Regression of the Carotid Intima Media Thickness by Propylthiouracil Therapy in Graves' Hyperthyroidism

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Abstract: *Introduction:* One of the cardiovascular effects of hyperthyroidism is increased carotid intima media thickness (CIMT). The aim of this study is to investigate the CIMT in patients with Graves' hyperthyroidism and the effect of propylthiouracil (PTU) therapy on CIMT. *Method:* Twenty-six patients with Graves' hyperthyroidism and 33 healthy controls were included in the study. CIMT was measured at the right and left external carotid arteries in every patient in both groups. CIMT was measured before and after the PTU therapy in patients with Graves' hyperthyroidism. *Results:* There was a significant difference in CIMT between the group of Graves' hyperthyroid patients and the control group (0.72 versus 0.55 mm, $P < 0.0001$) at baseline. Twenty-five of 26 patients with Graves' disease were followed up for 18 months prospectively. Euthyroidism has been achieved in 21 patients. After 18 months of treatment, CIMT decreased significantly compared with the baseline values [0.84 (0.54–1.3) to 0.72 (0.50–1.2), change 0.12 mm, $P < 0.001$]. *Conclusion:* Graves' hyperthyroidism is associated with atherosclerosis as assessed by CIMT. Treatment of Graves' hyperthyroidism with PTU decreases the CIMT.

Key Indexing Terms: Carotid intima media thickness; Propylthiouracil; Graves' disease; Regression. **[Am J Med Sci 2012;343(4):273–276.]**

Carotid intima media thickness (CIMT) is one of the predictors for upcoming vascular events.[1] It has been used as a surrogate marker of atherosclerosis and hence used in risk management of clinical end points for cardiovascular diseases, such as acute myocardial infarction, and especially for cerebrovascular events, such as stroke and transient ischemic attack.[2]

Thyroid function has effects on CIMT. Hypothyroidism with resulting dyslipidemia has been associated with atherosclerosis and cardiovascular disorders.[3] On the other hand, hyperthyroidism might also affect CIMT. The cardiovascular effects of hyperthyroidism, such as palpitation, atrial fibrillation, increasing systolic and mean arterial pressure and high cardiac output, are well known.[4]

There are not many studies investigating the association between CIMT and hyperthyroidism/Graves' hyperthyroidism. Völzke et al[5] found that subjects with low serum thyroid-stimulating hormone (TSH) levels had higher CIMT values compared with subjects with normal serum TSH levels. However, there has been no study about any change of CIMT by treatment in hyperthyroid patients/Graves' hyperthyroidism. Patients with toxic multinodular goiter or toxic adenoma are usually treated by radioactive iodine, whereas patients with Graves' disease usually receive long-term antithyroid drugs with sustained drug-free remission. The objectives of this study are[1] to evaluate whether CIMT increased in patients with Graves' hyperthyroidism compared with healthy controls and[2] if CIMT increased, whether treatment with propylthiouracil (PTU) would reverse this increase.

METHODS

Patients

The study population has been selected from a University Hospital internal medicine outpatient clinic between 2006 and 2007. Patients with coexisting hypertension, diabetes mellitus, coronary artery disease, obesity, pulmonary diseases (obstructive sleep apnea syndrome, chronic obstructive pulmonary disease, etc.), renal insufficiency or failure, and patients who have received any previous treatment for thyroid disorder, have been excluded. None of the women included in the study smoked. Only one man smoked 10 pack-years and has been an ex-smoker for 10 years. Informed consent was obtained from all patients on inclusion to the study. Thirty-five patients had clinical hyperthyroidism. Among these, 26 patients were diagnosed with Graves' disease and have been included in the study. Clinical, laboratory and ultrasound data of the patients were compared with 33 healthy controls from the same population. Patients had at least one of the clinical symptoms related to hyperthyroidism, including palpitations (55%), weight loss (45%), heat intolerance (35%) and nervousness (25%). Patients were followed up 18 months prospectively and clinical, laboratory and ultrasonography data were recorded.

Clinical Assessment

All patients had history and physical examination performed on presentation. Data on whether the patients underwent any medical treatment for their own basic diseases were included. Fasting morning blood glucose, blood urea nitrogen, creatinine, serum electrolytes, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, total bilirubin and fasting lipid profile were measured using a p800 system (Roche Diagnostics, Indianapolis, IN); TSH (thyrotropin), free T4 (FT4) and free T3 (FT3) were recorded using a Roche Modular Analytics E170 (Roche/Hitachi, Indianapolis, IN); and CBC and its differential were recorded using a Sysmex XT 2000i system (Roche Diagnostics). Creatinine clearance was calculated according to the Cockroft-Gault formula, and body mass index was calculated using age and height in centimeters for each patient. Serum TSH, FT4 and FT3 were measured using a Roche Modular Analytics E170 module. The diagnosis of Graves' disease was made through laboratory analysis, including thyroid ultrasound, and clinical signs, including hyperthyroidism and ophthalmopathy. Many drugs could influence the CIMT value (ie, statins, antihypertensive drugs, etc.) but none of the study popula-

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TABLE 1. Baseline characteristics of the 26 Graves' hyperthyroidism patients and 33 healthy controls

	Hyperthyroid (n = 26)	Healthy controls (n = 33)	P
Age, mean (SD)	47.8 (14.3)	46.7 (12.7)	>0.2
Sex			>0.5
Female, n (%)	21 (78)	22 (67)	
Male, n (%)	5 (22)	11 (33)	
TSH, mean (SD) or median (IR), mIU/mL	0.005 (0.004–0.005)	1.45 (0.59)	
FT4, mean (SD), median (IR), ng/dL	27.5 (21.25–36)	16.75 (1.93)	
FT3, median (IR), ng/dL	27.5 (21.3–36)	5.2 (3.1–6.1)	
Carotid IMT, mean (SD), median (IR), mm	0.72 (0.64–0.83)	0.55 (0.08)	<0.001

TSH, thyrotropin; FT4, free thyroxin; FT3, free triiodothyronin; SD, standard deviation; IR, interquartile range.

tion used any medication other than PTU and propranolol; thus, we excluded the possible effects of some drugs such as statins, antihypertensive drugs or amiodarone.

All patients had thyroid ultrasonography and scintigraphy to exclude toxic multinodular goiter or toxic adenoma. Treatment started with 150–300 mg/d PTU by mouth 3 times a day. Dose titration was made according to serum FT4, FT3 and thyrotropin. The maximum PTU dose was 600 mg/d by mouth. Failure to achieve FT4 and FT3 levels within the normal laboratory limits of our hospital was accepted as treatment failure.

Measurement of CIMT

CIMT was measured at the right and left external carotid arteries using a Hitachi EUB-6500 ultrasound device (Hitachi Medical Corporation, Tokyo, Japan) using a 7S high-sensitive 7.5- to 13.5-MHz multifrequency linear array probe transducer in the supine position with the patient's head 20° deviated to the opposite side. The same investigator who was blinded to the clinical characteristics of the patients performed the measurements in a dark and quiet room. A 1-cm arterial segment was chosen at 1 cm proximal to the carotid bulbus when there was no atheromatous plaque. In the presence of a plaque, the measurement point was at least 1 cm to it. Measuring on the gray scale, only the posterior wall was evaluated by using lumen/intima and media/adventitia characteristic echogenicities. Several measurements at every 1 mm were performed along the 1-cm arterial segment. Ten subjects had their measurements repeated to assess intraoperator variability, with a coefficient of variation of less than 5%. Mean CIMT for each patient was manually calculated from these measurements. Measurements were repeated on the other side, and the thicker one was recorded as the CIMT for that patient. Delta CIMT values were calculated as the difference between before treatment CIMT values and after treatment CIMT values.

The width, length and thickness of each lobe were measured, and the volumes of the lobes were calculated using an ellipsoid model formula (width × length × thickness × 0.52 for each lobe).

Statistical Analysis

Baseline and descriptive data were presented as mean (SD) for normally distributed data, and median and interquartile range for non-normally distributed data. Between-group analyses were performed using one-way analysis of variance. Before and after treatment values were analyzed using paired *t* test. Multiple stepwise linear regression analysis was used for continuous variables. All *P* values were calculated as 2-tailed. $P < 0.05$ was set as statistically significant. SPSS 15.0 was used for statistical calculations (SPSS, Chicago, IL).

RESULTS

The baseline clinical and laboratory characteristics of the patients are presented in Table 1. Age was similar between patients with Graves' disease and healthy controls ($P > 0.2$). There was a female preponderance in both groups (78% versus 67% in the hyperthyroid group and healthy controls, respectively). Sex did not differ between groups ($\chi^2_{2df} = 1.080, P > 0.5$). One patient left the follow-up because of relocation. Twenty-five of 26 patients with Graves' disease completed the study throughout 18 months. Euthyroidism (serum TSH and free T3/T4 in the hospital reference range) was achieved in 21 patients. Four patients remained hyperthyroid and were evaluated for other therapies, including radioiodine treatment or surgery. The 21 patients who achieved euthyroidism have been followed up for 12 months after PTU was discontinued, and all remained euthyroid during this period. Delta CIMT values of the patients, and before and after treatment measurements, were presented in Table 2 and Figure 1. One-way analysis of variance revealed that CIMT was significantly higher in the patients with Graves' disease than in healthy controls (0.72 mm versus 0.55 mm, respectively, $P < 0.001$). Stepwise analysis revealed that the independent predictors of CIMT in the Graves' group of the best model had 4 variables, and

TABLE 2. Before and after treatment values of 25 Grave's patients

	Before treatment	After treatment	P
Age, mean (SD)	47 (15)		
Male/female	5/21	4/21	
TSH, median (IR) (μIU/mL)	0.005 (0.005–0.9)	0.37 (0.21–1.4)	0.001
FreeT3, median (IR) (ng/dL)	18.8 (4–50)	5.7 (3–13.0)	<0.001
FreeT4, median (IR) (ng/dL)	43 (15–100)	15.5 (5–48)	0.001
CIMT, median (IR) (mm)	0.84 (0.54–1.3)	0.72 (0.50–1.2)	<0.001

SD, standard derivation; IR, interquartile range; CIMT, carotid intima media thickness.

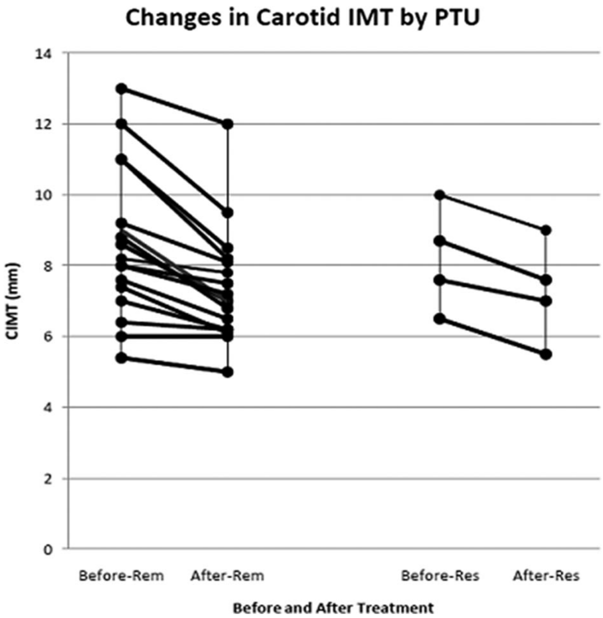

FIGURE 1. Changes in CIMT before and after treatment of PTU. Group A: 21 patients who achieved euthyroidism (remission group). Group B: 4 patients who did not achieve euthyroidism (resistance group).

multiple linear regression analysis showed that 3 of these were independent factors affecting CIMT: age, serum TSH and FT3.

After 18 months of treatment, CIMT decreased significantly (0.12 mm, $P < 0.001$). This change was also clinically significant because small increases in CIMT have important clinical consequences with a relative risk of myocardial infarction (1.15) and stroke (1.32) per 0.10-mm increase in CIMT. Further analysis of the data included stepwise multiple regression analysis of delta CIMT values and predictors. The model had 3 independent predictors with a predicted R^2 of 59.1% (Table 3). The predictors were age, delta free T3 and delta thyroid volume. The regression equation is delta CIMT $= -0.0288 + 0.00197$ Age $+ 0.00243$ dFT3 $+ 0.00791$ dTV.

DISCUSSION

In this study, we showed that patients with Graves' hyperthyroidism had significantly increased CIMT and that treatment with PTU significantly decreased CIMT in Graves' hyperthyroidism. Both the increase of CIMT in Graves' hyperthyroidism and the decrease of CIMT after treatment with PTU were clinically significant. Our results suggest that hyperthyroidism should be taken into account in the evaluation of increased CIMT. In addition, PTU might probably be preferred in patients with high cardiovascular risk.

Völzke et al[5] reported an independent association between thyroid function and CIMT according to data from a large cross-sectional study. They found increased CIMT in the low TSH population, and there was a significant relation between advanced age, male sex, diabetes mellitus, hypertension, medication of hypertension and previous cardiovascular events. We also detected a significant relation with age, free T3 and TSH, and because of our exclusion criteria, we did not find a relation between the diabetes mellitus, hypertension, cardiovascular events, sex and age.

There are clinical and experimental evidences explaining CIMT increase in hyperthyroidism, namely the renin-angiotensin system activation,[6] the related angiotensin stimulation of vascular smooth muscle cell growth and matrix synthesis, increased cardiac output related changes, the adaptive response to increased wall stiffness[7] and the direct vascular effect of thyroid hormones. Another mechanism would be the decreased growth hormone release in thyrotoxicosis[8,9] and related complex hormonal influences as seen in hypopituitarism-related increased CIMT.[8] Studies revealing the physiologic role of deiodinase in the regulation of local T3 production and the presence of deiodinase in vascular smooth muscle further suggest the selective effects of thyroid hormones on the vascular system.[10,11]

We showed that CIMT significantly decreased after treatment with PTU in patients with Graves' disease. In a stepwise regression model, age, delta free T3 and delta thyroid volume were statically significant. Free T3 is the most effective thyroid hormone in peripheral tissue; thus, it could be a cause of the decrease of CIMT in our study. Decreased thyroid volume could be a reason for a decreased thyroid artery flow. Furthermore, vascular hypertrophy is associated with increased vascular stiffness and increased stiffness of the carotid arteries reported in patients with hyperthyroid Graves' disease.[12–15] Increased CIMT might merely reflect an adaptive response of the vessel wall to the changes in shear stress and tensile stress.[14] Increased CIMT was also related to antibodies against thyroid tissues in Graves' disease. Such antibodies may cause inflammation and endothelial dysfunction, which may eventually lead to atherosclerosis and an increase in CIMT.[16] Ciccone et al[17] showed that the increase in CIMT in overweight and obese women affected by Hashimoto's thyroiditis could be related to thyroid antibodies and inflammation-based arteritis such as hyperthyroidism, although this has not been confirmed. Unfortunately, the antibody levels have not been measured previously.

In our study, there was no sex difference between the controls and the study participants, but women were significantly higher than men in the Graves' group (78% versus 22%, respectively). However, we also know that more women than men develop Graves' hyperthyroidism. This was a major limitation of our study.

PTU is widely used in the treatment of hyperthyroidism. It seems to have vascular effects independent of an antithyroid effect. Rahmani et al[15] showed inhibitory effects of PTU on phenylephrine-induced contractions. Several studies about the vascular effects of thyroid hormones revealed new aspects. Chen et al demonstrated that PTU has an inhibitory effect on vascular smooth muscle cell proliferation and migration in cholesterol-fed rabbits. In addition, PTU has been shown to inhibit atherogenesis.[18] They also suggested that PTU had a potent antiatherosclerotic effect, which was clearly independent

TABLE 3. Independent predictors for delta CIMT

Predictors	Coefficient	SE coefficient	P
Age	0.0019696	0.0008013	0.025
Delta free T3 (ng/dL)	0.0024280	0.0009708	0.023
Delta thyroid volume (mL)	0.007912	0.003150	0.022

Delta free T3: before treatment value minus after the treatment values; delta thyroid volume: before treatment value minus after the treatment values.

from its antithyroid effect.[18] In a recent study, PTU reversed the downregulation of contractile proteins and upregulated the phosphatase and tensin homolog protein in the neointima, which has been induced by balloon injury, in rats.[18] Our findings regarding the regression of CIMT by PTU were consistent with these studies. Furthermore, 4 patients who did not achieve euthyroidism had significantly decreased CIMT by PTU treatment.

This is the first study revealing a reversal of increased CIMT by PTU in patients with Graves' disease. Several drugs, such as statins and cilostazol, have been reported to decrease CIMT.[19] Our study showed 3 new findings: First, there was an increase in CIMT in Graves' hyperthyroidism; second, CIMT decreased after PTU treatment; and third, PTU treatment might have an independent effect on decreasing CIMT, and thus, improving the atherosclerotic process in humans. PTU might probably be preferred for patients with high cardiovascular risk.

Limitations

The limited number of patients might have resulted in a limited power of the study. Majority of the patients were women. We could not compare PTU with methimazole.

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