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The Evaluation of Left Ventricular Hypertrophy in Hypertensive Patients with Subclinical Hyperthyroidism

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Abstract. The aim of this prospective cross-sectional study was to investigate the hypertrophic effects of endogenous subclinical hyperthyroidism on myocardium and early development of left ventricular hypertrophy (LVH) in essential hypertensive patients accompanied by endogenous subclinical hyperthyroidism. A total of 31 consecutive patients with stage I hypertension were included in the study. Sixteen of them also had endogenous subclinical hyperthyroidism that they were unaware before. The patients and the controls formed out of ten healthy subjects all underwent an investigation of thyroid functions and cardiologic evaluation. The mean wall thickness of the left ventricle in the stage I hypertensive group with endogenous subclinical hyperthyroidism (group I) was significantly increased as compared with both hypertensive patients without thyroid disease (group II) and the control subjects. The mean left ventricle mass was also significantly higher in group I than group II. Both of the patients' groups had an increased prevalence of LVH as compared with the controls. In this study, hypertensive patients with subclinical hyperthyroidism presented more increase in left ventricular mass, suggesting that subclinical hyperthyroidism may contribute to left ventricular hypertrophy forming a natural progression to hypertension. The hypertensive population should always be screened for endogenous subclinical hyperthyroidism, and should be examined for the criteria of left ventricular hypertrophy by echocardiography in early stages.

Key words: Subclinical hyperthyroidism, Left ventricular hypertrophy, Hypertension

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SUBCLINICAL hyperthyroidism is characterized by persistently suppressed plasma thyroid stimulating hormone (TSH) concentrations and the presence of normal levels of free thyroxine (fT_4) and free triiodothyronine (fT_3) hormones. Subclinical hyperthyroidism can be the result of the same causes of overt clinical hyperthyroidism but patients with subclinical hyperthyroidism do not usually show specific symptoms and signs of hyperthyroidism [1, 2].

It has been demonstrated that exogenous subclinical hyperthyroidism, in which patients treated with TSH-suppressive doses of levothyroxine, may affect the heart as in subjects with overt hyperthyroidism, but it remains controversial whether endogenous subclinical hyperthyroidism affects the heart [3–5].

Situations in which thyroid hormones were increased have been shown to stimulate myocardial hypertrophy. Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality. Hypertension may also cause left ventricular myocardial hypertrophy. The importance of LVH in the prognosis of hypertension is well known because it clearly shows the duration and the severity of high blood pressure [6–8].

Since hypertension and hyperthyroidism both may result in myocardial hypertrophy, we designed a cross-sectional study to investigate the early development of LVH in essential hypertensive patients accompanied by endogenous subclinical hyperthyroidism. It could

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also elucidate whether an early anti-thyroid treatment should be considered.

Subjects and Methods

A large number of outpatients at the Hypertension Unit of our Endocrinology and Metabolism Department were investigated for secondary hypertension. A total of 289 consecutive hypertensive patients with suppressed TSH levels were included in the study. After a physical examination, all patients went through a detailed investigation of body mass index calculation, blood pressure measurements both while standing and at supine position and also biochemical measurements of fasting blood glucose, urea, creatinine, potassium, calcium, lipid profile, TSH, fT_4, fT_3, whole blood count and urine analysis. Standard 12-lead electrocardiograms (ECG) were recorded and chest X-rays were taken from all patients.

Subjects with overt thyroid disease or probable secondary hypertension or symptoms and/or history of any kind of systemic disease were discharged from the study. Patients having positive ECG criteria for LVH were also kept out.

Subclinical hyperthyroidism diagnosis was based on the finding of low serum TSH levels (<0.27 μIU/ml, normal range: 0.27–4.20 μIU/ml) with normal fT_4 (normal range: 12–22 pmol/L) and fT_3 (normal range: 3.65–6.8 pmol/L) values. TSH was assessed by a solid phase, two-site chemiluminescent immunometric method using Immulite 2000 Third Generation TSH kit in Immulite Analyzer by DPC Diagnostic Products Corp., Los Angeles, CA. Free T_4 and fT_3 were assessed by Immulite 2000 free T_4 and free T_3 solid-phase, chemiluminescent, competitive analog immunoassays in Immulite Analyzer by DPC Diagnostic Products Corp., Los Angeles, CA.

Early stage or stage I hypertension was accepted as systolic blood pressure value between 140–159 mmHg and diastolic blood pressure value between 90–99 mmHg, with also a hypertensive past not longer than five years, according to JNC-7 report [9].

After all these screening procedures, two study groups with mild to moderate hypertension (stage I) were formed: 17 subjects also with subclinical hyperthyroidism (group I) and 15 subjects without any thyroid disease (group II). Eleven of 17 subjects in group I were affected by multinodular goiter and the other 6 were affected by solitary thyroid nodule. Stable endogenous subclinical hyperthyroidism diagnosis was confirmed in all 17 patients of group I by screening for anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies once and by measuring TSH, fT_4 and fT_3 twice more within the following two months. Three dimensional ultrasound examination of thyroid tissue was performed for all subjects. None of the subjects in both groups, except one female in group I, had clinical and/or biochemical evidence of overt thyroid or nonthyroidal systemic disease, nor a family history of thyroid disease. One female patient with multinodular goiter had thyroid antibodies in group I, was excluded from the study.

A third group formed by ten control subjects, sex- and age-matched as far as possible with the patients in other groups, were selected from a number of outpatients complaining nonspecifically at the internal medicine unit. The controls also underwent the same biochemical and radiological investigations and ECG analysis, all of which were normal.

All patients gave their informed consent according to the Declaration of Helsinki.

Cardiological evaluation

Standard 12-lead ECGs were recorded in all subjects as mentioned above. Evidence of LVH was assessed by transthoracic echocardiography. Complete M-mode and two-dimensional echocardiographical inspection was performed for each of 42 subjects forming the three study groups. The observer was unaware of the clinical data and the following parameters were obtained by the observer using an ultrasound system (Acuson 128 XP, High Technology Inc., Walpole, MA) equipped with a 3.5-mHz transducer: Left ventricle end-diastolic diameter (LVEDD), left ventricle end-systolic diameter (LVESD), left ventricle posterior wall thickness (LVPWT) and interventricular septum thickness (IVST) at diastole. Left ventricular mass was calculated according to the Devereux formula [10].

Statistical analysis

Data obtained both by physical examination and by measurements are reported as the mean ± SD. Mann Whitney U test and Fisher's exact test was used for statistical analysis. Data were analyzed by using the computer program SPSS for Windows V.10.

Results

All subjects in patients' groups and the controls were well matched for age, sex and body mass index (BMI, Table 1). Systolic and diastolic blood pressures of both patients' groups were also well matched; mean blood pressure values of controls were normal. Electrocardiograms did not show any specific abnormalities in either the controls or patients. All subjects were in sinus rhythm and ECG criteria of LVH were not detected in any of the subjects. Chest radiographies were not pathological. Analysis of urine specimens was normal. The measurements of biochemical parameters were within normal range. Free T_4 and fT_3 measurements were between normal ranges in all three groups. The mean value of TSH was significantly lower in group I than group II and control group (Table 2).

In the measurements obtained by M-mode echocardiography, as seen in Table 3, mean LVPWT and IVST were found higher in group I than group II and the controls. In group I, 4 (25%) out of 16 patients IVST were measured over 11 mm. Left ventricular end-systolic diameter measurements of these 4 patients were closer to the lower limits (mean LVESD: 27.9 ± 3.0 mm).

Mean values of LVPWT and IVST of the patients in group II were 8.3 ± 1.1 mm and 8.7 ± 1.0 mm, respectively. Only one patient in this group (6.6%) had an IVST over 11 mm.

Echocardiographical measurements were between normal ranges in the control group. Mean left ventricular mass was 149.7 ± 34.9 g in this group.

Mean wall thickness of the left ventricle in the stage I hypertensive group with endogenous subclinical hyperthyroidism (group I) was significantly increased as compared with both group II and the control subjects ($p<0.05$). Mean left ventricle mass was also significantly higher in group I than group II ($p<0.01$).

Discussion

It is well known that LVH is an independent risk factor for cardiovascular morbidity and mortality. Hypertension and overt hyperthyroidism may cause to LVH in the course of their natural progression [11–14]. The cardiac effects of exogenous subclinical hyperthyroidism have been widely studied. In this cross-sectional study, we aimed to investigate the hypertrophic effects of endogenous subclinical hyperthyroidism on myocardium.

Stage I (mild to moderate) primary hypertensive patients with endogenous subclinical hyperthyroidism who were unaware of their condition before this, were compared with same stage hypertensive patients and healthy controls both without any thyroid disease in our study.

Table 1. Demographic characteristics of subjects

	Group I (n:16)	Group II (n:15)	Controls (n:10)	p
Age (years)	54.9 ± 11.4	52.4 ± 9.2	54.2 ± 10.1	NS*
Gender (M/F)	4/12	5/10	3/7	NS
BMI (kg/m^2)	27.4 ± 2.2	28.2 ± 1.5	27.2 ± 1.9	NS

* NS: Not significant

Table 2. Mean values of blood pressure and thyroid hormones in the patient groups

	Group I (n = 16)	Group II (n = 15)	p
Systolic BP (mmHg)	153 ± 6	152 ± 6	NS*
Diastolic BP (mmHg)	93 ± 5	91 ± 5	NS
TSH (μIU/ml)	0.15 ± 0.1	2.34 ± 0.6	<0.001
fT4 (pmol/L)	18.12 ± 1.9	16.54 ± 2.4	NS

* NS: Not significant

Table 3. Echocardiography findings of the study groups

	Group I (n:16)	Group II (n:15)	Controls (n:10)	P
LV posterior wall (mm)	9.3 ± 1.1	8.3 ± 1.1	7.5 ± 0.6	<0.05[1] <0.001[2] <0.01[3]
Interventricular septum (mm)	9.5 ± 1.3	8.7 ± 1.0	8.0 ± 0.7	<0.05[1] <0.01[2] NS*[,3]
LV end-systolic diameter (mm)	27.9 ± 3.0	33.1 ± 3.2	36.4 ± 3.4	<0.001[1] <0.001[2] <0.05[3]
LV end-diastolic diameter (mm)	52.4 ± 4.6	49.3 ± 4.1	47.4 ± 3.9	<0.05[1] <0.01[2] NS*[,3]
Left ventricular mass (g)	227.1 ± 56.7	183.7 ± 51.2	149.7 ± 34.9	<0.01[1] <0.01[2] NS*[,3]

* NS: Not significant
[1] Group I vs Group II
[2] Group I vs Control
[3] Group II vs Control

It has been shown that patients with commonly encountered cardiac disorders, should be screened for potentially contributing subclinical thyroid diseases, since thyroid hormones may exert cardiovascular actions by direct effects on the myocardium by interacting with the sympathetic nervous system and through alterations of the peripheral circulation, even though patients are not complaining of full-blown thyroid disease [6, 15, 16]. Persistent subclinical hyperthyroidism by TSH-suppressive doses of levothyroxine has been shown to affect heart morphology and function in different groups of patients. Biondi *et al.* showed that subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased left ventricular mass with marginal concentric remodeling, impaired ventricular relaxation, reduced exercise performance and increased risk for cardiovascular death [17]. Another study by Donatelli *et al.*, on women with overt and subclinical hyperthyroidism, indicated a global impairment of diastolic heart performance, complicated in overt hyperthyroidism by left ventricular concentric hypertrophy [18]. Subclinical hyperthyroidism may affect elderly patients' hearts more adversely, especially in patients older than 60 years [19, 20].

Mancia *et al.* reported that many studies have shown that in the population, only a minority of treated hypertensive patients achieves blood pressure control. He showed that left ventricular mass index, left ventricular wall thickness, and prevalence of left ventricular hypertrophy were markedly increased not only in untreated hypertensive patients but also in treated hypertensives with inadequate blood pressure control, compared with values in the normotensive groups. Echocardiographic abnormalities were less in treated hypertensives with blood pressure control than in patients with inadequate blood pressure control, but values were still clearly greater than in normotensive subjects in the Mancia study [21]. Early interventions to prevent LVH in early stages of primary hypertension, and also to treat the other contributing diseases, seem to be more logical strategy.

In the study of Faber *et al.*, treatment of endogenous subclinical hyperthyroidism resulted in significant changes in several haemodynamic parameters regarding the heart and vascular system. They indicate that endogenous subclinical hyperthyroidism might be regarded as a mild form of hyperthyroidism and should be treated more aggressively [22]. In a review by Kek *et al.*, subclinical hyperthyroidism is defined as mild form of tissue thyrotoxicosis because of the occurrence of cardiovascular abnormalities [1]. Actually, Sgarbi *et al.* showed that after six months treatment with methimazole in endogenous subclinical hyperthyroidism, significant reduction in the heart size was observed [23].

In our study held in a normal iodine state region, hypertensive patients with subclinical hyperthyroidism presented more increase in left ventricular mass, reflected by increased interventricular septum and left ventricular posterior wall thickness. This seems to be able to contribute to the formation of left ventricular hypertrophy in natural progression of hypertension. As a result, hypertensive population should always be screened for endogenous subclinical hyperthyroidism, and should be examined for the criteria of left ventricular hypertrophy by echocardiography in early stages. As our work is a cross-sectional observational study, follow-up studies with treatment strategies in larger groups can also elucidate on whether an early antithyroid treatment could influence LVH or not.

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