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Small doses of triiodothyronine can change some risk factors associated with abdominal obesity

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OBJECTIVE: To elucidate whether the administration of small doses of triidothyronine (T3) can increase concentrations of sex hormone binding globulin (SHBG) in obese women with different types of obesity and to evaluate the potential metabolic benefits of such treatment.
DESIGN: Daily administration of 20 μg of T3 during six weeks while maintaining habitual food intake and physical activity.
SUBJECTS: Seventy premenopausal obese women (age: 41.2 ± 1.5y mean ± s.e.m., body mass index (BMI): 34.4 ± 0.7).
MEASUREMENTS: Plasma concentrations of SHBG, lipids, insulin, thyroid hormones, sex hormones, blood glucose and insulin sensitivity (by euglycemic insulin clamp in 12 patients) at base line after six weeks of treatment.
RESULTS: Six weeks treatment with small doses of T3 resulted in a significant increase in plasma SHBG. The increase of SHBG was higher in abdominal obesity and not associated with a significant change in body weight, plasma insulin concentration, insulin/glucose ratio of plasma insulin sensitivity (glucose disposal during insulin clamp). In patients with initially high SHBG the significant increase of insulin removal (as judged from the increase of c-peptide/insulin ratio) was observed. Treatment resulted in a reciprocal increase of T3, decrease of thyroxine (T4), and a more than double increase of T3/T4 ratio.
CONCLUSIONS: Administration of small doses of T3 can increase the concentration of SHBG without changing insulin concentrations or sensitivity. As there was a significant decrease (by 36%) of T4 and parallel increase of T3 with a clear increase of T3/T4 ratio it seems possible that rather than lack of thyroid hormones a lower peripheral deiodination of T4 might be a factor contributing to the low SHBG concentration in abdominal obesity. Treatment with small doses of T3 may be considered to ameliorate some of the risk factors associated with abdominal obesity, particularly in some subgroups of obese women with a relative resistance to thyroid hormones possibly dependent on decreased peripheral deiodination of thyroxine.

Keywords: Supplementation with T3; deiodination of thyroxin; SHBG; obesity

Introduction

The serum concentrations of sex hormone-binding globulin (SHBG) are low in obesity and correlate negatively with waist to hip ratio (WHR) and positively with the cardiovascular risk factors[1] and non-insulin dependent diabetes mellitus (NIDDM).[2,3]

It is generally assumed that the cause of the low SHBG concentrations might be the hyperinsulinaemia which is characteristic of abdominal obesity, since SHBG production in vitro is inhibited by insulin.[4]

Apart from the influence of insulin, the synthesis of SHBG is also believed to be affected by thyroid hormones.[5,6] The major aim of the present study was to determine if administration of small doses of triiodothyronine (T3) increase the low concentrations of SHBG in women with different types of obesity. Abdominal (A) obesity in contrast to gluteal femoral (GF) is characterised by low SHBG and high free testosterone concentrations. We also wanted to elucidate whether the effects of T3 are expressed more in this type of obesity.

Another purpose of the study was to determine if small supplementations with T3 may influence beneficially other metabolic aberrations associated with obesity, including the possible influence on SHBG.

Material and methods

Seventy premenopausal obese women of age 41.2 ± 1.5y were recruited. Their general characteristics and anthropometric data are given in the Table 1. All participants completed the study. No side effects were reported.

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All women were asked to maintain their habitual food intake during the six week treatment with 20 μg triiodothyronine (T3) (Liothyronine®, Nycomed Pharma AS, Norway) daily. Treatment was arranged so that measurements could be taken during the same phase of the menstrual cycle in each individual.

The study was accepted by the local ethical committee (at Göteborg University and Sahlgren's Hospital). All patients received detailed information regarding the study and gave their written formal consent.

Body weight was recorded in underwear to the nearest 0.1kg, height to the nearest cm and the body mass index (BMI) calculated. Waist and hip circumferences were recorded in the morning after a light breakfast with the patient in the supine position[7] and the WHR calculated.

The women were divided into two equal groups. BMI (weight (kg)/height (m^2)), age and body composition were carefully matched to be equal but the waist to hip circumference ratios (WHR) were different. This was performed to obtain one group with high WHR (A obesity) and one with low WHR (GF obesity). This division was performed utilising as an arbitrary division value of 0.84 for the WHR. A similar division (median value) was used to obtain a low and high SHBG group.

Cholesterol was measured using the CHOD PAP enzymatic colorimetric kit and triglycerides were measured as esterified glycerol using the enzymatic colorimetric kit (Boehringer Mannheim Diagnostics, Ingelheim, Germany).

Insulin and C-peptide were measured by radioimmunoassays (RIA) using a double antibody separation method (Pharmacia Diagnostics, Uppsala, Sweden).

Free testosterone, 17 beta-oestradiol, progesterone as well as SHBG were measured in serum by commercially available radioimmunoassays (Orion, Åbo, Finland). Blood glucose was determined by an enzymatic method (Boehringer). The measurements were performed after fasting overnight before treatment and were repeated on the day of examinations after treatment. The last dose of T3 being administered 16h before.

The concentration of plasma creatinine, urine creatinine, urine cortisol, sodium, calcium and potassium were determined according to the hospital routine. Serum TSH was determined with a luminometric immunoenzymetric assay (Amerlite TSH-30, Kodak Clinical Diagnostics Ltd, Amersham, UK).

Serum free thyroxine was determined by Amerlite MAB FT4 assay (Kodak Clinical Diagnostics). Serum T3 was measured by double antibody RIA with reagents from the Diagnostic Products Corp. (LA, USA). SHBG was determined by an immunoradiometric assay (Farmos Group Ltd, Oulunsalo, Finland), serum testosterone by a nonextraction competitive RIA (Coat-a Count, Diagnostic Products Corp.) oestradiol by enzyme immunoassay using luminometry (Amerlite E2 - GO - Amersham International, UK).

Serum T4, T3 and TSH were measured by specific radioimmunoassays.

Insulin euglycaemic clamp measurements were performed on 12 patients after an overnight fast, before and after T3 treatment. Insulin and glucose infusions were given in an antecubital vein and samples for analyses taken from a dorsal hand-vein, where arterialised blood was obtained after heating the arm. Insulin (Actrapid MC, Novo, Copenhagen, Denmark) was infused at a concentration of 5007 mU/ml in isotonic saline solution containing 2ml of plasma from the subjects to prevent losses of insulin. Insulin was infused at a rate of 0.12U/kg body weight min for 110min after a primed infusion for 10min. A 10% glucose solution containing potassium and phosphate was infused through a venous catheter, the tip of which was placed at the level of the axilla. The infusion rate was adjusted to maintain a constant blood glucose concentration of about 5mM, analysed every 10min during infusions in an automatic analyser. Insulin was determined before and after 80, 90, 100, 110 and 120min of insulin infusion. The values at 120min were 151 ± 12 (means $\pm$ s.e.m.) uU/ml before and 145 ± 8uU/ml after hormonal treatments, and the assessment of insulin sensitivity was based on the exogenous glucose infusion rate during the last 20 min when a steady state had been reached.

Table 1 Effects of low-dose T3 treatment in all 70 volunteers

	Before	*After*	*P*
Body weight (kg)	94.3 ± 0.7	94.0 ± 1.8	NS
BMI	34.4 ± 0.7	34.3 ± 0.7	NS
WHR	0.83 ± 0.01	0.83 ± 0.01	NS
Systolic blood pressure (mmHg)	134.3 ± 2.4	131.3 ± 2.3	NS
Diastolic blood pressure (mmHg)	85.8 ± 0.9	86.1 ± 1.1	NS
Cholsterol (mmol/l)	5.98 ± 0.22	5.60 ± 0.16	< 0.01
HDL cholesterol (mmol/l)	1.31 ± 0.05	1.37 ± 0.05	NS
Triglycerides (mmol/l)	2.24 ± 0.52	2.05 ± 0.37	NS
Insulin (μU/l)	14.8 ± 1.1	15.1 ± 1.5	NS
C-peptide (nmol/l)	3.18 ± 0.25	3.08 ± 0.20	NS
S-TSH (m/IU/l)	2.58 ± 0.24	2.28 ± 0.16	NS
S-triiodthyronine (nmol/l)	2.28 ± 0.07	2.28 ± 0.09	< 0.01
Free thyroxine (pmol/l)	16.8 ± 0.8	10.9 ± 0.8	< 0.01

T3, triiodothyronine; BMI, body mass index; WHR, waist to hip ratio; NS, not statistically significant.

Statistics

Data are presented as Mean ± s.e.m.

The entire group was divided into subgroups, with the median of the SHBG concentration as the point of arbitrary division.

The group with low SHBG (mean concentration 22.4 ± 1.3) and high SHBG (mean concentration 53.2 ± 3.3) were compared using the nonparametric Mann-Whitney test of the Statview Macintosh statistical program. The same test was used for the comparison of low (GF) and high (A) WHR obesity groups. All metabolic variables, blood pressure, body weight, body composition and anthropometric variables have been compared before and after treatment using the paired student t-test. Multiple regression analysis was performed according to SPSS-program.

Table 2 List of correlations ($n = 70$) with SHBG

	r	P
Body fat (kg)	−0.29	NS
Fat free mass (kg)		NS
Waist girth (cm)	−0.29	< 0.01
Hip girth (cm)		NS
WHR	−0.31	< 0.01
HDL cholesterol (mmol/l)	0.26	< 0.05
Systolic blood pressure (mmHg)	−0.28	< 0.05
Diastolic blood pressure (mmHg)		NS
Glucose (mmol/l)	−0.34	< 0.01
Insulin (μU/l)	−0.39	< 0.001
C-peptide (nmol/l)	−0.41	< 0.001
Glucose disposal (μ = 12)	0.68	> 0.01
Free testosterone (pmol/l)	−0.58	< 0.001
Triiodthyronine (nmol/l)	0.39	< 0.01
Free thyroxine (pmol/l)	0.39	< 0.01
Oestradiol (nmol/l)	0.39	< 0.01

SHBG, sex hormone binding globulin; WHR, waist to hip ratio; NS, not statistically significant; HDL,

Results

The general characteristics of participants and the effects of T3 treatment in the 70 patients is shown in Table 1.

The six weeks treatment influenced neither body weight, WHR nor BMI. Apart from small but significant reductions in plasma total cholesterol levels, there were no major changes inmost of variables examined (Table 1 and Figure 1). In spite of an insignificant trend toward a lower blood glucose concentration (not shown), the insulin/glucose ratio was unchanged (2.96 ± 0.03 before and 3.02 ± 0.04 after).

There was a significant increase of SHBG which parallelled the increase in oestradiol, decrease in free testosterone and increase in T3, decrease in thyroxine and trend to a decrease in serum TSH (Table 1), and a significant increase ($p < 0.001$) in the T3/T4 ratio.

There were no side effects reported and all patients completed the planned treatment period.

The concentration of SHBG before treatment with T3 correlated negatively with the concentrations of insulin, C-peptide, glucose, systolic blood pressure, free testosterone and WHR. A positive correlation was found between the basal level of SHBG and the concentrations of free T4, T3, HDL cholesterol and oestradiol (Table 2).

The group of 70 patients was divided into two subgroups with the point of arbitrary division corresponding to the median of SHBG at the base line.

The higher WHR group had low SHBG and higher systolic and diastolic blood pressure, triglyceride, glucose, insulin and free testosterone concentrations.

Treatment for six weeks with T3 resulted in a decrease in plasma cholesterol, increase in SHBG and oestradiol concentrations in both groups. C-peptide concentrations increased in the high SHBG group only.

Free T4 decreased and T3 increased in both groups, but the concomitant decreased in TSH reached statistical significance only in the low SHBG group (Table 3).

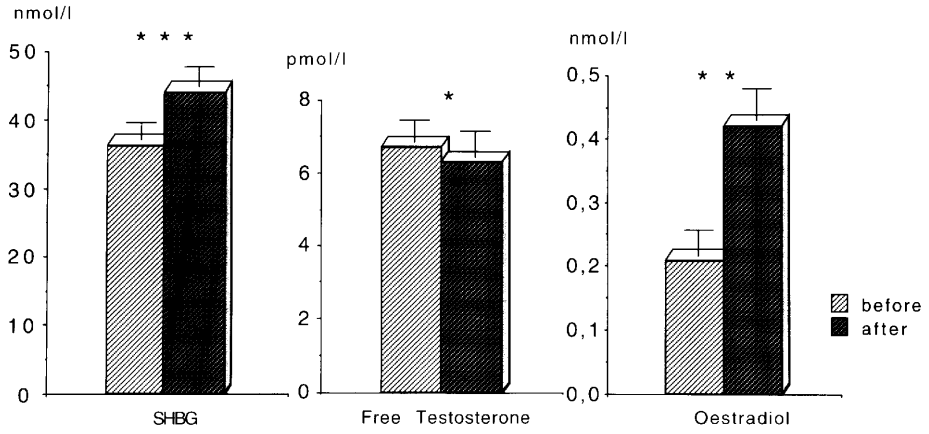

Figure 1 Changes in the concentrations of sex hormone binding globulin (SHBG), free testosterone oestradiol in obese women before and after treatment with triiodothyronine (T3) (20 μg/d), $n = 70$. Blood sampling was undertaken in the same phase of the menstrual cycle, means ± s.e.m. units as in Table 1 and Table 5.

Table 3 Effects of low-dose T3 treatment

		Low SHBG group n = 35	*High SHBG group n = 35*	*Differences between groups*
Body weight (kg)	Before	95.4 ± 2.1	93.1 ± 3.0	NS
	After	95.2 ± 2.2	92.6 ± 2.9	NS
BMI	Before	35.2 ± 0.8	33.5 ± 1.1	NS
	After	35.2 ± 0.8	33.3 ± 1.0	NS
WHR	Before	0.85 ± 0.01	0.82 ± 0.01	< 0.05
	After	0.84 ± 0.01	0.81 ± 0.01	< 0.05
Systolic blood pressure (mmHg)	Before	139.5 ± 3.6	128.9 ± 2.9	< 0.05
	After	136.2 ± 3.7	126.3 ± 2.9	< 0.05
Diastolic blood pressure (mmHg)	Before	86.8 ± 1.1	84.5 ± 1.2	< 0.05
	After	86.6 ± 1.2	85.1 ± 1.3	NS
Cholesterol (mmol/l)	Before	6.38 ± 0.34	5.58 ± 0.19	< 0.05
	After	5.74 ± 0.25**	5.41 ± 0.15*	NS
HDL cholesterol (mmol/l)	Before	1.26 ± 0.06	1.138 ± 0.08	NS
	After	1.32 ± 0.05	1.44 ± 0.08	NS
Triglycerides (mmol/l)	Before	2.92 ± 0.68	1.42 ± 0.10	< 0.05
	After	2.46 ± 0.69	1.60 ± 0.16	NS
Glucose (mmol/l)	Before	5.41 ± 0.33	4.54 ± 0.15	< 0.05
	After	5.52 ± 0.42	4.48 ± 0.15	< 0.05
Insulin (μU/ml)	Before	16.7 ± 1.5	12.5 ± 1.0	< 0.05
	After	18.8 ± 2.6	11.0 ± 1.0	< 0.05
C-peptide (nmol/l)	Before	3.71 ± 0.31	2.60 ± 0.14	< 0.001
	After	3.64 ± 0.33	5.72 ± 0.86*	< 0.05
Free testosterone (pmol/l)	Before	8.35 ± 0.80	4.72 ± 0.70	< 0.001
	After	7.57 ± 0.87	4.62 ± 0.82	< 0.01
Oestradiol (nmol/l)	Before	0.242 ± 0.06	0.196 ± 0.03	NS
	After	0.318 ± 0.06*	0.405 ± 0.06*	NS
SHBG (nmol/l)	Before	22.6 ± 1.30	52.34 ± 2.84	< 0.001
	After	28.56 ± 1.45*	60.29 ± 2.92***	< 0.001
Free T4 thyroxine (pmol/l)	Before	15.7 ± 0.60	17.7 ± 1.0	NS
	After	10.9 ± 0.7***	11.0 ± 1.1***	NS
T3 (nmol/l)	Before	2.23 ± 0.06	2.34 ± 0.13	NS
	After	2.65 ± 0.18*	2.98 ± 0.25*	NS
TSH (m IU/l)	Before	2.69 ± 0.35	2.45 ± 0.33	NS
	After	2.24 ± 0.20*	2.32 ± 0.27	NS

T3, triiodothyronine; SHBG, sex hormone binding globulin; BMI, body bass index; WHR, waist to hip ratio; HDL,; T4,; NS, not statistically significant.
* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$ for changes before/after within groups.

When divided according to the median of WHR (0.84) the A obesity had significantly lower SHBG and higher free testosterone than the GF obesity group. Treatment with T3 resulted in the significant increase of SHBG in both groups (by 20% in A and by 11.6% in GF obesity). A trend (insignificant) toward a decreased free testosterone was observed in both groups (Table 4).

A separate group of 12 patients was randomly chosen from the 70 volunteers and examined with the euglycaemic insulin clamp (Table 5). Their body weight, body fat and fat free mass were not changed by treatment (not shown).

There was no significant change in plasma lipids (not shown), but a small significant decrease of blood glucose (Table 5).

Treatment with T3 resulted in decreased concentrations of plasma creatinine, but no changes in its urinary excretion. There were no changes in the concentrations of plasma or urinary cortisol or plasma concentrations of progesterone. Plasma testosterone and oestradiol showed only trends to decrease and increase respectively (not shown). Plasma concentration of malonyldealdehyde (MDA) (indirect indicator of lipid peroxides concentrations) did not change after treatment. Glucose disposal when calculated for each kg of body weight or kg of fat free mass (FFM) showed a slight trend to increase but the changes did not reach statistical significance (Table 5). Glucose disposal during the insulin clamp was positively correlated to the concentration of SHBG before treatment ($r = 0.65$ $P < 0.01$), but not after. There was also a positive correlation to the concentration of HDL cholesterol ($r = 0.64$) and negative to the concentration of trigylcerides ($r = -0.61$ $P < 0.01$). Glucose disposal calculated for each kg

Table 4 Changes in SHBG and testosterone in abdominal (A) and gluteal-femoral (GF) obesity

		A	*P*	*GF*	*P*	*P between groups*
SHBG (nmol/l)	Before	24.2 ± 2.9	–	41.2 ± 5.1	-	< 0.001
	After	29.8 ± 3.6	xx	46.6 ± 5.0	xx	< 0.001
Free testosterone (pmol/l)	Before	11.6 ± 0.9	–	6.4 ± 1.0	–	< 0.001
	After	9.9 ± 1.6	ns	5.8 ± 1.1	ns	< 0.001

SHBG, sex hormone binding globulin; NS, not statistically significant; xx = $P < 0.01$, for differences before – after within groups.

Table 5 Effect of low-dose T3 in 12 patients who have been examined with insulin euglycemic clamp

	Before	*After*	P
Glucose (mmol/l)	5.31 ± 0.28	5.06 ± 0.23	< 0.05
Insulin (mU/l)	17.6 ± 1.7	19.9 ± 2.9	NS
Glucose disposal (mg/kg body weight × min)	4.16 ± 0.10	5.00 ± 0.10	NS
Glucose disposal (mg/kg FFM × min)	8.95 ± 1.31	9.42 ± 1.54	NS
SHBG (nmol/l)	24.3 ± 3.1	29.5 ± 3.8	< 0.05
Thyroxine (pmol/l)	13.2 ± 0.5	11.0 ± 0.9	< 0.05
TSH (m IU/l)	2.22 ± 0.2	1.57 ± 0.2	< 0.05
T3 (nmol/l)	1.84 ± 0.09	2.49 ± 0.12	< 0.05
Progesterone (nmol/l)	8.49 ± 1.99	7.6 ± 0.35	NS
Cortisol (nmol/l)	347.0 ± 49.7	310.1 ± 25.26	NS
Malonyldialdehyde (mmol × 1^{-1})	0.823 ± 0.06	0.916 ± 0.07	NS
Creatinine (nmul/l)	70.8 ± 2.6	67.3 ± 2.7	< 0.05
Urine creatinine (mmol/24 h)	12.13 ± 0.93	11.41 ± 0.98	NS
Urine cortisol (mmol/24 h)	174.0 ± 24.8	172.1 ± 36.8	NS

T3, triiodothyronine; SHBG, sex hormone building globulin; NS, not statistically significant.

of FFM was also significantly correlated with the concentration of oestradiol ($r = 0.76$ $P < 0.001$).

To evaluate an independent association between SHBG, T3 and insulin, stepwise multiple regression analysis was performed with the basal concentration of SHBG as the dependent variable and the basal level of T3, insulin, body weight and WHR as the independent variables. T3, insulin and body weight significantly contributed to the variations of the concentration of SHBG at the basal level (adjusted $R^2 = 0.42$, $P < 0.001$). The analysis was also performed with the difference in SHBG after the treatment as the dependent variables and the difference in T3, insulin, glucose disposal rate and body weight as the independent variables. Only the difference in the concentrations of T3 was independently correlated with the changes in SHBG concentrations (adjusted $R^2 = 0.45$, $P < 0.001$). The insulin/glucose ratio in a whole group of 70 volunteers did not change after the treatment.

Discussion

Decreased concentration of SHBG is a characteristic feature of abdominal obesity,[8] and polycystic ovary syndrome[9–16] and an indirect index of abdominal obesity.[16] Low SHBG concentrations have also been described as an independent risk factor for the development of NIDDM[2] and is associated with glucose intolerance and hyperinsulinaemia in female populations with varying BMI and WHRs.[15–17] Low SHBG has also been associated with several indices of insulin resistance in muscle tissue[18–20] and impairment of insulin extraction.[21] On the other hand thyroid hormones and oestrogen have been found to contribute to the increase of plasma SHBG concentration.[6]

These observations are in agreement with present findings of a negative association between the concentration of SHBG and blood glucose, plasma insulin, C-peptide and WHR, and a positive correlation with glucose disposal (insulin sensitivity). Furthermore, there was a significant negative correlation between the SHBG and systolic blood pressure and a positive correlation with HDL cholesterol. There was also a significant correlation with thyroid hormones–the higher the concentration of thyroxine and T3, the higher the concentration of SHBG.

Impact of T3 on SHBG

In this study, the administration of T3 in a very low dose of 20 mg/day resulted in a significant increase of the SHBG concentration. In the whole group (irrespective of the initial SHBG concentration and the types of adipose tissue distribution), T3 treatment resulted in no change in insulin and C-peptide concentrations and no significant change in insulin sensitivity as judged from the results of the insulin euglycemic clamp (Table 5). In addition, multiple regression analysis found that neither changes in insulin nor changes in insulin sensitivity contributed to the T3-induced increases in SHBG.

Results according to WHR and SHBG status

When divided according to the median of WHR (0.84), SHBG concentrations were nearly half those in A obesity than in GF obesity (Table 4). Treatment with T3 induced increases in both groups. Plasma insulin concentrations were higher in A than in GF obesity and did not change after treatment in either of the groups. This observation also confirms that T3 evokes its effect on SHBG independently of plasma insulin.

The concentration of C-peptide significantly increased without an increase in plasma insulin concentration in the high SHBG group. From this it is suggested that T3 treatment may have resulted in an increase in insulin secretion (as judged from the increased C-peptide). This, however, was not associated with a change in insulin sensitivity, but with possibly an improved hepatic removal of insulin (as judged from the decreased insulin/C-peptide ratio). Although the clamp studies were performed in only 12 patients, these results support the conclusion drawn from the analysis of insulin/glucose ratios which

remained unchanged in all 70 patients. This raises the question whether the concentration of SHBG can be treated as a general marker for hyperinsulinaemia and insulin resistance in humans.[13]

SHBG is synthesised in the liver and the regulation of its synthesis is known from studies in a hepatoma cell line.[4] The liver is exposed to much higher insulin concentrations than other organs and insulin is a potent inhibitor of SHBG production in hepatocytes.[4] Moreover, when added together, insulin is capable of blocking the stimulatory effect of oestradiol and T4.[4]

In obese individuals, the concentration of SHBG is inversely correlated to WHR and positively correlated to local insulin sensitivity, capillarisation and the percentage of slow-twitch insulin-sensitive muscle fibres, the main target of glucose utilisation in muscle tissue.[2,3,7] Thus hypersecretion and/or insulin resistance caused by the presence of insulin resistant muscle tissue, seem to play a regulatory role in the synthesis of SHBG in the liver.

However, in lean individuals, there is a conflicting information about the relationship between insulin and SHBG.[22,23] In contrast to obese women with polycystic ovary syndrome, in lean women suppression of insulin secretion by diazoxide is not associated with increased SHBG concentrations.[24] Moreover, in insulin-treated diabetic women, SHBG concentrations are not suppressed and may even be elevated.[25,26] In addition, insulin infusions do not alter SHBG concentrations in normal women[27] and there is no association between SHBG concentrations and insulin secretion rate in normal healthy premenopausal women[13] and men.[28]

Low tissue concentration of T3?

Since T4 concentrations significantly decreased, the increased concentration of T3 is certainly one factor responsible for the change in concentrations of SHBG. As the percent decrease in T4 was higher than the increase in T3, it is tempting to speculate that obesity, particularly A obesity, is associated with a relative low responsiveness (resistance) and/or a relative deficiency of T3 in several specific organ(s).[29] We chose intentionally a ratio of total T3 to free T4 to avoid interpretation problems as the concentration of free T4 is to a higher extent dependent on the binding of this hormone to prealbumins (TBPA) and thyroxine binding globulin (TBG). Anyhow in another group of patients treated in similar way the ratio of free T3 to T4 was found to be increased as a result of parallel increase of free T3 and a decrease of free T4 (not shown).

This concept is quite in line with recent findings that the replacement therapy for hypothyroidism with T4 alone does not ensure euthyroidism in all tissues, and observations that the T3 concentration in the liver and other tissues can be too low to be quantified from serum T4 and T3 levels.[33]

In humans the production of T3, which has much higher biological activity than T4, depends mainly on the extrathyroidal deiodination of T4 to T3.[30] It has been suggested that the impairment of the deiodination system and reduced conversion of T4 to T3, is a characteristic feature of obesity.[31,32] It has also been suggested that hypometabolism may be treated as one of the contributing factors in the development of overweight and its complications.[22,33,34] We have found that low deiodination activity especially in the liver could be a reasonable contributing factor to lowering of SHBG concentration.

Theoretically, insulin and glucose phosphate increase deiodinase activity.[21] Consequently the improvement of glucose metabolism and/or insulin sensitivity, could be expected to increase T3 concentration. However, we did not observe any significant changes in either insulin or blood glucose concentration.

Androgens/oestrogen balance and treatment by T3

It seems that T3 treatment also improves androgens/oestrogen balance, as both a slight decrease of free testosterone and significant increases in the concentration of oestradiol were observed. Decreases in SHBG are associated with a greater rise in free testosterone than in free oestradiol because the affinity of SHBG for testosterone is greater than for oestradiol.[24] Moreover, other androgens also bind to SHBG, and a decline in SHBG would be associated with increases in free concentrations of other androgens as well. Thus, despite a rise in free oestradiol with decreased SHBG, reduced concentration of SHBG shifts the relative androgen to oestrogen balance towards increased androgenicity.

Treatment with T3 was associated with a significant rise in oestradiol. This rise was not due to the timing of blood sampling, as the blood samples were taken during the same phase of the menstrual cycle.

Thus, a plausible explanation could be that the decreased free oestradiol, secondary to the increased SHBG, could activate gonadotropin secretion and/or that the observed increase is a direct effect of T3 on the total oestradiol concentration. Whatever the cause, an increase in the concentration of oestradiol is a rather unexpected finding, in contrast to a decrease of free testosterone, which could be treated as an expected and direct consequence of increased binding to SHBG. A separate study with measurements of gonadotrophin concentrations and aromatose activity in adipose tissue is obviously needed to elucidate the possible mechanisms. Interesting in this connection is the observation that the increase in oestradiol was not associated with a change in plasma progesterone level. The increase in oestradiol concentrations together with the decrease in testosterone could result in decreased androgenisation in A (high WHR/low SHBG) obesity.

It was interesting to follow the effects of T3 treatment for a longer period of time. Thirty patients who participated in this study were followed for three

months while taking their habitual energy intake and the same dose of T3. The SHBG concentrations were even higher than following this six weeks treatment. No measurements of insulin sensitivity were made. Providing that androgenisation is responsible as a contributing factor to the development of insulin resistance, one would expect improvement in insulin sensitivity as a consequence of the decreased free testosterone and increased oestradiol concentrations. Further studies are needed to confirm or reject this concept so vigorously discussed in the literature.[9–13.]

Thus, it seems that thyroid function and possibly the rate of deiodination of thyroxine in the liver may contribute to the lower SHBG levels and the secondary androgenisation of A obesity.

Treatment with 20m T3 did not result in changes in body weight in our group. It has been previously reported that treatment with small doses of T4 resulted in very slight increases of T4 and T3 concentrations, and increased resting energy expenditure by 5%.[31] In a recent study[34] by Astrup *et al*, it was shown that physiological variations in plasma androstenedione and T3 concentrations contributed to the interindividual variance in energy expenditure of normal women, and their role is not different in obese women. These variations could account for individual differences in sleeping energy expenditure of 594kJ/day. Obviously, the treatment period of our study was too short to show any statistically significant decrease of body weight.

The present study resulted in a reduction in total cholesterol in the absence of significant changes in HDL cholesterol. This result is in accordance with those of the small number of published reports on subclinical hypothyroidism and the effects of thyroid hormones treatment upon lipoprotein fractions in patients with mild hypothyroidism.[35] The lack of 'favourable' increase in HDL cholesterol probably depends on the effect of T3 on the hepatic lipase activity.[36]

Conclusion

In summary, treatment for six weeks with small doses of T3 resulted in a significant increase of SHBG in spite of unchanged plasma insulin levels and insulin sensitivity. This was accompanied by a decrease in plasma total cholesterol and in some patients the probable improvement of hepatic insulin extraction (as judged from the C-peptide/insulin ratio). It is possible that low concentrations of T3 and/or low T4 deiodination in some tissues or organs contribute to the observed low concentration of SHBG in A obesity. The concomitant decreased free testosterone together with increased oestradiol concentration are likely to contribute to the amelioration of the androgenisation observed in A obesity.[7,8,10,11,14,18] This study seems to show that administration of small doses of T3 evokes several favourable beneficial effects. The improved hormonal profile, decreased plasma cholesterol and increased SHBG concentrations may motivate the use of small doses of T3 as an adjunct in the dietary treatment of abdominal obesity, particularly in some subgroups of obese women with indirect indications of relative resistance to thyroid hormones possibly dependent on slower deiodination of thyroxine.

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