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The Beneficial Effect of L-Thyroxine on Cardiovascular Risk Factors, Endothelial Function, and Quality of Life in Subclinical Hypothyroidism: Randomized, Crossover Trial

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Context: Subclinical hypothyroidism (SCH) is defined as raised serum TSH levels with circulating thyroid hormones within the reference range. It is uncertain whether treatment of SCH with L-thyroxine improves cardiovascular (CV) risk factors and quality of life.

Objective: The objective of the study was to assess CV risk factors and patient-reported outcomes after treatment.

Design: This was a randomized, double-blind, crossover study of L-thyroxine and placebo.

Setting: The study was conducted with community-dwelling patients.

Patients: One hundred patients [mean age (SD) 53.8 (12) yr, 81 females] with SCH [mean TSH 6.6 (1.3) mIU/liter] without previously treated thyroid or vascular disease.

Intervention: Intervention consisted of 100 μg L-thyroxine or placebo daily for 12 wk each.

Measurements: Primary parameters were total cholesterol (TC) and endothelial function [brachial artery flow-mediated dilatation (FMD)], an early marker of atherosclerosis. Patient-reported outcomes were also assessed.

Results: L-thyroxine treatment reduced TC (*vs.* placebo) from 231.6 to 220 mg/dl, $P < 0.001$; low-density lipoprotein cholesterol from 142.9 to 131.3 mg/dl, $P < 0.05$; waist to hip ratio from 0.83 to 0.81, $P < 0.006$; and improved FMD from 4.2 to 5.9%, $P < 0.001$. Multivariate analysis showed that increased serum free T_4 level was the most significant variable predicting reduction in TC or improvement in FMD. Furthermore, the symptom of tiredness improved on L-thyroxine therapy, but other patient-reported outcomes were not significantly different after correction for multiple comparisons.

Conclusion: SCH treated by L-thyroxine leads to a significant improvement in CV risk factors and symptoms of tiredness. The CV risk factor reduction is related to the increased level of achieved free T_4 concentration. **(*J Clin Endocrinol Metab* 92: 1715–1723, 2007)**

SUBCLINICAL HYPOTHYROIDISM (SCH) is a common condition affecting 6–17% of the general population (1). It is defined as a serum free T_4 (FT4) level within the reference range and an elevated serum TSH level. It is controversial whether SCH can lead to increased risk of cardiovascular (CV) disease and whether treatment with L-thyroxine reverses this risk (2, 3). Furthermore, it is uncertain whether L-thyroxine therapy improves symptoms of hypothyroidism or health status in SCH (4–9).

A population-based survey concluded that SCH was associated with aortic atherosclerosis and myocardial infarction in elderly women, independent of serum cholesterol levels (10). Several subsequent investigations have also shown an association of poor vascular outcome with SCH (11, 12). However, contrary to these findings, there have been several other studies that have shown no increased CV risk in SCH (11, 13, 14). Such conflicting results may stem from heterogeneity of the studies in terms of the definition of SCH, the wide degree and duration of thyroid failure in the patients examined, varying age, gender, ethnicity, and other risk factors of the patients studied (15). Furthermore, the effects of SCH on vascular risk may be of a modest degree, such that no study so far may have been adequately powered to provide an unequivocal outcome. Several factors may contribute to CV risk in SCH, including body mass index, fat distribution, lipid profile, and vascular dysfunction (16). The present study was designed to evaluate whether L-thyroxine treatment improves CV risk profile in people with SCH. In addition, the effect of L-thyroxine on patient-reported outcomes was also investigated.

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Abbreviations: apo, Apolipoprotein; CV, cardiovascular; FMD, flow-mediated dilatation; FT3, free T_3; FT4, free T_4; GTN, glyceryltrinitrate; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; QoL, quality of life; RCT, randomized, controlled trial; SCH, subclinical hypothyroidism; SF-36v2, 36-item Short-Form 36, version 2; TC, total cholesterol; TFT, thyroid function test; TG, triglyceride; ThyDQoL, Underactive Thyroid-Dependent QoL; ThySC, Underactive Thyroid Symptom Checklist; ThyTSQ, Underactive Thyroid Treatment Satisfaction Questionnaire; TPO, thyroid peroxidase autoantibody.

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Patients and Methods

Participants

Patients, from 27 general practices in Gateshead, an urban UK population, with stable SCH (TSH > 4 mIU/liter and FT4 levels in the normal reference range) and aged 18–80 yr of age, were identified from the laboratory database after they had had at least two thyroid function tests (TFTs) (n = 322) measured, at least 3 months apart (median 5 months, range 3–41 months). General practitioners had given their consent for their patients to be contacted if they met the initial biochemical criteria. TFTs had been undertaken due to symptoms that could be attributed to hypothyroidism (n = 179) or coincidental finding (n = 103) or due to family history of thyroid disease (n = 24). No reason for undertaking TFTs could be ascertained in 16 people. Two hundred twenty-two people were excluded, after initial assessment or after a screening visit, until 100 patients were recruited into the study (Fig. 1). Exclusion criteria were previous thyroid disease and its treatment, medications that could cause thyroid hormone dysfunction, diabetes mellitus (by history and a fasting plasma glucose test), serum creatinine greater than 1.36 mg/dl (120 μmol/liter), vascular disease (history and electrocardiogram), psychiatric conditions or their treatment (by history), and current or previous pregnancy in the last 2 yr. All participants gave their informed written consent and the local research ethics committee approved the study.

Intervention

One hundred participants were randomized to receive either 100 μg L-thyroxine or matching placebo (Royal Hallamshire Hospital Pharmacy, Sheffield, UK) for 12 wk before being crossed over to the other treatment. The participants were asked to swallow the treatment capsules whole with water early in the morning, half an hour before food. Compliance as assessed at each visit by counting the number of capsules remaining in the container, was judged to be good (median 94%, range 83–100%).

Hypothesis and end points

Hypothesis: treatment of SCH with L-thyroxine improves CV risk factors. Primary end points included: improvement in brachial artery flow-mediated dilatation (FMD) as a marker of vascular endothelial function and total cholesterol (TC) levels after 12 wk of L-thyroxine treatment.

Secondary end points. These included changes in weight and its distribution (assessed by body mass index and waist to hip ratio) and patient-reported outcomes (assessed by questionnaires), such as perceived health status, hypothyroidism-specific quality of life (QoL), and hypothyroid symptoms.

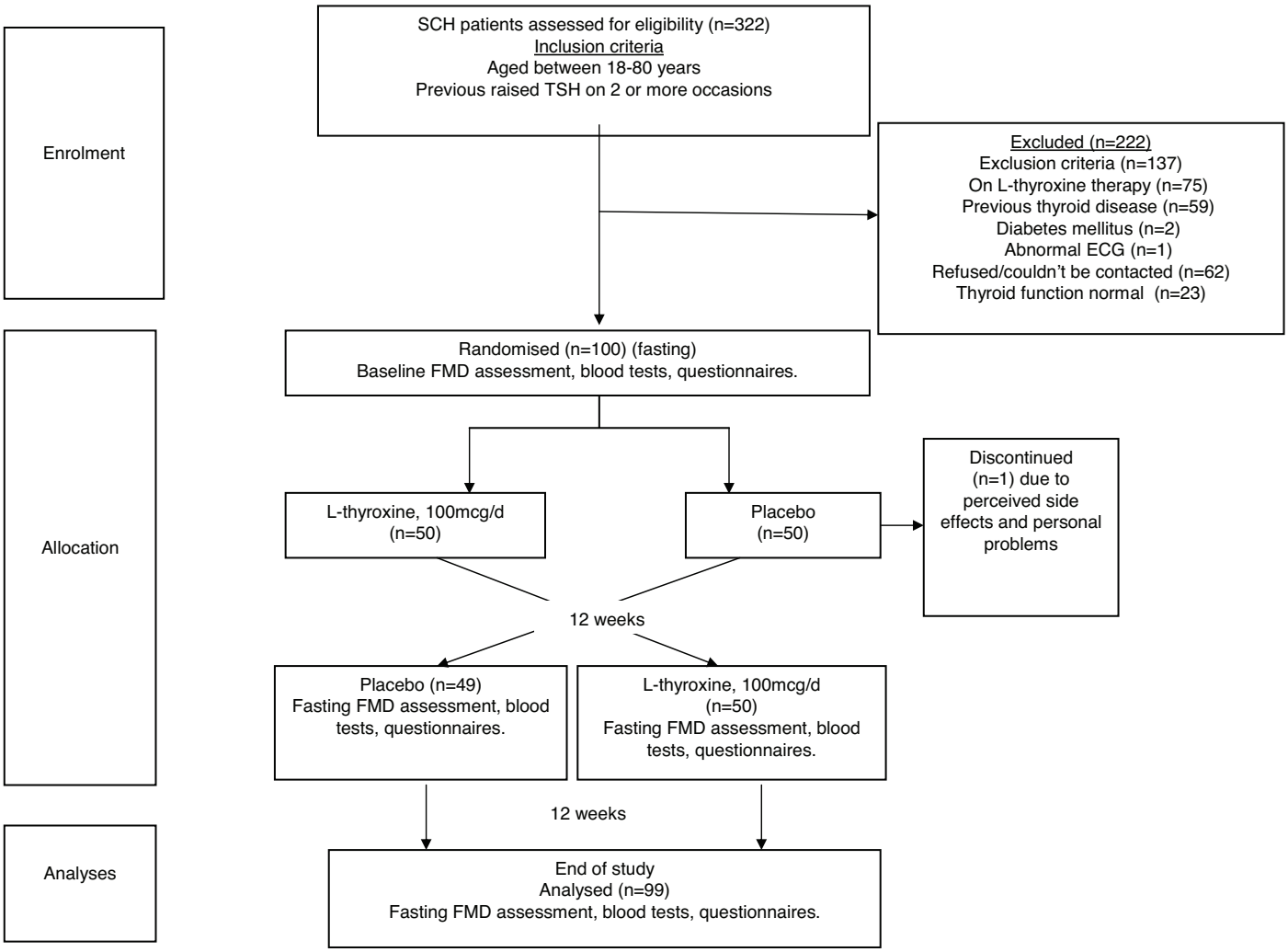

FIG. 1. Flow of patients through each stage of the study.

FMD assessment

Brachial arteries were investigated by high-resolution ultrasonography, using HDI 5000 system (ATL, Bothell, WA) and a 5- to 12-MHz linear transducer. The same investigator (S.R.) performed all examinations, which were in accordance with international guidelines (17). All measurements were obtained in the morning, with participants having fasted and having stopped any medication for minimum 12 h and, for premenopausal women, in the same phase of the menstrual cycle. The right brachial artery was scanned continuously, 2–10 cm above the elbow, with the participant lying supine after an initial 15-min rest. Transient vascular occlusion was obtained (5 min) with a blood pressure cuff, situated at the proximal forearm, inflated to 250 mm Hg. Pulsed Doppler assessed arterial flow at rest and immediately after tourniquet deflation. FMD was automatically calculated as the ratio of mean diastolic vessel diameters, 55–65 sec after reactive hyperemia, to the baseline diameter, and expressed as a percentage change. Endothelium-independent dilatation was calculated as the ratio of the mean diastolic diameter, 4 min after 400 μg of sublingual glyceryltrinitrate (GTN) administration, to the baseline diameter. The ultrasound system was connected to a computer equipped with a frame grabber and artificial neural network wall-tracking software, allowing optimized real-time analyses for a more accurate measurement of vessel diameter and reduction in observer error (18, 19). Intraobserver variability (SD) on 29 controls was 0.1% (2.1%).

Biochemical measurements

Blood samples were drawn after at least 12 h of fasting and before taking the intervention capsule and immediately centrifuged. Samples were then stored at −40 C until analysis. Samples from the same participants were analyzed as one batch, in duplicate. Serum FT4, free T_3 (FT3), and TSH concentrations were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Lewes, UK). Thyroid autoimmunity was assessed by the quantitative measurement of antithyroid peroxidase autoantibodies (TPO) by ELISA (Orgentec Diagnostika GmbH, Mainz, Germany). Serum TC, high-density lipoprotein cholesterol (HDLc), and triglycerides (TGs) were assayed using automated enzymatic methods (Roche Diagnostics). Low-density lipoprotein cholesterol (LDLc) was calculated using Friedewald's formula. Serum apolipoprotein (apo) A1 and apoB were determined by immunoturbidimetric methods (Roche Diagnostics). Normal ranges are as follows: FT4 = 0.7–1.9 ng/dl (9–25 pmol/liter); FT3 = 0.3–0.6 ng/dl (5–8.5 pmol/liter); TSH = 0.4–4 mIU/liter; and anti-TPO antibody less than 50 IU/ml. Coefficients of variation were less than 5% for all tests except FT3, which was 5.5%.

Physical examination (by single observer). Blood pressure (right arm) was measured after the participants had rested for at least 10 min. Waist circumference was measured at the midpoint between lower rib margins and the iliac crest and hip circumference at its widest point.

Patient-reported outcomes

A number of validated instruments were used to assess patient-reported outcomes (20). The 36-item Short-Form 36, version 2 (SF-36v2) measured perceived health status; it has eight subscales (physical functioning, general health, vitality, mental health, social functioning, bodily pain, role-emotional, and role-physical) (21). The 18-item Underactive Thyroid-Dependent QoL (ThyDQoL) questionnaire was used to assess the perceived impact of hypothyroidism on QoL (22, 23), the 15-item Underactive Thyroid Symptom Checklist (ThySC) to measure frequency and perceived severity of symptoms of hypothyroidism (23), and the seven-item Underactive Thyroid Treatment Satisfaction Questionnaire (ThyTSQ) to assess satisfaction with present treatment (22, 24). The order of questionnaire administration was as follows: SF-36v2, ThyDQoL, ThySC, and ThyTSQ.

Randomization and blinding

Independent external pharmacists drew up a computer-generated randomization list, and the treatment was then distributed in sequentially numbered identical containers. The investigators allocated the next available number on entry to the trial. All study investigators and participants remained blinded to treatment assignment for the duration of both study and analysis. The blinded nature of participants was assessed at the end of the two treatment periods by asking patients to identify the L-thyroxine phase. Forty-four percent of patients correctly identified the active treatment period, 32% did not, and 24% were unsure ($P = 0.12$).

Statistical methods

Data analyses were performed by one investigator (S.R.) and then confirmed by another (J.U.W.). All analyses were performed as per preestablished plan and with an intention to treat. Because intention-to-treat analyses does not always reflect clinical practice, we also analyzed the data after excluding patients with discordant TFT results (TSH and FT4 levels outside the expected values during the course of the study). The data were analyzed in accordance with previous guidance on the analyses of crossover trials (25). This method (difference of differences) adjusts for period and subject effects and also checks for any carry-over effect (residual effect of treatment in first period persisting into the second period as assessed by treatment * period interaction). Normally distributed data were analyzed using Student's t test and Pearson's r correlation coefficient. Nonnormally distributed data were analyzed using Wilcoxon's rank sum test and Spearman's rho correlation coefficient. Because the order of administration of L-thyroxine or placebo did not alter the results, the results for each were combined. Two-sided significance tests were used throughout. Adjustment for multiple comparisons was made using Bonferroni correction for analysis [six variables comprising the two primary end points (TC and FMD) and four questionnaires]: required P value was < 0.008). Treatment effects are reported as the mean difference between the two treatment periods, with both 95% confidence intervals and both raw and corrected P values. Multivariate analyses were conducted by general linear model with backward selection, after assessment for colinearity and interactions, using the two primary end points as dependent variables and correlated factors as independent variables. The binomial sign test was used to estimate whether there were significant differences between the two treatment periods in a consistent direction within a questionnaire, even if the magnitude of the difference were small. The statistical software SPSS 11.0 for Windows (SPSS, Chicago, IL) was used to perform analyses.

Sample size calculation. The sample size needed to show an intended treatment benefit was based on the primary outcomes (FMD and TC), $\alpha = 0.05$ and $\beta = 0.20$. For FMD, to detect a minimal improvement of 1%, SD of 2.1, the required sample size was 81. The obtained sample size of 100 would give the study a power of 0.99 to detect the above difference. For TC, to detect a difference of 7.7 mg/dl (0.2 mmol/liter), SD of 19.3, sample size was calculated as 101 patients.

The funding source had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Results

The study protocol is outlined in Figure 1. Participants attended for randomization (baseline visit) after a first treatment period at 12 wk and then at 24 wk after crossover to the other treatment allocation. Outcome measures were obtained at each visit. Ninety-nine participants completed the full study protocol. One person dropped out of the study after reporting side effects after 12 d of placebo treatment; therefore, baseline results were carried forward in the final data analyses. There was no significant carry-over effect in any of the outcomes or measurements.

Baseline visit demographic and clinical characteristics of the patients are given in Table 1. There were no significant differences in the two groups at randomization. Fifty-one

TABLE 1. Baseline demographic and clinical characteristics of study sample

	All patients (n = 100)	Randomized to L-thyroxine first (n = 50)	Randomized to placebo first (n = 50)
Age (yr)	53.8 (12.6)	53.5 (13.3)	54.2 (12.1)
Male (n)	18	10	8
Weight (kg)	76.5 (16.4)	75.9 (15.9)	77 (16.9)
Smokers (n)	25	14	11
Medications (n)			
Antihypertensive	18	10	8
Statins	6	3	3
SBP (mm Hg)	132.5 (21.5)	135.7 (22.6)	129.4 (20.1)
DBP (mm Hg)	79.9 (9.2)	80.8 (8.3)	79.1 (10)
Waist to hip ratio	0.83 (0.1)	0.84 (0.1)	0.83 (0.1)
TSH (mIU/liter)	5.3 (3.7–15.8)	5.4 (3.8–15.8)	5.3 (3.7–13.9)
FT4 (pmol/liter)	13.6 (2)	13.5 (2.1)	13.7 (2)
FT3 (pmol/liter)	4.7 (0.6)	4.7 (0.7)	4.7 (0.6)
TC (mmol/liter)	6.0 (1.2)	6.1 (0.9)	6.0 (1.4)
LDLc (mmol/liter)	3.6 (1)	3.6 (0.8)	3.6 (1.2)
HDLc (mmol/liter)	1.7 (0.5)	1.7 (0.5)	1.6 (0.4)
Triglycerides (mmol/liter)	1.2 (0.5–3.7)	1.2 (0.7–3.7)	1.2 (0.5–3.1)
apoB (mg/dl)	104.4 (33.8)	104.7 (34)	104.1 (33.6)
apoA1 (mg/dl)	152 (30)	157.2 (31.3)	147 (28)
apoB to apoA1	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)
FMD (%)	4.8 (3.2)	5.1 (3.3)	4.6 (3)

Values are expressed as mean (SD) or median (range). To convert FT4 from picomoles per liter to nanograms per deciliter, divide by 12.87. To convert FT3 from picomoles per liter to nanograms per deciliter, divide by 15.4. To convert TC, HDLc, and LDLc from millimoles per liter to milligrams per deciliter, multiply by 38.6. To convert triglycerides from millimoles per liter to milligrams per deciliter, multiply by 88.6. SBP, Systolic blood pressure; DBP, diastolic blood pressure.

patients were positive for anti-TPO antibodies, 18 were on treatment for hypertension and six were on statin therapy for hyperlipidemia.

Twenty-nine patients had discordant TFTs during the course of the study: normal TSH at randomization (n = 8), less than 0.4 mIU/liter and above 4.0 mIU/liter on L-thyroxine therapy (n = 10 and 2, respectively), normal TSH and above 15 mIU/liter on placebo therapy (n = 14 and 2, respectively); seven patients fell into this category on more than one occasion (for example, patients that had normal TSH at randomization also had low TSH on L-thyroxine therapy). No patient had a FT3 level recorded outside the reference range. The results were reanalyzed after excluding these 29 patients and are shown in Tables 2–4 (n = 71) alongside the results for the entire 100 patients.

Intention-to-treat analyses showed that during L-thyroxine therapy TC, LDLc, HDLc, weight, waist to hip ratio, apoB, apoA1, and apoB to apoA1 ratio were all reduced, although only TC, LDLc, and waist to hip ratio remained significant after Bonferroni correction (Table 2). The reduction from baseline in serum TC and LDLc averaged 5.5 and 7.3%, respectively.

FMD increased significantly on L-thyroxine without any significant change in baseline vessel diameter, blood flow, or endothelium-independent vascular dilatation in response to GTN (Table 3).

There was a significant inverse relationship between reduction in TC levels and an increase in FT4 levels ($r = -0.43$, $P < 0.01$) and a positive relationship between increase in FMD and increase in FT4 levels ($r = 0.3$, $P < 0.05$), one significant outlier not excluded for either. There were no significant correlations between change in FT4 levels and reduction in weight and reduction in waist to hip ratio. TSH was not correlated with baseline TC levels or change in TC levels during treatment. Multivariate general linear model analyses, for changes in LDLc or FMD (dependent variables) and blood pressure, weight, TSH, FT4, and apoB to apoA1 ratio (independent variables), showed that the change in FT4 concentrations was the only common variable that predicted these two outcomes [change in LDLc: adjusted $r^2 = 0.50$ for whole model with change in FT4 ($t = -3.1$, $\beta = -0.25$, $P < 0.005$) (Fig. 2) and change in FMD: adjusted $r^2 = 0.1$ for whole model and change in FT4 ($t = 2.0$, $P < 0.05$), respectively]. The other two variables that predicted change in LDLc were changes in diastolic blood pressure and apoB to apoA1 ratio (data not shown).

During L-thyroxine treatment, there were significant improvements in some patient-reported outcomes. The proportion of patients reporting tiredness (ThySC questionnaire) was reduced from 89 to 78% during thyroxine therapy; $P < 0.006$. QoL questionnaires showed reduced perception of the negative impact of hypothyroidism (ThyDQoL overview item) and on sex life (ThyDQoL domain) by thyroid hormone therapy, although these no longer remained significant after Bonferroni correction (Table 4). Most other domains of QoL and reported hypothyroid symptoms showed a trend toward improvement but did not reach statistical significance. Health status (SF-36v2) and treatment satisfaction (ThyTSQ) did not show any significant change. The sign test showed a significant difference in favor of L-thyroxine for the 18 ThyDQoL domains ($P = 0.03$) but not perceived health status ($P = 0.07$), symptom bother scores ($P = 0.6$), and satisfaction with treatment ($P = 0.68$).

Post hoc subgroup analyses showed that there were no significant differences between patients with positive *vs.* negative anti-TPO antibodies with respect to any measured outcome. Similarly there were no differences between patients with baseline TSH values greater than 6.1 mIU/liter (the mean for the entire group) when compared with those with baseline TSH levels less than 6.1 mIU/liter.

TABLE 2. The effect of L-thyroxine *vs.* placebo on anthropometric and biochemical markers

Outcome measured	All patients (n = 100)					Discordant TFTs excluded (n = 71)				
	L-thyroxine	Placebo	Adjusted difference (95% CI)[a]	*P* value	Corrected *P* value[b]	L-thyroxine	Placebo	Adjusted difference (95% CI)[a]	*P* value	Corrected *P* value[b]
Weight (kg)	75.8 (16.5)	76.5 (16.7)	−0.6 (−1.1 to −0.1)	0.02	0.12	77.9 (17.5)	78.4 (17.9)	−0.5 (−0.85 to −0.15)	0.04	0.24
SBP (mm Hg)	132.8 (22.8)	134.6 (22.9)	−1.8 (−4.6 to 1.0)	0.21		134.5 (22.7)	136.2 (22.8)	−1.9 (−4.4 to 0.6)	0.28	
DBP (mm Hg)	78.8 (10.3)	79.9 (9.6)	−1.1 (−2.8 to 0.5)	0.16		79.4 (10.4)	80.6 (9.9)	−1.4 (−2.9 to 0.04)	0.16	
Waist to hip ratio	0.81 (0.1)	0.83 (0.1)	−0.01 (−0.02 to −0.01)	0.001	0.006	0.82 (0.1)	0.83 (0.1)	−0.01 (−0.01 to −0.004)	0.009	0.05
TSH (mIU/liter)	0.5 (0.01–12.1)	5.2 (0.9–63.4)	−5.6 (−7.2 to −4.1)	<0.001	<0.001	0.8 (0.4–3.9)	5.2 (4.1–12.1)	−4.7 (−5.1 to −4.3)	<0.001	<0.001
FT4 (pmol/liter)	20.5 (4.8)	13.5 (2.3)	7.0 (6.0 to 8.0)	<0.001	<0.001	20.2 (4.2)	13.8 (2.2)	6.4 (5.7 to 7.1)	<0.001	<0.001
FT3 (pmol/liter)	5.3 (1)	4.7 (0.7)	0.6 (0.4 to 0.8)	<0.001	<0.001	5.2 (0.8)	4.7 (0.6)	0.4 (0.3 to 0.5)	<0.001	<0.001
TC (mmol/liter)	5.7 (1)	6.0 (1)	−0.35 (−0.5 to −0.2)	<0.001	<0.001	5.7 (1.1)	6.0 (1)	−0.28 (−0.4 to −0.1)	0.008	<0.05
LDLc (mmol/liter)	3.4 (0.8)	3.7 (0.9)	−0.2 (−0.4 to −0.1)	0.008	<0.05	3.4 (0.9)	3.7 (0.9)	−0.2 (−0.3 to −0.1)	0.02	0.12
HDLc (mmol/liter)	1.6 (0.5)	1.7 (0.5)	−0.06 (−0.1 to −0.01)	0.02	0.12	1.7 (0.5)	1.7 (0.5)	−0.01 (−0.04 to 0.02)	0.98	
Triglycerides (mmol/liter)	1.3 (0.5–4.1)	1.3 (0.4–5.1)	−0.06 (−0.2 to 0.1)	0.26		1.3 (0.5–4.1)	1.4 (0.5–4.3)	−0.1 (−0.2 to 0)	0.09	
apoB (mg/dl)	101.6 (34)	108.8 (38)	−7.2 (−12.7 to −1.7)	0.01	0.06	102.2 (33.9)	106.5 (35.7)	−6.4 (−12.5 to −0.3)	0.04	0.24
apoA1 (mg/dl)	152.1 (30.6)	156.8 (34.4)	−4.8 (−8.9 to −0.6)	0.02	0.12	152.1 (32.1)	153.8 (34.3)	−2.1 (−5.7 to 1.4)	0.41	
apoB to apoA1	0.69 (0.2)	0.72 (0.3)	−0.04 (−0.1 to −0.01)	0.04	0.24	0.70 (0.3)	0.72 (0.3)	−0.04 (−0.09 to 0.01)	0.05	0.30

Values are expressed as mean (SD) or median (range). To convert FT4 from picomoles per liter to nanograms per deciliter, divide by 12.87. To convert FT3 from picomoles per liter to nanograms per deciliter, divide by 15.4. To convert TC, HDLc, and LDLc from millimoles per liter to milligrams per deciliter, multiply by 38.6. To convert triglycerides from millimoles per liter to milligrams per deciliter, multiply by 88.6. SBP, Systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval.

[a] Adjusted for subject and period effects.

[b] Bonferroni correction for multiple testing for six variables. Only the significant raw *P* values are corrected.

TABLE 3. The effect of treatment with L-thyroxine *vs.* placebo on brachial artery vascular parameters

	All patients (n = 100)					Discordant TFTs excluded (n = 71)				
	L-thyroxine	Placebo	Adjusted difference (95% CI)[a]	*P* value	Corrected *P* value[b]	L-thyroxine	Placebo	Adjusted difference (95% CI)[a]	*P* value	Corrected *P* value[b]
Baseline flow (ml/min)	58.5 (43.8)	55.1 (42.4)	3.4 (−4.9 to 11.7)	0.42		60.5 (46.4)	59.3 (45.2)	1.9 (−6 to 9.7)	0.69	
Peak flow (ml/min)	147.3 (59.2)	142.7 (56.5)	4.6 (−8.1 to 17.3)	0.48		147.2 (56.1)	150.3 (61.4)	−2.4 (−13.9 to 9.1)	0.76	
Baseline diameter (mm)	3.4 (0.6)	3.5 (0.6)	0.02 (−0.0 to 0.05)	0.11		3.5 (0.6)	3.5 (0.6)	−0.0 (−0.0 to 0.1)	0.06	
FMD (%)	5.9 (3.1)	4.2 (3)	1.6 (1.2 to 2.1)	<0.001	<0.001	5.8 (3.1)	4.2 (3.2)	1.6 (1.2 to 2.0)	<0.001	<0.001
Absolute change in diameter (mm)	0.2 (0.1)	0.1 (0.1)	0.06 (0.02 to 0.08)	<0.001	<0.001	0.2 (0.1)	0.15 (0.1)	0.06 (0.04 to 0.07)	<0.001	<0.001
GTN response (%)	21.3 (6.3)	20.6 (7.1)	0.7 (−0.3 to 1.6)	0.15		21.1 (6.1)	20.2 (6.6)	0.7 (−0.2 to 1.5)	0.23	

Values are expressed as mean (SD). CI, Confidence interval.

[a] Adjusted for subject and period effects.

[b] Bonferroni correction for multiple testing for six variables. Only the significant raw *P* values are corrected.

TABLE 4. The effect of treatment with L-thyroxine *vs.* placebo on QoL[a]

Questionnaire (ThyDQoL)	All patients (n = 100)					Discordant TFTs excluded (n = 71)				
	L-thyroxine (SD)	Placebo (SD)	Adjusted difference (95% CI)[b]	*P* value	Corrected *P* value[c]	L-thyroxine (SD)	Placebo (SD)	Adjusted difference (95% CI)[b]	*P* value	Corrected *P* value[c]
T-QoL	−1.1 (1)	−1.2 (0.9)	0.2 (0.02 to 0.36)	0.04	0.24	−1 (0.9)	−1.2 (1)	0.3 (0.08 to 0.52)	0.01	0.06
Sex life	−2.3 (2.7)	−2.7 (2.8)	0.3 (0.02 to 0.7)	0.03	0.18	−1.9 (2.6)	−2.4 (2.9)	0.3 (0.05 to 0.7)	0.01	0.06
Motivation	−3.6 (2.7)	−3.7 (2.7)	0.4 (−0.4 to 0.9)	0.16		−3.1 (2.8)	−3.8 (2.8)	0.9 (0.1 to 1.7)	0.009	0.05
Worries about future	−2.5 (3)	−2.8 (2.9)	0.2 (−0.2 to 0.7)	0.23		−2 (2.9)	−2.6 (3)	0.4 (−0.2 to 1.1)	0.07	
AWI-18	−2.7 (2.4)	−2.8 (2.3)	0.1 (−0.3 to 0.5)	0.45		−2.3 (2.3)	−2.7 (2.3)	0.3 (0.01 to 0.6)	0.01	0.06

Maximum score range: ThyDQoL individual QoL domains: −9 to +3 (maximum negative to maximum positive perceived impact of hypothyroidism on that QoL domain); T-QoL (hypothyroid-dependent QoL) score range: −3 to +1 (maximum negative to maximum positive perceived weighted impact of hypothyroidism on QoL); AWI-18 (average weighted impact of all 18 domains) score range −9 to +3, provides a total summative score; the more negative the score, the greater the perceived negative impact of hypothyroidism on QoL. CI, Confidence interval.

[a] Only the significant or close to significant domains are presented.

[b] Adjusted for subject and period effect.

[c] Bonferroni correction for multiple testing for six variables. Only the significant raw *P* values are corrected.

The results changed a little when patients with discordant TFTs were excluded (Table 2).

If the set of patients in the first 12-wk period were examined as a parallel group (L-thyroxine *vs.* placebo), the primary end points still remained significantly improved on L-thyroxine.

Discussion

To our knowledge this is the largest randomized, controlled trial (RCT) in which patients received both L-thyroxine and placebo and in whom CV risk factors and patient-reported outcomes were measured. The present study has

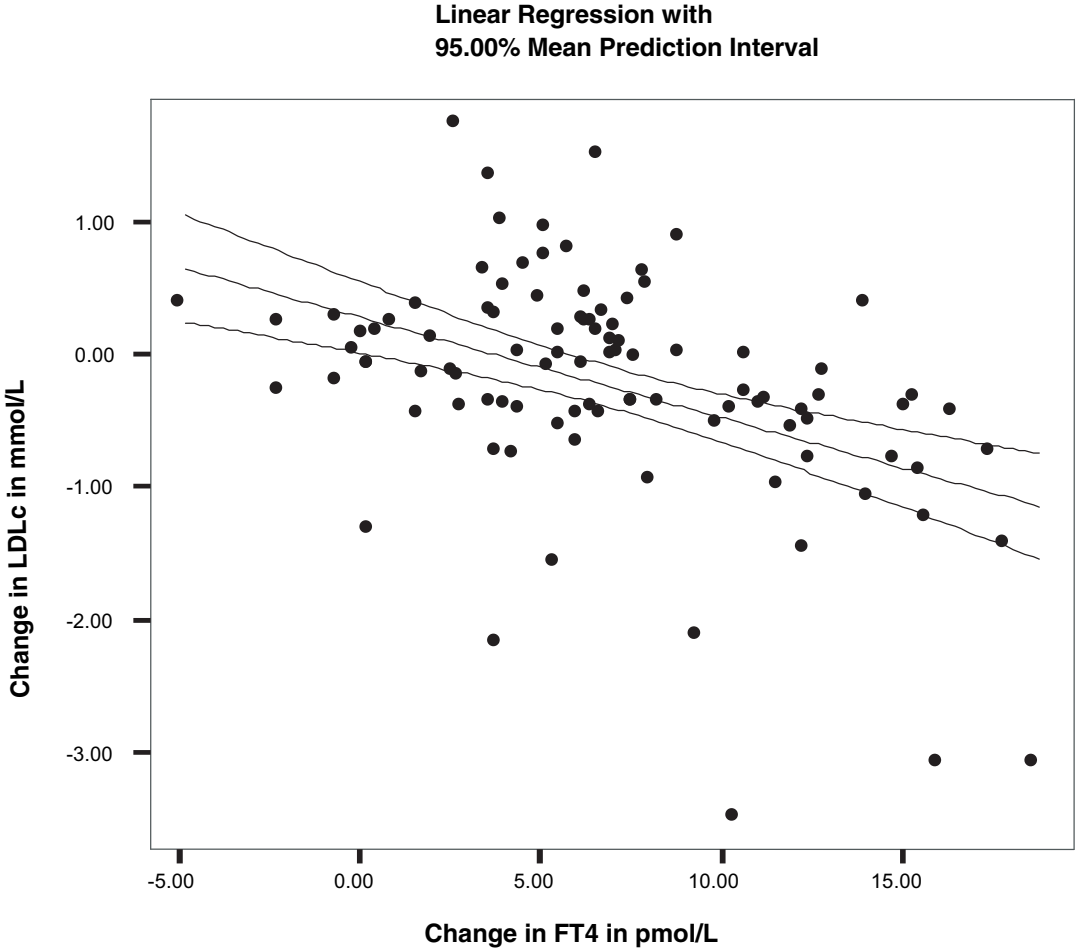

FIG. 2. Linear regression with 95% mean prediction interval. The regression equation that predicted the change in LDLc in relation to the change in FT4 levels was −0.27 + (0.08 multiplied by change in FT4). For example, an increase in FT4 by 5, 10, or 15 pmol/liter would reduce LDLc by 0.13, 0.53, and 0.93 mmol/liter, respectively. To convert FT4 from picomoles per liter to nanograms per deciliter, divide by 12.87 and to convert LDLc from millimoles per liter to milligrams per deciliter, multiply by 38.6.

shown that treatment of SCH with L-thyroxine is associated with significant, although modest, improvement across a wide spectrum of CV risk factors.

A crossover design was chosen for this study because it has the advantage of requiring a smaller sample size to detect a significant difference because interpatient variability is removed. The disadvantage of this design is that it takes double the time period as well as having the possibility of having a carry-over effect, although not evident in this study.

Previous research in this area has shown contradictory results, with some RCTs (number of patients ranging from 45 to 63) showing an improvement in the atherogenic lipid profile (7, 26, 27) but others (number of patients ranging from 17 to 35) showing no difference (4–6, 8). This may be due to small numbers, different upper limits of serum TSH used to define SCH and differences in study design (28). The reduction in TC of 11.6 mg/dl (0.3 mmol/liter) with L-thyroxine treatment in the present study is more than that the average taken from a systematic review of 13 studies. The review concluded that treatment of SCH with L-thyroxine reduced TC, LDLc, and apoB with no significant change in apoA1 and HDLc, although the reduction in TC was of greater magnitude in patients who were undertreated for overt hypothyroidism (16.9 mg/dl or 0.44 mmol/liter) rather than in *de novo* treatment for SCH (5.4 mg/dl or 0.14 mmol/liter) (15).

Rather surprisingly, when considering the short treatment period, we found a significant effect of L-thyroxine on reducing central adiposity as measured by waist to hip ratio, which is an independent risk factor for CV disease (29). This reduction persisted even on exclusion of patients with evidence of hyper- and hypothyroidism. To our knowledge this has not been shown by any previous RCT. This could be due to the fact that in comparison with other investigations, we studied more patients and used a larger daily dose of L-thyroxine. Previous studies used doses less than 100 μg, with one exception (8). Our study has shown that a significant increase in FT4, although within the normal reference range, may be a better marker for risk factors for CV disease in monitoring response to treatment in SCH than TSH level alone. This is in agreement with previous research that has shown that changes in serum lipoproteins, in both hypothyroid and hyperthyroid patients, are correlated with changes in FT4 levels (30).

Brachial artery FMD, a validated surrogate marker for coronary artery endothelial function, is emerging as an independent predictor of future cardiac events (31). The present study has confirmed the beneficial effect of treatment with L-thyroxine on brachial artery endothelial function in people with SCH, independent of other CV risk factors, as found in a previous smaller study (32). An improvement in FMD response may suggest better nitric oxide bioavailability and an associated improvement in vasoprotection in clinically relevant areas of the vasculature, such as coronary and carotid circulation (33). This improvement in endothelial function could translate into reduction in CV morbidity and mortality (34), although this has yet to be proved in prospective clinical trials. We chose to measure endothelial function by FMD and distal occlusion because it is a better marker of nitric oxide bioavailability and is noninvasive, compared with other techniques (*e.g.* brachial artery acetylcholine infusion) (33).

The effect of L-thyroxine treatment on patient-reported outcomes was mixed. Before correction for multiple comparisons, the perceived negative impact of hypothyroidism on QoL and sex life was reduced by L-thyroxine therapy (as measured by the disease-specific ThyDQoL). However, this did not remain significant after Bonferroni correction. Nevertheless, there was a trend toward improvement in the perceived negative impact of hypothyroidism on sex life, which is interesting and warrants further research into the underlying mechanism. This may be due to the effect of thyroid hormones on psychological aspects (*e.g.* reducing tiredness). However, this is not an isolated finding as L-thyroxine has been shown to improve impaired sexual function and performance in men with overt hypothyroidism (35). However, although all subscales of the generic health status measure, the SF-36v2 (apart from Role emotional), tended toward an improvement with L-thyroxine therapy, none reached statistical significance. This may not be surprising, given that generic instruments are less sensitive than disease-specific ones in assessing response to treatment (20) and that our study was not powered to detect differences in patient-reported outcomes. For example, if one assumes the improvement in vitality (the subscale that showed the most improvement in the SF-36v2) was sustained in a larger patient group, we calculated that more than 300 subjects would have been needed to detect a significant difference. It is also indeed possible that no difference was detected in many of the patient-reported parameters by L-thyroxine therapy because no such difference exists. The present study indicates that fewer patients report tiredness after L-thyroxine therapy, although patients' scores for symptom severity did not improve. There is no direct explanation for this and may be due to patients having adapted to their symptoms.

The limitations of the present study are that patients were not identified after population screening and thus may have been more symptomatic, treatment was for 3 months only, and the dose of L-thyroxine was a fixed 100 μg per patient. The patient sample was obtained primarily from those presenting to primary care physicians and selected to reflect mild SCH because this is the most common and most controversial area of clinical practice (36). The treatment period of 12 wk duration was deemed adequate for the present study because it takes about 4–6 wk of full replacement therapy with L-thyroxine to correct the dyslipidemia of overt hypothyroidism (37). However, it may be insufficient time for some benefits (such as perceptible reduction in some symptoms and psychological factors) to become apparent to patients. Previously it has been suggested that the dose of L-thyroxine required to treat SCH is between 50 and 75 μg/d (38). This is based on three studies that used mean doses ranging from 68 to 150 μg/d and the treated group's TSH values ranged from 1.9 to 4.6 mIU/liter (4, 5, 8). However, another study that used 100 μg/d in biochemically euthyroid patients with hypothyroid symptoms found that mean TSH levels did not drop below the reference range (39). Thus, 100 μg of L-thyroxine

per day was an adequate empirical dose to treat the majority of patients in our study, with only 10% showing biochemical evidence of either subclinical (n = 8) or mild thyrotoxicosis (n = 2).

In conclusion, our study suggests that people with SCH with no apparent vascular disease can obtain improvement in their CV risk factor profile (weight loss with reduction in central adiposity, a favorable shift in lipoprotein pattern and improvement in endothelial function) and reduced tiredness after treatment with 100 μg L-thyroxine. If the reduction in LDLc alone were sustained long term in SCH patients taking T_4, we estimate this would result in a relative reduction in 10-yr CV mortality of about 10% (40). Our data also suggest that serum FT4 levels are the strongest correlate of changes in CV risk, and we would recommend their use when monitoring such treatment. Long-term studies are required to confirm whether these apparent short-term benefits will translate into reduction in CV mortality and morbidity.

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