



Associations between the levels of thyroid hormones and abdominal obesity in euthyroid postmenopausal women

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Abstract

Introduction: The aim of this study was to explore the association between thyroid hormones and abdominal fat quantities in euthyroid post-menopausal women.

Material and methods: Serum levels of thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) as well as body mass index (BMI) and waist circumference (WC) were collected from 540 euthyroid post-menopausal women aged 45–65 years. Magnetic resonance imaging (MRI) was performed to measure visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) area. Multivariate linear regression analysis was used to determine whether abdominal fat was associated with thyroid hormones.

Results: Weight, BMI, WC, fasting plasma glucose (FPG), fasting insulin (Fins), homeostasis model assessment of insulin resistance (HOMA-IR), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), TSH, and fT4 were higher in the obese group than in the non-obese group ($p < 0.05$). The study participants were divided into four groups according to quartiles in the light of TSH reference range (0.1–4.2 mU/L). Subcutaneous adipose tissue and VAT increased with the TSH levels. Adjusted for age, years since menopause (YSM), BMI, and HOMA-IR, VAT was negatively correlated with fT4 and positively correlated with fT3 and fT3-to-fT4 ratio (fT3/fT4) ($p < 0.05$), while no association was found between SAT and thyroid hormones. Similarly, we found no relation between body fat distribution and TSH. Furthermore, the association of common indicators of obesity and thyroid hormones showed no significance.

Conclusions: In euthyroid post-menopausal women, VAT rather than SAT was negatively correlated with fT4, and positively correlated with fT3 and fT3/fT4. (Endokrynol Pol 2020; 71 (4): 299–305)

Key words: post-menopausal; thyroid hormones; abdominal obesity; visceral adipose tissue; subcutaneous adipose tissue

Introduction

Obesity has been identified as a major modifiable risk factor associated with morbidity and mortality. The prevalence of obesity has increased dramatically as one of the most common worldwide health problems in recent decades. More than 1.4 billion adults aged 20 years or older are overweight. Of these, over 200 million men and nearly 300 million women are obese [1]. The prevalence of overweight and obesity among Chinese adults was 42.6% in 2010 [2], and it increased with age.

The prevalence of obesity is even more serious in post-menopausal women due to the decline of oestrogen levels [3], the increase of follicle-stimulating hormone (FSH) levels [4], and the reduction in energy expenditure [5]. Furthermore, other endogenous hormones like thyroid hormones also contributed to post-menopausal obesity [6–8]. However, it was complicated to evaluate the effect of thyroid hormones on weight gain in the post-menopausal status, especially when using traditional indicators of fat mass like body mass index (BMI) and waist circumference (WC). Firstly,

the serum thyroid stimulating hormone (TSH) concentration and prevalence of thyroid dysfunction increased along with aging and menopause for the diminution of size, iodine absorption ability, and daily production of triiodothyroxine (T3) and thyroxine (T4) of the thyroid gland [9, 10]. Secondly, the post-menopausal women underwent body fat changes characterised by weight gain in general fat mass and, mainly, central adiposity [11, 12]. Toth et al. [13] reported an increase of 49% in abdominal fat and 22% in subcutaneous fat in post-menopausal comparing to premenopausal women. Body mass index and WC, used as common indicators of obesity, could hardly distinguish the distribution of body fat in post-menopausal women. Based on the above-mentioned reasons, the relationship between thyroid hormones and general obesity (BMI, WC) as well as regional adiposity indicated as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) area remain a focus of debate both in thyroid dysfunction and euthyroid individuals [14–18].

Because obesity is known as a risk factor of cardiovascular disease and all-cause mortality, the determination



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of potential risk factors of anatomical fat accumulation during this period of women's lives is an important health target. To our knowledge, the evidence of the relationship between normal thyroid function and central obesity assessed by MRI remain scarce. With this background, the present research explored the relationship between serum thyroid hormones and obesity determined by MRI in a sample of euthyroid post-menopausal women.

Material and methods

Subjects

Data were obtained from a cross-sectional survey in post-menopausal women aged 45–65 years in the community of Banknote Printing Company of Chengdu. Age, years since menopause (YSM), and chronic medical histories of subjects were recorded in a face-to-face questionnaire survey conducted by trained medical staff before enrolment. Women with a history of post-menopause for 1–9 years, who were willing to participate in this study, were included. Patients were excluded in any of the following circumstances: hysterectomy, hormone replacement therapy, thyroidectomy, taking medications affecting thyroid function, and heart, renal, or liver failure. Finally, a total of 540 women were recruited to the investigation. All the subjects signed informed consent for the questionnaire survey and data collection for research purposes. This study was approved by the Ethics Committee of the Fifth People's Hospital of Chengdu and was conducted in accordance with the Declaration of Helsinki.

Diagnosis criteria

Menopause referred to 12 consecutive months of amenorrhoea without using hormonal contraception, according to the National Institute of Health and Care Excellence guideline [19]. Overweight and obesity prevention and control guideline for Chinese adults (2003 edition) formulated by the Ministry of Health was used as the diagnostic criteria for obesity [20]. Obesity was defined as BMI ≥ 28 kg/m². Euthyroidism was defined as serum TSH (0.1–4.2 mU/L), fT3 (2–6 pmol/L), and fT4 (12–24 pmol/L) levels within our laboratory references ranges, without history of thyroid diseases, taking TH replacement therapy, and anti-thyroid drugs.

Clinical and biochemical measurements

All the subjects were submitted to take a physical examination including height, weight, and waist circumference (WC) measurement with unlined clothes and barefoot with an empty stomach. WC was assessed at the horizontal circumference between the midline of the iliac crest and the lower edge of the 12th rib. Body mass index was calculated as weight [kg]/height [m]². After sitting for 15 minutes, the blood pressure of the brachial artery in the right arm was measured with a mercury sphygmomanometer three times, with intervals of more than five minutes, and the mean value was obtained. After 12 hours of fasting, blood samples were taken from the forearm vein at 8–10 a.m. the next morning. The serum fasting plasma glucose (FPG), fasting insulin (Fins), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and glycated haemoglobin (HbA_{1c}) were measured by an Olympus AU 5400 automatic biochemical analyser (Japan). Serum TSH and fT4 were measured by Enzyme Linked Immunosorbent Assay (Bayer Co., Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows:

$$\text{HOMA-IR} = (\text{Fins [mIU/L]}) \times (\text{FPG [mmol/L]} / 22.5)$$

Serum levels of oestradiol (E2), luteinising hormone (LH), and follicle stimulating hormone (FSH) were measured by radioim-

unoassay kits (Tianjin Jiuding Medical Bioengineering Co., Ltd., Tianjin, China).

MRI quantification of the VAT and SAT

MRI examination was performed by a 1.5-T scanner (Magnetom Open Viva, Siemens AG, Erlangen, Germany). The quantification of abdominal fat was detected at the level of the L3–L4 discs. SliceOmatic image analysis software (version 4.3, Tomovision, Montreal, CA) was used to analyse MRI slices. VAT and SAT areas (cm²) were measured separately by two observers. The correlation coefficient of observer variation was 0.816 ($p < 0.001$). A repeated measurement was conducted by a third observer to assess the repeatability.

Statistical analysis

The data of normal distribution were expressed as mean \pm SD, while the data of non-normal distribution were presented as medians with inter-quartile range. The comparison of two groups was performed by Student's *t*-test for normal distribution and by Mann-Whitney *U* test for non-normal distribution. A test for linear trend was conducted with the quartiles of median values of serum TSH as a continuous variable in the models. A multiple liner regression analysis was constructed to investigate the relationship between abdominal obesity indices measured by MRI (SAT area and VAT area) and thyroid hormones. Model 1 is the crude model. Model 2 is adjusted for age, years since menopause, and oestrogens. Model 3 is further adjusted for HOMA-IR and BMI. Statistical analysis was performed by SPSS17.0 software. All variables with a *p*-value less than 0.05 were considered as statistically significant.

Results

A total of 540 post-menopausal women (55.00 ± 9.15 years) were included in the study. All the subjects were divided into an obese group and non-obese group according to whether their BMI was greater than 28 kg/m² or not. 224 (41.48%) and 316 (58.52%) objects were obese and non-obese. No significant differences were seen in variables such as age, YSM, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), HDL-C, HbA_{1c}, and fT3 ($p > 0.05$). Weight, BMI, WC, FPG, Fins, HOMA-IR, LDL-C, TG, TSH, and fT4 were higher in the obese group than in the non-obese group ($p < 0.05$) (Tab. 1).

Thyroid stimulating hormone was divided into four groups according to quartiles in light of the TSH reference range (0.1–4.2 mIU/L). The numbers of objects were 97 (18%), 152 (28%), 155 (29%), and 136 (25%), respectively, in four groups. The SAT and VAT areas increased with the TSH levels ($p < 0.05$), while age, BMI, WC, HOMA-IR, LDL-C, and TG levels increased with TSH levels without any significant difference ($p > 0.05$). However, other variables in the four groups showed no significant differences (Tab. 2).

A multiple liner regression analysis was performed to identify which thyroid hormones had a major role in determining the VAT and SAT. Visceral adipose tissue was negatively correlated with fT4 and positively correlated with fT3 and fT3-to-fT4 ratio (fT3/fT4) ($p < 0.05$), even after adjusting for possible confounders of age, years since menopause, oestrogens (model 2),

Table 1. Comparison of clinical characteristics of none-obese and obese participants

Variables	All	None-obese	Obese	p
N (%)	540	316 (58.52%)	224 (41.48%)	NS
Age [years]	55.00 ± 9.15	54.74 ± 7.43	56.23 ± 10.03	0.081
YSM [years]	4.17 ± 1.56	5.11 ± 1.21	4.07 ± 1.42	0.561
Height [cm]	157.08 ± 16.40	156.4 ± 14.61	158.11 ± 17.72	0.668
Weight [kg]	68.51 ± 11.32	57.89 ± 10.52	71.26 ± 9.27	0.060
BMI [kg/m ²]	24.48 ± 3.52	21.63 ± 3.37	28.27 ± 4.41	< 0.001
WC [cm]	80.55 ± 10.34	77.71 ± 9.98	84.25 ± 9.61	< 0.001
SBP [mmHg]	131.89 ± 21.67	134.27 ± 20.63	130.07 ± 22.27	0.054
DBP [mmHg]	79.43 ± 13.15	82.16 ± 13.02	77.35 ± 12.86	0.615
E ₂ [pg/mL]	13.12 ± 8.34	14.82 ± 8.54	12.51 ± 7.69	0.227
LH [mIU/mL]	24.52 ± 14.06	25.67 ± 23.09	23.16 ± 31.09	0.089
FSH [mIU/mL]	59.39 ± 37.02	62.95 ± 41.09	58.95 ± 39.47	0.055
HbA _{1c}	6.38 [1.31]	5.75 [1.17]	7.14 [1.27]	0.067
FPG [mmol/L]	8.15 ± 1.16	5.31 ± 1.09	8.97 ± 2.12	0.028
Fins [mU/L]	9.11 ± 1.98	8.18 ± 1.51	15.87 ± 4.42	0.042
HOMA-IR*	1.18 (0.91)	0.88 (0.79)	1.23 (0.82)	0.019
LDL [mmol/L]	3.27 ± 0.61	3.10 ± 0.66	3.68 ± 0.92	0.026
HDL [mmol/L]	1.61 ± 0.42	1.74 ± 0.52	1.41 ± 0.45	0.782
TG [mmol/L]*	1.29 (0.97)	1.32 (0.74)	1.91 (1.02)	0.014
TSH [mU/L] *	3.15 (1.42)	2.16 (1.28)	4.15 (2.58)	0.045
ft3 [pmol/L] *	3.84 (1.09)	3.24 (0.88)	4.72 (1.48)	0.059
ft4 [pmol/L] *	15.89 ± 3.12	14.21 ± 4.34	21.11 ± 3.57	0.042
SAT area [cm ²]	166.8 ± 82.7	152.4 ± 39.1	197.4 ± 58.2	0.023
VAT area [cm ²]	75.4 ± 31.1	65.4 ± 20.1	84.4 ± 26.1	0.018

Data were expressed as mean ± SD unless indicated otherwise. Normal distribution variables were compared by Student's t-test. YSM — years since menopause; BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG — triglycerides; HDL-C — high-density lipoprotein-cholesterol; LDL-C — low-density lipoprotein-cholesterol; FPG — fasting plasma glucose; HbA_{1c} — glycated haemoglobin; Fins — fasting insulin; TSH — thyrotropin; ft³ — free triiodothyronine; ft⁴ — free thyroxine; E₂ — oestradiol; LH — luteinising hormone; FSH — follicle-stimulating hormone; SAT — subcutaneous adipose tissue; VAT — visceral adipose tissue. p < 0.05 is considered as significant level. *Non-normal distribution data are presented as medians with inter-quartile range and compared by Mann-Whitney U test

HOMA-IR, and BMI (model 3). In contrast, SAT area was not associated with thyroid hormones (p > 0.05) (Tab. 3). Similarly, the association of common indicators of obesity (BMI, WC) and thyroid hormones showed no significance (data not shown).

Discussion

In this cross-sectional study of 540 euthyroid post-menopausal women, we have demonstrated that VAT rather than SAT was negatively correlated with ft4 and positively correlated with ft3 and ft3/ft4. However, common parameters of obesity assessed by BMI and WC were not associated with thyroid hormones. Furthermore, we found no relation between body fat distribution and TSH.

The association of thyroid hormones with fat distribution has been studied previously [17, 18, 21]. Muscogiuri et al. [17] demonstrated that VAT quantified by CT was the best predictor of TSH concentration in obesity. Akbaba et al. [18] found that VAT was positively correlated with ft4 in subclinical hypothyroidism. Min et al. [21] indicated that ft3 and ft4 were significantly associated with increased pericardial fat volume and BMI in non-obese euthyroid men. In concordance with those investigations, we found that ft3 and ft4 levels were inversely correlated with VAT in euthyroid post-menopausal women. The pathogenesis of the relationship between thyroid hormones and obesity in post-menopausal states has not yet been fully elucidated. Some underlying mechanisms might be explored as follows: First, both thyroid hormones and leptin af-

Table 2. Clinical and biochemical characteristics of euthyroid subjects according to the quartiles of serum thyroid-stimulating hormone (TSH) levels within the reference range

Variables	TSH [mU/L]				P ^b _{Trend}
	1 st quartile	2 nd quartile	3 rd quartile	4 th quartile	
N	97(18%)	152(28%)	155(29%)	136(25%)	NS
TSH [mU/L]	1.88 (0.79)	2.95 (0.61)	3.11 (0.81)	4.09 (0.76)	0.012
Age (years)	48.34 ± 11.43	53.92 ± 10.22	57.04 ± 9.69	68.34 ± 11.12	0.063
YSM (years)	4.20 ± 1.12	5.01 ± 0.98	4.77 ± 1.25	6.58 ± 1.78	0.451
BMI [kg/m ²]	23.81 ± 2.18	24.89 ± 2.42	27.22 ± 4.18	29.12 ± 3.11	0.062
WC [cm]	80.92 ± 8.94	82.13 ± 11.13	86.09 ± 10.21	88.18 ± 9.21	0.067
SBP [mm Hg]	129.13 ± 18.33	129.94 ± 19.27	131.09 ± 20.52	133.22 ± 21.03	0.084
DBP [mm Hg]	80.19 ± 10.12	79.99 ± 12.63	81.23 ± 12.36	80.72 ± 10.56	0.081
FPG [mmol/L]	80.19 ± 10.12	79.99 ± 12.63	81.23 ± 12.36	80.72 ± 10.56	0.081
E ₂ [pg/mL]	13.09 ± 7.11	14.00 ± 6.98	12.83 ± 6.60	14.14 ± 7.61	0.227
LH [mIU/mL]	25.12 ± 13.89	25.99 ± 24.09	24.06 ± 20.19	23.88 ± 29.19	0.089
FSH [mIU/mL]	61.39 ± 37.02	60.95 ± 31.29	58.95 ± 39.55	57.79 ± 30.01	0.055
HbA _{1c}	6.12 (1.74)	5.95 (1.07)	6.82 (1.12)	7.01 (1.56)	0.441
Fins [mU/L]	8.89 ± 1.26	10.08 ± 1.05	14.11 ± 2.93	18.21 ± 2.52	0.689
HOMA-IR ^a	0.75 (0.53)	1.16 (0.67)	1.29 (0.87)	1.32 (0.79)	0.055
LDL-C [mmol/L]	3.09 ± 0.37	3.18 ± 0.79	3.44 ± 1.09	3.81 ± 0.98	0.068
HDL-C [mmol/L]	1.51 ± 0.23	1.49 ± 0.52	1.54 ± 0.66	1.47 ± 0.62	0.073
TG [mmol/L]	1.21 (0.77)	1.52 (0.82)	1.78 (0.89)	1.98 (0.74)	0.094
FT3 [pmol/L] ^a	4.15(0.79)	3.62(1.28)	4.02(1.16)	3.881(1.48)	0.129
FT4 [pmol/L] ^a	19.19 ± 4.55	16.28 ± 3.78	15.45 ± 4.12	14.11 ± 4.42	0.062
SAT area [cm ²]	149.81 ± 44.17	155.14 ± 41.21	170.04 ± 48.22	181.71 ± 50.28	0.046
VAT area [cm ²]	62.45 ± 26.32	71.92 ± 35.16	81.42 ± 29.16	95.72 ± 32.36	0.021

Data were expressed as mean ± SD unless indicated otherwise; ^aNon-normal distribution data; ^bTest for trends across ordered groups. Abbreviations listed in Table 1

Table 3. Association of thyroid hormones as independent variables with visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) area by multiple regression analysis

Variables	Model 1		Model 2		Model 3	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
VAT area [cm ²]						
TSH [mU/L]	1.003 (0.832,1.128)	0.089	0.755 (0.592,1.008)	0.051	0.811 (0.735,1.105)	0.063
FT3 [pmol/L]	1.103 (1.032,1.341)	0.013	1.213 (1.187,1.355)	0.045	1.147 (1.099,1.248)	0.048
FT4 [pmol/L]	-1.562 (-1.271,-1.692)	0.038	-1.312 (-1.063,-1.452)	0.044	-1.420 (-1.203,1.595)	0.040
FT3/FT4	1.141 (1.072,1.253)	0.016	1.377 (1.282,1.465)	0.021	1.198 (1.002,1.312)	0.033
SAT area [cm ²]						
TSH [mU/L]	1.013 (0.742,1.109)	0.545	0.883 (0.946,1.273)	0.665	0.932 (0.844,1.004)	0.832
FT3 [pmol/L]	1.603 (0.942,1.818)	0.618	1.121 (0.712,1.308)	0.753	0.877 (0.615,1.017)	0.673
FT4 [pmol/L]	1.403 (0.927,1.605)	0.463	1.223 (0.804,1.415)	0.662	0.993 (0.716,1.118)	0.553
FT3/FT4	0.803 (0.682,1.024)	0.849	0.553 (0.421,1.001)	0.728	0.613 (0.599,1.128)	0.940

Values of β are standardised regression coefficients; Model 1 — crude model; Model 2 — adjustment for age, years since menopause, estrogens; Model 3 — further adjustment for HOMA-IR and BMI; Abbreviations listed in Table 1

affected each other and regulated body composition [22, 23], but the changes of serum leptin in post-menopausal women remained contradictory as either increased [24], identical [25] or decreased [26]. Hence, further studies are needed to demonstrate how leptin influences thyroid hormones in post-menopausal women. Second, a decreased expression of DIO2 in adipose tissues of obese individuals led to a lower local conversion of T4 to T3, resulting in elevated serum fT3 as a compensation of peripheral hormone resistance [27]. Third, clinically euthyroid obese patients had decreased expression of TSHR and TR 1 in VAT and SAT in the face of higher plasma fT3 and TSH, which would be reversed after major weight loss [28].

Interestingly, we did not find any correlation between SAT and thyroid hormones. Alevizaki's [15] findings showed that SAT was negatively associated with fT4 and positively associated with TSH among euthyroid overweight individuals. Westerink et al. [29] observed that TSH levels in the normal range were associated with an increase in VAT in patients with vascular diseases over 66 years old. Firstly, this could be partially explained by the different functional characteristics of abdominal VAT and SAT with diverse physiological and metabolic responses in handling excess fat [30]. VAT was a major endocrine organ that secreted a variety of cytokines and adipocytokines, which interfered with the HPT axis. On the basis of this findings, whether post-menopausal status might modify the relationship between anatomic body fat and thyroid hormones continues to be debated. Further longitudinal studies are needed to assess the interrelationship between the hypothalamic–pituitary–thyroid axis and fat redistribution in post-menopausal women over time.

In addition, studies have shown that abdominal VAT and SAT are major contributors to insulin resistance [31, 32], while gluteofemoral fat is protective against diabetes and cardiovascular disease [33]. However, the current study focuses on abdominal adipose and does not include the thoracic adipose and peripheral subcutaneous adipose in upper and lower extremities. Meanwhile, we evaluated only the abdominal section of SAT instead of the total subcutaneous fat volume. Hence, it was difficult to extend our results to the relationship between other ectopic fat distribution and thyroid hormones. Accordingly, further investigations are needed to clarify the association of thyroid function parameters with other anatomic fat accumulation.

The correlations between serum TSH within the reference range and obesity revealed conflict. Several studies indicated that TSH was positively correlated with obesity in euthyroid subjects [8, 34]. However, a meta-analysis showed that only 18 out of 29 studies found a positive association between TSH and obesity,

while others did not [35]. Our study was in accordance with previous research that showed no association between TSH and obesity assessed by both general (BMI and WC) [36] and abdominal (VAT and SAT) indicators [18]. The discrepant results among different studies can be attributed to different study designs, analyses, and varying control of confounding variables. First, aging was considered as a potential confounder of the association between obesity and thyroid hormones. Accordingly, various cross-sectional and longitudinal studies suggested an age-related increase in the TSH set point and a reduction of fT4 level for decreased synthesis and catabolism of fT4 [37–39]. The present study only enrolled post-menopausal women aged 45–65 years to reduce the confounding factor of aging, although it is difficult to fully control the influence in a cross-sectional design. Second, it was observed that the association between TH and obesity was different among individuals with varying degrees of obesity [40]. The correlations of BMI and serum TSH concentration was shown among morbidly obese participants [41], which would be attenuated in lean women. The average BMI of our sample was 24.48, far less than other studies. Third, the normal range of the TSH has been the subject of intense debate among numerous studies. This variability in the reference interval might explain the lack of association between TSH and indicators of obesity. Forth, there is a special, individual set point for pituitary-thyroid axis function, and the reference ranges of TSH are altered with age.

The strengths of this study are that quantitative determination of VAT and SAT were precisely assessed by MRI, which more accurately described the body fat distribution in post-menopausal women. We performed multivariable adjusted analyses for age, years since menopause, oestrogens, HOMA-IR, and BMI in healthy euthyroid post-menopausal women, which provided well-characterised data and ensured relatively reliable evaluations. However, there were some limitations to the present study. First, we cannot indicate causality between VAT and SAT area and thyroid hormones for the cross-sectional design. Second, all the participants enrolled were Chinese post-menopausal women. Third, thyroid antibodies considered as common confounders were not taken into account. Forth, we only included subjects with euthyroidism rather than without thyroid disorders because thyroid ultrasonography and anti-thyroid antibodies were not checked in the present study. Thus, follow-up research with expanded sample sizes and with patients of normal thyroid structure and function should be conducted to obtain more scientific data to clarify the impact of hormone changes, age, and other factors on SAT and VAT.

Taken together, our study highlighted that VAT rather than SAT was negatively correlated with fT4 and positively correlated with fT3 and fT3-to-fT4 ratio (fT3/fT4) in Chinese euthyroid post-menopausal women. Our results suggest that slight differences in thyroid function parameters might reflect increasing intra-abdominal fat. Further longitudinal studies are needed to better understand the causality between serum levels of fT4 or fT3 and regional adiposity in euthyroid post-menopausal women.

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Author's contribution

H.W. and S-D.H. are co-senior authors.

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