylated Apo A1 is present in normal human serum at a proportion of 1.0–7.4 % of N-Hcy-Apo A1 among total Apo A1 [11]. With increasing levels of Hcy in patients with HO levels of N-Hcy-Apo A1 may be increased. A recent study found that N-Hcy-Apo A1 promotes LDL-C oxidation, and HcyT-treated HDL-C also loses its antioxidant activity. Therefore, increased levels of Apo A1 and HDL-C do not affect antioxidant ability because N-homocysteinylation of Apo A1 impairs this function [22]. Dyslipidemia and HHcy may both be associated with endothelial dysfunction and cardiovascular disease.

To investigate the association between HHcy and blood lipid indexes, the levels of CHOL, HDL-C, LDL-C and Apo A1 in the HO group were higher. The differences in HDL-C and Apo A1 values were not significant, and Apo A1 only showed a difference between them. Levels of HDL-C and Apo A1 were significantly lower in the hyperhomocysteinemic patients with HO. Apo A1 and HDL-C can reduce the risk of cardiovascular disease by promoting reverse cholesterol transport and modulating inflammation [9,10]. Hcy can inhibit reverse cholesterol transport by reducing circulating HDL-C via the inhibition of the expression and protein synthesis of Apo A1 [30, 31]. This finding suggests that Hcy inhibited the expression of Apo A1 and HDL-C in patients with HO which could increase the risk of cardiovascular disease.

Our study showed that Hcy was negatively correlated with levels of FT3 and FT4 in the HO group and positively correlated with levels of TSH in the HO groups. Several other studies have proposed that HO reduces hepatic levels of the enzymes involved in Hcy metabolism. This hypothesis has been supported by the finding that HO are associated with alterations in plasma levels of Hcy [34, 35]. We observed that plasma levels of Hcy were negatively correlated with those of HDL-C in the HO and were negatively correlated with levels of Apo A1 among them. With an increased level of Hcy, there was a concurrent reduction in the levels of HDL-C and Apo A1. Similar correlations have been reported in other diseases [30, 31]. To the best of our knowledge, we have established for the first time that plasma Hcy levels show a significant, negative correlation with Apo A1 concentrations in patients with HO. Our findings suggest that HHcy impairs the antioxidant ability of Apo A1 and inhibits the expression of Apo A1 and HDL-C; these events are associated with an increased risk of cardiovascular disease in patients with Hypothyroidism.

Conclusions

Plasma Hcy levels were significantly increased in patients with HO. These increased levels of Hcy may impair cardiovascular function by impairing the antioxidant ability of Apo A1 and inhibiting the expression of Apo A1 and HDL-C. Our findings suggest that HHcy may increase cardiovascular risk via multiple effects, especially through a mechanism that can induce dyslipidemia in patients with HO. Thus, our findings provide new insights into the pathogenesis of Hypoyhroidism induced metabolic disorders.

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