

The impact of acute hypothyroidism on lipid levels in athyreotic patients

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Background: We investigated the effect of acute hypothyroidism on lipid concentrations especially on high density lipoprotein (HDL-cholesterol) level in athyreotic patients. **Materials and Methods:** Thirty-one patients, with a history of differentiated thyroid carcinoma and total thyroidectomy, who were candidates of radioiodine therapy, enrolled in the study. Their lipid profiles and serum thyrotropin stimulating hormone (TSH) levels were measured before and two-to-six weeks after thyroid hormone withdrawal. The lipid concentrations were compared with the paired t test and serum TSH using the Wilcoxon signed rank test. *P* values < 0.05 were considered statistically significant. **Results:** The median of TSH concentration was 0.06 mU / liter on thyroid hormone suppressive therapy and 102 mU / liter at the thyroid hormone withdrawal phase (*P* < 0.0001). The serum concentrations of all lipids were significantly increased after withdrawal (*P* < 0.0001). The mean (SD) of the HDL-cholesterol concentration rose from 44 ± 9 mg / dL to 58 ± 17 mg / dL. The levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride increased by 58, 75, 30, and 59%, respectively, during acute hypothyroidism. **Conclusion:** The present study showed that thyroid hormone withdrawal altered the lipid concentrations significantly, in a short period of time. The levels of both atherogenic (LDL-cholesterol) and cardioprotective (HDL-cholesterol) particles increased concurrently. Their clinical importance should be investigated in future.

Key words: Cholesterol-HDL, hypothyroidism, lipid metabolism, thyroid hormones, thyroid neoplasms

INTRODUCTION

Thyroid hormones have various effects on the intermediary metabolic pathway, such as, lipolysis and lipogenesis.^[1] Thyroid hormones affect both the synthesis and the degeneration of lipids (lipogenesis and lipolysis).^[1] Longstanding overt hypothyroidism is associated with several effects on lipid metabolism, including a marked increase in cholesterol and low density lipoprotein-cholesterol (LDL-cholesterol) concentrations.^[2] However, the triglyceride levels might be normal or increased in these patients.^[3] Studies have reported variable effects of overt hypothyroidism on high-density lipoprotein (HDL)-cholesterol levels. Some of them have reported increased HDL-cholesterol, while the others have shown its decrease or no change in level.^[4-6]


Thyroidectomy, thyroid hormone suppression therapy, and radioactive iodine therapy are the

established forms of treatment for differentiated thyroid cancer (papillary and follicular).^[7] Thyroid hormone withdrawal before therapeutic radioiodine administration in athyreotic patients makes for a unique model of acute overt hypothyroidism, to investigate the effects of thyroid hormones on metabolic pathways such as lipid metabolism. To the best of our knowledge, there are just a few studies to point out the effect of short-term or acute overt hypothyroidism on the lipid profile. This is why we decided to investigate the effects of acute hypothyroidism on HDL-cholesterol and other lipid concentrations before and after thyroid hormone withdrawal in athyreotic patients.

MATERIALS AND METHODS

This prospective trial study was performed at the Isfahan Endocrine and Metabolism Research Center, from September 2011 to March 2012.

Forty-two patients, with a history of differentiated thyroid carcinoma, who had undergone total thyroidectomy, accepted our invitation to enroll in the study. These patients were taking thyroid hormone suppression therapy. They were candidates for thyroid hormone withdrawal, to have radioiodine therapy. Before recruitment, patients with a history of diabetes mellitus (*n* = 6) and hyperlipidemia (*n* = 1) were excluded. No

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one had hypertension, smoking, renal and liver disease, or history of taking medications for these disorders. However, our plan was to exclude those people with these disorders. Finally, 35 patients were enrolled. Patients were visited for the first time when they were on thyroid hormone suppression therapy (visit 1) and two-to-six weeks^[7] after thyroid hormone withdrawal (visit 2). After visit 1, two patients did not want to continue the study and two more patients were excluded. The cause of exclusion was a serum TSH > 10 mU / liter on thyroid hormone therapy, as they had already been hypothyroid on levothyroxine therapy. Finally, 31 patients completed the study [(6 males and 25 females); mean age, 38 years (range, 19 – 78 years)]. The sample size ($n = 31$) had been calculated with the power of 80%, at a 5% significance level ($\alpha = 0.05$), according to a pilot study that was previously done with us.

At each visit, blood samples were taken after 10 – 12 hours of overnight fasting, to measure the concentration of the thyroid stimulating hormone (TSH), total cholesterol, triglyceride, and HDL-cholesterol. LDL-cholesterol was calculated by using the Friedewald formula when total triglyceride was less than 400 mg / dl.^[8] Total cholesterol and HDL-cholesterol were measured by the CHOD-PAP method and triglyceride was measured by the GPO-PAP method, using the Biotecnica BT-3000 Plus Chemistry analyzer, Italy. TSH was measured by a chemiluminescence assay on the Siemens Advia Centaur CP immunoassay analyzer (reference range 0.35 – 5.50 mU / liter; Siemens Healthcare Diagnostics Inc., Tarrytown, NY).

The tenets of the Declaration of Helsinki were followed. All participants signed their informed consent. The study was approved by the Isfahan University of Medical Sciences Medical Ethics Committee (Isfahan research project number: 391072).

Normality of the data distribution was evaluated by the Kolmogorov–Smirnov (KS) test. All the data had a normal distribution, but for TSH. The data were expressed as mean and SD (standard deviation). The serum TSH concentration was expressed as median and quartiles (the first quartile and the third quartile). To compare the variables before and after thyroid hormone withdrawal, the paired sample *t*-test or the Wilcoxon signed rank test were used. The relative

change was calculated according to this formula – (new value - reference value) ÷ reference value.^[9]

Statistical analysis was done with the SPSS software version 16 for Windows (SPSS, Chicago, IL). A *P* value < 0.05 was considered to be statistically significant.

RESULTS

The lipid profiles and relative change of lipid profile, before and after overt short-term hypothyroidism, are listed in Table 1.

The median (the first quartile and the third quartile) of TSH concentration was 0.06 (0.02, 0.2) mU / liter on thyroid hormone suppressive therapy and 102 (49,150) mU / liter at the withdrawal phase. After hormone withdrawal, the levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides increased significantly during acute hypothyroidism ($P < 0.0001$).

The LDL-cholesterol levels, as atherogenic particles, increased from a mean (SD) of 94 ± 24 to 163 ± 5 mg / dL. Furthermore, the mean (SD) of HDL-cholesterol concentrations, as an anti-atherogenic particle, increased from 44 ± 9 to 58 ± 17 mg / dL.

DISCUSSION

Thyroid hormones affect the metabolism of lipids.^[1] Several studies have assessed these effects in patients with hypothyroidism. These studies have reported increased levels of total cholesterol and LDL-cholesterol,^[2,3,10] but the exact effects of thyroid hormone deficiency on triglyceride and HDL-cholesterol were inconsistent.^[3-6] Thyroid hormone withdrawal, before therapeutic radioactive iodine administration, in athyreotic patients, made a unique model for acute hypothyroidism, to help us to investigate these effects.

The outstanding finding in our study was the increase in HDL-cholesterol concentration by 30%. It could be a consequence of the decreased activity of the cholesteryl-ester transfer protein (CETP)^[11] and hepatic lipase (HL).^[12] These enzymes are regulated by the thyroid hormones.

Table 1: The lipid profiles and relative change of lipids before and after thyroid hormone withdrawal in athyreotic patients

	Before thyroid hormone withdrawal	After thyroid hormone withdrawal	<i>P</i> value	Relative change (%)
TSH (mU / liter)	0.06 (0.02,0.2)	102 (49,150)	0.0001 ^b	
Total cholesterol (mg / dL)	158 ± 30	250 ± 65	0.0001	58
Triglycerides (mg / dL)	96 ± 39	155 ± 70	0.0001	59
LDL-cholesterol (mg / dL)	94 ± 24	163 ± 51	0.0001	75
HDL-cholesterol (mg / dL)	44 ± 9	58 ± 17	0.0001	30

Values are expressed as the mean ± SD and median (the first quartile, the third quartile), *P* value comes from paired *t* test and ^b by Wilcoxon signed rank test for TSH, TSH = Thyrotropin stimulating hormone, LDL-cholesterol = Low density lipoprotein-cholesterol, HDL-cholesterol = High-density lipoprotein-cholesterol

On the other hand, the expression of HDL-cholesterol scavenger receptor class-B, type I (SR-BI) is regulated by thyroid hormones.^[13]

Our data showed that the triglyceride was increased by 59%. The thyroid hormone increases lipoprotein lipase activity.^[12] The higher concentration of serum triglyceride may be due to lower lipoprotein lipase activity.

Total cholesterol and LDL-cholesterol were increased by 58 and 75%, respectively. Increase in total cholesterol and LDL-cholesterol occurred due to several mechanisms in hypothyroidism. The thyroid hormone induced the expression of cell surface LDL-cholesterol receptors. The sterol regulatory element-binding protein 2 (SREBP-2) was critical for the expression of the LDL receptor.^[14] The *SREBP-2* gene was directly regulated by the thyroid hormones and *SREBP-2* gene expression diminished in hypothyroidism^[14] Furthermore, intestinal cholesterol absorption increased in hypothyroidism due to the thyroid hormone actions on Niemann-Pick C1-like 1 protein in the gut.^[15]

There is some evidence that hypothyroidism is related to atherosclerosis and cardiovascular diseases.^[16] This association may partly be explained by the effects of hypothyroidism on the induction of diastolic hypertension, altered coagulopathy, and changes in lipid metabolism, such as, increase in the circulating levels of LDL-cholesterol, a highly atherogenic particle.^[16]

Indeed, our study showed that both atherogenic and antiatherogenic particles, LDL-cholesterol, and HDL-cholesterol increased significantly in overt hypothyroidism.

Historically, HDL-cholesterol particles have been subdivided by size into larger HDL2 and smaller HDL3 subparticles. Pearce *et al.*, showed that large HDL subparticle (HDL2) concentrations increased, but small and medium HDL subparticle (HDL3) concentrations decreased in overt hypothyroid subjects.^[10] The shift toward larger HDL subparticle sizes may be due to a decrease in the activity of hepatic lipase during hypothyroidism, which alters the HDL-cholesterol subfractions.^[2] HDL-cholesterol levels, as antiatherogenic particles, increased in the hypothyroidism phase in our study and in some studies done previously.^[5,10] However, if this increase in the level of HDL-cholesterol, especially large HDL subparticles (HDL2) can be cardioprotective in hypothyroid patients, further investigation will be required.

Our study has some possible limitations. The sample size of the study is relatively small, and it does not have a randomized controlled trial design. The patients who

participated had thyroid cancer and had to be on suppressive dosage of thyroid hormones. However, they were not euthyroid when they enrolled for the study, before hormone withdrawal. These factors could influence the findings.

In conclusion, the present study showed that thyroid hormones play a considerable role in HDL-cholesterol and other lipid metabolism. Thyroid hormone withdrawal altered the lipid concentrations, significantly. The levels of both atherogenic particles (LDL-cholesterol) and cardioprotective particles (HDL-cholesterol) increased, concurrently. However, the net effect of these changes on the cardiovascular system needs further investigation.

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