RESEARCH LETTER

Changes of lipid profile in subclinical hyperthyroidism and following restoration of euthyroidism

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Introduction Subclinical hyperthyroidism (sHT) is characterized by low thyroid-stimulating hormone (TSH) serum concentration and normal levels of free thyroxine (fT4) and free triiodothyronine (fT3), and it affects 0.2% to 15.4% of the general population.[1] sHT can be detrimental to the human body and can develop into clinically overt hyperthyroidism (HT).[1] Although the condition is called "subclinical," in a recent study 83.7% of patients with sHT manifested symptoms of HT.[2]

sHT is associated with an increased risk of arrhythmias, acute myocardial infarction, pulmonary embolism, and cardiovascular and all-cause mortality.[3] Patients with sHT present increased heart ventricle volume and mass, disturbed left ventricle relaxation, increased diameter of the ascending aorta, as well as worse physical capacity.[4,5]

Lipid metabolism, total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, and lipoprotein(a) levels are decreased in sHT and HT, mainly due to an increased LDL receptor expression in the liver and enhanced cholesterol turnover. High-density lipoprotein cholesterol (HDL-C) serum concentration tends to decline because of a direct effect of thyroid hormones on cholesteryl ester transfer protein and hepatic lipase activity.[6] Increased oxidative stress and enhanced LDL-C oxidation may promote atherosclerosis and thus be one of the factors contributing to increased cardiovascular risk in hyperthyroid state.[7]

However, it is still unclear if and to what extent the treatment of sHT impacts lipid metabolism. To address this knowledge gap, we prospectively evaluated how the transition from sHT to euthyroidism, achieved by radioiodine treatment, influenced lipid profile parameters.

Patients and methods The studied group consisted of 44 patients (37 women, 7 men), diagnosed with endogenous sHT in the course of toxic multinodular goiter (TMNG), diffused thyroid autonomy (DTA), or autonomously functioning thyroid nodule (AFTN). The patients were included in the study based on the following criteria: 1) decreased TSH serum concentration (<0.36 mIU/l). To exclude the patients with temporarily suppressed TSH, it was measured at least 2 times, at intervals of at least 6 weeks; 2) normal fT3 and fT4 levels: 3.5–7.9 pmol/l and 7.64–19.7 pmol/l, respectively, also measured twice at intervals of at least 6 weeks; 3) results of the thyroid ultrasound examination and Tc-99m scintiscan, suggesting one of the following diagnoses: TMNG, DTA, or AFTN.

We measured antithyroid autoantibodies to exclude the patients with sHT in the course of autoimmune thyroid disease.

Tc-99m thyroid scintiscan, radioiodine uptake testing, and thyroid ultrasound examination were performed in every patient at admission.

All the patients were subsequently treated with radioiodine. The individual therapeutic radioiodine activity was calculated with the equation described elsewhere.[3]

The patients were evaluated every 3 months of following the therapy. We measured TSH, fT3, fT4, total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG), and sex hormone binding globulin (SHBG) serum concentration at admission, and at every check-up visit until the last visit 6 months after euthyroidism restoration. To determine TSH, fT3, and fT4 serum concentrations, we used the AutoDELFIA Immunoassay system kits (PerkinElmer, Turku, Finland). To analyze the lipid profile parameters, we utilized the enzymatic colorimetric method with

TABLE 1 Complete thyroid function test results and lipid profile parameters before and after treatment

Parameter		Mean	SD	*P* value
TSH, mIU/l	Before treatment	0.16	0.10	<0.001
	After treatment	1.32	0.75	
FT3, pmol/l	Before treatment	6.48	0.69	<0.001
	After treatment	5.77	0.57	
FT4, pmol/l	Before treatment	14.16	2.37	<0.001
	After treatment	13.05	1.85	
HDL-C, mg/dl	Before treatment	64.02	15.68	0.04
	After treatment	66.25	16.34	
LDL-C, mg/dl	Before treatment	114.32	33.50	0.02
	After treatment	121.89	36.52	
TG, mg/dl	Before treatment	95.16	39.86	0.28
	After treatment	102.57	61.90	
TC, mg/dl	Before treatment	204.59	39.07	0.11
	After treatment	211.09	39.56	

SI conversion factors: to convert cholesterol to mmol/l, multiply by 0.0259, trigycerides to mmol/l, by 0.0113

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone

the COBAS INTEGRA (Basel, Switzerland) analyzer and Roche (Basel, Switzerland) reagents.

The protocol of the study is in accordance with the Declaration of Helsinki and was approved by the local bioethics committee (5/2003). All patients provided written informed consent to participate in the study.

Statistical analysis The statistical analysis was carried out with STATISTICA package, version 12.0 (StatSoft, Tulsa, Oklahoma, United States). We assumed a *P* value below 0.05 to be significant. The Kolmogorov–Smirnov test was used to check the normality of the distribution of the variables and their differences. The paired *t* test was employed to compare paired groups with normally distributed variables. The Wilcoxon test compared paired samples with variables not normally distributed. Pearson linear correlation coefficient was used to test for correlation of the data with normal distribution.

Results A total of 44 patients (37 women, 7 men) with sHT participated in the study. Their mean (SD) age was 45.9 (11.0) years (range, 22–65). The underlying thyroid pathologies causing sHT were: TMNG in 38 patients, DTA in 4 and AFTN in 2. Radioiodine treatment resulted in the restoration of biochemical euthyroidism. Detailed thyroid function test results and lipid profile parameters before and after the treatment are presented in TABLE 1. At the moment of the diagnosis 14 patients had their TSH level suppressed below 0.1 mIU/l, while 30 patients showed partial suppression (0.1–0.36 mIU/l).

All the patients achieved euthyroidism after a 36-month follow-up. Only 3 patients had transient HT that required a short course of methimazole therapy, however, after the drug was stopped, the patients were either euthyroid or hypothyroid and no recurrence of sHT was observed. Three patients presented transient exacerbation of HT 3 months after radioiodine administration, requiring a short period of methimazole treatment. Two patients developed hypothyroidism, which was treated with levothyroxine substitution and led to the restoration of euthyroidism.

The mean (SD) time from the diagnosis of sHT till radioiodine treatment was 12.7 (9.8) months, while the mean time between radioiodine treatment and the achievement of euthyroidism was 6.9 (4.8) months. Control laboratory tests assessing the lipid profile status were performed after a mean time of 5.7 (4.2) months after confirmation of euthyroidism. The mean total time from radioiodine treatment until control measurement was 12.6 (6.1) months.

The restoration of euthyroidism was associated with a significant increase in LDL-C and HDL-C. An increase in TG and TC serum concentrations was also observed but it was not significant (TABLE 1). We also calculated non-HDL-C levels and noted a rise in this parameter from 141.11 mg/dl to 145.05 mg/dl. We found a weak but significant correlation between posttreatment fT3 and serum HDL-C concentrations ($r = -0.303$, $P = 0.046$). No significant correlations were found between any other pre- or posttreatment lipid profile parameters and TSH, fT4, or fT3 levels. We also evaluated SHBG levels. The posttreatment SHBG serum concentration (median, 35.7 [IQR, 25.2; 47] nmol/l) was significantly lower ($P < 0.001$) than before the treatment (median, 51 [IQR, 33.1; 64.9] nmol/l).

Discussion The latest American Thyroid Association guidelines recommend treating patients with persistently suppressed TSH levels below 0.1 mIU/l and: 1) older than 65 years, 2) those who are symptomatic, 3) patients with heart diseases, cardiac risk factors, osteoporosis, or postmenopausal women who are not on estrogen or bisphosphonate therapy. Treatment of sHT should be, however, individually considered in all patients without the abovementioned risk factors, if TSH is persistently below 0.1 mIU/l.[8] The 2015 European Thyroid Association guidelines similarly recommend treatment of sHT in older patients, with certain risk factors, thyroid pathologies or significant TSH suppression, and an individualized approach in younger patients, with a lower degree of TSH suppression and lack of signs of thyroid pathology.[9] Our study provides further data that can be used by clinicians in the process of decision making in therapy of patients with sHT.

There is a general agreement that the treatment of overt HT is associated with an increase in TC, LDL, HDL, and apolipoprotein B levels, while TG tend to stay unchanged.[10] The magnitude of changes in HDL-C and LDL-C serum

concentrations after the restoration of euthyroidism were found to correlate with the fT4 level.[11] According to the latest meta-analysis[10] on the influence of thyroid dysfunction treatment on serum lipid metabolism, the treatment of HT results in a rise of TC by 44.50 mg/dl, LDL-C by 31.13 mg/dl, HDL-C by 5.52 mg/dl, apolipoprotein A by 15.6 mg/dl, apolipoprotein B by 26.12 mg/dl, and lipoprotein(a) by 4.18 mg/dl. Data on the effect of sHT treatment on the lipid profile are scarce and heterogeneous. The mentioned meta-analysis[10] reported no changes in TC, LDL-C, HDL-C, and TG after the treatment with radioiodine, surgery, or antithyroid drugs. However, a subgroup analysis of studies that included a follow-up longer than 6 months revealed a significant increase in TC, LDL-C, HDL-C, and TG.[10] The latter observation is in concordance with our study, which comprised a similar follow-up and yielded similar results. A study by Bel Lassen et al[12] showed that patients with multinodular goiter and sHT suffered from a rise in body weight and LDL-C levels after thyroidectomy. The changes observed in those parameters were significantly greater than in the group of euthyroid individuals who also underwent thyroidectomy.[12] However, in another study no relevant differences in lipid metabolism were found 6 months after restoration of euthyroidism in patients with longstanding sHT treated for differentiated thyroid carcinoma.[13] This suggests that depending on the treatment modality and the underlying cause of sHT, the restoration of euthyroidism can differently impact serum lipid metabolism.

According to a study by Greenlund et al,[14] sHT treatment causes an increase in body mass (including both fat and fat-free mass). This can further contribute to the development of hyperlipidemia seen during treatment of HT and sHT. Interestingly, in our study we did not observe any changes in body mass before and after the treatment, however, we did not perform a body composition analysis.

A paper by Sigal et al[15] examined the changes in plasma lipid metabolism in a group of patients treated for differentiated thyroid carcinoma after the transition from euthyroidism to exogenous sHT, which is a reverse process to the one described in our paper. They detected an increase in HDL-C by 21.6%, in unesterified cholesterol by 12.3%, and in lipoprotein(a) by 33.3% after achieving sHT. There were no significant changes in TC, LDL-C, non-HDL-C, TG, apolipoprotein A-I, and apolipoprotein B.[15]

We showed that the treatment of sHT results in a significant increase in LDL-C and HDL-C serum concentrations. The rise in serum TG and total serum cholesterol did not reach statistical significance. Further studies assessing the impact of sHT treatment on lipid metabolism are still needed, especially since none of those conducted so far assessed changes in lipoproteins. It is also still not clear if different treatment modalities and different causes of sHT exert the same effect on lipid metabolism, and whether the observed changes are clinically relevant in terms of cardiovascular risk.

ARTICLE INFORMATION

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