0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 85, No. 12
Printed in U.S.A.

Endogenous Subclinical Hyperthyroidism Affects Quality of Life and Cardiac Morphology and Function in Young and Middle-Aged Patients*

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ABSTRACT

To determine the clinical impact of endogenous subclinical hyperthyroidism, specific symptoms and signs of thyroid hormone excess and quality of life were assessed in 23 patients (3 males and 20 females; mean age, 43 ± 9 yr) and 23 age-, sex-, and lifestyle-matched normal subjects by using the Symptoms Rating Scale and the Short Form 36 Health Survey questionnaires. Because the heart is one of the main target organs of the thyroid hormone, cardiac morphology and function were also investigated by means of standard 12-lead electrocardiogram (ECG), 24-h Holter ECG, and complete Doppler echocardiography. Stable endogenous subclinical hyperthyroidism had been diagnosed in all patients at least 6 months before the study (TSH, 0.15 ± 0.1 mU/L; free T_3, 6.9 ± 1.1, pmol/L; free T_4, 17.2 ± 2.3, pmol/L). Fifteen patients were affected by multinodular goiter, and eight patients by autonomously functioning thyroid nodule. The mean Symptoms Rating Scale score (9.8 ± 5.5 *vs.* 4.3 ± 2.2, $P < 0.001$) and both the mental (36.1 ± 9.5 *vs.* 50.0 ± 8.5, $P < 0.001$) and physical (42.6 ± 8.0 *vs.* 55.6 ± 4.1, $P < 0.001$) component scores of Short Form 36 Health Survey documented a significant prevalence of specific symptoms and signs of thyroid hormone excess and notable impairment of quality of life in patients. Holter ECG showed a higher prevalence of atrial premature beats in endogenous subclinical hyperthyroid patients than in the controls, but the difference was not statistically significant, although the average heart rate was significantly increased in the patients ($P < 0.001$). An increase of left ventricular mass (162 ± 24 *vs.* 132 ± 22 g, $P < 0.001$) due to the increase of septal ($P = 0.025$) and posterior wall ($P = 0.004$) thickness was observed in patients. Systolic function was enhanced in patients as shown by the significant increase of both fractional shortening ($P = 0.005$) and mean velocity of heart rate-adjusted circumferential fiber shortening ($P = 0.036$). The Doppler parameters of diastolic function were significantly impaired in the patients as documented by the reduced early to late ratio of the transmitral flow velocities ($P < 0.001$) and the prolonged isovolumic relaxation time ($P = 0.006$).

These data indicate that endogenous subclinical hyperthyroidism has a relevant clinical impact and that it affects cardiac morphology and function. Moreover, they suggest that treatment of persistent endogenous subclinical hyperthyroidism should be considered also in young and middle-aged patients to attenuate specific symptoms and signs of thyroid hormone excess, ameliorate the quality of life, and avoid the consequences to the heart of long exposure to a mild excess of thyroid hormone. (*J Clin Endocrinol Metab* **85:** 4701–4705, 2000)

PERSISTENT SUBCLINICAL hyperthyroidism is characterized by the presence of low or undetectable plasma TSH concentrations and normal circulating free thyroid hormones. The clinical impact of subclinical hyperthyroidism has yet to be established. Subclinical hyperthyroid patients show few and often not specific symptoms and signs of hyperthyroidism. Indeed, subclinical hyperthyroidism is relevant in elderly patients, the risk of developing cardiac arrhythmias being increased in this age group (1). However, the treatment of endogenous subclinical hyperthyroidism in young and middle-aged patients is controversial (2–6). Furthermore, it is not known whether subclinical hyperthyroidism affects quality of life.

Subclinical hyperthyroidism is often present in patients treated with TSH-suppressive doses of Levo-thyroxine (L-thyroxine) for thyroid nodular disease or as postoperative treatment for differentiated thyroid carcinoma to prevent local and/or metastatic progression (exogenous subclinical hyperthyroidism). However, it is also seen in patients with autonomously functioning thyroid nodule or multinodular goiter (endogenous subclinical hyperthyroidism). Its prevalence, in several large community and clinical surveys, has been reported to range from 2–16% (2). The difference in reported rates of subclinical hyperthyroidism may be explained by the difference in sensitivity of TSH assays and by the different iodine intakes in the populations studied. In particular, endogenous subclinical hyperthyroidism represents a common disease in areas of iodine insufficiency (7).

The natural history of untreated multinodular goiter is characterized by progressive growth of one or more autonomous nodules and by a prolonged period of subclinical hyperthyroidism before development of overt thyrotoxicosis (7–11). The appearance of thyrotoxicosis may be precipitated by an increase in iodine intake from iodine-containing drugs

Received April 27, 2000. Revision received August 10, 2000. Accepted August 30, 2000.

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* Presented in part at the 72nd Annual Meeting of the American Thyroid Association, Palm Beach, Florida, 1999.

or radiographic contrast agents. Iodine-induced thyrotoxicosis has been reported after the introduction of iodine prophylaxis in populations with endemic goiter (12, 13). Bourdoux *et al.* (14) have reported that after 2 yr of prophylaxis with iodine salt in Zaire, Africa, TSH was undetectable in the serum of 14% of 190 patients.

It has been demonstrated that overt hyperthyroidism affects cardiac performance and morphology (15, 16). In addition, the minimal but significant and persistent increase of thyroid hormone observed in patients with exogenous subclinical hyperthyroidism may affect the heart (17–25). However, it is not known whether there is the same effect in subjects with endogenous subclinical hyperthyroidism.

Therefore, in the present cross-sectional study, we have investigated whether, in young and middle-aged patients, endogenous subclinical hyperthyroidism: 1) induces specific symptoms and signs of thyroid hormone excess; 2) affects quality of life; and 3) produces cardiovascular abnormalities. This information is also important to establish whether this condition needs clinical surveillance or treatment.

Subjects and Methods

Endogenous subclinical hyperthyroid patients, all from areas of mild to moderate iodine deficiency and with normal serum antithyroglobulin and antithyroperoxidase antibody concentrations, were selected from a larger number of outpatients with low TSH and thyroid nodules or nodular goiters. Patients entered the study only if they had shown stable endogenous subclinical hyperthyroidism for at least 6 months before study (as demonstrated by two thyroid hormonal profiles) and if they had a sedentary lifestyle. Patients who were taking regular medications and/or who had clinical or anamnestic evidence of nonthyroidal illnesses were excluded from the study. At the end of the screening procedure, 23 endogenous subclinical hyperthyroid patients were eligible for the study: 15 were affected by multinodular goiter and 8 by autonomously functioning thyroid nodule (Table 1).

Twenty-three control subjects, sex- and age-matched as far as possible with the endogenous subclinical hyperthyroid patients, were selected from a larger number of outpatients undergoing diagnostic protocol for chest pain. None of the subjects had clinical and/or biochemical evidence of thyroid or nonthyroidal disease, nor a family history of thyroid disease (Table 1). All had a sedentary lifestyle. The study was approved by the Ethics Committee of the University of Naples "Federico II."

Assessment of thyroid status. The evaluation of thyroid morphology and function was performed by clinical examination, assessment of serum free thyroid hormone and TSH levels, ^{131}I scintiscan, and ultrasound examination of the thyroid. Antithyroglobulin antibodies (normal range, <100 U/mL) were assayed with an immunoradiometric technique (Ares Serono kit set; Ares Serono, Milan, Italy), and antiperoxidase antibodies (normal range, <10 U/mL) were measured with a RIA kit (kit set; DiaSorin, Inc., Saluggia, Italy). Serum TSH levels were assessed by the sensitive TSH-immunoradiometric assay method (Delfia, Wallac, Inc. Finland), which has a detection limit of 0.03 mU/L (normal range, 0.3–3.8 mU/L; intraassay coefficient of variation, 3.7–5.4%). Serum free T_4 and free T_3 levels were assessed with the Lisophase kit (Technogenetics, Milan, Italy). The intra- and interassay variation and sensitivity was 2.9%, 4.7%, and 0.8 pmol/L for free T_3 and 5.0%, 9.0%, and 1.0 pmol/L for free T_4. Reference ranges in our laboratory are: free T_3, 4.0–9.2 pmol/L; free T_4, 7.7–20.6 pmol/L.

Assessment of symptoms and signs of thyroid hormone excess and quality of life. To evaluate the occurrence of specific symptoms and signs of thyroid hormone excess and to investigate general health, patients and control subjects were assessed by using the Symptom Rating Scale (SRS) (26) and were asked to complete (unaided) the Short Form 36 Health Survey (SF 36) (27). The SRS questionnaire was applied by two physicians, unaware of the study protocol (interphysician agreement: 92 ± 4%), higher scores indicating higher occurrence of specific symptoms and signs of thyroid hormone excess. The SF 36 was chosen on the basis of previous studies that showed its reliability, validity, and internal consistency in estimating quality of life (28). It analyzes both the mental [mental health, role-emotional, social-functioning scales (MCS)] and physical [physical functioning, role-physical, bodily pain scales (PCS)] components of well being, with higher scores indicating better health status.

Assessment of cardiac morphology and function

Electrocardiography. Standard 12-lead electrocardiograms (ECG) were recorded in all subjects. Evidence of left ventricular (LV) hypertrophy and conduction and repolarization abnormalities was assessed. Eighteen of the 23 endogenous subclinical hyperthyroid patients underwent 24-h ECG monitoring to detect rhythm disturbances; the tapes were printed with a full disclosed unit. After coding, the printouts were analyzed blindly by two observers (E.A.P. and C.C.). The subjects were then categorized according to the number and complexity of atrial premature beats as previously reported (18).

Doppler echocardiography. Complete M-mode and two-dimensional Doppler echocardiographic analysis was performed with an ultrasound mechanical system equipped with a 3.5-MHz transducer (Apogee CX, Interspec, Inc., Ambler, PA). M-mode and two-dimensional recordings were acquired with the patients in the lateral recumbent position, according to previously described methods (29). The investigator reading the echoes was blinded as to whether the recordings were of subclinical hyperthyroid or normal subjects. The following parameters were assessed on the M-mode recordings: LV end-diastolic and end-systolic diameters (LVEDD and LVESD, respectively), and LV posterior wall and interventricular septum thickness (PWT and IVST, respectively). LV mass was calculated by using the Penn convention, with the following

TABLE 1. Characteristics of the study population

	Controls (n = 23)	ESH (n = 23)			*P*
		1st examination (9–7 months)	2nd examination (5–2 months)	Enrolled	
Age (yr)	40 ± 10			43 ± 9	0.291
Sex (m/f)	3/20			3/20	
Body surface area (m^2)	1.66 ± 0.15			1.66 ± 0.14	1
Systolic blood pressure (mm Hg)	123 ± 15			128 ± 16	0.280
Diastolic blood pressure (mm Hg)	76 ± 7			79 ± 7	0.153
Free T_4 (pmol/L)	15.5 ± 1.9	17.7 ± 1.5	18.1 ± 2.2	17.2 ± 2.3	0.009
Free T_3 (pmol/L)	6.1 ± 1.0	6.7 ± 1.5	7.1 ± 1.6	6.9 ± 1.1	0.013
TSH (mU/L)	1.55 ± 0.9	0.16 ± 0.11	0.14 ± 0.10	0.15 ± 0.10	<0.001
SRS	4.3 ± 2.2			9.8 ± 5.5	<0.001
SF-36 (MCS)	50.0 ± 8.5			36.1 ± 9.5	<0.001
SF-36 (PCS)	55.6 ± 4.1			42.6 ± 8.0	<0.001

Data are reported as mean ± SD; the *P* values are between controls and hyperthyroid patients at inclusion time. ESH, Endogenous subclinical hyperthyroidism; SF-36 (MCS), short form 36 (Mental Component Score); SF-36 (PCS); short form 36 (Physical Component Score).

regression-corrected cube formula (30): LVM = 1.04[(IVST + LVEDD + PWT)^3 - (LVEDD)^3]-14 g. LV fractional shortening (FS) was obtained by the following formula: FS = (LVEDD - LVESD)/LVEDD. Heart rate-adjusted mean velocity of circumferential fiber shortening was calculated by dividing the fractional shortening by the ejection time.

Doppler tracings were acquired during quiet respiration with the transducer positioned at, or slightly to the left of the cardiac apical impulse, according to a previously reported method (23). The following parameters were measured and calculated on mitral flow velocimetry: maximal early diastolic flow velocity (E), maximal late diastolic flow velocity (A), and the E/A ratio. Isovolumic relaxation time (*i.e.* the time interval from aortic valve closure to the onset of early diastolic flow) was obtained by simultaneous recording of aortic and mitral flow by continuous-wave Doppler at 100 mm/sec speed. Aortic peak flow velocity and mean aortic acceleration were obtained by aortic flow velocimetry. In particular, mean aortic acceleration was obtained by dividing the peak flow velocity by the acceleration time.

Statistical analysis. Data are reported as the mean ± SD. The two-tailed unpaired Student's *t* test and linear regression were used for statistical analysis. The Fisher's exact test was used to compare the prevalence of arrhythmias between groups. *P* less than 0.05 was considered significant.

Results

The clinical characteristics and the biochemical thyroid hormonal patterns of the study population are listed in Table 1. The patients and the control subjects were well matched for body surface area and systolic and diastolic blood pressure. Although in the normal reference ranges mean serum free T_3 and free T_4 estimates were significantly increased in the patients as compared with the control subjects, whereas basal mean serum TSH concentration was significantly lower.

Assessment of symptoms and signs of thyroid hormone excess and quality of life

The mean SRS score, which evaluates specific symptoms and signs of hyperthyroidism, was significantly higher in the group of patients than in the control group ($P < 0.001$; Table 1). This was principally accounted for by the higher prevalence of palpitations, nervousness, tremor, heat intolerance, and sweating. The SF 36 scores for both mental (MCS) and physical (PCS) components were also significantly lower (both $P < 0.001$; Table 1) in the patients than in the control subjects. A significant inverse correlation was found between the SRS scores and the sums of the MCS and PCS scores (r = -0.84, $P = 0.008$). No correlation was found between thyroid function and the sums of the MCS and PCS scores (data not shown).

Assessment of cardiac morphology and function

Electrocardiography. No ECG abnormality was detected in either the controls or patients. All subjects were in sinus rhythm, and none fulfilled the ECG criteria of LV hypertrophy. Holter analysis (Table 2) showed a significant increase in the average heart rate in the patients as compared with that of the normal subjects (82 ± 6 *vs.* 70 ± 6 bts; $P < 0.001$). The prevalence of atrial premature beats was higher in patients than in controls, but the difference was not significant (78% *vs.* 67%; $P = 0.852$). No difference was observed in the prevalence of ventricular arrhythmias.

Doppler echocardiography. As reported in Table 3, the mean interventricular septal thickness and, to a greater extent, the mean LV posterior wall thickness were significantly higher in the patients than in the controls ($P = 0.025$ and $P = 0.004$, respectively). As expected, the mean LV mass was significantly increased in the patient group (162 ± 24 *vs.* 132 ± 22 g; $P < 0.001$). The mean value of end-diastolic diameter did not differ between the two groups ($P = 0.401$), whereas the mean value of end-systolic diameter was significantly decreased in hyperthyroid patients (29 ± 3 *vs.* 31 ± 3 m;, $P = 0.029$).

Doppler-echocardiographic indices of LV systolic function were significantly higher in patients than in controls: fractional shortening was increased by about 14%, mean velocity of heart rate-adjusted circumferential myocardial fiber shortening by about 7%, mean aortic acceleration by about 40%, and peak aortic flow velocity by about 19%. Conversely, the pulsed-wave Doppler-derived mitral inflow pattern clearly showed abnormalities of myocardial relaxation in the patient group, as indicated by the significant reduction of the E/A ratio (1.2 ± 0.5 *vs.* 1.7 ± 0.4; $P < 0.001$), mainly accounted for by an increased A-wave of mitral flow velocity (63 ± 14 *vs.* 47 ± 10 cm/sec; $P < 0.001$). Furthermore, isovolumic relaxation time was significantly prolonged (95 ± 18 *vs.* 83 ± 9 msec; $P = 0.006$) in the patients. No significant correlation was found between left ventricular mass and TSH or thyroid hormone levels. Among indices of diastolic function, only the E/A ratio showed a trend toward a slight but not significant inverse correlation with left ventricular mass (r = 0.368; $P = 0.06$).

TABLE 2. Incidence of arrhythmias in the study population

	Control n = 18 (%)	ESH n = 18 (%)	*P*
Mean 24-h heart rate (beats/min)	70 ± 6	82 ± 6	<0.001
Atrial premature beats	12 (67)	14 (78)	=0.852
<100/24-h	11 (61)	12 (67)	=0.892
>100/24-h	1 (6)	2 (11)	=0.415
Ventricular premature beats	10 (56)	10 (56)	=0.652
<50/24-h	9 (50)	7 (39)	=0.946
>50/24-h	1 (6)	3 (17)	=0.758

Twenty-four-hour heart rate is reported as mean ± SD. ESH, Endogenous subclinical hyperthyroidism.

TABLE 3. Echocardiographic parameters of left ventricular morphology and function

	Control (n = 23)	ESH (n = 23)	*P*
Left ventricular mass (g)	132 ± 22	162 ± 24	<0.001
End-diastolic diameter (mm)	48 ± 4	49 ± 4	0.401
End-systolic diameter (mm)	31 ± 3	29 ± 3	0.029
Interventricular septum (mm)	9.1 ± 1.5	10.0 ± 1.5	0.025
Posterior wall (mm)	8.5 ± 1.3	9.8 ± 1.6	0.004
Fractional shortening (%)	35 ± 4	40 ± 7	0.005
mVCFc (circ/sec)	1.21 ± 0.14	1.32 ± 0.20	0.036
Peak aortic velocity (m/sec)	0.9 ± 0.1	1.1 ± 0.1	<0.001
Aortic acceleration (m/sec^2)	10 ± 1.5	14 ± 3.0	<0.001
E (cm/sec)	80 ± 12	75 ± 15	0.219
A (cm/sec)	47 ± 10	63 ± 14	<0.001
E/A ratio	1.7 ± 0.4	1.2 ± 0.5	<0.001
Isovolumic relaxation time (msec)	83 ± 9	95 ± 18	0.006

Data are reported as mean ± SD; ESH, Endogenous subclinical hyperthyroidism; mVCFc, rate-adjusted mean velocity of circumferential fiber shortening; E, maximal early diastolic flow velocity; A, maximal late diastolic flow velocity.

Discussion

This cross-sectional study demonstrates that young and middle-aged subjects affected by stable endogenous subclinical hyperthyroidism have an increased prevalence of symptoms and signs of thyroid hormone excess and impaired quality of life. Furthermore, cardiac morphology and function is affected in these patients as demonstrated by increased heart rate and LV mass, enhanced LV function, and impaired LV diastolic filling.

The patients with endogenous subclinical hyperthyroidism evaluated in this study, as well as the patients with exogenous subclinical hyperthyroidism, had symptoms and signs of hyperthyroidism evaluated by the SRS score (18, 22, 25, 31). Similarly, a group of elderly patients with TSH levels less than 0.1 mU/L had a higher Wayne score (a clinical index of hyperthyroidism) compared with a group 10 euthyroid subjects (32). Our patients with endogenous subclinical hyperthyroidism also had lower mental and physical scores as assessed by the SF 36, indicating that their quality of life was impaired compared with control subjects. Interestingly, SRS and SF 36 scores were significantly and inversely correlated ($r = -0.84$; $P < 0.01$), thus suggesting that the impairment of quality of life observed in these patients was principally due to the higher prevalence of thyroid hormone excess-related symptoms and signs. Conversely, there was no significant correlation between thyroid function and the sums of the mental and the physical component scores of the SF 36. However, this result is not surprising because each patient probably had a different sensitivity to the mild excess of thyroid hormone.

The cardiac effects of exogenous subclinical hyperthyroidism induced by long-term L-thyroxine suppressive TSH therapy (17–25) have been widely studied. In these patients it has been demonstrated that chronic exposure to a mild excess of thyroid hormones was responsible for an increase in LV mass (18, 21, 22, 25). We previously showed that the increase in LV mass was principally the consequence of the chronic increase in cardiac workload, and was responsible for the attendant diastolic dysfunction and impaired systolic function during exercise (23, 24). These abnormalities were significantly reverted by β-blocking drugs (31). The prognostic significance of the demonstrated increase in LV mass in patients with exogenous and endogenous subclinical hyperthyroidism remains unknown because of the lack of epidemiological studies of the cardiovascular risk in these patients. However, it is well known that LV hypertrophy is an independent risk factor for cardiovascular morbidity and mortality (33). In addition, increased LV mass, not necessarily above the hypertrophic threshold, has been found to be associated with increased risk of sudden death in subjects 45 yr of age or older(34).

Results concerning the increase of heart rate and the incidence of supraventricular arrhythmias in patients with exogenous subclinical hyperthyroidism are not consistent (1, 18–22, 25, 31, 35). Our previous data obtained with Holter ECG in patients affected by exogenous subclinical hyperthyroidism revealed higher 24-h mean heart rates, increased prevalence of premature atrial contractions, and, in predisposed subjects, episodes of reentrant atrioventricular nodal tachycardia (18–20). In endogenous subclinical hyperthyroidism, despite a significant increase in heart rate, we did not find a significant prevalence of atrial premature contractions. In this regard, it must be emphasized that endogenous subclinical hyperthyroidism may be significantly different from exogenous subclinical hyperthyroidism in terms of both rate and duration of rise in thyroid hormones. This might explain why the incidence of supraventricular arrhythmias was higher in patients with exogenous subclinical hyperthyroidism than in those with endogenous hyperthyroidism. However, also in these patients, the mild excess of thyroid hormone was, in all likelihood, sufficient to directly stimulate sino-atrial node function and to account for the increase in heart rate reported in the present study and in the pioneering study of Boutin *et al.* (35).

The regulation of heart rate by thyroid hormone is complex. The effects of an excess of thyroid hormone are related, in part, to an indirect adrenergic effect and, in part, to a direct intrinsic positive chronotropic effect (36, 37). In fact, in rat myocardium, thyroid hormone regulates the shaker-related potassium channel mRNA levels, and recently it has been reported that myocardial hyperpolarization-activated cyclic nucleotide-gated channel (HCN2) mRNA is thyroid hormone dependent (38).

The significant increase in heart rate has implications in young and middle-aged patients affected by subclinical hyperthyroidism. Indeed, enhanced heart rate has been shown to be associated with increased risk of cardiovascular and noncardiovascular mortality also in middle-aged subjects (39, 40).

Taken together, the results of the present study, coupled with those previously reported, suggest that many patients with subclinical hyperthyroidism, be it exogenous or endogenous, are symptomatic and support the claim that the term "subclinical" hyperthyroidism is a misnomer (11, 41). Moreover, the occurrence of cardiovascular abnormalities in subclinical hyperthyroid patients emphasizes that subclinical hyperthyroidism should be considered *de facto* a mild form of tissue thyrotoxicosis.

Treatment of subclinical hyperthyroidism is still controversial, particularly as regards young and middle-aged people (2–6). Treatment is recommended in older patients with even mild symptoms of thyrotoxicosis, and risk factors for cardiovascular or skeletal diseases, or a large goiter. Exogenous or endogenous subclinical hyperthyroidism in older patients represents an important risk factor for atrial fibrillation (1). Because increased morbidity and mortality from thromboembolic events is associated with atrial fibrillation, subclinical hyperthyroidism in older patients may be considered a risk factor for thromboembolism. However, also young and middle-aged patients with untreated endogenous subclinical hyperthyroidism are at risk of untoward events: 1) impairment of quality of life, related to the persistence of symptoms and signs of hyperthyroidism; 2) adverse cardiac effects, related to both the increased LV mass and increased heart rate; 3) cardiovascular risks, related to the onset of overt thyrotoxicosis in hearts previously exposed to prolonged periods of subclinical hyperthyroidism.

In conclusion, these data suggest that early treatment of persistent endogenous subclinical hyperthyroidism should

be considered not only in older but also in young and middle-aged patients to improve their quality of life and avoid the consequences of long-term exposure of the cardiovascular system to small increases in thyroid hormone.

Acknowledgments

We are grateful to Jean Ann Gilder for editing the text.

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