

CLINICAL STUDY

Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals

Maria Alevizaki^{1,2}, Katerina Saltiki^{1,2}, Paraskevi Voidonikola³, Emily Mantzou¹, Christos Papamichael³ and Kimon Stamatelopoulos³

¹Endocrine Unit, Department of Endocrinology and Metabolism, 'Evgenidion' Hospital, Athens University School of Medicine, 18, Papdiamantopoulou, 11528 Athens, Greece, ²Endocrine Unit, Department of Medical Therapeutics, Alexandra Hospital, Athens University School of Medicine, 80 Vass Sofias Avenue, 11528 Athens, Greece and ³Vascular Laboratory, Department of Medical Therapeutics, Alexandra Hospital, Athens University School of Medicine, 80 Vass Sofias Avenue, 11528 Athens, Greece

(Correspondence should be addressed to M Alevizaki; Email: mani@otenet.gr)

Abstract

Objective: Thyroid function parameters have been associated with obesity, but associations with the type of adiposity have not been examined. We used ultrasound (US) to assess regional adiposity and investigated associations of thyroid function with parameters of central obesity.

Design: Cross-sectional study.

Methods: A total of 303 apparently healthy individuals (age 42.9 ± 8.8 , body mass index (BMI) 19.0–43.3, median 26.2 kg/m², 181 women) were examined for indices of the metabolic syndrome. BMI, waist and hip circumference, abdominal subcutaneous fat (SF), and preperitoneal fat (PF) layer was estimated. TSH, free thyroxine (fT₄), triiodothyronine (T₃), thyroid autoantibodies, insulin, glucose, and lipid levels were measured. Subjects receiving T₄ (9.2%) were excluded.

Results: SF and SF/PF ratio were inversely correlated with fT₄ levels ($r = -0.169$, $P = 0.023$, $r = -0.193$, $P = 0.009$ respectively). In multivariate analysis, fT₄ was a predictor of SF and SF/PF, independently of age, sex, and smoking. SF correlated with TSH levels ($r = 0.149$, $P = 0.037$). PF and SF were positively associated with T₃ levels ($r = 0.245$, $P = 0.004$ and $r = 0.189$, $P = 0.019$ respectively). T₃ levels were positively associated with BMI ($r = 0.257$, $P = 0.0004$), waist perimeter ($r = 0.324$, $P < 0.0001$), and waist-to-hip ratio (WHR; $r = 0.363$, $P < 0.0001$). The T₃/fT₄ ratio was positively correlated with SF ($r = 0.182$, $P = 0.028$), WHR ($r = 0.267$, $P = 0.0003$), and BMI ($r = 0.146$, $P = 0.043$).

Conclusions: Increasing SF accumulation as assessed by US is associated with lower fT₄ and higher TSH levels among euthyroid slightly overweight individuals. These associations indicate that subtle variation in thyroid function may participate in regional adiposity.

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Introduction

Thyroid function has been associated with obesity in several reports, but this relationship is not etiologically clear (1). Overt hypothyroidism may be associated with increased body weight (2) as well as with various adverse cardiovascular effects. Similarly, subclinical hypothyroidism has also been associated with higher body mass index (BMI), especially in older women (3), but this finding is not consistent (4).

Furthermore, even in the normal population, there are studies that have reported associations between thyroid function parameters such as TSH and thyroid hormone levels, within the normal range, and changes in BMI (5), weight (6), and fat distribution (7). A large population study showed that TSH levels were positively and free thyroxine (fT₄) levels negatively associated with BMI (5). In two large population studies, among

non-smokers, BMI was also positively correlated with TSH (8) and inversely with fT₄ (9). Finally, TSH was correlated with BMI in older females (10). However, these results have not been confirmed by all investigators; Manji *et al.* reported no associations of TSH or fT₄ levels with BMI in euthyroid individuals (11).

The association of thyroid function parameters with fat distribution has not been studied in detail. De Pergola *et al.* (7) reported that central fat accumulation, as assessed by waist circumference measurement, was positively and independently associated with TSH and free triiodothyronine (fT₃) levels in overweight and obese euthyroid women.

Thyroid function parameters even within the normal range have also been associated with alterations in metabolic and cardiovascular parameters such as arterial pressure, endothelial function and coronary heart disease (4, 12–14). Moreover, even slightly

impaired thyroid function might be associated with dyslipidemia and insulin resistance (13).

It is well known that adipose tissue and especially visceral fat is implicated in the pathogenesis of the metabolic syndrome (MS). Subjects with increased central fat distribution are at higher risk for the development of cardiometabolic disease (15). Visceral and subcutaneous fat (SF) expresses thyroid hormone receptors (16–19) as well as TSH receptors that may also directly influence various functions of adipose cells (20). However, it is not known whether the type of adiposity could be implicated in the associations of thyroid function parameters with obesity.

The aim of our study was to investigate in apparently healthy individuals possible associations of thyroid function with measurements of central and peripheral obesity and parameters of the MS. For this purpose we used ultrasound (US), a reliable low-cost method, to assess regional adiposity.

Subjects and methods

We studied 303 apparently healthy individuals (181 women, 122 men, mean age 42.9 ± 8.8 , BMI $19.0\text{--}43.3$, median 26.2 kg/m^2) who were examined for indices of the MS. All subjects were attending a preventive medicine program that offered investigation for the presence of unrecognized MS in the outpatients clinic of our hospital over a period of 11 months. The inclusion criteria of our study were the absence of a history of diabetes (previously diagnosed according to the American Diabetes Association criteria), as well as the absence of overt cardiovascular or other systemic disease. A total of 41.1% were current smokers or had recently (<6 months) ceased smoking. Thyroid function tests (fT_4 , TSH, T_3 , antiTG autoantibodies and antiTPO autoantibodies) were included in the protocol.

Subjects receiving T_4 or drugs possibly affecting thyroid function (such as lithium, amiodarone, interferon-gamma) or circulating free thyroid hormone levels (such as continuous treatment with high doses of salicylate or non-steroid anti-inflammatory drugs) were excluded from the analysis (9.2%, $n=28$), so the population finally analyzed included 275 subjects (163 women and 112 men). The study was approved by the institutional Ethics Committee and all subjects gave their informed consent.

Height and weight were measured with subjects wearing indoor clothes without shoes. BMI was calculated according to the formula weight (kg)/height (m^2). Waist and hip perimeter (cm) measurements were also performed. WHR was used to evaluate fat distribution. Arterial pressure was measured in a sitting position using a standard mercury sphygmomanometer.

Classical predisposing risk factors for cardiovascular disease, MS (arterial hypertension, dyslipidemia, smoking etc.), and current drug therapy were also recorded. Ninety-one (55.8%) of women out of the total participating in the study were premenopausal. The presence of the MS was defined using the ATP III criteria, i.e. the presence of any three of the following metabolic traits: abdominal obesity (waist circumference $>102 \text{ cm}$ for men and $>88 \text{ cm}$ for women); triglycerides ($\geq 150 \text{ mg/dl}$, high-density lipoprotein (HDL) $<40 \text{ mg/dl}$ for men and $<50 \text{ mg/dl}$ for women); blood pressure ($\geq 130/85 \text{ mmHg}$); and fasting glucose ($\geq 100 \text{ mg/dl}$; 5.55 mmol/l) (21).

Fasting blood samples were obtained by venipuncture between 0800 and 0900 h. Serum TSH, fT_4 and T_3 were measured using chemiluminescent immunometric assays with the DPC Immulite 2000 (Siemens, Gwynedd, UK). Serum anti-thyroid antibodies (antiTPO, antiTG) analysis was performed by RIA using the reagents Brahms DINO test (BRAHMS Diagnostica GmbH, Berlin, Germany). The reference ranges were: TSH $0.36\text{--}4 \text{ mU/l}$; fT_4 $9\text{--}26 \text{ pmol/l}$; T_3 $1.1\text{--}2.9 \text{ nmol/l}$; antiTPO $<60 \text{ IU/ml}$; and antiTG $<60 \text{ IU/ml}$. The T_3/fT_4 ratio was calculated as an index of the activity of peripheral $5'$ -deiodinase.

The levels of glucose, total cholesterol, HDL, low-density lipoprotein (LDL), triglycerides, and uric acid were measured immediately (using an automated analyzer, Integra 400, Roche). Insulin levels (in specimens kept frozen at -20°C until analysis was performed by IRMA, Biosource Europe SA, Nivelles, Belgium) were also estimated. Basal insulin resistance index (homeostasis model assessment-insulin-resistance-index, HOMA-IR) was calculated according to the formula: insulin resistance = $FI \times G/22.5$, where FI = fasting insulin ($\mu\text{U/ml}$) and G = fasting glucose (mmol/l).

Abdominal SF and preperitoneal fat (PF) layers were estimated by B-mode US imaging (US, 7.0 MHz, linear array transducer, Acuson 128 XP, Mountain View, CA, USA). The measurements that were obtained were the following: minimum SF, defined as the minimum distance from the skin to linea alba, and maximum PF, defined as the maximum distance from linea alba to the interior surface of the liver. The ratio of SF to PF layer (S/P) was then calculated. Coefficient of variation of these measurements obtained by the same investigator was 6.8% and was quite similar to that previously reported (22). The measurement of the maximum PF layer that highly correlated with visceral fat has been previously shown (22). US is considered a reliable method for the assessment of regional adiposity compared to other diagnostic procedures such as computed tomography, dual energy x-ray absorptiometry (DEXA), magnetic resonance imaging and at the same time it is a simpler and inexpensive procedure (22–25).

Statistical analysis

Statistical analysis was done using the SPSS statistical package. All descriptive data are presented as mean \pm s.d.. Pearson's correlation coefficient was used to investigate correlations between continuous variables. Multiple regression analysis was performed to investigate the simultaneous effect of different variables on the adiposity parameters. In the initial simple regression analysis, a threshold of $P < 0.05$ was used to identify candidate variables for inclusion in the final model. The multiple regression analyses were performed using the enter procedure. All covariates included in the final models were tested for interactions with each other. Because the tolerance values for each covariate were > 0.5 , no correction for the co-linearity of data were necessary. Student's *t*-test was used to compare mean values between groups where the distribution was normal.

Results

TSH range was 0.18–5.9, median 1.4 mU/l; fT_4 range was 11.5–25.9, median 17.4 pmol/l. T_3 range was 0.72–1.7, median 1.17 nmol/l. Eight subjects had TSH levels between 0.18 and 0.35 mU/l and were considered as having subclinical hyperthyroidism, while seven subjects had TSH levels between 4.1 and 5.9 mU/l and were considered as having subclinical hypothyroidism. The clinical and biochemical characteristics of the population are shown in Table 1.

SF was inversely correlated with fT_4 levels ($r = -0.168$, $P = 0.017$); the SF/PF ratio was also inversely, rather weakly correlated with fT_4 levels ($r = -0.194$, $P = 0.006$; Fig. 1). These associations

Table 1 Characteristics of the studied population ($n = 275$).

	Mean \pm s.d.	Median	Range
Age (years)	46.71 \pm 8.9	48.00	34.3–52.2
Gender (female) <i>n</i> (%)	163 (59.3%)		
BMI	26.9 \pm 4.77	26.21	19.0–43.3
Weight (kg)	77.02 \pm 16.5	75.00	49–125
Waist perimeter	90.50 \pm 14.8	90.00	53–130
Waist-to-hip ratio	0.87 \pm 0.13	0.87	0.5–1.4
Pre-peritoneal fat layer (mm)	12.16 \pm 4.6	12.10	0.8–30.5
Subcutaneous fat layer (mm)	12.05 \pm 5.38	11.25	0.7–32
Metabolic syndrome <i>n</i> (%)	37 (13.4%)	–	–
TSH (mU/l)	1.56 \pm 0.94	1.40	0.18–5.9
Free T_4 (pmol/l)	17.57 \pm 2.5	17.40	11.5–25.9
T_3 (nmol/l)	1.18 \pm 0.18	1.17	0.72–1.71
HOMA-IR index	1.85 \pm 1.4	1.46	0.4–11.0
Total cholesterol (mg/dl) (mmol/l)	209.3 \pm 40.1	208.0	123–372
HDL (mg/dl) (mmol/l)	59.26 \pm 15.8	58.0	3.18–9.60
LDL (mg/dl) (mmol/l)	145.24 \pm 38.41	141.0	71.0–233.0
	3.75 \pm 0.99	3.64	1.83–6.0

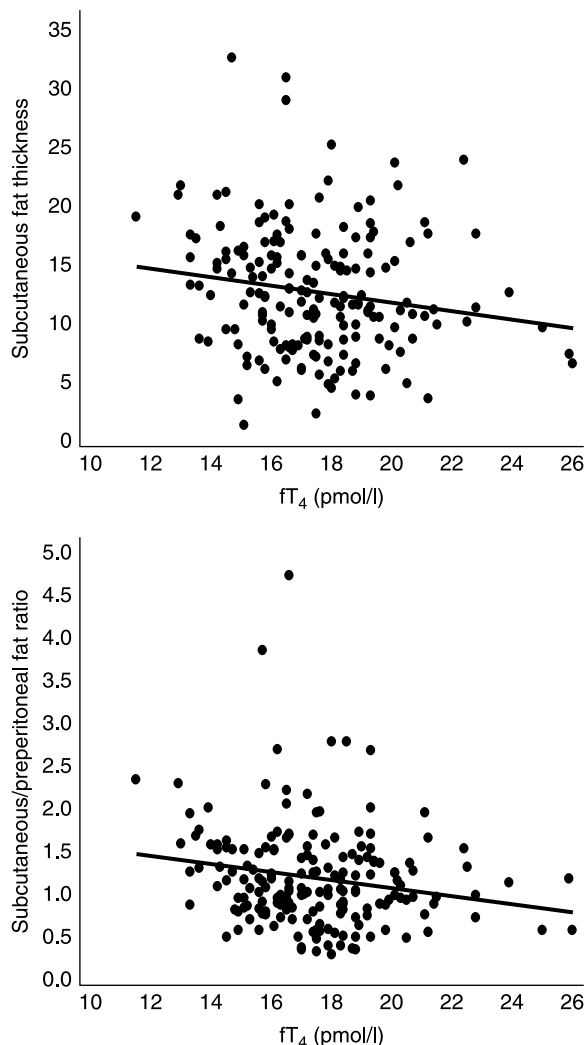


Figure 1 Association of free T_4 with subcutaneous fat thickness ($r = -0.169$, $P = 0.023$) and subcutaneous/preperitoneal fat ratio ($r = -0.193$, $P = 0.009$) in euthyroid apparently healthy individuals.

remained significant only when subjects with $BMI \geq 25$ were analyzed ($r = -0.25$, $P = 0.009$ and $r = -0.21$, $P = 0.026$ respectively), while they were not significant in the subjects with $BMI < 25$. When only male subjects were analyzed, SF and SF/PF were inversely correlated with fT_4 levels ($r = -0.247$, $P = 0.027$ and $r = -0.2193$, $P = 0.05$ respectively). When only female subjects were examined there was no significant association between SF and fT_4 levels while there was a weak negative association between the ratio SF/PF and fT_4 levels ($r = -0.14$, $P = 0.14$ and $r = -0.19$, $P = 0.044$ respectively).

By multivariate regression analysis, fT_4 levels among age, smoking, HOMA-IR, and gender were a significant independent predictor of SF (Table 2). fT_4 was also an independent predictor of the ratio SF/PF (Table 2).

Table 2 Multivariate linear regression analysis for the association between subcutaneous fat layer (a) and subcutaneous/preperitoneal fat ratio (b) and parameters associated with adiposity in euthyroid individuals.

Variable	Parameter	Partial regression coefficient, <i>B</i> (95% CI)	<i>t</i>	<i>P</i>	<i>r</i> ²
(a)					
Subcutaneous fat layer	Age	0.136 (0.056 to 0.217)	3.343	0.001	0.229 <i>P</i> <0.001
	Gender	1.506 (−0.026 to 3.038)	1.941	0.054	
	HOMA-IR ^a	5.115 (2.821 to 7.410)	4.401	<0.001	
	Smoking	0.709 (−0.304 to 1.722)	1.382	0.169	
	Free T ₄	−0.414 (−0.698 to −0.130)	−2.882	0.004	
Variable	Parameter	β-Partial regression coefficient, <i>B</i> (95% CI)	<i>t</i>	<i>P</i>	<i>r</i> ²
(b)					
Subcutaneous/ pre-peritoneal fat ratio	Age	0.012 (0.003 to 0.021)	2.50	0.013	0.144 <i>P</i> <0.001
	Gender	0.317 (0.140 to 0.495)	3.52	0.001	
	Smoking	0.058 (−0.061 to 0.177)	0.957	0.340	
	Free T ₄	−0.051 (−0.085 to −0.018)	−3.041	0.003	

^aHOMA-IR was log transformed to reduce skewness.

Thus, for a change of 1 pmol/l in fT₄, a decrease of 0.414 mm and 0.051 units is expected in the SF and in the ratio SF/PF respectively.

In the univariate analysis SF showed a positive association with TSH levels in all subjects (Pearson's correlation, $r=0.149$, $P=0.037$) as well as in those with BMI ≥ 25 ($r=0.19$, $P=0.035$); however, this association was no longer significant in the multivariate analysis when other confounding factors were taken into account (age, gender, smoking, HOMA-IR).

SF was positively associated with WHR ($r=0.213$, $P=0.003$), HOMA-IR ($r=0.346$, $P<0.001$), total cholesterol levels ($r=0.16$, $P=0.022$), LDL levels ($r=0.154$, $P=0.026$), and triglyceride levels ($r=0.1611$, $P=0.020$).

PF was also associated with WHR ($r=0.434$, $P<0.0001$), HOMA-IR ($r=0.2519$, $P=0.0003$), and lipid levels. There was no association between PF layer thickness and fT₄ or TSH levels.

There were no significant associations of fT₄ and TSH levels with waist perimeter, WHR or BMI. No association between fT₄ and HOMA-IR or lipid levels was found. Higher TSH levels were associated with higher total cholesterol, LDL levels and HOMA-IR ($r=0.16$, $P=0.006$, $r=0.15$, $P=0.008$ and $r=0.124$, $P=0.035$ respectively).

SF and PF were positively associated with T₃ levels ($r=0.189$, $P=0.019$ and $r=0.245$, $P=0.004$ respectively, Fig. 2). However, by multivariate regression analysis T₃ levels did not determine SF or PF fat independently of other confounding factors (age, gender, smoking, HOMA-IR). T₃ levels were also positively correlated with weight ($r=0.197$, $P=0.006$), BMI ($r=0.257$, $P=0.0004$), waist perimeter ($r=0.324$, $P<0.0001$), and WHR ($r=0.363$, $P<0.0001$). Mean T₃ levels and HOMA-IR were higher in subjects with PF ≥ 11 mm compared to those with PF < 11 mm (T₃ levels 1.23 ± 0.19 vs 1.15 ± 0.18 ,

$P=0.023$ and for HOMA-IR 2.25 ± 1.6 vs 1.59 ± 1.3 , $P=0.002$, *t*-test).

The T₃/fT₄ ratio (T₃/fT₄) was positively correlated with SF ($r=0.182$, $P=0.028$), waist perimeter ($r=0.217$, $P=0.003$) and the WHR ($r=0.267$, $P=0.0003$), as well as with BMI ($r=0.146$, $P=0.043$). By multivariate regression analysis, T₃/fT₄ was marginally associated with SF ($B=5.7$, 95% CI -0.443 to 11.92 , $P=0.068$, *r* square for model = 0.227 , P for model <0.001) independently of other confounding factors (age, gender, HOMA-IR, and smoking); this association indicates that for every 0.1 change of the ratio a change of 5.7 mm in SF is expected.

No associations were found between the titers or positivity of thyroid autoantibodies (antiTG or antiTPO) and the various measurements of adiposity such as SF, SF/PF, PF, WHR or BMI.

Finally, mean fT₄, T₃, and TSH levels did not differ between subjects fulfilling the criteria of the MS ($n=37$, 13.4%) and those who did not. Subjects with MS versus without MS: fT₄ 18.25 ± 3.5 vs 17.6 ± 2.3 pmol/l; TSH 1.43 ± 0.8 vs 1.57 ± 1.1 mU/l; T₃ 1.23 ± 0.3 vs 1.19 ± 0.2 nmol/l; all non significant.

Discussion

In this cohort of euthyroid apparently healthy individuals, we have demonstrated, for the first time, that thyroid function parameters are associated with measurements of regional adiposity obtained by US imaging. We have shown that fT₄ levels are negatively associated with the abdominal SF layer thickness as well as with the SF/PF ratio. These associations were rather weak but were independent of age, sex, and other obesity parameters. Moreover, we found that TSH levels, although not independently, showed a positive association with the abdominal SF layer thickness. Thus, it

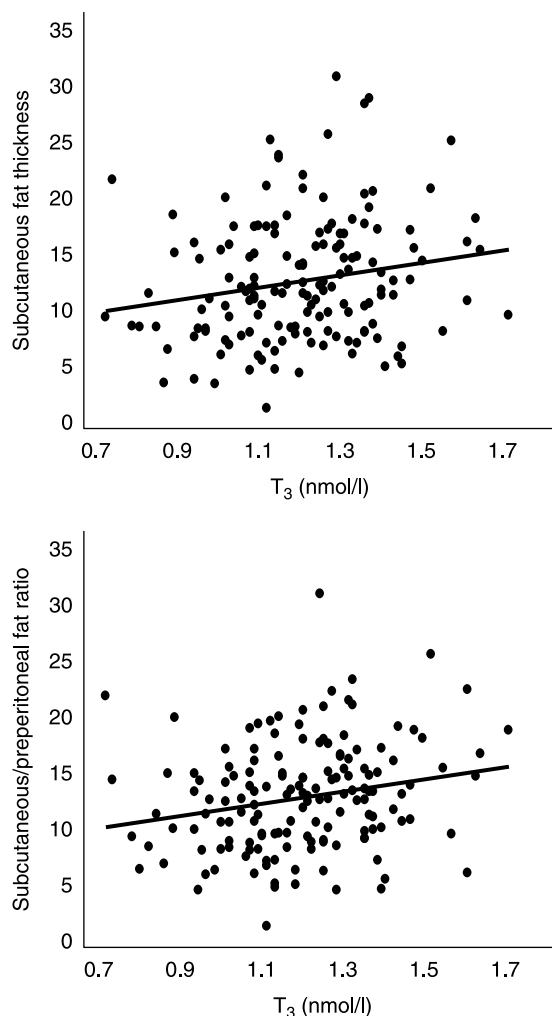


Figure 2 Association of T_3 levels with subcutaneous ($r=0.189$, $P=0.019$) and preperitoneal fat thickness ($r=0.245$, $P=0.004$) in euthyroid apparently healthy individuals.

seems that subtle differences in thyroid function parameters may participate in regional adiposity even in clinically euthyroid individuals. This finding is in accordance with the report of Al-Adsani *et al.* who described that resting energy expenditure responds to small variations of thyroid status within the subclinical range (26).

We did not find any significant association between PF and fT_4 or TSH levels. This could be attributed to the fact that the subcutaneous compartment has an increased capacity to store fat compared to visceral fat (27). This finding is compatible with a very recent report which showed that the expression of the thyroid hormone receptor $TR\alpha 1$ gene is much higher in SF compared to omental fat and that this difference is much more striking in obese individuals (19). Our finding in the subgroup of overweight and obese subjects concerning the inverse association of SF layer

with fT_4 levels further agrees with this report (19). Thus, it seems that the associations of slightly impaired thyroid function with components of the MS that has been reported may reflect associations with adiposity in general as this may be represented by SF (12). It thus appears that lower fT_4 levels even within the normal range may influence fat accumulation only in the subcutaneous layer, without affecting the preperitoneal layer.

Associations concerning thyroid function and regional adiposity measurements have not been previously reported; however, there are several reports in the literature which examine associations of thyroid function with other obesity parameters. fT_4 levels have been recently associated with BMI, waist perimeter and other components of the MS in both sexes (28). Two large population studies showed a positive association of TSH levels with BMI and with weight gain (5, 6) as well as a negative association between fT_4 levels and BMI (5). In another older-population study, a similar association of TSH with BMI, over a wide range, was reported; however, when only the subgroups of euthyroid and subclinically hypothyroid subjects were considered, no difference in BMI was found (29). Similarly, higher TSH levels have been found in subjects with morbid obesity compared to normal weight or mildly obese subjects (30, 31). These results point to the same direction as our findings concerning regional adiposity parameters. It is likely that the previously mentioned reports in the literature, concerning the associations of TSH or fT_4 levels with BMI in euthyroid individuals, possibly reflect associations with subtle alterations in thyroid function. In our study, we did not find associations of fT_4 or TSH levels with BMI. This could be due to the relatively smaller number of subjects studied. Similarly, there are reports in the literature where no associations between TSH or fT_4 levels and BMI were found (4, 11). However, it is likely that SF layer thickness is more sensitive than BMI as an early index of obesity.

When analysis was performed according to gender, these associations remained significant mainly in male participants. Central obesity in men is more extensive compared to women and thus these findings are probably more obvious in men than in women. Data concerning male subjects are rare in the literature. Nyren *et al.* have reported higher BMI in non-smoking euthyroid males with TSH levels in the highest quartile of the normal range compared to those in the lowest (8). In another large study TSH levels were associated with body weight in men as well as in women (6). It should be stressed that all of these studies examined rough indices of obesity and that none of them examined associations with regional fat measurements as in the current study. In the studies concerning females, as has already been mentioned, thyroid function has indeed been associated with obesity parameters (7, 10, 30).

Another interesting finding in our study concerns the positive association of T_3 levels with SF and the PF layer thickness. Moreover, T_3 levels were positively correlated with weight, BMI, waist perimeter, and WHR. There are several studies in the literature which examined associations of T_3 levels with obesity parameters. In the study by Knudsen *et al.* (5) no association of fT_3 levels with BMI was found. However, it is likely that in our study where the subjects were rather overweight, such association was easier to identify. Our findings are in the same direction as the study by de Pergola *et al.*, performed in overweight and obese women where fT_3 and TSH levels were positively associated with waist perimeter (7). In particular morbidly obese subjects have been recently shown to have higher fT_3 levels compared to normal weight subjects (32). Several possible mechanisms have been proposed to explain these findings; T_3 increases energy expenditure and thermogenesis in parallel with increases in body weight (7, 33–35). Other possible explanations could be a possible resistance to the action of thyroid hormones (36) or a reset of the hypothalamic and pituitary 'thyrostat' (32). Leptin that is produced mainly by the SF adipocytes (37), may be also involved (10, 37).

The T_3/fT_4 ratio was also positively but not independently associated with SF thickness. This finding agrees with the report of de Pergola *et al.* in which the fT_3/fT_4 ratio showed a positive association with waist perimeter (7). It has been suggested that in a mild hypothyroid state where there is a slight decrease in T_4 levels, the efficiency of the conversion of T_4 – T_3 by 5'-deiodinase may be increased (38). The finding of our study where fT_4 levels were negatively associated with subcutaneous abdominal adiposity might concur with these hypotheses. Thus, a variety of mechanisms may be involved in the associations of thyroid function with regional adiposity parameters.

Furthermore, we found that biochemical parameters of the MS were associated with higher TSH levels, despite the fact that associations with the presence of the MS itself were not found. These findings are partly in accordance with the results previously reported (12, 30, 39). Finally, there were no associations between the presence of thyroid autoantibodies and measurements of fat layer thickness. Similarly, no association has previously been reported between thyroid autoantibodies and BMI (11). Rotondi *et al.* have also reported that obese subjects with subclinical hypothyroidism, compared to normal weight ones, have a lower rate of thyroid autoantibody positivity (31).

Taken together, our results might suggest that slightly impaired thyroid function may increase regional adiposity in apparently healthy individuals. One of the limitations of our study is that it does not represent an entirely random population: the subjects included in the study volunteered to attend the preventive medicine program. These individuals might be more motivated to health problems, or they might be aware of the presence

of increased risk factors. This is indeed reflected in the fact that the population sample was, on average, overweight. One cannot exclude the possibility that this is one reason why these associations were indeed revealed. It is thus possible that these associations may not apply to a population with a lower medium weight and BMI.

In conclusion, SF thickness as assessed by US is associated with lower fT_4 and higher TSH levels among slightly overweight euthyroid individuals. These findings may indicate that the reported associations of thyroid function parameters with BMI are not due to differences in visceral fat and may indeed reflect the biological significance of small variations in thyroid function for general adiposity as assessed with SF accumulation. However, one should stress that these results do not by any means justify the administration of thyroid preparations in obesity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Tourli P & Alevizaki M. Obesity and thyroid. *Obesity and Metabolism* 2007 **3** 116–130.
- 2 Hoogwerf BJ & Nuttall FQ. Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. *American Journal of Medicine* 1984 **76** 963–970.
- 3 Lindeman RD, Romero LJ, Schade DS, Wayne S, Baumgartner RN & Garry PJ. Impact of subclinical hypothyroidism on serum total homocysteine concentrations, the prevalence of coronary heart disease (CHD), and CHD risk factors in the New Mexico Elder Health Survey. *Thyroid* 2003 **13** 595–600.
- 4 Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A & Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Annals of Internal Medicine* 2000 **132** 270–278.
- 5 Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L & Jorgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4019–4024.
- 6 Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN & Vasan RS. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Archives of Internal Medicine* 2008 **168** 587–592.
- 7 De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P & Giorgino R. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. *Clinical Endocrinology* 2007 **67** 265–269.

- 8 Nyrnes A, Jorde R & Sundsfjord J. Serum TSH is positively associated with BMI. *International Journal of Obesity* 2006 **30** 100–105.
- 9 Makepeace AE, Bremner AP, O'Leary P, Leedman PJ, Feddema P, Michelangeli V & Walsh JP. Significant inverse relationship between serum free T₄ concentration and body mass index in euthyroid subjects: differences between smokers and nonsmokers. *Clinical Endocrinology* 2008 **69** 648–652.
- 10 Ruscica M, Dozio E, Gandini S, Gnocchi P, Devalle GG, Motta M, Roti E & Magni P. Total, free and bound leptin and thyroid function in elderly women with different body weights. *Clinical Endocrinology* 2008 **68** 1002–1008.
- 11 Manji N, Boelaert K, Sheppard MC, Holder RL, Gough SC & Franklyn JA. Lack of association between serum TSH or free T₄ and body mass index in euthyroid subjects. *Clinical Endocrinology* 2006 **64** 125–128.
- 12 Roos A, Bakker SJ, Links TP, Gans RO & Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 491–496.
- 13 Biondi B & Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocrine Reviews* 2008 **29** 76–131.
- 14 Saltiki K, Voidonikola P, Stamatelopoulos K, Mantzou E, Papamichael C & Alevizaki M. Association of thyroid function with arterial pressure in normotensive and hypertensive euthyroid individuals: a cross-sectional study. *Thyroid Research* 2008 **1** 3.
- 15 Chan JM, Rimm EB, Colditz GA, Stampfer MJ & Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994 **17** 961–969.
- 16 Oregon MJ. Thyroid hormone and adipocyte differentiation. *Thyroid* 2008 **18** 185–195.
- 17 Villicev CM, Freitas FR, Aoki MS, Taffarel C, Scanlan TS, Moriscot AS, Ribeiro MO, Bianco AC & Gouveia CH. Thyroid hormone receptor beta-specific agonist GC-1 increases energy expenditure and prevents fat-mass accumulation in rats. *Journal of Endocrinology* 2007 **193** 21–29.
- 18 Viguerie N, Millet L, Avizou S, Vidal H, Larrouy D & Langin D. Regulation of human adipocyte gene expression by thyroid hormone. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 630–634.
- 19 Ortega FJ, Moreno-Navarrete JM, Ribas V, Esteve E, Rodriguez-Hermosa JJ, Ruiz B, Peral B, Ricart W, Zorzano A & Fernandez-Real JM. Subcutaneous fat shows higher thyroid hormone receptor-alpha1 gene expression than omental fat. *Obesity*, 2009 In Press DOI: 10.1038/oby.2009.110.
- 20 Antunes TT, Gagnon A, Chen B, Pacini F, Smith TJ & Sorisky A. Interleukin-6 release from human abdominal adipose cells is regulated by thyroid-stimulating hormone: effect of adipocyte differentiation and anatomic depot. *American Journal of Physiology. Endocrinology and Metabolism* 2006 **290** E1140–E1144.
- 21 Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Journal of the American Medical Association* 2001 **285** 2486–2497.
- 22 Suzuki R, Watanabe S, Hirai Y, Akiyama K, Nishide T, Matsushima Y, Murayama H, Ohshima H, Shinomiya M, Shirai K, Saito Y, Yoshida S, Saisho H & Ohto M. Abdominal wall fat index, estimated by ultrasonography, for assessment of the ratio of visceral fat to subcutaneous fat in the abdomen. *American Journal of Medicine* 1993 **95** 309–314.
- 23 Ribeiro-Filho FF, Faria AN, Kohlmann O Jr, Ajzen S, Ribeiro AB, Zanella MT & Ferreira SR. Ultrasonography for the evaluation of visceral fat and cardiovascular risk. *Hypertension* 2001 **38** 713–717.
- 24 Sabir N, Pakdemirli E, Sermez Y, Zencir M & Kazil S. Sonographic assessment of changes in thickness of different abdominal fat layers in response to diet in obese women. *Journal of Clinical Ultrasound* 2003 **31** 26–30.
- 25 Stamatelopoulos KS, Lekakis JP, Vamvakou G, Katsichti P, Protogerou A, Revela I, Karatzi K, Alevizaki M, Zakopoulos N & Papamichael CM. The relative impact of different measures of adiposity on markers of early atherosclerosis. *International Journal of Cardiology* 2007 **119** 139–146.
- 26 al-Adsani H, Hoffer LJ & Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 1118–1125.
- 27 Tchernof A, Belanger C, Morisset AS, Richard C, Mailloux J, Laberge P & Dupont P. Regional differences in adipose tissue metabolism in women: minor effect of obesity and body fat distribution. *Diabetes* 2006 **55** 1353–1360.
- 28 Kim BJ, Kim TY, Koh JM, Kim HK, Park JY, Lee KU, Shong YK & Kim WB. Relationship between serum free T₄ (fT₄) levels and metabolic syndrome (MS) and its components in healthy euthyroid subjects. *Clinical Endocrinology* 2009 **70** 152–160.
- 29 Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M & Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *Journal of the American Medical Association* 2004 **292** 2591–2599.
- 30 Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV & Leonetti F. Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. *Clinical Endocrinology* 2005 **62** 487–491.
- 31 Rotondi M, Leporati P, La Manna A, Pirali B, Mondello T, Fonte R, Magri F & Chiovato L. Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism? *European Journal of Endocrinology* 2009 **160** 403–408.
- 32 Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, Psyrogiannis AI, Kalfarentzos FE & Kyriazopoulou VE. Thyroid function in humans with morbid obesity. *Thyroid* 2006 **16** 73–78.
- 33 Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid* 2008 **18** 141–144.
- 34 Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Annals of Internal Medicine* 2003 **139** 205–213.
- 35 Rosenbaum M, Hirsch J, Murphy E & Leibel RL. Effects of changes in body weight on carbohydrate metabolism, catecholamine excretion, and thyroid function. *American Journal of Clinical Nutrition* 2000 **71** 1421–1432.
- 36 Matzen LE, Kvetny J & Pedersen KK. TSH, thyroid hormones and nuclear-binding of T₃ in mononuclear blood cells from obese and non-obese women. *Scandinavian Journal of Clinical and Laboratory Investigation* 1989 **49** 249–253.
- 37 Zimmermann-Belsing T, Brabant G, Holst JJ & Feldt-Rasmussen U. Circulating leptin and thyroid dysfunction. *European Journal of Endocrinology* 2003 **149** 257–271.
- 38 Bianco AC, Salvatore D, Gereben B, Berry MJ & Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenoenzymes. *Endocrine Reviews* 2002 **23** 38–89.
- 39 Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ & Gans RO. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 1206–1211.

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