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A DOUBLE-BLIND CROSS-OVER 12-MONTH STUDY OF L-THYROXINE TREATMENT OF WOMEN WITH 'SUBCLINICAL' HYPOTHYROIDISM

E. NYSTRÖM, K. CAIDAHL, G. FAGER, C. WIKKELSÖ, P.-A. LUNDBERG AND G. LINDSTEDT

From the Departments of Medicine II, Clinical Physiology, Medicine 1, Neurology, and Clinical Chemistry, Gothenburg University, Göteborg, Sweden

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SUMMARY

Twenty women, who had been randomly selected from women with subclinical hypothyroidism identified in a population study were treated with L-thyroxine and placebo in a double-blind cross-over design during 2 × 6 months. Three women did not complete the study, one because she moved to another part of the country, and two because of nervousness and sense of tachycardia. None of these 'drop-outs' had any objective signs of overtreatment; they had normal pulse rate and a serum T3 concentration within the reference interval. During L-thyroxine treatment serum procollagen-III-peptide concentration increased in 13 women out of the 17 women completing the study and at the end of treatment the mean concentration was significantly raised ($P < 0{\cdot}001$). Serum concentrations of procollagen-III-peptide then correlated with those of free thyroxine ($P < 0{\cdot}01$), total thyroxine ($P < 0{\cdot}05$), and reverse triiodothyronine ($P < 0{\cdot}05$). The same comparison revealed little or no effect on the concentrations of serum creatine kinase activity, transcortin or sex-hormone binding globulin. Heart rate-corrected preejection period and symptom score decreased ($P < 0{\cdot}05$). Four women starting with L-thyroxine showed a marked and prolonged (4–6 months) rise in thyrotrophin concentration during the subsequent placebo period, but remained clinically euthyroid. Four women (of 17) improved during therapy as judged by psychometric testing and their own rating. We could not by pretreatment observations identify these four women apart from serum free and total 3,5,3′-triiodothyronine concentrations in the lower part of the health-associated reference interval. Subclinical hypothyroidism is common among middle-aged and old women, and our findings indicate that approximately one

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Correspondence: Dr Ernst Nyström, Department of Medicine II, Gothenburg University, Sahlgrens Hospital, S-413 45 Göteborg, Sweden.

woman in four with this 'subclinical' condition will benefit from L-thyroxine treatment.

Autoimmune thyroid disease is common in women, particularly after the menopause, as also indicated by the increased prevalence of antibodies directed against a microsomal antigen presumed to be thyroid peroxidase. Moderately increased basal thyrotrophin (TSH) concentration has been reported to occur in about 5% of women after the age of 50 (Tunbridge *et al.*, 1977; Nyström *et al.*, 1981a). The TSH response to thyroliberin is high but serum thyroxine (T4) and 3,5,3′-triiodothyronine (T3) concentrations are usually within reference limits; there are normally none of the symptoms classically associated with hypothyroidism, with the possible exception of common and non-specific complaints such as tiredness, depression, etc. This condition, most commonly called subclinical or preclinical hypothyroidism (Evered *et al.*, 1973; Croxson & Ibbertson, 1980), may be associated with minor deviations in thyroid hormone end-organ responses of unknown practical consequence as, e.g., prolonged cardiac systolic-time interval or Achilles-tendon reflex time (Croxson & Ibbertson, 1980; Ooi *et al.*, 1980).

The present double-blind cross-over study of L-thyroxine in subclinical hypothyroidism aimed at elucidating whether early treatment of individuals with slightly raised TSH would be beneficial. Since the central nervous system appears to be affected at an early stage by hypothyroidism (organic psychosyndrome, depression) we put emphasis on the use of psychometric and neurophysiological tests, but we also attempted to find circulating indicators of possible use in the evaluation of T4 substitution therapy.

METHODS

Patients

We recruited 20 women, aged 51–73 years, from a population study carried out in 1980–1981 (Lapidus *et al.*, 1984). This population study was the third stage in a longitudinal study of women in five age strata started in 1968–1969 in Gothenburg, a city on the Swedish west coast. The sampling method and high participation rate (90·1% in 1969; 78·9% of those studied in 1969 participated in 1980–1981) ensured that the participants were a representative cross-section from the community of the ages studied. In the population study 88 women out of 1192 had TSH concentration above 4·0 mU per litre; 78 women (6·5%) had TSH 4·0–15 mU/l and these were invited to a thyroliberin stimulation test. From the participants we randomly selected 22 women (of which 20 volunteered to participate) without clinical evidence of thyroid disease, having T4, free T4, and T3 concentrations within the reference interval but exaggerated TSH response (ΔTSH above 30 mU per litre) upon thyroliberin administration. The women had no history of cardiovascular disease nor exhibited any signs of hypothyroidism in the more detailed examination immediately preceding the substitution study. Informed consent was obtained and each woman received a written statement of the study protocol, which had been approved by the Ethical Comittee of Gothenburg University.

Study protocol

The study had double-blind cross-over design with each treatment period lasting at least 6 months. L-Thyroxine (0·10 mg) and placebo tablets were kindly supplied by Nyegaard &

Co. (Oslo, Norway). The code was broken after completion of the study. Observations immediately preceding the period of active treatment and at the end of this period were designated 'pretreatment' and 'posttreatment' observations, respectively. The women underwent a detailed clinical examination before each test period (6 months) and at the end of the study. The women, in a random design, received placebo or 0·05 mg of L-thyroxine daily for the first 2 weeks, 0·10 mg for the next 2 weeks, and 0·15 mg daily for the rest of the study period. They were instructed to interrupt the substitution and contact us in case of unpleasant tachycardia or chest pain.

Blood sampling and biochemical methods

We sampled blood before the first test period, at cross-over, and after the second test period. Blood was drawn between 0800 h and 1000 h after the women had fasted overnight. We also sampled blood at 1100–1300 h (non-fasting subjects) at approximately monthly intervals within each test period. The women were instructed to take their daily dose (thyroxine/placebo) after the blood sampling. In the thyroliberin stimulation test we sampled blood 10 min and 1 min before and 10, 20 and 30 min after an i.v. injection of 200 μg thyroliberin (TRH, Hoffman-La Roche, Switzerland). One aliquot of the serum sample was stored at −20°C until the study was finished when we simultaneously analysed all samples. The concentration of thyroid hormones was also directly determined on another aliquot after each visit during the test periods; this information was available only to the assayist but was revealed for the three subjects who discontinued the study. We determined serum TSH (upper reference limit 4·0 mU/l), T4 (reference interval 90–160 nmol/l), and T3 (reference interval 1·5–3·0 nmol/l) with reagents from Diagnostic Products Corp. (Los Angeles, CA, USA; NHS-TSH RIA 'double antibody', T4 RIA 'double antibody', and T3 RIA 'double antibody', respectively). We assayed serum free T4 (reference interval 10·8–23 pmol/l) and serum free T3 (reference interval 4·3–7·1 pmol/l) by ligand analog assays with reagents from The Radiochemical Centre (Amersham International plc, Amersham, Bucks, UK; 'Amerlex free T4' and 'Amerlex-M free T3', respectively), and serum 3,3′,5′-triiodothyronine (reverse T3; reference interval 0·07–0·47 nmol/l) with reagents from Serono Diagnostic SA (1267 Coinsins, Switzerland). We determined serum creatine kinase activity with reagents from Boehringer (Mannheim, FRG; 'CKNAC Aktiviert'); procollagen-III-peptide with reagents from Behringwerke AG (Marburg, BRD; RIA-gnost Prokollagen-III-Peptid') with a modified calibration procedure (Lindstedt *et al.*, 1984); and anti-microsomal antibodies by haemagglutination (Fujizoki Microsome Test obtained as Seratek Microsomal Antibody Test through Ames Division, Miles Laboratories, Inc., Elkhart, IA, USA). Sex-hormone binding globulin and transcortin were assayed by our own methods (Lapidus *et al.*, 1986).

Clinical and neurophysiological examinations

Before and after each test period we examined and interviewed the women for the presence of hypothyroid symptoms using a questionnaire modified from Billewicz *et al.* (1969) We scored the following symptoms (absent = 0; doubtful = 1; or present = 2): physical tiredness, mental lethargy, dry skin, cold intolerance, dry hair, and constipation. After the end of the second study period the women were asked to identify — if possible —

the period of active treatment and whether they had felt better. Systolic and diastolic blood pressure as well as pulse rate was measured after 5 min rest and after 5 min of standing immediately after the rest period.

The women also had a detailed clinical neurological examination followed by three psychometric tests: (a) *Identical forms test according to Thurstone (1943)* which measures the speed of complex, perceptual functions. The test consisted of 60 items, each containing a row of 6 figures. In each row 2 figures were identical and the patient was asked to find out which two. The test time was limited to 6 minutes. The number of correct items minus 0·25 points for every wrong answer gave the test score. (b) *Bingley's memory test* (Bingley, 1958). The patient was shown a chart with 12 common objects which were to be memorized for 30 seconds. The number of objects immediately recalled was noted and the mean of 2 forms calculated. (c) *Reaction time.* An apparatus with combined light and sound stimuli was used and the patients were asked to press a button at stimulus. The accumulated reaction time for a cycle (15 irregularly distributed stimuli during 90 seconds) was noted and the mean score from three identical cycles calculated.

We calculated the difference in results for each test after the placebo period for the 10 individuals who started the study with placebo treatment and calculated its standard deviations (SD). A significant improvement after L-thyroxine treatment was defined as increased performance of ≥ 2 SD in at least two of the three psychometric tests.

Systolic-time intervals

We registered electrocardiograms and carotid pulse curves on a direct writing ink-jet 7-channel recorder. Details on instrumentation, recording, and analysing techniques have been reported (Wikstrand *et al.*, 1978).

The left ventricular ejection time (LVET) was measured from the carotid upstroke to the incisure. We measured the Q-A2 interval from the earliest QRS activity noted in any of the leads aVL, I, -aVR, II, aVF, III, to the first deviation from the baseline of the hearing-like (including high frequencies) phonocardiographic recording of the second heart sound, corresponding to the aortic valve closure (A2). We used the mean value from measurements on five consecutive beats and subtracted the mean value of LVET from the mean value of Q-A2 to obtain the preejection period (PEP) and calculated the ratio PEP/LVET. We adopted the regression formulas for women given by Weissler *et al.* (1968) to correct for heart rate and calculated the indices (I) of each systolic-time interval (Q-A2 I, PEP I, and LVET I), as well as the ratios between the measured and expected values expressed as percentages (Q-A2%, PEP%. and LVET%).

Examinations during the study periods

At intervals of approximately one month, we made a brief clinical examination of the women including measurement of blood pressure and pulse rate. We sampled blood for the determination of TSH, T4, free T4, T3, creatine kinase, procollagen-III-peptide, sex-hormone binding globulin, transcortin, and antimicrosomal antibodies. The clinical examination was carried out by the same clinician (EN) during the entire study. The thyroid hormone concentrations were analysed monthly (PAL) and checked for presence of unexpectedly high values for T3 which might indicate autonomous thyroid function.

Statistical methods

Fisher's test for pairwise comparison (Bradley, 1968) was used to compare values immediately before and after the active period. We compared the 'improved' patients with the 'non-improved' as regards observations immediately before active treatment and changes during active treatment. The significances of the correlations between thyroid hormones and parameters expressing their peripheral effects were tested applying Pitman's non-parametric test. The 95% confidence limits for the relationship between free T4 and procollagen-III-peptide concentrations were illustrated by a tolerance ellipse for the population (Lentner, 1982).

RESULTS

During the first study period three women (all on L-thyroxine) left the study. One woman moved from Gothenburg and two experienced nervousness and sense of tachycardia (no increase in basal pulse rate could be recorded by us; serum T3 concentrations were 1·5 and 1·8 nmol/l, respectively, i.e. within the reference interval). No woman left the study during the second period; thus 17 women completed the study.

When recruited, i.e. 6–12 months before the start of the study, all women fulfilled the criteria for subclinical hypothyroidism stated in the Introduction. Table 1 gives hormone concentrations of all participants at the initiation of the study. Three women then had serum TSH concentration below 4·0 mU/l but titres of anti-microsomal antibodies were high.

Symptoms and biochemical tests during the test periods

During the monthly examinations we observed no abnormality in the clinical presentation of the women; neither did the women experience any symptoms with the exception of the two women mentioned above.

A pattern of biochemical results typical for the seven individuals starting the study with L-*thyroxine* is shown by Fig. 1, panel A (case 12 in Table 1). A prolonged and pronounced concentration increase in serum TSH with low free and total thyroxine concentrations was seen during the ensuing placebo period in four out of seven women (cases 10, 12, 13, 16 in Table 1). A pattern typical for the women with initial *placebo* period is also shown in Fig. 1, panel b (case 4 in Table 1). Both panels demonstrate the expected depression of serum TSH and rise of serum T4 and free T4 concentrations in the period with active drug. However, in one-half of the individuals with active drug treatment free T4 concentrations tended to decrease after the initial rise (*cf* case 12, Fig. 1, Panel a). Increased concentrations ($> 30\%$) of serum procollagen-III-peptide were noted in 13 of the women during the period with active drug (not in cases 3,8,9, and 14), whereas serum creatine kinase activity tended to be lower with active drug then with placebo. Only single cases displayed depression of serum transcortin concentration during L-thyroxine, whereas a transient increase in sex-hormone binding globulin was observed in six individuals. Mean and SEM values for all analytes during the two study periods and the two protocols are shown in Fig. 1 (panels c and d).

Table 1. Initial hormone concentrations and clinical outcome of 6-month treatment with L-thyroxine of women with 'subclinical' hypothyroidism

		Biochemical data at the initiation of the study							Post-treatment psychometric performance§ and individual rating of the test period				
Case no.	Age* (years)	TSH (mU/l)	T_4 (nmol/l)	Free† T_4 (pmol/l)	T_3 (nmol/l)	Free† T_3 (pmol/l)	Reverse T_3 (nmol/l)	MSA‡	Reaction time	12 Object memory test	Figure identification	Feeling of improvement	Identification of test period¶
Improved													
1	63	6·0	86	13·8	1·40	5·4	0·37	25 600	+	+	+	+	+
2	64	9·9	80	12·8	1·54	4·5	0·30	6 400	+	+	+	+	+
3	59	7·6	90	15·5	1·63	4·4	0·31	6 400	+	+	−	+	+
4	51	4·8	71	11·0	1·69	4·7	0·23	1 600	+	+	−	+	+
Not improved													
5	59	7·6	93	12·7	1·79	4·8	0·27	1 600	+	−	−	+	+
6	59	3·8	100	13·6	1·94	5·2	0·31	1 600	−	−	−	+	+
7	60	5·5	70	15·1	1·60	4·9	0·31	0	−	−	−	+	+
8	52	9·4	68	10·5	1·76	4·9	0·23	400	−	−	−	+	+
9	51	7·2	101	12·0	2·36	6·4	0·33	400	+	−	−	−	0
10	63	5·8	111	14·8	1·78	6·0	0·45	102 400	−	−	−	−	+
11	51	6·1	110	16·0	1·92	6·3	0·44	100	−	−	−	−	0
12	51	13·2	78	11·7	1·77	5·6	0·27	6400	−	−	−	−	+
13	63	16·3	95	14·4	1·76	5·3	0·35	25 600	−	−	−	−	0
14	63	3·0	118	18·4	2·24	6·3	0·33	6400	−	−	+	−	−
15	63	2·9	100	14·0	1·70	5·1	0·34	1600	−	+	−	−	0
16	63	9·1	82	10·1	1·63	4·6	0·34	1600	+	−	−	+	−
17	51	12·4	87	11·7	2·23	5·9	0·26	102 400	−	−	+	−	0

*Age at the start of the study.

†Free T_4 and free T_3 denote free serum thyroxine and triiodothyronine, respectively, as analysed by an analog method.

‡MSA denotes microsomal antibodies, reciprocal titre.

§+, improved; −, not improved.

¶0, no opinion; +, correct; −, wrong.

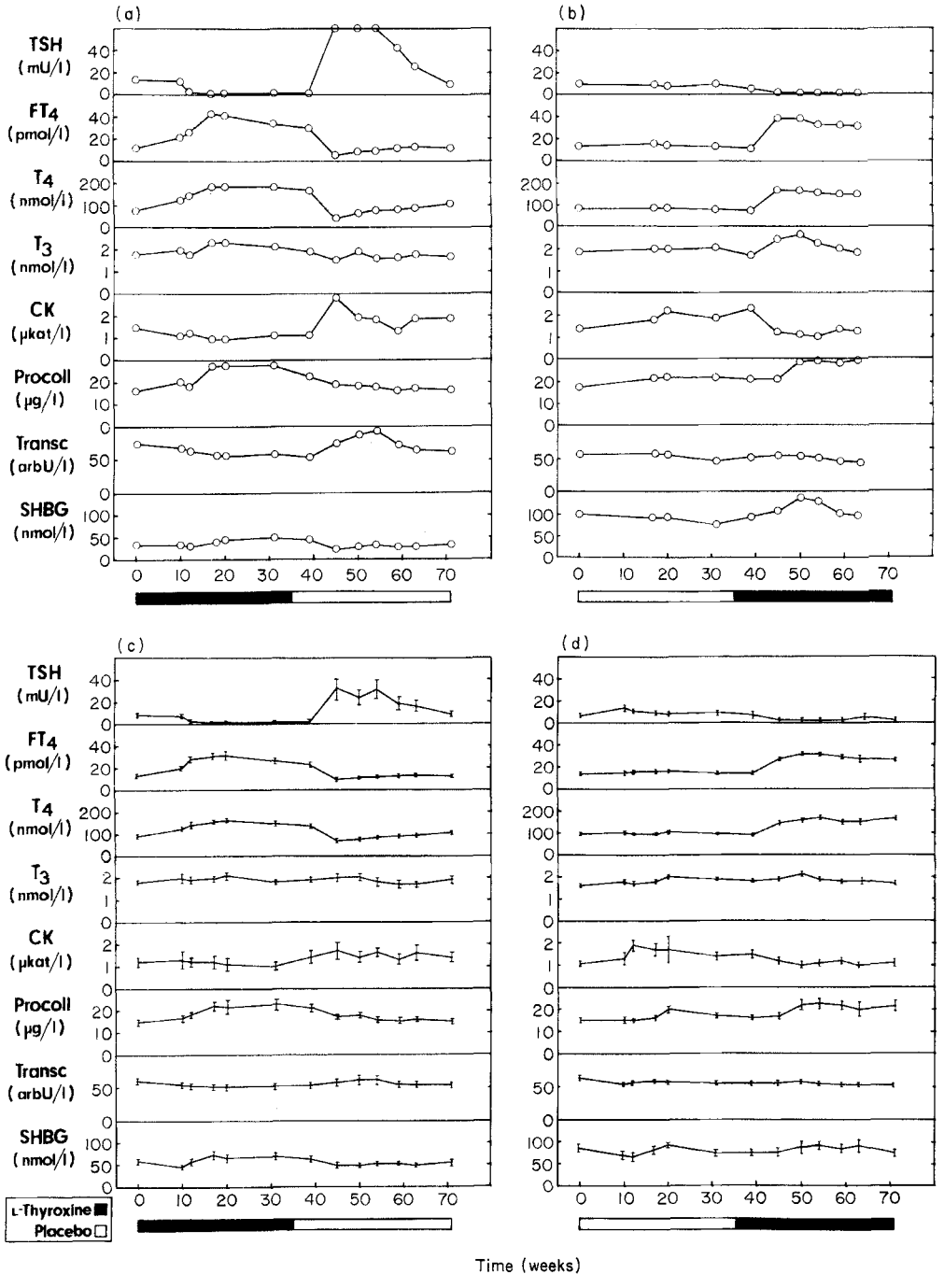

Fig. 1. TSH, thyroid hormone (FT4, T4, T3), creatine kinase (CK), procollagen-III-peptide (Procoll), transcortin (Transc), and sex-hormone binding globulin (SHBG) concentrations in an individual starting the study with L-thyroxine (a; number 12 in Table 1) or with placebo (b; number 4 in Table 1).Observations of serum TSH concentrations exceeding 60 mU/l have in the the graph been represented at a concentration of 60 mU/l. The mean values (±SEM) of the variables are also shown for the subjects starting with L-thyroxine (c) or with placebo (d).

Table 2. Clinical and laboratory data (mean (SD)) in 17 patients immediately before and at the end of 6 month treatment with L-thyroxine

	Before T4	6 month T4
TSH (mU/l)	7·7 (3·7)	1·9 (1·8)***†
T4 (nmol/l)	91 (15)	154 (30)***
Free T4 (pmol/l)†	13·4 (2·2)	24·7 (6·1)***
T3 (nmol/l)	1·8 (0·26)	1·7 (0·29)
Free T3 (pmol/l)†	5·3 (0·66)	5·8 (1·3)
Reverse T3 (nmol/l)	0·32 (0·062)	0·41 (0·10)***
Creatine kinase (μkat/l)	1·4 (0·62)	1·2 (0·67)
Procollagen-III-peptide (μg/l)	16 (3·2)	20·5 (5·2)***
Cholesterol (mmol/l)	6·8 (0·58)	6·6 (0·95)
Pulse rate (supine‡) (beats/min)	69 (11)	68 (11)
Q-A_2 I (ms)§	543 (20)	531 (10)*
Q-A_2%	99 (4·7)	96 (2·5)*
LVET I (ms)	413 (11)	410 (11)
LVET%	98 (3·6)	97 (3·4)
PEP I (ms)	130 (14)	121 (9·2)**
PEP%	98 (14)	89 (9·0)**
PEP/LVET	0·34 (0·05)	0·31 (0·04)**
Symptom score	3·25 (2·4)	1·44 (1·8)**¶

*$P<0·05$, **$P<0·01$, ***$P<0·001$; denote significant differences compared to values obtained immediately before the active period. (Fisher's test for pairwise comparison).

†Free T4 and Free T3 denote serum free thyroxine and triiodothyronine, respectively, as analysed by an analog method.

‡After 5 min rest.

§Q-A2, LVET and PEP are systolic time intervals explained in the text.

¶One outlier excluded.

Pretreatment versus posttreatment psychometric tests

In the psychometric tests two individuals improved significantly in all three tests and two improved in two tests (Table 1). After the end of the second period the women were asked to identify (if possible) the active test period and whether they had felt better. Ten out of 12 women who had believed they could identify the period were correct; eight of them considered themselves improved. Of the other two, one woman considered herself improved, i.e. she reacted to the placebo treatment. We arbitrarily chose to define a treatment as being beneficial when the woman had scored significantly better in two or more psychometric tests, and had correctly identified the test period with a subjective impression of improvement of her physical condition.

Pretreatment versus posttreatment group comparisons: serum analytes and cardiovascular parameters

As expected, we found significant differences in TSH, T4, and free T4, and reverse T3

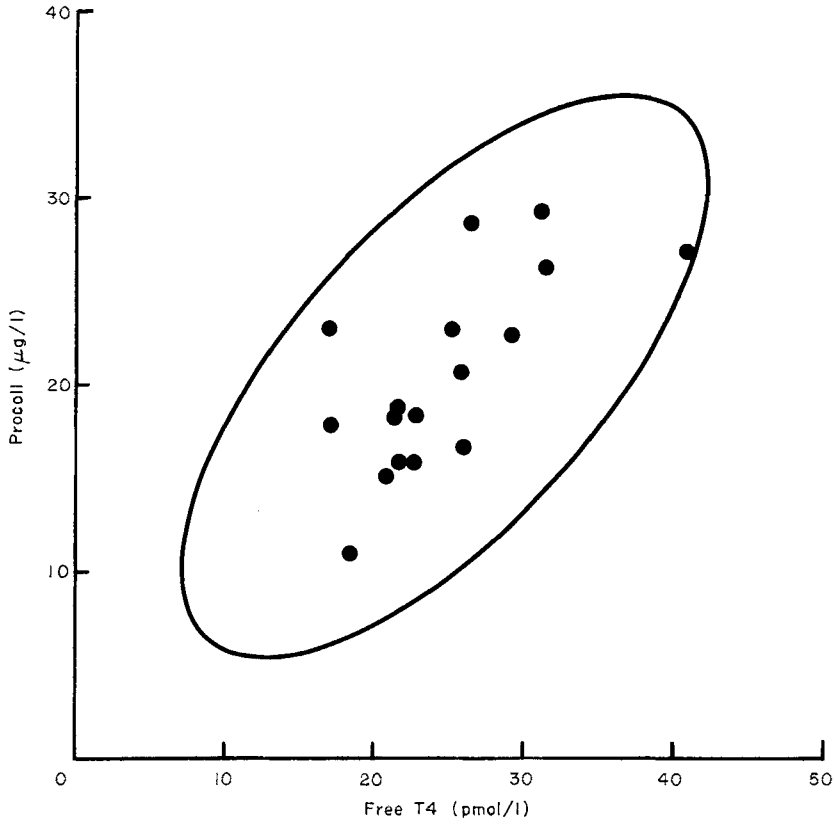

Fig. 2. Relationship between post-treatment concentrations of procollagen-III-peptide (procoll) and free T4 (analog method) concentrations in 17 women with preclinical hypothyroidism after administration of L-thyroxine for 6 months. The ellipse illustrates the 95% confidence area.

concentrations ($P < 0{\cdot}001$) and significant rises in procollagen-III-peptide concentration ($P < 0{\cdot}001$), whereas the L-thyroxine treatment had no effect on mean serum concentrations of T3, free T3, cholesterol, creatine kinase activity, or heart rate at rest (Table 2). L-thyroxine treatment did not affect serum concentrations of transcortin, sex-hormone binding globulin, or triglycerides or body mass, heart rate at rest, blood pressure, orthostatic pulse reaction, or haemoglobin concentration (not shown in Table 2). The systolic-time intervals were significantly changed (PEP I, PEP%, PEP/LVET, $P < 0{\cdot}01$: Q-A2%, $P < 0{\cdot}05$). LVET I however, not affected ($P > 0{\cdot}05$). Most women only presented with occasional clinical symptoms. If the combined scores for the group before and after the active period were compared, a significant decrease was seen ($P < 0{\cdot}01$, one outlier excluded).

TSH and thyroid hormones versus peripheral effects

Among pretreatment observations we did not find serum concentrations of TSH, T4, free T4, T3, free T3, or reverse T3 to be correlated to serum concentrations of creatine kinase activity, procollagen-III-peptide, sex-hormone binding globulin, or systolic time intervals

(LVET I, PEP I, PEP/LVET). After 6 months of treatment with L-thyroxine, the serum concentration of procollagen-III-peptide significantly correlated to serum concentration of free T4 ($r=0{\cdot}68$, $P<0{\cdot}01$) (Fig. 2). A less pronounced relationship was seen between procollagen-III-peptide and T4 ($P<0{\cdot}05$) and reverse T3 ($P<0{\cdot}05$), and between serum creatine kinase activity and TSH ($P<0{\cdot}05$) and T4 (inverse relationship, $P<0{\cdot}05$).

Comparisons between improved and not-improved cases

Pretreatment serum T3 and free T3 concentrations were lower in the improved group than in the remainders ($P<0{\cdot}01$), whereas the pretreatment concentrations of T4, free T4, and TSH did not differ between the groups (Table 1). Pretreatment antimicrosomal antibody titres did not predict improvement as only three out of eight women with high titre (1:6400 or above) appeared to benefit from L-thyroxine treatment.

DISCUSSION

This is the first double-blind cross-over study reported so far of women with subclinical hypothyroidism receiving L-thyroxine. Two previous studies (Cooper *et al.*, 1984; Bell *et al.*, 1985) in this field have mainly comprised subjects previously treated for hyperthyroidism and their results, therefore, cannot be directly transferred to the presently studied individuals who were recruited from a population study and had no prior knowledge of thyroid disease. We chose to investigate women with TSH concentrations 4–15 mU/l; as judged from our previous experience (Nyström *et al.*, 1981b) women with higher TSH concentration run such a high risk of developing hypothyroidism that it seems appropriate to treat them without further investigation.

In the present study we put some emphasis on psychometric tests, since neurasthenic-depressive symptoms may appear early in the development of hypothyroidism. Furthermore, the observations that a majority of nuclear T3 in the brain (Larsen *et al.*, 1981) appears to be derived from circulating T4 rather than T3 suggests that the function of central nervous system might be affected early in hypothyroidism when serum T4 decreases gradually in contrast to serum T3 concentration. The psychometric tests were chosen to allow psychometric measurement over a wide range and not to be time-consuming. The differences in individual performance were considerable and the results of the tests could only be used for intra-individual comparisons.

The advantage of a double-blind cross-over design of a study of the treatment of a state with atypical—if any—symptoms and well-informed participants with certain expectations of the treatment is obvious. Furthermore, this study design is important in the interpretation of the results of tests, particularly the psychometric tests, for which there is only little experience in hypothyroidism. However, the finding of a pronounced rise in TSH concentration lasting up to 6 months in several individuals who had their placebo period preceded by active treatment, indicated that these individuals had a long-lasting adaptation period after withdrawal of L-thyroxine. A similar adaptation pattern, although of shorter duration, is seen during recovery from severe hypothyroxinaemia of critical illness (Hamblin *et al.*, 1986). Therefore, we could not as regards statistical calculations take full benefit from the cross-over model, but were limited to conventional pre-post treatment comparisons. Evidently, a clinical and laboratory assessment of an individual receiving thyroxine for presumed hypothyroidism, in whom the need for this

therapy has been questioned, can only be valid after at least 6 months without thyroxine substitution. Previous studies (Vagenakis *et al*, 1975; Krugman *et al.*, 1975) have extended over 4–8 weeks and therefore have not detected this long-term recovery of thyroid function in individuals with autoimmune thyroid disease.

Due to the double-blind design we could not increase the L-thyroxine dosage until return to normal of TSH or TSH response to TRH administration, as has been done in the two previous studies (Cooper *et al.*, 1984; Bell *et al.*, 1985). In fact, this procedure may be questioned since the pituitary gland may differ in sensitivity to T4 compared to, e.g. the heart (Brajkovitch *et al.*, 1983). Instead, all participating subjects finally received 0·15 mg of L-thyroxine daily, which is the average dose routinely given to adults in this country. None of the subjects completing the study showed any signs or symptoms of overtreatment.

The slow decrease in serum free T4 concentration after the initial rise, seen both in individuals with normal (<23 pmol/l) or markedly high (>40 pmol/l) peak free T4 concentrations, might reflect an increase in the rate of elimination of T4 from the circulation (*cf.*, Brown & Refetoff, 1980).

The finding that procollagen-III-peptide concentration increased in a large number of individuals, stayed essentially unchanged throughout the period of thyroxine supplementation and then correlated to the T4, free T4, and reverse-T3 concentrations indicates that this analyte might be useful as an indicator of the metabolic effects of thyroid hormones, at least when the study period is similar to the one used here. Collagen metabolism, however, is influenced by a number of metabolic and hormonal factors, thus changes in procollagen-III-concentration are nonspecific for thyroid hormone action.

Hypothyroid patients have reduced myocardial function (Crowley *et al.*, 1977; Ooi *et al.*, 1980; Willimas & Braunwald, 1984), with prolonged systolic-time intervals. The previously observed reduction of systolic time intervals in individuals with subclinical hypothyroidism (Croxson & Ibbertson, 1980; Ooi *et al.*, 1980) is in agreement with our results, where no difference between 'improved' and 'non-improved' study subjects was observed.

Due to the design of the study, the number of participants had to be limited to a small number, and this should be borne in mind when interpreting the results. Still, it was evident that some, but not all, women did benefit from L-thyroxine treatment. However, some women might have identified the correct active period due to side effects not reported to us and, similarly, some might have experienced slight withdrawal symptoms. We therefore chose to classify the women from results of psychometric testing which might reflect performance of practical consequence to the individual. The 4 improved women (Table 1) could not, however, be identified by any pretreatment observation other than low-normal serum T3 and free T3 concentrations. Since they did not differ from the remainders as regards reverse-T3 concentration the possibility of a confounder such as temporarily inhibited T4-to-T3 conversion from nonthyroidal illness at the start of the active period appears remote.

We conclude that individuals with subclinical hypothyroidism who would benefit from L-thyroxine therapy might so far only be identified by a somewhat low serum concentration of T3 (free T3). Since there was a decrease in symptom score after substitution in some individuals it might be appropriate to give L-thyroxine for a test period of 6 months to individuals with at least some symptoms suggesting hypothyroidism (*cf.* Cooper *et al.*, 1984). Because of the rather long test period needed, and the

possible influence of confounding factors in the environment of the individual, it would be of great value if the clinician had some kind of supporting laboratory data during the test treatment. However, the results from the present study do not permit us to give any recommendations.

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