Clinical aspects of endogenous hypothyroidism and subclinical hyperthyroidism in patients with differentiated thyroid carcinoma

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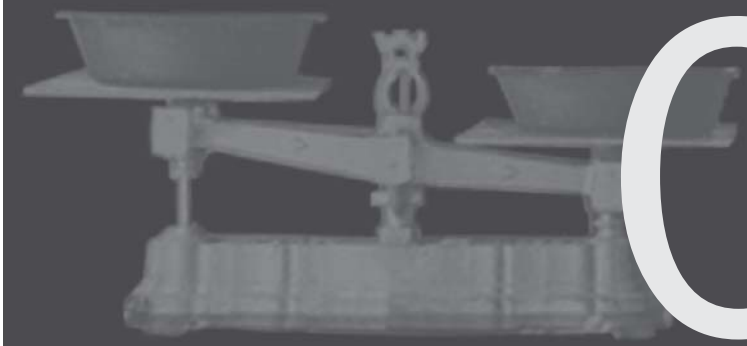

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Glucose Tolerance and Lipid Profile in Long-term Exogenous Subclinical Hyperthyroidism and the Effects of Restoration of Euthyroidism, a Randomised Controlled Trial

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Abstract

Objective: The impact of prolonged subclinical hyperthyroidism on glucose and lipid metabolism is unclear. Therefore, we evaluated glucose and lipid metabolism in patients with differentiated thyroid carcinoma (DTC) on TSH suppressive thyroxin therapy as a model for subclinical hyperthyroidism and investigated whether restoration to euthyroidism affects metabolism.
Design: We performed a prospective, single-blinded, placebo-controlled, randomised trial of 6 months duration with 2 parallel groups.
Patients: Twenty-five subjects with a history of differentiated thyroid carcinoma with >10 years TSH-suppressive therapy with L-thyroxin completed the study. L-thyroxin dose was replaced by study medication containing L-thyroxin or L-thyroxin plus placebo. Medication was titrated to establish continuation of TSH suppression (low-TSH group, 13 patients) and euthyroidism (euthyroidism group, 12 patients).
Measurements: We evaluated glucose metabolism by glucose tolerance test and HOMA (IR) and lipid metabolism by lipid profile. In addition, we measured plasma concentrations of glucoregulatory hormones.
Results: At baseline, glucose tolerance, HOMA (IR), lipid profile and plasma concentrations of glucoregulatory hormones were within the normal range. No significant differences between the low TSH and euthyroidism group were observed. After 6 months, neither glucose- nor lipid metabolism in the low TSH group were different from baseline values.
Conclusion: In summary, glucose- and lipid metabolism in patients with DTC and long-term subclinical hyperthyroidism in general are not affected. Restoration of euthyroidism in general does not affect glucose and lipid metabolism.

Introduction

In *overt hyperthyroidism*, impaired glucose tolerance and increased insulin resistance have long been observed as a frequent complication (1-7)(Table 1), predominantly at the level of the liver (1). The underlying mechanisms have not been completely elucidated, but have been ascribed to a combination of multiple factors, like decreased pancreatic secretion of insulin (8,9), decreased suppression of glucagon by glucose (10) and increased adrenergic activity (11)(Table 1). Regarding lipid metabolism, overt hyperthyroidism is associated with decreased plasma concentrations of total and/or LDL cholesterol (3,12-16), that normalize after correction of hyperthyroidism (17-19) (Table 2).
Subclinical hyperthyroidism is a state, in which the patient has a suppressed thyrotrophin (TSH) level (below 0.4 mU/l), although the free T4 level is within the normal range. This condition affects several organ systems, including bone (20-23) and the cardiovascular system (24-28). Only scarce data are available on the consequences of subclinical hyperthyroidism for glucose- and lipid metabolism. Glucose metabolism in subclinical hyperthyroidism has been studied only by Yavuz *et al.*, who observed a decreased insulin sensitivity index by oral glucose tolerance test in patients with exogenous subclinical hyperthyroidism compared to values after restoration of euthyroidism and compared to controls (29) (Table 1). Most studies report no differences in lipid profile in subclinical hyperthyroidism (29-30), with the exception of 2 studies, that report decreased total and LDL cholesterol levels (32,33). In the study of Franklyn *et al.*, total cholesterol concentrations were decreased only in patients older than 55 years and LDL cholesterol levels were decreased only in patients older than 65 years (32). Most of the above described studies contained patients with endogenous (subclinical) hyperthyroidism. A disadvantage of those studies can be that the duration and degree of (subclinical) hyperthyroidism are not known. Exogenous subclinical hyperthyroidism is a good model to study the effects of subclinical hyperthyroidism on metabolism, because the duration and degree of subclinical hyperthyroidism are known.
In the present study, we therefore conducted a randomised, controlled trial in patients with differentiated thyroid carcinoma to compare the effects of restoration of exogenous subclinical hyperthyroidism to euthyroidism on glucose- and lipid metabolism.

Material and methods

Subjects
Consecutive patients were recruited from the outpatient clinic of the Department of Endocrinology of Leiden University Medical Centre. This department is a tertiary referral centre for differentiated thyroid carcinoma. Patients were included who had been diagnosed with DTC, who had received initial therapy consisting of total-thyroidectomy and radioiodine ablation therapy. Additional therapies were allowed, as long as they resulted in cure of DTC. Cure was documented by the absence of measurable serum thyroglobulin (Tg) during TSH stimulation as well as by a negative total-body scintigraphy with 4 mCi 131-I. The patients had to be on TSH suppressive therapy, defined as TSH levels below the lower reference value for TSH (0.4 mU/l), for at least 10 years. The adequacy of the TSH suppressive therapy had to be documented by yearly TSH measurements.
Patients who had diabetes mellitus according to the WHO criteria (34) or a BMI >30 were excluded. Patients who used any drugs known to influence the metabolic parameters we studied were also excluded. The local ethics committees approved the study, and written informed consent was obtained from all subjects.

Table 1. Overview of the Literature: impact of (subclinical) hyperthyroidism on glucose metabolism

Study	Number of patients	Diagnosis	TSH	Duration subclin. HT	Control group	Design	Outcome
Subclinical hyperthyroidism							
Yavuz (29)	20	Exogenous (T4) MNG	0.2 ±0.3	6 months	20 age- and sex-matched controls	Prospective	ISI (OGTT) ↓
Overt hyperthyroidism							
Tosi (6)	12 healthy subjects	Exogenous (T3)	< 0.1	10 days	-	Prospective	IGT (OGTT)
Jenkins (5)	6	Endogenous	not detectable	?	6 controls	Prospective	4/6 IGT(OGTT)
Karlander (40)	6	Endogenous	<0.1	?	6 controls	Cross-sectional	glucose tolerance = (OGTT)
Ikeda (4)	18	Endogenous	?	?	6 age-matched controls	Prospective	IGT(OGTT)
Gimenez-Palop (2)	24	Endogenous	0.01 ± 0.00	?	45 controls	Prospective	HOMA-IR ↑
Iglesias (3)	20	Endogenous	0.05 ± 0.004	?	20 controls	Prospective	HOMA-IR ↑
Yaturu (7)	69	Endogenous	0.087 ± 0.05	?	-	Prospective	HOMA-IR ↑
Cavallo-Perin (1)	12	Endogenous	?	?	12 sex-, age- and weight-matched controls	Prospective	hepatic insulin resistance (hyperinsulinemic euglycemic clamp)

MNG = Multinodular goitre, HOMA-IR= Homeostatic Model Assessment Insulin Resistance, OGTT= Oral Glucose Tolerance Test, ISI= Insulin Sensitivity Index, IGT= Impaired Glucose Tolerance

Table 2. Overview of the Literature: impact of (subclinical) hyperthyroidism on lipid metabolism

Subclinical hyperthyroidism							
Yavuz (29)	20	Exogenous (T4) MNG	0.2 ±0.3	6 months	20 age- and sex-matched controls	Prospective	TC, TG, LDL, HDL =
Langer (30)	149	Endogenous	011-0.30	?	1750 controls	Cross-sectional	TC, TG =
Lee (31)	35	Endogenous	0.07 ± 0.03	?	100 age- and sex matched controls	Cross-Sectional	TC, LDL, HDL, TG =,
Parle (33)	27	Endogenous	<0.4	?	27 age-, sex- and BMI- matched controls	Prospective	TC, LDL ↓
Franklyn (32)	59	Exogenous (T4)	< 0.5 mU/l	> 1 year (median 7.9 years, range 1-18 years)	Sex, age and menopausal state matched controls	Cross-sectional	TC↓>55 years, LDL ↓> 65 years.
Overt hyperthyroidism							
Riis (46)	9	Endogenous GD	0	?	8 age- and sex- matched controls	Prospective	FFA↑
Muller (45)	6 healthy subjects	Exogenous (T4)	?	10-14 days	-	Prospective	FFA =
Mantzoros (15)	22 healthy subjects	Exogenous (T3)	0.25 ± 0.14	7 days	-	Prospective	TC ↓
Iglesias (3)	20	Endogenous	0.05 ± 0.004	?	20 controls	Prospective	TC↓
Kung (14)	40	Endogenous	< 0.05	?	119 controls	Prospective	TC, LDL, HDL ↓
Cachefo (12)	5	Endogenous	?	?	20 controls	Cross-sectional	TC, HDL ↓ TG ↑
Sundoram (16)	7	Endogenous	< 0.04	?	-	Prospective	TC, LDL ↓
Costantini (13)	16	Endogenous	0.02 ± 0.035	?	16 age- and sex- matched controls	Cross-sectional	TC, LDL, HDL ↓
Lam (42)	16	Endogenous	< 1.3 µi.u/ml	?	24 controls	Cross-sectional	TC, HDL, TG =
Abrams (44)	13	Endogenous	2.6 ± 0.2 units	?	Controls	Prospective	TG ↑ VLDL-TG ↓
Raiszadeh (43)	24	Endogenous	0.07 ± 0.08	?	23 age- and sex- matched controls	Prospective	TG ↓ after treatment: TC,TG ↑
Azizi (17)	50	Endogenous	< 0.3	?	50 age- and sex-matched controls	Cross-sectional	TG ↓
Diekman (18)	47	Endogenous	< 0.01	?	-	Prospective	after treatment: HDL, LDL, TG, TC↑
Oge (19)	16	Endogenous	0.01 ± 0.2	?	-	Prospective	after treatment: C, LDL ↑

TC = Total Cholesterol, TG = Triglycerides, LDL = LDL cholesterol, HDL = HDL cholesterol, FFA= Free Fatty Acids

Study design

The study was a prospective, single-blinded randomised controlled trial with 2 parallel groups with a duration of 6 months. After inclusion, patients were randomised in a single-blinded way to continue TSH suppressive therapy (low TSH group, target TSH level < 0.4 mU/L) or to restore euthyroidism by decreasing the L-thyroxin dose (euthyroidism group, target TSH levels within the normal reference range (0.40-4.8 mU/L)).

After randomisation, standard thyroxin therapy of all patients was replaced in part by study medication according to an algorithm. Study drugs consisted of either 25 µg thyroxin or placebo tablets with similar appearance. Serum TSH levels were checked every 6 weeks in every patient, and study medication was adjusted if necessary to obtain the target TSH levels. Before and after 6 months, a physical examination was performed and fasting blood samples were drawn for hormonal and metabolic parameters.

Experimental protocol

Subjects were admitted to the clinical research unit, where they handed in the urine collected over the previous 48 hours. Patients were asked to follow a diet free of potential catecholamine stimulating food or medication (excluding coffee, alcohol, bananas, nuts and acetaminophen) from two days before urine collection. All subjects fasted from the preceding evening (18.00 hr) until the end of the study. On the study day, at 08.00 hr, height (meters [m]) and weight (kilograms [kg]) were measured. Body composition was measured by DEXA (Hologic 4500, Hologic Inc., Bedford, MA, USA). Patients were subsequently requested to lie down on a bed in a semi recumbent position. A catheter was inserted in a dorsal hand vein to collect plasma samples for measurement of glucose, insulin, cortisol, growth hormone, leptin, free fatty acids (FFA), total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. To investigate insulin sensitivity an Oral Glucose Tolerance Test (OGTT) was performed. After an overnight fast patients were given 75 gram of glucose. At 0, 30, 60, 90 and 120 minutes serum glucose and insulin was measured. Plasma and serum samples were handled immediately and stored at –20o C in Sarstedt tubes.

Blood Chemistry

All plasma and serum samples were measured in one batch. Serum free thyroxin (FT4) and TSH were measured with an electrochemoluminescentic immunoassay with a Modular Analytics E-170 system with an intraassay CV of 1.6-2.2 % and 1.3-5.0 % respectively (Roche, Almere, The Netherlands). Serum free triiodothyronine (FT3) was measured with a fluorescentic polarisatic immunoassay, CV 2.5-9.0 %, on an ImX system (Abbott, Abbott Park, IL, USA). Serum insulin was measured by IRMA (Medgenix, Fleurus, Belgium) with a CV of 4.8-8.5 %, leptin by RIA (Linco Research, St. Charles, MO, USA) with an intraasaay CV of 3.0-5.1 %, growth hormone by IFMA on a Delfia system (Wallac OY, Turku, Finland), cortisol by TDX (Abbott) with an intraassay CV of 3.5-6.5 %, ACTH by IRMA (Nichols Institute, san Juan Capistrano, CA, USA) and FFA by spectrofotometry by a validated kit (Boehringer, Mannheim, Germany). Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were measured with a fully automated Modular P800 system (Roche).

Twenty-four hour excretion of urinary catecholamines (epinephrine, norepinephrine) was measured by HPLC with electrochemical detection.

Calculations

Insulin resistance was assessed by HOMA score (HOMA-IR) with the formulas as described by Matthews *et al.* (35). Insulin Sensitivity Index (ISI) was calculated as described by Matsudo and DeFronzo (36).

Statistical Analysis

Values are presented as mean ± standard deviation (SD). Data between groups were analysed using an unpaired T-test. Data within groups were analysed using a paired T-test. All calculations were performed using SPSS 12.0 for windows (SPSS. Inc., Chicago, IL, USA). Differences were considered statistically significant at $P<0.05$.

Results

Patient characteristics

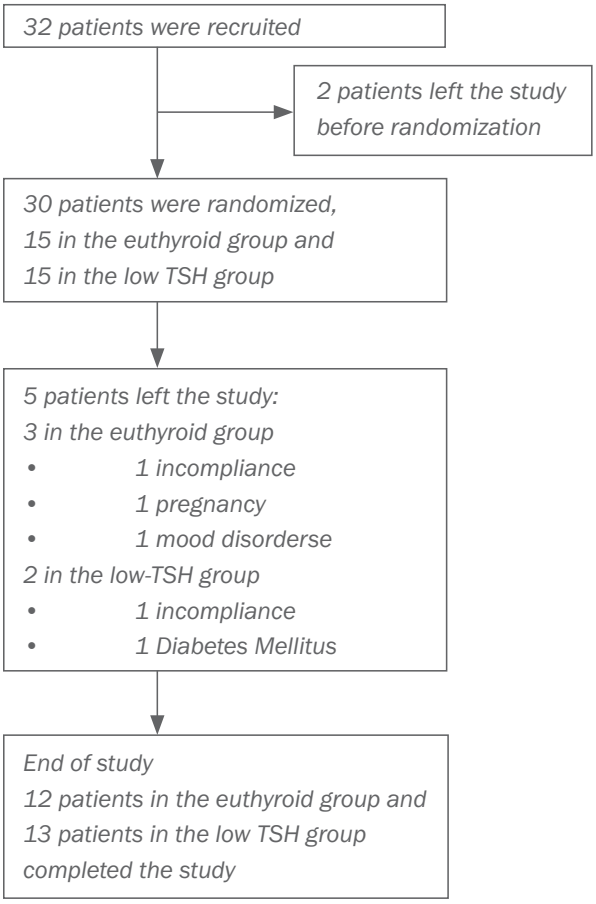
Thirty-two patients were recruited initially (Figure 1). Before randomisation 2 patients left the study; one patient because of comorbidity and the other patient without a clear reason. The other 30 patients were randomised in two groups of 15 patients. Two patients in the euthyroidism group left during the study, one because of pregnancy, the other because of mood disorders. In the subclinical hyperthyroidism group one patient left the study, because diabetes mellitus was diagnosed on the basis of a fasting glucose > 7 mmol/l. At the end of the study 2 patients, one in each group, were excluded because of incompliance. Consequently, 25 patients were included in the calculations, 8 men and 17 women (Table 3). Thirteen patients (9 women and 4 men, mean age 48.18 ± 8.60 years) were treated with thyroid hormone to suppress TSH level below 0.4 mU/l. Mean dose of thyroid hormone before randomisation was 179 ± 31 µg per day. Twelve patients (8 women and 4 men, mean age 50.81 ± 9.99 years) were treated to restore euthyroidism. Mean dose of thyroid hormone treatment before randomisation was 185 ± 39 µg.

Table 3. Patient Characteristics at baseline

	Low TSH (n=13)	Euthyroidism (n=12)	p-value
Age (yr)	48.18 ± 8.60	50.81 ± 9.99	0.487
Sex (m/f)	4 : 9	4 : 8	0.891
Weight (kg)	68.07 ± 19.84	74.8± 9.9	0.302
Length (m)	1.70 ± 0.08	1.73 ± 0.07	0.458
BMI (kg/m^2)	23.46 ± 6.74	24.98 ± 2.20	0.463
DEXA LBM (kg)	49.8 ± 8.5	48.8 ± 13.0	0.809
DEXA total fat (kg)	21.9 ± 6.4	21.1 ± 3.0	0.693
Tumor Stage			0.328
T2 N0 M0	9	5	
T2 N1 M0	3	3	
T3 N0 M0	1	2	
T3 N1 M0	0	2	
Histology Tumor			0.564
Papillary	10	10	
Papillary-follicular variant	2	1	
Follicular	0	1	
Follicular Hurthle	1	0	
Dose I-131	3174 ± 1817[#]	2418 ± 602	0.183
Duration of TSH suppressing treatment (years, (range))	13 ± 2	13 ± 2	0.724

[#] *1 patient received 6900 MBq I-131 for persisting thyroid remnants*

Figure 1 Study Flow Chart



Thyroid hormone levels

Thyroid hormone levels are summarized in Table 4. All patients had suppressed TSH levels at baseline. TSH, free T4 (FT4) and free T3 (FT3) concentrations were not different between the 2 groups at baseline. At 6 months no differences were observed in TSH, FT4 and FT3 concentrations and thyroxin dose in the subclinical hyperthyroid group compared to baseline. In the euthyroidism group, TSH, FT4 and FT3 concentrations were significant different at 6 months compared to baseline. Serum TSH concentrations were significantly lower (0.07 ± 0.10 vs. 4.35 ± 3.63 µmol/ml, p=0.002) and serum free T4 (22.97 ± 4.23 vs. 18.29 ± 4.76 nmol/l, p=0.012) and FT3 (3.59 ± 0.65 vs. 2.63 ± 0.60 pmol/l, p=0.001) concentrations were significantly higher in the low-TSH group compared with the euthyroidism group.

Anthropometric data

At baseline, BMI, DEXA total fat and DEXA Lean Body Mass were not different between the subclinical hyperthyroidism group and the euthyroidism group (Table 3). In addition, these parameters were not different within each groups at 6 months compared to baseline, or between groups at 6 months.

Glucose metabolism

At baseline, 2 of 13 patients in the subclinical hyperthyroidism group had impaired glucose tolerance on the basis of the OGTT according to the WHO criteria (34). In the euthyroidism group, 2 of 12 patients had impaired glucose tolerance. There were no differences between both groups. At 6 months, 1 of 13 patients in the subclinical hyperthyroidism group had impaired glucose tolerance. In the euthyroidism group, 1 of 12 patients had impaired glucose tolerance and 1 patient had type 2 diabetes mellitus based on the OGTT. There were no differences between groups or compared to baseline in both groups.

Table 4. Thyroid hormone parameters

	Baseline					6-months		
	Low TSH (n=13)	Euthyroidism (n=12)	p-value vs. Low TSH	Low TSH (n=13)	p-value vs. baseline	Euthyroidism (n=12)	p-value vs. baseline	p-value vs. Low TSH
Thyroxin dose (µg/day)	170 ± 30	185 ± 39	0.308	180 ± 32	0.077	129 ± 37	0.000	0.001
TSH (mU/l)	0.20 ± 0.25[a]	0.19 ± 0.29[a]	0.943	0.07 ± 0.10	0.063	4.35 ± 3.63	0.002	0.002
FT4 (pmol/l)	22.08 ± 5.71	22.60 ± 4.09[a]	0.777	22.97 ± 4.23	0.484	18.29 ± 4.76	0.004	0.018
FT3 (pmol/l)	3.30 ± 0.79	3.55 ± 0.39	0.336	3.59 ± 0.65	0.200	2.63 ± 0.60	0.000	0.001

[a] *p <0.05 in independent t-test compared to placebo group*

Table 5. Glucose and lipid metabolism

	Subclinical hyperthyroidism (n= 13)			Restoration to euthyroidism (n=12)		
	0 months	6 months	p-value	0 months	6 months	p-value
Glucose Metabolism						
Glucose (mmol/l)	5.1 ± 0.8 (4.0-6.8)	4.7 ± 0.7 (4.0-6.3)	0.510	5.2 ± 0.5(4.3-5.9)	5.1 ± 0.5(4.4-6.1)	0.696
Insulin (pmol/l)	69.5 ± 41.7 (20.8-173.6)	55.6 ± 13.9 (27.8-83.3)	0.226	76.4 ± 13.9 (27.8-83.3)	69.5 ± 17.8 (27.8-111.1)	0.302
HOMA-IR (median 2.8, interquartal range 1.55)(24)	2.39 ± 1.90 (0.54-7.40)	1.70 ± 0.58 (0.77-2.69)	0.193	2.73 ± 1.57 (0.85-6.21)	2.23 ± 1.07 (0.80-3.88)	0.268
Insulin Sensitivity Index (2.28±1.2)(14)	4.62 ± 1.75(1.77-7.38)	5.35 ± 2.17(2.34-9.44)	0.104	3.80 ± 1.14	4.60 ± 2.19	0.140
Lipid metabolism						
Cholesterol (mmol/l)	5.26 ± 0.71(4.38-6.93)	5.03 ± 0.96(3.94-7.37)	0.118	5.30 ± 1.35(3.46-7.80)	5.44 ± 0.99(3.96-7.54)	0.581
HDL-cholesterol (mmol/l)	1.51 ± 0.31(0.99-2.03)	1.49 ± 0.17(0.85-2.10)	0.588	1.75 ± 0.77(1.06-3.96)	1.68 ± 0.51(1.04-2.87)	0.518
LDL-cholesterol (mmol/l)	3.53 ± 0.72(2.34-5.09)	3.27 ± 0.71(2.45-4.28)	0.559	3.50 ± 1.11(2.09-5.85)	3.69 ± 1.07(2.58-5.97)	0.159
Triglycerides (mmol/l)	1.05 ± 0.48(0.51-2.24)	1.04 ± 0.64(0.39-2.76)	0.902	0.91 ± 0.43(0.47-2.09)	0.95 ± 0.49(0.43-2.03)	0.643
FFA (mmol/l)	0.55 ± 0.17(0.31-0.90)	0.52 ± 0.20(0.28-1.07)	0.602	0.45± 0.21(0.11-0.85)	0.43 ± 0.09(0.28-0.58)	0.781

Baseline plasma insulin concentrations, HOMA-IR and ISI were not different between the subclinical hyperthyroidism and euthyroidism group (Table 5). At 6 months, plasma insulin concentrations, HOMA-IR and ISI were not different compared to baseline values in both experimental groups and not different between groups. In our study, basal glucose concentrations and HOMA-IR were within the normal range of a Dutch study including 277 healthy controls with normal glucose tolerance with a median BMI of 25.6 kg/m^2 (37).

Lipid metabolism

At baseline, concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and FFA were not different between the subclinical hyperthyroidism group and the euthyroidism group (Table 5). After 6 months, no differences were seen in these parameters in both groups compared to baseline values. In addition, there were no differences between the two groups in any of these parameters at 6 months.

Hormone concentrations

At baseline and after 6 months plasma concentrations of cortisol, ACTH, growth hormone, leptin and 24 hour urinary excretion of catecholamines were not different between both groups. At 6 months those values were not different within each groups.

Discussion

The present study was performed to investigate the effects of restoration of euthyroidism after long-term subclinical hyperthyroidism on glucose- and lipid metabolism. The study was a prospective, placebo-controlled randomised study and as such the first using this design. The findings indicate, that restoration to euthyroidism in patients with long-term subclinical hyperthyroidism had no appreciable influence on several parameters of glucose- and lipid metabolism.

In our study, according to reference values using WHO criteria, 4 of 26 patients (15.4%) had impaired glucose tolerance at baseline. These percentages are in accordance with previous studies in The Netherlands and USA. Mooy *et al.* (38) found a prevalence of impaired glucose tolerance of 10.3% in the Dutch population, Harris *et al.* (39) a prevalence of 15.6% in the USA population. Two patients had a familiarity for type 2 diabetes mellitus. However, these patients did not have impaired glucose tolerance at baseline or at 6 months. The findings of our study on glucose metabolism are in conflict with the study of Yavuz *et al.* (29), which reports a decreased insulin sensitivity index after 6 months of exogenous subclinical hyperthyroidism compared to matched controls. Basal glucose values are not reported in that study. Most studies, performed in overt hyperthyroidism (1-7) found insulin resistance, whereas one study found no difference in glucose tolerance (40). An explanation for these differences in outcome of subclinical hyperthyroidism on glucose metabolism could be the duration of subclinical hyperthyroidism. We studied a population, that was treated for over 10 years with TSH suppressive therapy which might result in adaptation, whereas Yavuz *et al*. studied 20 patients with multinodular goitre who were treated for 6 months (29). Alternatively, it might imply that the “dose” (the extent of subclinical hyperthyroidism) in our study was not relevant to result in a “response” (glucose intolerance), However, this is unlikely, because TSH values in our study were comparable to values in the study of Yavuz *et al.* (29).

Table 6. Glucoregulatory hormones.

	Subclinical hyperthyroidism (n= 13)			Restoration to euthyroidism (n=12)		
	0 months	6 months	p-value	0 months	6 months	p-value
Cortisol (nmol/l)	428.5± 173.2(160.0-720.0)	419.9 ± 174.0(160.0-870.0)	0.839	445.8 ± 126.6(300.0-660.0)	476.7 ± 169.4(220.0-730.0)	0.493
ACTH (pmol/l)	3.74 ± 2.64 (1.10-11.44)	2.86 ± 1.32 (1.54-6.38)	0.219	4.84 ± 2.42 (1.98-9.90)	5.50 ± 4.84 (1.54-18.48)	0.694
GH (mU/l)	4.90 ± 6.03(0.50-18.63)	7.16 ± 9.01(0.07-29.72)	0.215	5.46 ± 6.92(0.07-18.09)	5.29 ± 5.55(0.39-18.54)	0.911
Leptin (µmol/l)	12.4 ± 7.4(2.7-24.0)	12.9 ± 7.9(3.5-28.7)	0.626	16.0 ± 7.4(5.6-32.2)	16.3 ± 6.6(4.4-27.4)	0.714
Adrenaline-U (µmol/24 hour)	0.02 ± 0.01(0.00-0.06)	0.02 ± 0.02(0.00-0.07)	0.439	0.02 ± 0.02(0.00-0.08)	0.02 ± 0.02(0.00-0.05)	0.391
Noradrenalin-U (µmol/24 hour)	0.24 ± 0.12(0.09-0.53)	0.24 ± 0.08(0.14-0.43)	0.948	0.30 ± 0.10(0.18-0.44)	0.25 ± 0.06(0.15-0.35)	0.188

Alternatively, it might indicate the absence of a direct relationship between plasma levels of hormones and tissue specific hormone effect parameters (41). It might be argued that the number of patients included in our study was too low, resulting in underpowering of the study. A posthoc power analysis, however, for some important items of the different questionnaires, showed a sufficient power, e.g. range 70-97 %. Therefore, it seems unlikely that underpowering of our study plays a major role in the negative findings.

Restoration of subclinical hyperthyroidism to euthyroidism did not affect lipid profile. This is in accordance with previous studies (29-31). Only one study in 27 patients with endogenous subclinical hyperthyroidism (33) and one study in 59 patients with exogenous subclinical hyperthyroidism (32) found a decrease in total- and/or LDL cholesterol. In the latter study, also a decrease in LDL-cholesterol was observed.

In overt hyperthyroidism, total cholesterol was mostly decreased (3,12-16). Only one study (42) found a total cholesterol level within the normal range. Triglycerides are either decreased (17,18,43), within the normal range (42), or increased (44,12). Free fatty acids were within the normal range (45) or increased (46).

In our study, basal glucoregulatory hormones were all within the normal range and were not different after restoration of subclinical hyperthyroidism. In contrast to our findings, Hsieh *et al*. (47) noticed a significant increase in serum leptin in patients with exogenous subclinical hyperthyroidism. This change was more profound in females.

Successful restoration of subclinical hyperthyroidism to euthyroidism, as indicated by normalization of TSH concentration and a decrease in FT3/FT4 concentration by approximately 40% and 30%, respectively, did not result in any changes in parameters of glucose metabolism or lipid profile, which is comparable with baseline observations that glucose- and lipid metabolism are not affected to a considerable extent in subclinical hyperthyroidism. In addition, minimally if any changes were observed in any other of the studied metabolic parameters. We cannot exclude that a period of 6 months of restoration of euthyroidism is too short to detect differences in metabolic parameters.

In summary, we investigated the effects of subclinical hyperthyroidism in patients treated for differentiated thyroid carcinoma on several metabolic parameters. A prospective, single-blinded, randomised controlled trial was performed to investigate whether restoration of euthyroidism has effects on these metabolic parameters. We observed no relevant differences in glucose- and lipid metabolism during long-term subclinical hyperthyroidism and after restoration of subclinical hyperthyroidism to euthyroidism.

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