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Subclinical Hyperthyroidism: Physical and Mental State of Patients

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Summary. We investigated whether subclinical hyperthyroidism [subnormal basal thyroid-stimulating hormone (TSH) level, attenuated TSH response to thyrotropin-releasing hormone (TRH) stimulation, peripheral thyroid hormones within normal range] is accompanied by physical and mental changes. Thirty-five subclinically hyperthyroid patients (27 female, 8 male) were compared with 60 overtly hyperthyroid patients (51 female, 9 male) and with 28 euthyroid control patients (18 female, 10 male) with respect to physical symptoms, affective state, short-term memory, ability to concentrate and psychomotor performance. Patients with subclinical hyperthyroidism ranged between the other two groups. The major difference between controls and subclinically hyperthyroid patients was an increase in frequency of nervous symptoms and symptoms due to an increase of metabolic rate and thermal regulation changes. The major differences between subclinically hyperthyroid and overtly hyperthyroid patients were psychomotor impairment and symptoms of increased metabolic rate. Self-ratings of affective state tended to be similar in patients with subclinical and overt hyperthyroidism. The ability to concentrate and short-term memory were not impaired in any group. Symptoms in patients with subclinical hyperthyroidism probably result from central changes which lead to attenuated TSH responses to TRH, or from elevated but still normal thyroxine levels, which possibly enhance the effect of catecholamines.

Key words: Subclinical hyperthyroidism – Psychometry – Mental state – Physical state

Introduction

A large number of studies have reported that the thyrotropin-releasing hormone (TRH)-induced thyroid-stimulating hormone (TSH) response is attenuated in about 25% of depressed patients (Loosen 1987). Blunted responses are probably not specific to depression. They have also been found in 50% of patients undergoing acute alcohol withdrawal (Loosen et al. 1979), during prolonged abstinence (Loosen et al. 1983), and in patients with borderline personality disorders (Garbutt et al. 1983). They obviously do not occur in patients suffering from schizophrenia (Loosen 1987). The mental states with TSH blunting have in common profound affective disturbances. No endocrinological explanation has yet been found.

Attenuated TSH responses to TRH stimulation typically occur in patients with overt hyperthyroidism [basal TSH levels below the normal range, attenuated TSH responses to stimulation with TRH, serum levels of triiodothyronine (T_3) and/or thyroxine (T_4) above the normal range]. In these patients, highly elevated levels of T_3 and/or T_4 lead to a diminished secretion of TSH from the pituitary via negative feedback loops (Reichlin 1978). Patients frequently suffer from a number of physical and affective symtoms, while cognitive and behavioural disorders may occur as well (Hall 1983; Whybrow 1985). The reported prevalence of psychiatric syndromes among hyperthyroid patients ranges from 1% to 20% (Hall 1983).

The diagnosis of thyroid disorders has increasingly become a laboratory diagnosis (Kaumeier 1987). Within this realm, attention has been drawn to patients who exhibit normal levels of peripheral thyroid hormones, while baseline TSH levels are subnormal and TSH responses to TRH stimulation are blunted. This hormonal constellation has been called "subclinical" or "preclinical" hyperthyroidism in English-speaking countries and "latent" hyperthyroidism in German medicine. It resembles the endocrine state which is considered a marker for endogenous depression. Mürtz and Usadel (1986) reported 285 patients with subclinical hyperthyroidism among 44,770 inpatients and 11,500 outpatients (0.51%) of a

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large hospital in Mannheim (Upper Rhine Valley), while Bottermann et al. (1989) found 4.58% of inpatients to be subclinically hyperthyroid in a large Munich hospital. The difference in prevalence rates may be due to higher cut-off levels in the latter study and a higher prevalence rate of goitre in Bavaria (Pfannenstiel 1985), since treatment of goitre with T_4 may produce subclinical hyperthyroidism. Screening of 6,884 workers at a large chemical plant in the Upper Rhine Valley revealed that 228 workers had basal TSH levels above 0.21 mU/l (3.31%). Further investigations showed that more than one-third took thyroid hormones, and some individuals suffered from a severe chronic disorder (Schlote et al., in preparation).

Previous experience suggests that patients with subclinical hyperthyroidism exhibit physical and mental symptoms (Röckel 1987; Röckel et al. 1987). Thus not only thyroid hormones have to be held responsible for the development of symptoms but also a dysfunction of the hypothalamus-pituitary axis. The present study attempts to prove this assumption by systematically investigating physical and mental symptoms in three groups of subjects: patients with overt hyperthyroidism, patients with subclinical hyperthyroidism, and euthyroid controls.

Materials and Methods

All the participants of the study were either inpatients admitted to the "Klinikum Mannheim" between September 1987 and September 1989 or outpatients treated there during the same period. The thyroid hormone status was determined in patients who came to the hospital with symptoms of unknown origin (e.g, gastrointestinal or cardiovascular symptoms, loss of hair, weight loss, tremor, sweating) and/or if they possibly had to undergo surgical treatment. The groups were defined as follows:

Overt hyperthyroidism: Basal TSH level < 0.2 mU/l; TSH response to TRH stimulation (200 µg, i.v.) < 2.5 mU/l; $T_3 > 2.0$ µg/l and/or $T_4 > 130$ µg/l; thyroxine-binding globulin (TBG) 15–30 mg/l.

Subclinical hyperthyroidism: Basal TSH level < 0.2 mU/l; TSH response to TRH < 2.5 mU/l; $T_3 < 2.0$ µg/l and > 0.6 µg/l; $T_4 > 45$ µg/l and < 130 µg/l; TBG 15–30 mg/l.

Euthyroidism: Basal TSH level > 0.2 mU/l and < 3.5 mU/l; TSH resposne to TRH > 2.5 mU/l and < 25 mU/l; $T_3 > 0.6$ µg/l and < 2.0 µg/l; $T_4 > 45$ µg/l and < 130 µg/l; TBG 15–30 mg/l.

TSH was determined using the Enzymun-Test TSH (Boehringer, Mannheim, FRG); T_3 and T_4 determinations were performed using the Enzymun-Test T3 and the Enzymun-Test T4 (Boehringer). For TBG determinations we used the TBG-RIA (Henning, Berlin, FRG). For differential diagnosis of overt hyperthyroidism, microsomal and thyreoglobulin antibody determinations were included (ELISA: Elias Müller, Freiburg, FRG). Microsomal and thyroglobulin autoantibody concentrations above 400 units/ml were considered positive. Antibodies against the TSH receptor (TRAK) were determined semit-quantitatively by the radioligand assay of Henning (Berlin). Value above 10 units/ml were taken to be positive.

Medical records were checked. Patients were excluded from the study if they had a psychiatric history or a disease which could alter either thyroid hormone levels or their mental state or if they took medication known to have similar effects. Patients were also excluded if treatment of the thyroid disorder – which often involves giving β-blocking agents – had already started more than 2 days previously.

Within the study period of 25 months, 88 of 11,732 patients (0.77%) were given a diagnosis of subclinical hyperthyroidism as one of their first five diagnoses. Thirty-five patients with *subclinical hyperthyroidism* (27 female, 8 male; average 56.6 years, range 37–79) were eligible for the study. Their diagnoses at admission were goitre and/or cardiovascular and gastro-intestinal disorders, non-insulin-dependent diabetes and, in a few cases, mild forms of degenerative bone disorders. (The patients who were not included in the study most often suffered from a consumptive or neurological disease, took medication which influences thyroid hormone levels, mood or alertness, and/or were unable to undergo psychological testing – even when visited at the bedside – due to considerable physical and mental impairment. Often they were very old.) Within the same time-span 60 patients with *overt hyperthyroidism* (51 female, 9 male; average age 58.2 years, range 21–84) were found. Their diagnoses at admission were hyperthyroidism and the same types of disorders as in subclinically hyperthyroid patients. Female patients were more numerous among patients with subclinical as well as among those with overt hyperthyroidism. The predominance of female patients among subclinically and overtly hyperthyroid patients seems to be characteristic of this kind of disorder (e.g. Bommer et al. 1990; Kaumeier 1987; Krüskemper and Krüskemper 1970; Perrild et al. 1986). Overt hyperthyroidism was due to Graves' disease in 50% of cases, to autonomous adenoma in 45.8% of cases, to iodine excess and hyperthyreosis factitia in 2.1% each. Non-autoimmune thyroid disorders occurred in 57.1% of cases with subclinical hyperthyroidism. An autoimmune process was present in 4.8% of this group. We found 28 *euthyroid controls* (18 female 10 male; average age 53.5 years, range 22–88) who had been admitted for treatment of disorders similar to those listed for the two other groups, except for 2 patients who came for clarification of symptoms of unknown origin (recurrent fever; erythema). None of the controls had a thyroid disorder. We were unable to match controls for sex, because it proved to be impossible to find enough female patients between 40 and 70 years of age who only suffered from cardiovascular or gastrointestinal disorders, and who were willing to answer a number of questionnaires.

All the patients underwent a standardized battery of medical and psychological tests. We tested for physical and mental changes suspected to occur in subclinical hyperthyroidism and reported to be frequently present in overtly hyperthyroid patients (Artunkal and Togrol 1964; Heinik 1986; Kathol et al. 1986; Krüskemper and Krüskemper 1970; Vinson and Robbins 1960; Wallace et al. 1980; Whybrow et al. 1969; Zeitlhofer et al. 1984). As far as possible, instruments had to correspond to those used by Röckel et al. (1987). They had to be suitable for repeated application (results will be published elsewhere) and must not overburden the elderly. Physical and psychological investigation procedures comprised:

1. A standardized check-up for hyperthyroid symptoms and signs developed by Crooks et al. (1959), translated into German, and modified by Kaumeier (1987).
2. A complaint questionnaire (*Gießener Beschwerdebogen;* Brähler 1978) which asks subjects to evaluate their degree of impairment by various physical symptoms.
3. A depression scale (*Depressivitätsskala DS'*: von Zerssen 1976) for self-evaluation of affective state.
4. Two visual analogue scales for self-evaluation of irritability and touchiness;
5. The German version of the *State-Trait-Anxiety Inventory* by Spielberger (Laux et al. 1981);
6. Number repetition, a subtest of the Hamburg-Wechsler Intelligence Scale designed to test short-term memory (Wechsler 1982);
7. An attention-concentration test (*Aufmerksamkeits-Belastungstest d2;* Brickenkamp 1978) which comprises visual discrimination tasks similar to those of the Tolouse-Pieron Concentration Attention Test of Szeleky (1966; cf. Alvarez et al. 1983).
8. Two psychomotor tests (*Psychomotorische Leistungsserie nach Schoppe;* Hamster 1980): a steadiness test (diameter of the open-

ing: 4.8 mm) was used to evaluate objectively the tremor of the left and right hand. A track tracing task was used to test the precision of arm-hand coordination.

Patients over 60 years of age did not do the attention-concentration test because many of them suffered from considerable presbyopia. They performed an easier form of the steadiness test (diameter of the opening 5.8 mm) and modified versions of the complaint questionnaire, the depression scale, and the state-trait-anxiety inventory. The format of these tests had been altered to meet the needs of the elderly (McDonald unpublished work).

Group comparisons were made by means of the Wilcoxon rank sum test, because the premises for the performance of ANOVA were not fulfilled: there was no interval scale level for some tests; random samplings of controls, overtly and subclinically hyperthyroid patients probably did not derive from a population with the same variance (cf. Kaumeier 1987). Norms (standard score, T-score) were used for statistical calculations to exclude effects of age and sex as far as possible. Since the average age of the groups differed and since some test results showed a low but significant relation to age, the age effect was partialled out. Statistical between-group comparisons of these test results were carried out with residual values. (This method was used because no non-parametric procedure was available). Correlations between hormonal variables and test results were calculated by means of Kendall's tau.

Table 1. Hormone levels in patients with overt and subclinical hyperthyroidism and in euthyroid controls

	Overt hyperthyroidism $n = 53$	Subclinical hyperthyroidism $n = 34$	Euthyroid controls $n = 15$	Overt hyperthyroidism $n = 53$
Basal TSH	0.06	0.07 < ***	1.51 > ***	0.06
Delta TSH	0.12	0.43 < **	6.50 > **	0.12
T_3	3.1 > ***	1.3	1.2 < ***	3.1
T_4	177.4 > ***	86.7 > *	78.9 < ***	177.4
TBG	23.5	21.8	23.2	23.5
T_4/TBG	8.8 > ***	4.1 >	3.7 < ***	8.8

Wilcoxon scores (rank sums)
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Results

For several reasons it was impossible to base statistical treatment of test results on the total number of patients who participated in the study. We usually heard of possibly eligible patients from reports of thyroid hormone levels. Since we had to find out about exclusion criteria first and since patients were often difficult to interview at once (because of other physical examinations, visits to the patient, temporary discharge etc.), the time-lag between collection of serum and the application of tests sometimes exceeded 2 days and hormonal data were discarded. It was very difficult to have a specialist do another check-up following Crooks' criteria within the short timespan between tests and the beginning of treatment which influences Crooks' index and/or discharge from the hospital. Psychomotor tests or the attention-concentration test were not carried out if patients were strictly confined to bed or suffered from severe eye trouble (presbyopia, exophthalmos); sometimes paper-and-pencil tests were not filled out correctly (ambiguous checks of alternative answers, lack of answers).

Average Hormone Concentrations (Table 1)

Basal TSH levels and the TSH response to TRH did not differ between patients with subclinical and overt hyperthyroidism but were significantly lower than in euthyroid

Table 2. Total modified Crooks' index, total score of weighted signs and weighted symptoms of hyperthyroidism, and prevalence of selected symptoms and signs in patients with overt and subclinical hyperthyroidism, and in euthyroid controls

	Overt hyperthyroidism $n = 28$	Subclinical hyperthyroidism $n = 12$	Euthyroid controls $n = 13$	Overt hyperthyroidism $n = 28$
Total Crooks' index	12.1 > *	6.0 > **	−4.6 < ***	12.1
Weighted symptom score	7.0	4.6 > *	−3.3 < ***	7.0
Weighted score of signs	4.6 > *	1.4 >	−1.3 < ***	4.6
Symptoms:				
Palpitations	66	50 > **	0 < ***	66
Weight decrease	66 >	42 >	15 < **	66
Dyspnoea on effort	62 > *	25	15 < *	62
Preference for cold	59	42 > *	8 < **	59
Excessive sweating	55	58 > *	15 < **	55
Appetite increase	10 < *	33 >	8	10
Signs:				
Palpable thyroid	86	75 > *	27 < ***	86
Fine finger tremor	76 >	50 > *	15 < ***	76
Hyperkinetic movement	38	17	0 < **	38
Systolic blood pressure	135	130 >	120 < *	135
Diastolic blood pressure	76	80	74	76
Pulse rate	89	79	74	89

Wilcoxon scores (rank sums):
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3. Psychomotor test results of patients with overt and subclinical hyperthyroidism and of euthyroid controls: number of errors, duration of errors in seconds × 10

	Overt hyper-thyroidism	Subclinical hyper-thyroidism	Euthyroid controls	Overt hyper-thyroidism
Steadiness (< 61 years)	$n = 22$	$n = 21$	$n = 15$	$n = 22$
Number of errors, rh	45 > *	35	10 < **	45
Duration of errors, rh	40 > *	18	12	40
Number of errors, lh	55 > *	26 >	12 < ***	55
Duration of errors, lh	38 > *	16 > **	6 < ***	38
Track tracing	$n = 36$	$n = 25$	$n = 19$	$n = 36$
Number of errors, rh	36	29	25 < *	36
Duration of errors, rh	48	32	28	48
Number of errors, lh	37	36	30	37
Duration of errors, lh	50	45	35 < *	50

Wilcoxon scores (rank sums):
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$
rh, right hand; lh, left hand

controls ($P < 0.01$). Patients with subclinical hyperthyroidism had significantly higher T_4 levels ($P < 0.05$) than euthyroid controls – though still within the normal range. A similar trend was found for the T_4/TBG ratio. T_3 levels did not differ between subclinically hyperthyroid and euthyroid patients, but they were significantly higher in overtly hyperthyroid patients than in the other two groups ($P < 0.001$).

Signs and Symptoms of Hyperthyroidism (Crooks' index; Table 2)

Patients with subclinical hyperthyroidism differed from euthyroid controls with respect to palpitations ($P < 0.01$), weight loss (trend), preference for cold, excessive sweating (both $P < 0.05$) and increase in appetite (trend). More often a palpable thyroid, fine finger tremor (both $P < 0.05$) and a higher systolic blood pressure (trend) were found in patients with subclinical hyperthyroidism than in controls. Differences between patients with subclinical and overt hyperthyroidism became a trend or were statistically significant with respect to dyspnoea on effort, weight loss, increase in appetite (less in overtly hyperthyroid patients) and fine finger tremor. In patients with subclinical as well as with overt hyperthyroidism several signs and symptoms were confirmed in more than 50% of patients: palpitations, excessive sweating, palpable thyroid and fine finger tremor. There was no elevated frequency of signs or symtpoms of hyperthyroidism in euthyroid patients.

The sum of weighted signs and symptoms of hyperthyroidism gradually increased from euthyroid controls to subclinically hyperthyroid and, finally, overtly hyperthyroid patients. Group differences between patients with subclinical hyperthyroidism and euthyroid controls were significant at the 1% level for the total Crooks' index (Table 2). Individuals with subclinical hyperthyroidism exhibited a significantly lower score for weighted signs than patients with overt hyperthyroidism ($P < 0.05$) and tended to have a higher score than euthyroid controls. The difference in the weighted symptom score only reached significance between patients with subclinical hyperthyroidism and controls ($P < 0.05$).

The complaint questionnaire *(Gießener Beschwerdebogen)* revealed that patients with subclinical hyperthyroidism tended to feel more annoyed by symptoms of exhaustion (67th percentile) and by heart symptoms (73rd percentile) than control patients (52nd and 63rd percentiles). The results of the subclinically hyperthyroid group were similar to those of patients with overt hyperthyroidism (exhaustion: 68th percentile; heart complaints: 75th percentile). Patients with subclinical hyperthyroidism suffered significantly more ($P < 0.05$) than euthyroid patients from heat sensitivity (1.3 versus 0.6 on a five-point scale ranging from 0 = "not at all" to 4 = "very much"), tremor (1.0 versus 0.3), sweating (1.6 versus 0.7) and from having to cry (1.5 versus 0.8). Patients with overt hyperthyroidism differed from subclinically hyperthyroid patients only by suffering more from weight loss ($P < 0.05$).

Psychomotor Performance (Table 3)

Steadiness test results have only been calculated for patients below 61 years of age. Since no norms are available for the standard opening (4.8 mm) of the test, results have to be tentatively compared with data gathered from 200 inpatients on internal medicine and dermatology wards who did not exhibit neurological symptoms. They were tested with the next opening size, 5.8 mm (Sturm and Büssing 1985): i.e. an easier task. In patients with overt hyperthyroidism, subclinical hyperthyroidism and in euthyroid controls performances corresponded to the following percentiles: number of errors with the right hand 4.5, 6.7 and 46 (raw scores: 45, 35, 10 errors); duration of errors with the right hand 3.5, 5.5 and 15.9 (raw scores: 40, 18, 12); number of errors with the left hand 2.3, 13.6 and 34.4 (raw scores: 55, 26, 12 errors); duration of errors with the left hand 0.6, 9.7 and 30.9 (raw scores: 38, 16, 6). The number and duration of errors tended to be higher in patients with subclinical hyperthyroidism than in controls if the test was performed

Table 4. Psychometric results of patients with overt and subclinical hyperthyroidism and of euthyroid controls

	Overt hyper-thyroidism $n = 52$	Subclinical hyper-thyroidism $n = 31$	Euthyroid controls $n = 27$	Overt hyper-thyroidism $n = 52$
Self-ratings of affective state:				
Depression (TS)	58.5	60.4 >	57.0 <	58.5
Touchiness (RS)	6.7	7.5 > *	4.3 < *	6.7
Irritability (RS)	8.4	8.2 > *	5.9 < *	8.4
State anxiety (RS)	44.5	44.4	41.5	44.5
Trait anxiety (TS)	48.5	56.7 > *	50.1	48.5
Concentration test:				
Percent of errors	13.6	10.4	11.7	13.6
Ability to concetrate (ZS)	96.1	98.7	99.0	96.1
Number repetition:				
Forward (RS)	6.3	6.0	6.2	6.3
Backward (RS)	3.9	4.1	4.3	3.9

Wilcoxon scores (rank sums):
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$
TS, T score; RS, raw score; ZS, Z score

with the left hand ($P < 0.10$, $P < 0.05$ respectively). The overtly hyperthyroid group exhibited a significantly higher ($P < 0.05$) number and duration of errors for both hands than the two other groups.

The track tracing task did not reveal significant increases in arm-hand coordination errors either between controls and patients with subclinical hyperthyroidism or between patients with subclinical and overt hyperthyroidism, though there was a slight increase in errors made by controls as compared with overtly hyperthyroid patients. Achievements of patients with overt hyperthyroidism, subclinical hyperthyroidism and euthyroid controls corresponded to the following percentiles when compared with internal medicine and dermatology inpatients, who were tested with the same task (Sturm and Büssing 1985): 38.2, 54 and 65.5 (raw scores: 36, 29, 25) for number of errors with the right hand; 5.5, 21.2 and 30.9 (raw scores: 48, 32, 28) for the duration of errors with the right hand; 65.5, 65.5, and 84.1 (raw scores: 37, 36, 30) for number of errors with the left hand, 9.7, 15.9 and 34.5 (raw scores: 50, 45, 35) for durtion of errors with the left hand.

Self-ratings of Emotional Well-being (Table 4)

Subclinically and overtly hyperthyroid patients achieved similar scores on the depression scale (T-scores: 60.4 and 58.5) and tended to describe themselves as more depressed than euthyroid controls (T-score: 52.0) State-anxiety scores did not differ between groups: 44.5 in patients with overt hyperthyroidism, 44.4 in patients with subclinical hyperthyroidism and 41.5 in euthyroid controls. Scores of all three groups ranged within one standard deviation of average scores obtained in a representative sample of 696 women aged 55–75 years (mean: 37.66, SD 10.14: cf. McDonald and Suchy in Laux et al. 1981). Self-ratings of touchiness on the visual analogue scale were 6.7 for overtly hyperthyroid patients, 7.5 for subclinically hyperthyroid patients and 4.3 for euthyroid controls. Ratings of irritability were 8.4, 8.2 and 5.9, respectively. Patients with overt hyperthyroidism, subclinical hyperthyroidism and euthyroid controls had trait-anxiety scores (T-scores) of 48.5, 56.7 and 50.1. Self-ratings of trait-anxiety, touchiness and irritability were significantly higher in patients with subclinical hyperthyroidism than among euthyroid controls ($P < 0.05$) and did not differ significantly between overtly hyperthyroid patients and subclinically hyperthyroid patients.

Concentration

The results of the attention-concentration test were normal in all three groups. Patients with overt hyperthyroidism, subclinical hyperthyroidism and euthyroid controls achieved normal Z scores with respect to the number of signs checked within the given time-span (99.4, 99.6 and 101.5) and their ability to concentrate (96.1, 98.7 and 99.0). The percentage of errors was 13.6, 10.4 and 11.7, respectively. None of the differences between groups reached significance.

Number Repetition

Group averages for number repetition were 6.3 for patients with overt hyperthyroidism, 6.0 for patients with subclinical hyperthyroidism and 6.2 for euthyroid controls. Group averages for number repetition in revers order were 3.9, 4.1 and 4.3, respectively. Differences between groups were not significant. Tables by Wechsler (1982) indicate that the totals of numbers repeated forward and backward (10.2., 10.1 and 10.5) are within the normal range.

Correlative Relationships Between Hormonal Variables

Basal TSH levels correlated significantly with delta TSH levels (0.70; $P < 0.001$) and with T_4 (-0.31; $P < 0.01$).

The TSH responses to TRH exhibited significant inverse relationships with T_3 (-0.42; $P < 0.001$), T_4 (-0.37; $P < 0.001$) and T_4/TBG (-0.33; $P < 0.01$).

Correlative Relationships Between Hormonal Data and Questionnaire Results

Basal TSH levels correlated negatively with the weighted score of signs of hyperthyroidism (-0.38; $P < 0.01$) and with the total modified Crooks' index (-0.33; $P < 0.01$). Delta TSH levels were inversely related to the weighted score of signs of hyperthyroidism (-0.39; $P < 0.05$), the weighted score of symptoms of hyperthyroidism (-0.33; $P < 0.05$), the total Crooks' index (-0.37; $P < 0.05$) the average duration of errors (right hand) on the track tracing task (-0.32; $P < 0.01$), the average duration of errors (left hand) on the steadiness task (-0.41; $P < 0.05$) and the number of errors (left hand) on the steadiness task (-0.39; $P < 0.05$), the percentage of errors in the concentration test (-0.44; $P < 0.01$), and the fluctuation of ability to concentrate (-0.38; $P < 0.05$). T_4 levels exhibited significant positive relationships with the weighted score of signs of hyperthyroidism (0.39; $P < 0.001$), the total Crooks' index (0.46; $P < 0.001$), the number of errors in the steadiness test (patients 61 years: right hand 0.32; $P < 0.01$ / left hand 0.33; $P < 0.01$) and the duration of errors in the steadiness test (patients < 61 years: 0.34; $P < 0.001$). T_3 levels correlated significantly with the number of signs (0.39; $P < 0.001$) and symptoms (0.34; $P < 0.001$) of hyperthyroidism and the total Crooks' index (0.40; $P < 0.001$) only. We have not reported significant correlation coefficients below $r = |0.3|$, because the explained variance would be below 10%.

Discussion

Patients with subclinical hyperthyroidism can be placed between euthyroid and overtly hyperthyroid patients with respect to their physical and mental state. Our results compare well with those of Röckel et al. (1987), who found that subclinical hyperthyroidism seems to be accompanied mainly by symptoms in areas which are centrally controlled, such as thermal regulation, or autonomously controlled via catecholamines, such as palpitations and tremor. Overtly hyperthyroid patients exhibited a considerable increase in symptoms in both areas. In contrast to the much younger patients studied by Röckel et al. (average age of groups between 37.5 and 38.2 years) our older patients with subclinical hyperthyroidism exhibited some changes in metabolic rate. In our older patients with overt hyperthyroidism we observed a shift in symptomatology from an increase in appetite to a decrease in appetite, while the frequency of weight loss increased – a phenomenon which seems to be particularly pronounced after the fifth decade of life (Nordyke et al. 1988). Results of self-rating scales were similar in subclinically hyperthyroid patients studied by Röckel et al. (1987) and in our older subclinically hyperthyroid group: state-anxiety raw score, 45.1; depression T-score, 58.5 (calculated from raw scores); self-ratings of touchiness (Multidimensional Scale of Well-being of Janke and Debus 1978) were elevated. In contrast to our overtly hyperthyroid patients, the young group of patients with overt hyperthyroidism examined by Röckel et al. presented self-ratings of state-anxiety (raw score 53.8) and depression beyond the normal range (T-score: 63.2, calculated from reported raw scores).

Hormonal differences between groups may account for the presence of symptoms in subclinically hyperthyroid patients. To our knowledge, there have been no reports of direct mental or physical effects of a lack of TSH. Hypersecretion of TRH, however, may lead to a decrease of TSH due to a reduction of sensitivity of TSH-secreting cells (Ahuja et al. 1980). TRH is known to have an activating effect on the central nervous system, and it may even produce some hyperthyroid symptoms, as shown in animal studies (Breese et al. 1981; Prange and Utiger 1981). Elevated normal T_4 concentrations may play a crucial role in the development of symptoms. Röckel et al. (1987) assumed that down-regulation of TSH and a higher sensitivity of the organism to thyroid hormones may occur if peripheral thyroid hormone concentrations are elevated but still within the normal range (i.e. they are too high in a given individual). Földes et al. (1986) reported that subclinically hyperthyroid patients who exhibited clinical signs and symptoms had significantly higher, though still normal, T_3 and T_4 levels than subclinically hyperthyroid patients without symptoms. Thyroid hormones have been found to produce alterations in feeling tone. T_4 levels, in particular, showed a strong association with MMPI-(Minnesota Multiphasic Personality Inventory) pathology (Wallace et al. 1980), Sickness Impact Profile scores (Rockey and Griep 1980), poorer performance in tasks requiring concentration and memory (Wallace et al. 1980), the EEG variables β_3, β_1 and the psychological variables depression, paranoia, time estimation and anxiety (Zeitlhofer et al. 1984). Besides some direct effect of peripheral thyroid hormones, sympathomimetic symptoms in patients with subclinical and overt hyperthyroidism may possibly be explained by the fact that thyroid hormone excess enhances the effect of catecholamines (Landsberg and Young 1985; Whybrow and Prange 1981). Trzepacz et al. (1988) demonstrated that treatment of hyperthyroid patients with propranolol for 2 weeks led to an improvement in all depression scales, to a significant decrease on the hyperthyroid symptom scale, and a decrease of heart rate and motor activity, though endocrine parameters did not change. A slight elevation of T_4 levels in subclinical hyperthyroidism possibly affects β-adrenergic receptor densities and thus contributes to the nervous symptoms of this group of patients (Trzepacz et al. 1988).

Even though a number of results of tests and self-rating scales differed significantly between groups, average scores of subclinically as well as of overtly hyperthyroid patients lacked clinical significance. Possible reasons include the high average age of our patients. Almost all the patients were older than 40 years and most were over 50. A decrease in the number and severity of symptoms with age in overtly hyperthyroid patients has been documented by several authors (e.g. Köbberling 1984; Nor-

dyke et al. 1988; Tibaldi et al. 1986). One may speculate as to how far such a decrease as well as the normal test results may be related to the phenomenon that older individuals tend to answer items more often according to social desirability than younger individuals (Lawton et al. 1980; Nowotny et al. 1990; Oswald and Fleischmann 1983; Schlote et al. 1990). Another reason may be the type of scales used. Depression and anxiety scores of individuals with hyperthyroidism largely depend on whether or not the items refer to physical changes which typically accompany hyperthyroidism (Kathol and Delahunt 1986). Scores on these scales were unexpectedly low because we used scales for self-evaluation which more or less did not contain typical physical criteria for the diagnosis of hyperthyroidism.

Since a number of patients with subclinical hyperthyroidism did exhibit physical changes in the direction of overt hyperthroidism and suffered from syptoms, we are currently investigating whether these patients benefit from low-dose thyrostatic treatment.

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