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ORIGINAL RESEARCH

Impaired Sensitivity to Thyroid Hormones is Associated with Central Obesity in Euthyroid Type 2 Diabetes Mellitus Patients with Overweight and Obesity

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Background: Thyroid hormone levels are associated with the distribution of body components in humans.

Objective: This study aimed to investigate the associations between thyroid hormone (TH) levels, central sensitivity to THs, and body composition in overweight and obese patients with euthyroid type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study included 1215 euthyroid T2DM patients (721 men and 494 women) aged 20–80 years. The thyroid hormone sensitivity indices included the thyroid feedback quartile-based index (TFQI), thyrotroph T3 resistance index (TT3RI), thyrotroph T4 resistance index (TT4RI), and thyroid-stimulating hormone index (TSHI). The appendicular fat ratio, trunk fat ratio, android fat ratio, gynoid fat ratio, and appendicular skeletal muscle mass (ASM) were measured via dual-energy X-ray absorptiometry.

Results: The data revealed a greater proportion of subjects with impaired central sensitivity to THs in the obese group. $TFQI_{FT4}$ and $TFQI_{FT3}$ levels were positively correlated with the upper limb fat ratio, lower limb fat ratio, gynoid fat ratio, and total fat ratio. TSHI was positively correlated with body mass index (BMI), upper limb fat ratio, lower limb fat ratio, trunk fat ratio, android fat ratio, gynoid fat ratio, total fat ratio, and appendicular skeletal muscle mass index (ASMI) in women. In men, TSHI was only positively correlated with upper limb fat ratio, lower limb fat ratio, and total fat ratio. Logistic regression analysis indicated that TT3RI and $TFQI_{FT3}$ were independently and positively associated with central obesity and low muscle mass in overweight and obese men. No significant differences were found among the women.

Conclusion: THs central sensitivity is related to the body composition of euthyroid T2DM patients. Specifically, high levels of TT3RI and $TFQI_{FT3}$ are associated with central obesity and low muscle mass in T2DM men with overweight and obesity.

Keywords: thyroid hormones central sensitivity, euthyroid, body components, muscle mass, fat ratio, obese

Introduction

Obesity is a global health issue that has far-reaching implications. It not only increases the risk of cardiovascular disease, diabetes, and gallbladder disease but also increases mortality rates.[1,2] In particular, obesity plays a significant role in the prevalence of type 2 diabetes, a chronic disease characterized by insufficient insulin production or ineffective insulin utilization, leading to elevated blood sugar levels. The risk of type 2 diabetes increases linearly with increasing body mass index (BMI) and abdominal fat distribution.[3] The impact of obesity extends beyond fat content; it also affects body

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composition, including the ratio of fat to muscle.[4] Metabolic complications, such as increased fat mass and decreased lean body mass, are often associated with changes in body composition. Thyroid hormones (THs), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH), are vital in regulating metabolism, including energy homeostasis, thermogenesis, oxygen consumption, and lipid and glucose metabolism, all of which influence body composition.[5,6]

Research conducted by Ren et al revealed that fat mass, body fat percentage, and homeostasis model assessment for insulin resistance (HOMA-IR) significantly contribute to FT3 levels.[7,8] Another study involving 582 euthyroid subjects revealed that serum TSH levels are associated with visceral adipose tissue in lean men, whereas high FT3 levels are associated with increased fat in overweight and obese men.[4] Previous studies have utilized BMI, waist circumference, or body fat to investigate the associations between THs and obesity. Nam et al reported a positive association between T3 levels and visceral fat in overweight or obese individuals.[9] However, another study by Xiaomin Nie et al demonstrated that there was no correlation between visceral fat and either FT3 or FT3/FT4 in either sex. Instead, abdominal subcutaneous fat was independently associated with increased FT3 in a euthyroid population.[10] Few studies have evaluated the associations between TH and muscle mass among euthyroid individuals. In one study of euthyroid men, FT4 showed an inverse dose–response association with new-onset low muscle mass, as defined by weight and BMI. Conversely, euthyroid women did not exhibit a dose–responsive association between THs and incident low muscle mass.[11] Another study reported a negative correlation between FT4 and body weight, total muscle mass, and appendicular skeletal muscle mass index (ASMI) in diabetic men, whereas FT3/FT4 was positively correlated with the ASMI in both men and women.[12] However, another trial reported that FT3 was negatively associated with muscle mass in both age groups.[13] These discrepancies can potentially be attributed to the different methods used to measure fat and muscle mass. In our study, we adopted dual-energy X-ray absorptiometry (DXA), one of the most accurate and precise techniques for directly measuring body fat and muscle mass, to assess body composition.

Compared with a single index, composite-based indices are more effective at reflecting thyroid homeostasis. Laclaustra et al[14] proposed a new method for calculating the central sensitivity index, known as the thyroid feedback quartile-based index (TFQI), for THs. $TFQI_{FT4}$ is based on an empirical joint distribution of FT4 and TSH, and it has the advantage of not producing extreme values in the presence of thyroid dysfunction. Similarly, $TFQI_{FT3}$ is based on the empirical joint distribution of the FT3 and TSH levels. Other indices reflecting central TH sensitivity include the thyrotropin T4 resistance index (TT4RI), thyrotropin T3 resistance index (TT3RI), and TSH index (TSHI). Negative values of $TFQI_{FT4}$ and $TFQI_{FT3}$ indicate central sensitivity to THs, whereas positive values represent impaired TH sensitivity. Previous studies have shown a negative correlation between TSHI, TT3RI, and TT4RI values and thyroid central sensitivity.[15,16] Therefore, we defined TSHI, TT4RI, and TT3RI values higher than the upper quartile as indicating lower sensitivity to central THs. Previous studies have demonstrated that impaired central thyroid sensitivity may trigger adverse events. Heng Wan et al[17] proposed that $TFQI_{FT3}$ and $TFQI_{FT4}$ are positively related to the prevalence of diabetes, whereas another article[18] highlighted the association between impaired central sensitivity to FT3 and metabolic dysfunction–associated fatty liver disease (MAFLD) and its progression to liver fibrosis. Genfeng Yu et al[19] reported that decreased central sensitivity to THs is associated with an increased risk of all-cause mortality.

Type 2 diabetes mellitus (T2DM) is a common comorbidity of obesity. Patients with diabetes mellitus (DM) are at increased risk of thyroid disease, particularly those with poor glycemic control.[20] Gu et al[21] reported that patients with T2DM had significantly lower levels of FT3 and FT4 within the normal reference range than patients with normal glucose tolerance and prediabetes. Another study by Qin et al[22] revealed that diabetes in euthyroid adults was associated with an increased FT4/FT3 ratio. Thus, the association between THs and body composition in euthyroid T2DM patients may differ from that in euthyroid subjects without T2DM.

Currently, most investigations on THs and body composition are limited to the normal population. However, our study focused on overweight and obese individuals with T2DM. Furthermore, few studies have explored the correlation between compromised central TH sensitivity and human body composition. Therefore, our study aimed to explore the associations between THs, TH sensitivity, and human body composition in euthyroid T2DM patients who were overweight or obese.

Materials and Methods

Study Population

This cross-sectional study included a total of 1215 euthyroid T2DM patients (721 men and 494 women) aged 20–80 years who were Han Chinese adults. The patients were hospitalized at the First Affiliated Hospital of Wenzhou Medical University from February 2019 to May 2021. All participants had a BMI of ≥18.5 kg/m^2. The study protocol involving human participants was reviewed and approved by the Ethics Committee in Clinical Research (ECCR) of the First Affiliated Hospital of Wenzhou Medical University. Written informed consent was obtained from all patients prior to their participation in the study. The diagnostic criteria for T2DM included (1) fasting blood glucose of ≥7.0 mmol/l, (2) random blood glucose of ≥11.1 mmol/l or stimulated blood glucose of ≥11.1 mmol/L after a standard oral glucose tolerance test, and (3) hemoglobin A1c (HbA1c) of ≥6.5%. Euthyroid status was defined as having serum levels of TSH, FT3, and FT4 within the normal range. Patients with the following conditions were excluded from the study: (1) a history of hyperthyroidism, hypothyroidism, thyroid surgery, and family history of thyroid disease; (2) a history of taking TH or antithyroid medications; (3) a history of taking medications that affect thyroid function, such as contraceptives, estrogen, amiodarone, and other iodine-containing drugs and lithium agents; (4) the presence of malignant tumors; (5) pregnancy; (6) severe heart disease and impaired liver or kidney function; (7) active infection; and (8) a history of pituitary disease (Figure 1).

Parameters

The age and sex of the patients were recorded. Height and weight measurements were taken, and BMI was calculated as weight (kg) divided by height squared (m^2).

Laboratory Examination

Blood samples were collected from patients in the morning while they were in a seated position. Lipid metrics, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), were measured via a standard enzymatic method (AU580 Biochemical Analyzer, Beckman Coulter, Brea, CA, USA). Liver enzymes, including alanine aminotransferase (ALT), aspartate transaminase (AST), creatinine, and glucose, were measured via a standard enzymatic method (AU580 Biochemical Analyzer, Beckman Coulter, Brea, CA, USA). HbA1c was measured via high-performance liquid chromatography (Variant II turbo, Bio-Rad Laboratories, CA, USA) and expressed in National Glycohemoglobin Standardization Program units (%). FT3, FT4, and TSH levels were measured via an electrochemiluminescence immunoassay (UniCel DxI 800 Fully Automated Immunoassay Analyzer, Beckman Coulter, USA). The normal range for FT3 is 3.28–6.47 pmol/L. The normal range for FT4 is 7.64–16.03 pmol/L. The normal range for TSH is 0.38–5.33 mIU/L.

Dual-Energy X-Ray Absorptiometry (DXA)

DXA (GE Medical Systems Lunar, 3030 Ohmeda Drive Madison, WI 53718, USA) was used to measure various parameters, including total fat mass, appendicular fat mass, trunk fat mass, android fat mass, gynoid fat mass, appendicular skeletal muscle mass (ASM), total muscle mass, android muscle mass, and gynoid muscle mass.

Calculations and Definitions

BMI was calculated by dividing body weight in kilograms by height in meters squared (kg/m^2). The ASMI was calculated as the ASM (kg) divided by the height squared (m^2). The skeletal muscle index (SMI) was calculated as the total muscle mass (kg) divided by height squared (m^2). The calculation formulas for certain indicators of central TH sensitivity are as follows:

$TFQI_{FT4}$=cdf FT4−(1−cdf TSH)

$TFQI_{FT3}$=cdf FT3−(1−cdf TSH)

TSHI=ln TSH (mIU/L) +0.1345 × FT4 (pmol/L),

TT4RI=FT4 (pmol/L) × TSH (mIU/L)

TT3RI=FT3 (pmol/L) × TSH (mIU/L)

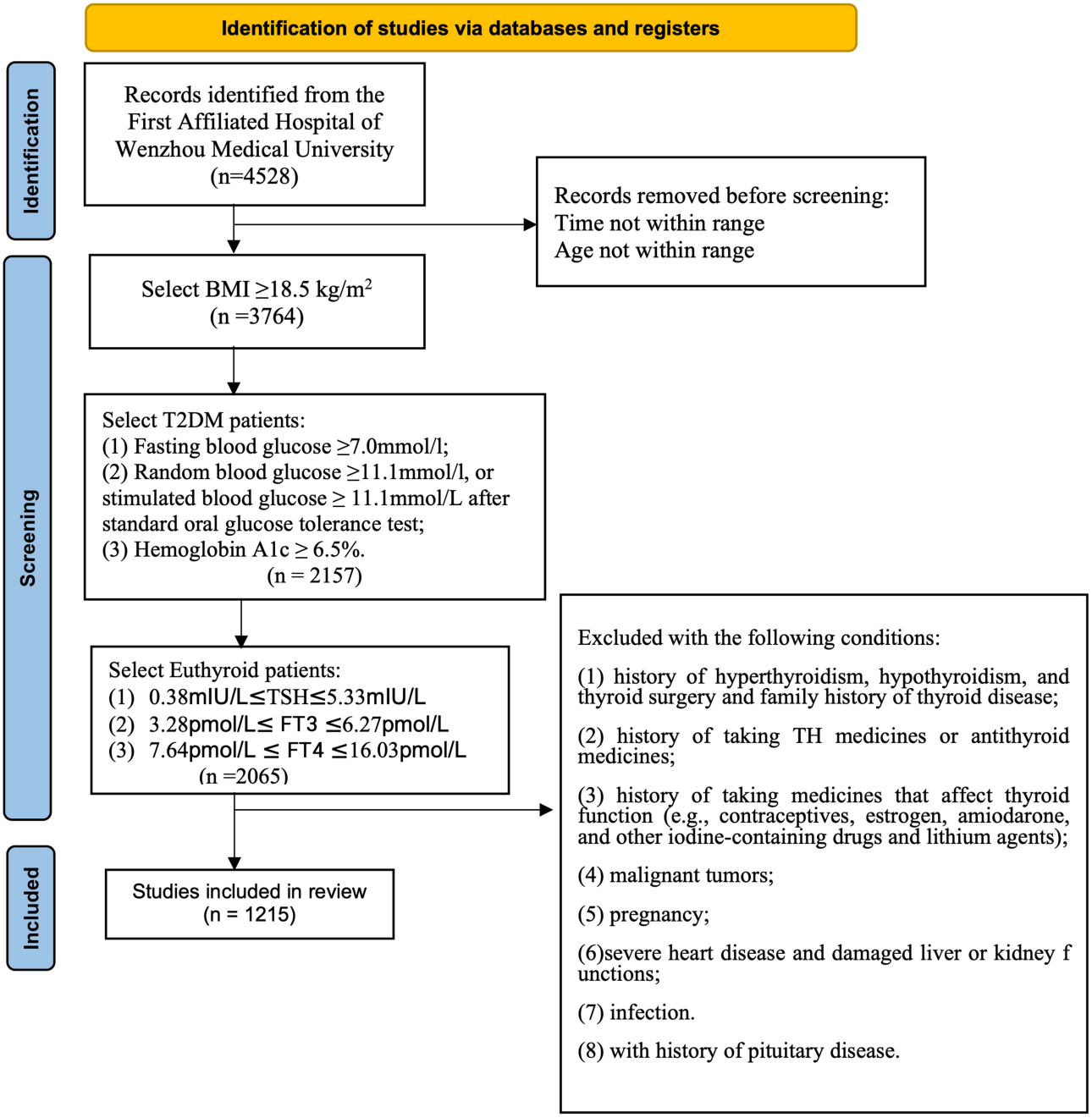

Figure 1 Study Population Screening Flowchart.

Grouping

The participants were divided into three groups on the basis of their BMI: the normal weight group (18.5–23.9 kg/m^2), the overweight group (24–27.9 kg/m^2), and the obesity group (≥28 kg/m^2). The overweight and obese groups were further segmented into three clusters on the basis of the results of BMI, the android fat ratio, and ASMI clustering analyses. As illustrated in Figure 2, the first cluster, designated "Moderates", comprised individuals with moderate BMIs, anroid fat ratio, and the ASMI. The second cluster, labeled "HMLA", included individuals with the lowest BMI and android fat ratio but the highest ASMI. The third cluster, labeled "HALM", represented individuals with the highest BMI and android fat ratio but the lowest ASMI.

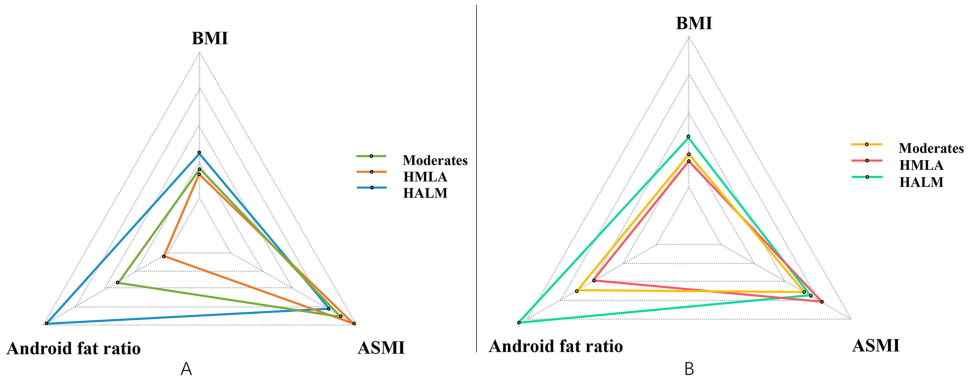

Figure 2 Overweight and Obese subjects cluster groups.
Notes: (**A**) presents the cluster groups of men and (**B**) presents the cluster groups of women. The moderate group included those with a moderate BMI, android fat, and ASMI. Patients in the HMLA group had the lowest BMI and android fat ratio, and the highest ASMI. Patients in the HALM group had the highest BMI and android fat ratio and lowest ASMI.
Abbreviations: BMI, body mass index; ASMI, appendicular skeletal muscle mass index.

Statistical Analyses

IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) was used for all the statistical analyses. Continuous variables are presented as the means ± standard deviations. Analysis of variance was used to assess differences between the groups. Pearson's correlation and partial correlation analyses were conducted to examine the associations between THs and body composition.

Cluster analysis was performed among overweight and obese patients on the basis of BMI, the android fat ratio, and ASMI scores. Multivariate logistic regression analysis was conducted using the identified independent variables. Fisher's exact test was used to compare categorical variables. The odds ratios (ORs) between the comparison groups were calculated with 95% confidence intervals (CIs). Statistical significance was set at $P<0.05$.

Results

All Participants

We have checked the normality of all continuous variables before conducting the analysis, and they all followed a normal distribution. Table 1 presents the characteristics of the male and female patients across the different groups, along with the observed differences. The data in Table 1 clearly indicate that in men, a high BMI is associated with significantly higher levels of FT3, $TFQI_{FT4}$, $TFQI_{FT3}$, TSH, TT3RI, TG, ALT, AST, the appendicular fat ratio, the trunk fat ratio, the android fat ratio, the gynoid fat ratio, the total fat ratio, the ASM, the ASMI, and low HDL levels. However, the results differ for women, where only the TT3RI, TSH level, appendicular fat ratio, trunk fat ratio, android fat ratio, gynoid fat ratio, total fat ratio, ASM, and ASMI are significantly different in patients with a high BMI. There is a trend test difference in the above indicators among the three groups (P for tend < 0.05). In addition, we further conducted multiple comparisons between each two groups, and the results are presented in the Supplementary Table 1.

We conducted an analysis of the correlation between THs and body composition, the results of which are presented in Table 2. For men, FT4 is positively correlated with the upper limb fat ratio, lower limb fat ratio, and gynoid fat ratio but negatively correlated with the SMI. In women, FT4 is positively correlated with the lower limb fat ratio and gynoid fat ratio but negatively correlated with the ASMI and SMI. FT3 was positively correlated with all the indicators in men, whereas in women, it was positively correlated with the trunk fat ratio, the android fat ratio, the gynoid fat ratio, the total fat ratio, and the android fat/android muscle ratio and negatively correlated with the android fat/gynoid fat ratio. Furthermore, FT3/FT4 levels are positively correlated with the ASMI and SMI in both men and women. TSH levels in men are positively correlated with BMI, the upper limb fat ratio, the lower limb fat ratio, the trunk fat ratio, the android fat ratio, the gynoid fat ratio, the total fat ratio, and the android fat/android muscle ratio. In women, TSH is positively correlated with all indicators except the android fat/gynoid fat ratio.

Table 1 Clinical Characteristics of the Whole Sample, Subdivided by Gender

	Men				P value for trend	*P*	women				P value for trend	*P*
	Normal n=366	Overweight n=289	Obesity n=66	Total n=721			Normal n=253	Overweight n=176	Obesity n=65	Total n=494		
FT4 (pmol/L)	12.18±6.71	11.6±1.98	12.16±2.28	11.94±5.00	0.414	0.315	11.72±1.99	11.52±2.00	11.57±2.20	11.63±2.02	0.598	0.600
FT3 (pmol/L)	4.49±0.74	4.70±0.70	4.76±0.75	4.60±0.73	**< 0.001**	**< 0.001**	4.49±0.66	4.57±0.67	4.50±0.60	4.52±0.66	0.568	0.494
TFQIFT4	−0.07±0.28	−0.05±0.27	0.04±0.28	−0.05±0.27	**0.004**	**0.015**	−0.07±0.33	−0.06±0.36	0±0.32	−0.06±0.34	0.135	0.322
TFQIFT3	−0.01±0.38	0.02±0.35	0.09±0.42	−0.04±0.38	**< 0.001**	**< 0.001**	−0.09±0.36	−0.01±0.39	0.01±0.35	−0.05±0.37	0.061	0.055
TSHI	1.85±1.10	1.86±0.59	2.04±0.65	1.87±0.89	0.440	0.273	1.83±0.58	1.93±0.65	2.01±0.60	1.89±0.61	**0.034**	0.065
TT4RI	18.85±35.51	18.28±11.69	21.62±15.61	18.87±26.78	0.112	0.659	17.62±11.91	20.16±14.14	20.98±12.16	18.97±12.83	0.059	0.062
TT3RI	6.59±4.61	7.48±4.90	8.71±6.54	7.14±4.97	**< 0.001**	**0.002**	6.82±4.53	8.17±6.31	8.47±5.34	7.52±5.37	**0.026**	**0.014**
TSH (mIU/L)	1.47±1.00	1.61±1.09	1.79±1.28	1.55±1.07	**< 0.001**	**0.036**	1.53±1.04	1.77±1.32	1.91±1.27	1.67±1.18	**0.007**	**0.024**
TG (mmol/L)	1.55±1.12	1.89±1.16	2.12±1.18	1.74±1.16	–	**< 0.001**	2.85±16.84	2.57±7.40	2.18±1.50	2.67±12.83	–	0.926
HDL (mmol/L)	1.09±0.70	0.99±0.31	0.97±0.20	1.04±0.54	–	**0.033**	1.55±6.79	1.11±0.27	1.11±0.26	1.33±4.86	–	0.606
LDL (mmol/L)	2.59±0.96	2.55±0.95	2.62±1.01	2.57±0.96	–	0.812	2.73±0.93	2.62±0.86	2.73±0.96	2.69±0.91	–	0.449
TC (mmol/L)	4.75±1.41	4.61±1.25	4.76±1.43	4.69±1.35	–	0.421	5.00±1.36	4.88±1.43	4.96±1.23	4.95±1.37	–	0.681
Fasting blood glucose (mmol/L)	8.32±4.13	8.52±3.99	7.82±3.54	8.35±4.02	–	0.424	8.11±3.23	8.06±3.22	8.28±3.53	8.11±3.26	–	0.889
ALT (U/L)	27.14±22.84	29.17±23.56	48.95±43.84	29.95±26.41	–	**< 0.001**	22.98±42.21	27.85±33.63	34.74±67.28	26.27±43.77	–	0.130
AST (U/L)	25.71±15.48	27.02±20.14	37.61±26.50	27.33±18.92	–	**< 0.001**	24.54±33.44	26.26±20.26	30.02±30.72	25.87±29.04	–	0.390
Creatinine (umol/L)	92.82±100.15	85.86±61.52	87.05±40.12	89.50±82.19	–	0.544	66.32±59.47	65.08±31.55	63.68±20.45	65.53±47.08	–	0.910
Hemoglobin A1c (%)	9.41±2.50	9.21±2.42	9.24±2.25	9.32±2.44	–	0.576	9.07±2.41	8.75±2.29	8.37±1.92	8.87±2.32	–	0.065
Age	57.83±13.31	57.11±13.40	53.58±15.72	57.15±13.62	–	0.065	63.57±11.61	63.96±12.37	63.71±14.30	63.73±12.24	–	0.950

BMI	21.87±1.44	25.71±1.14	30.54±2.27	24.20±3.07	–	**< 0.001**	21.71±1.55	25.86±1.11	30.42±2.35	24.33±3.41	–	**< 0.001**
Upper limb fat ratio	16.84±5.81	21.48±5.66	27.77±6.49	19.70±6.72	**< 0.001**	**< 0.001**	33.08±6.52	38.86±6.16	43.58±5.86	36.52±7.37	**< 0.001**	**< 0.001**
Lower limb fat ratio	17.58±5.46	20.99±5.59	25.43±5.07	19.67±5.99	**< 0.001**	**< 0.001**	28.31±6.55	33.16±5.68	37.74±6.86	31.28±7.13	**< 0.001**	**< 0.001**
Trunk fat ratio	25.06±8.43	32.78±6.53	39.09±5.48	29.44±8.86	**< 0.001**	**< 0.001**	33.61±7.05	40.64±5.15	45.16±4.92	37.64±7.55	**< 0.001**	**< 0.001**
Android fat ratio	30.60±9.19	37.59±6.91	43.05±5.84	34.54±9.13	**< 0.001**	**< 0.001**	40.50±7.35	46.67±6.15	50.13±4.71	43.98±7.59	**< 0.001**	**< 0.001**
Gynoid fat ratio	23.48±8.70	26.62±5.45	30.61±4.83	25.39±7.57	**< 0.001**	**< 0.001**	35.69±23.48	38.33±5.07	42.14±5.76	37.48±17.30	**0.007**	**0.020**
Total fat ratio	20.76±6.39	26.40±5.35	31.93±4.94	24.04±6.91	**< 0.001**	**< 0.001**	30.76±5.72	36.75±4.49	41.37±4.80	34.30±6.48	**< 0.001**	**< 0.001**
ASMI	7.58±0.86	8.34±0.81	9.16±0.88	8.03±0.98	**< 0.001**	**< 0.001**	6.21±0.81	6.84±0.80	7.32±0.90	6.58±0.91	**< 0.001**	**< 0.001**
SMI	14.95±1.36	16.50±4.11	17.71±1.45	15.82±2.96	**< 0.001**	**< 0.001**	12.91±1.09	14.03±1.09	15.29±1.41	13.62±1.41	**< 0.001**	**< 0.001**

Notes: Data are presented as mean ± SD. P < 0.05 considered statistically significant.

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; $TFQI_{FT4}$, Thyroid feedback quantile index of FT4; $TFQI_{FT3}$, Thyroid feedback quantile index of FT3; TT4RI, thyrotropin T4 resistance Index; TT3RI, thyrotropin T3 resistance index; TSHI, TSH index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, Total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index.

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Table 2 The Correlation Between Thyroid Hormones and Body Composition in All Participants

	FT4 (pmol/L)				FT3 (pmol/L)				FT3/FT4				TSH (mIU/L)			
	Men		Women		Men		Women		Men		Women		Men		Women	
	n=721		n=494		n=721		n=494		n=721		n=494		n=721		n=494	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
BMI	−0.019	0.609	0.017	0.701	0.193	**< 0.001**	0.062	0.170	0.159	**< 0.001**	0.051	0.255	0.134	**< 0.001**	0.132	**0.003**
Upper limb fat ratio	0.109	**0.004**	0.045	0.316	0.128	**0.001**	0.048	0.287	0.005	0.885	−0.018	0.694	0.099	**0.008**	0.113	**0.012**
Lower limb fat ratio	0.091	**0.015**	0.103	**0.023**	0.076	**0.041**	0.045	0.313	−0.013	0.737	−0.072	0.110	0.131	**< 0.001**	0.090	**0.047**
Trunk fat ratio	0.050	0.180	0.020	0.656	0.212	**< 0.001**	0.115	**0.010**	0.114	**0.002**	0.047	0.295	0.112	**0.003**	0.131	**0.004**
Android fat ratio	0.049	0.188	0.003	0.939	0.220	**< 0.001**	0.093	**0.039**	0.120	**0.001**	0.045	0.315	0.099	**0.008**	0.129	**0.004**
Android fat/Android muscle	0.046	0.215	0.007	0.877	0.227	**< 0.001**	0.091	**0.042**	0.126	**0.001**	0.042	0.353	0.093	**0.013**	0.124	**0.006**
Android fat / Gynoid fat	−0.023	0.536	−0.059	0.188	0.161	**< 0.001**	−0.101	**0.024**	0.140	**< 0.001**	−0.012	0.794	0.024	0.525	0.037	0.413
Gynoid fat ratio	0.081	**0.030**	0.090	**0.046**	0.108	**0.004**	0.093	**0.039**	0.014	0.698	−0.029	0.524	0.126	**0.001**	0.099	**0.028**
Total fat ratio	0.067	0.072	0.049	0.274	0.168	**< 0.001**	0.102	**0.024**	0.069	0.064	0.010	0.831	0.124	**0.001**	0.134	**0.003**
ASMI	−0.057	0.124	−0.113	**0.012**	0.203	**< 0.001**	0.019	0.667	0.195	**< 0.001**	0.132	**0.003**	0.026	0.482	0.155	**0.001**
SMI	−0.089	**0.016**	−0.117	**0.009**	0.112	**0.003**	0.010	0.826	0.145	**< 0.001**	0.135	**0.003**	0.021	0.568	0.106	**0.019**

Note: P < 0.05, considered statistically significant.

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; BMI, body mass index; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index.

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Table 3 presents the correlations between central TH sensitivity indicators and body composition in all participants. In men, $TFQI_{FT4}$, $TFQI_{FT3}$, and TT3RI are positively correlated with BMI, the upper limb fat ratio, the lower limb fat ratio, the trunk fat ratio, the android fat ratio, the gynoid fat ratio, and the total fat ratio. $TFQI_{FT3}$ expression is also positively correlated with ASMI. However, the TT4RI does not correlate with body composition in men. In women, $TFQI_{FT4}$, $TFQI_{FT3}$, TT4RI, TT3RI, and TSHI are positively correlated with the upper limb fat ratio, lower limb fat ratio, trunk fat ratio, gynoid fat ratio, and total fat ratio. Furthermore, the TT4RI, TT3RI, and TSHI are positively correlated with the ASMI in women.

Next, we compared the proportion of participants with impaired sensitivity to THs among the normal, overweight, and obese groups for each sensitivity index. The results indicate that among men, a greater proportion of individuals with impaired central sensitivity to THs, as assessed by the $TFQI_{FT4}$, $TFQI_{FT3}$, TSHI, TT3RI, and TT4RI, were found in the obesity group than in the normal and overweight groups (Figure 3A). However, this difference was not significant among women (Figure 3B).

Overweight and Obese Participants (BMI: ≥24 Kg/m^2)

Table 4 presents the clinical characteristics of the three cluster groups consisting of overweight and obese patients. As shown in Table 4, the HALM group presented higher levels of $TFQI_{FT4}$, $TFQI_{FT3}$, TT4RI, and TT3RI than the other groups did. Our findings revealed a positive correlation between FT4 and various fat ratios, including appendicular, trunk, android, gynoid, and total fat. Additionally, FT3 was positively correlated with the ASMI and the android fat ratio in men. However, no significant correlation was observed between TSH levels and these indicators (Table 5). Furthermore, Table 6 displays the correlation between TH sensitivity indices and body composition in overweight and obese men. Specifically, $TFQI_{FT3}$ and TT3RI levels were positively correlated with the ASMI and several regional fat ratios in men. In addition, we conducted logistic regression analysis of the clusters, comparing the HMLA and HALM methods. We have used variance inflation factor (VIF) to test the collinearity of the logistic regression model, and the result is that the VIF is less than 5. We conducted logistic regression after adjusting age for confounding factors. The results indicated that $TFQI_{FT3}$, TT3RI, and FT3 were significant indicators. Notably, in overweight and obese men, logistic regression analysis revealed independent and positive associations between $TFQI_{FT3}$, TT3RI, and FT3 and central obesity and low muscle mass. The standardized β values were 2.666 (95% CI; 1.527, 11.540; P=0.018), 0.526 (95% CI; 1.119, 2.559; P=0.013), and 1.695 (95% CI; 1.215, 9.416; P=0.027) (Table 7).

Discussion

This study aimed to investigate the associations between central TH sensitivity indicators and body composition in euthyroid T2DM patients. Specifically, our focus was on patients who were overweight or obese. To the best of our knowledge, this is the first study to explore the association between TH sensitivity and body composition in euthyroid T2DM patients who are overweight or obese. The results demonstrate that THs and central TH sensitivity are closely associated with the fat ratio and muscle mass in euthyroid T2DM patients. Moreover, high normal TT3RI and $TFQI_{FT3}$ levels are associated with central obesity and low muscle mass in overweight and obese T2DM men.

Our findings regarding the positive correlation between BMI and TSH or FT3 levels align with those of numerous studies in the literature.[4,23–27] The use of BMI is the most common method for studying obesity; however, it is not sufficient for accurately assessing body fat distribution.[4] Zhao et al reported that overweight and obese individuals have THs similar to those of normal weight individuals, but FT3 is associated with increased body fat, fasting insulin, and HOMA-IR.[8] Xiaomin Nie[10] reported that abdominal subcutaneous fat is independently related to increased FT3 in a euthyroid population. THs play a role in the synthesis and degradation of muscle proteins, yet few studies have explored the associations between THs and muscle mass in euthyroidism patients without overt thyroid disease, yielding inconsistent results. Cho et al recently demonstrated that the skeletal muscle mass index is inversely correlated with FT4 and positively correlated with FT3; however, these associations were not observed in elderly euthyroid women.[28] A prospective cohort study of 198,069 Korean adults revealed that FT4 has an inverse dose–response association with the new onset of low muscle mass among euthyroid men, whereas euthyroid women have no dose–responsive association between THs and incident low muscle mass.[11]

Table 3 The Correlation Between Thyroid Hormone Sensitivity Indices and Body Composition in All Participants

	$TFQI_{FT4}$				$TFQI_{FT3}$				TSHI				TT4RI				TT3RI			
	Men		Women		Men		Women		Men		Women		Men		Women		Men		Women	
	n=721		n=494		n=721		n=494		n=721		n=494		n=721		n=494		n=721		n=494	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
BMI	0.115	**0.002**	0.940	0.370	0.211	**< 0.001**	0.139	**0.002**	0.056	0.133	0.145	**0.001**	0.021	0.567	0.146	**0.001**	0.162	**< 0.001**	0.160	**< 0.001**
Upper limb fat ratio	0.161	**< 0.001**	0.118	**0.009**	0.180	**< 0.001**	0.123	**0.006**	0.089	**0.017**	0.141	**0.002**	0.044	0.238	0.133	**0.003**	0.144	**< 0.001**	0.132	**0.003**
Lower limb fat ratio	0.174	**< 0.001**	0.156	**< 0.001**	0.140	**< 0.001**	0.101	**0.025**	0.106	**0.004**	0.143	**0.001**	0.055	0.140	0.129	**0.004**	0.144	**< 0.001**	0.108	**0.016**
Trunk fat ratio	0.124	**0.001**	0.104	**0.020**	0.244	**< 0.001**	0.177	**< 0.001**	0.062	0.094	0.146	**0.003**	0.022	0.555	0.143	**0.001**	0.153	**< 0.001**	0.165	**< 0.001**
Android fat ratio	0.114	**0.002**	0.860	0.570	0.247	**< 0.001**	0.153	**0.001**	0.061	0.101	0.132	**0.001**	0.025	0.503	0.131	**0.004**	0.142	**< 0.001**	0.150	**0.001**
Android fat / Gynoid fat	-0.002	0.952	-0.320	0.481	0.123	**0.001**	-0.056	0.213	0.008	0.830	0.080	0.852	0.010	0.790	0.014	0.760	0.042	0.255	0.012	0.785
Gynoid fat ratio	0.121	**0.001**	0.146	**0.001**	0.117	**0.002**	0.144	**0.001**	0.057	0.129	0.145	**0.022**	0.018	0.636	0.133	**0.003**	0.102	**0.006**	0.130	**0.004**
Total fat ratio	0.152	**< 0.001**	0.136	**0.002**	0.217	**< 0.001**	0.173	**< 0.001**	0.082	**0.027**	0.163	**< 0.001**	0.036	0.339	0.156	**< 0.001**	0.159	**< 0.001**	0.166	**< 0.001**
ASMI	-0.037	0.319	0.050	0.918	0.154	**< 0.001**	0.094	0.370	-0.026	0.490	0.103	**0.022**	-0.022	0.557	0.127	**0.005**	0.047	0.204	0.153	**0.001**
SMI	-0.065	0.082	-0.280	0.529	0.043	0.251	0.660	0.143	-0.051	0.169	0.550	0.222	-0.032	0.394	0.074	0.101	-0.010	0.788	0.107	**0.017**

Note: P < 0.05 considered statistically significant.

Abbreviations: BMI, body mass index; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index; $TFQI_{FT4}$, Thyroid feedback quantile index of FT4; $TFQI_{FT3}$, Thyroid feedback quantile index of FT3; TT4RI, thyrotropin T4 resistance Index; TT3RI, thyrotropin T3 resistance index; TSHI, TSH index.

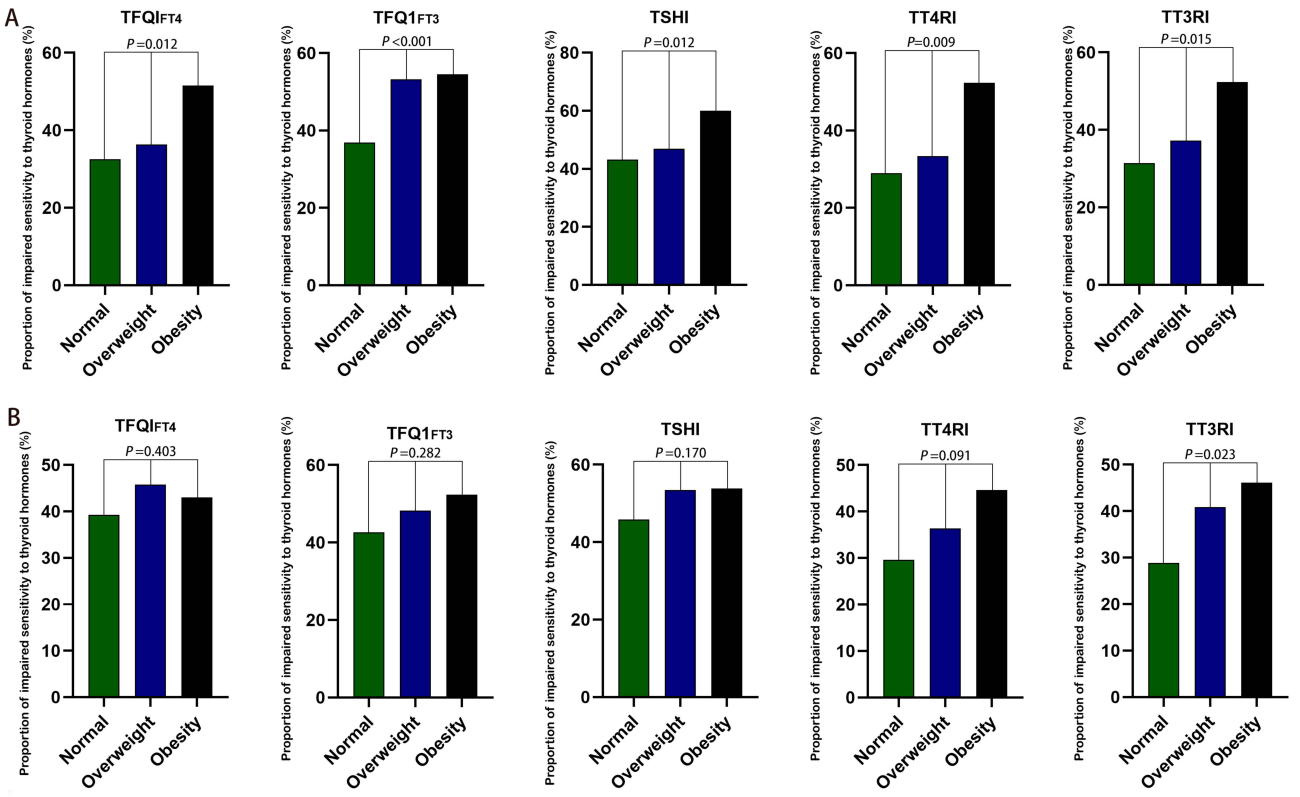

Figure 3 The proportion of participants in different group with impaired thyroid hormone sensitivity. (**A**) presents the groups of men and (**B**) presents the groups of women.
Note: P < 0.05 considered statistically significant.
Abbreviations: $TFQI_{FT4}$, Thyroid feedback quantile index of FT4; $TFQI_{FT3}$, Thyroid feedback quantile index of FT3; TT4RI, thyrotropin T4 resistance Index; TT3RI, thyrotropin T3 resistance index; TSHI, TSH index.

Previous studies have assessed thyroid function via traditional tests for circulating TH levels. TSH, FT4, and FT3 are closely regulated and influenced by each other. Sensitivity to THs is a newly proposed functional entity that considers TSH and TH (T3 or T4) levels. Sensitivity to TH provides a more comprehensive explanation of thyroid status.[29] Laclaustra et al[14] were the first to propose that the TFQI is a novel method to identify mild levels of acquired resistance in the general population. Various studies have demonstrated that the TFQI is more stable than the TSHI, TT4RI, and TT3RI are.[30] Laclaustra et al reported that for every 1 SD increase in the TFQI, the odds of diabetes increased by 1.13 (95% CI 1.02, 1.25), and the odds of metabolic syndrome increased by 1.16 (95% CI 1.02, 1.31). Other indices of resistance to TH, including TT4RI and TSHI, showed similar associations with diabetes-related deaths and metabolic syndrome.[14] Another study confirmed that higher normal FT3 and TSH levels, as well as impaired sensitivity to THs ($TFQI_{FT3}$, TT3RI, and TT4RI), were associated with metabolic dysfunction-associated fatty liver disease in euthyroid patients with newly diagnosed T2DM.[31] A recent study investigated the associations between sensitivity to THs, diabetes, and hypertension.[30] Wu et al[32] subsequently revealed that impaired sensitivity to THs was associated with hyperuricemia in the euthyroid population and emphasized the mediating effect of BMI.

In our study, our findings show that the associations between sensitivity to THs and BMI are consistent with the results reported by Zhou et al.[33] Specifically, we observed that $TFQI_{FT4}$ is positively correlated with the fat ratio in various parts of the body, including the upper limb, lower limb, trunk, gynoid, and total fat ratio. Similarly, $TFQI_{FT3}$ was positively correlated with BMI, the upper limb fat ratio, the lower limb fat ratio, the trunk fat ratio, thyroid fat ratio, the gynoid fat ratio, and the total fat ratio. In other words, increased impairment of central sensitivity to THs (as indicated by higher $TFQI_{FT4}$ and $TFQI_{FT3}$ levels) is associated with a greater fat ratio in different areas of the body.

Furthermore, our study revealed that a greater proportion of overweight and obese individuals had impaired central TH sensitivity. This aligns with the findings of Fang et al[34] who reported that the levels of TSHI and TFQI were

Table 4 Clinical Characteristics of 3 Cluster Groups in Overweight and Obese Patients

	Men				*p*	Women				*p*
	Moderates	HMLA	HALM	Total		Moderates	HMLA	HALM	Total	
	n=184	n=24	n=147	n=355		n=111	n=50	n=80	n=241	
FT4 (pmol/L)	11.50±1.90	11.48±2.08	12.00±2.19	11.70±2.05	0.072	11.48±2.07	11.33±1.89	11.74±2.13	11.54±2.05	0.498
FT3 (pmol/L)	4.70±0.58	4.3±0.76	4.78±0.82	4.71±0.71	**0.008**	4.63±0.71	4.41±0.62	4.53±0.56	4.55±0.65	0.131
TSH (mIU/L)	1.65±1.16	1.99±1.34	1.55±0.95	1.63±1.09	0.175	1.88±1.34	1.67±1.24	1.81±1.31	1.81±1.30	0.631
TFQIFT4	−0.01±0.27	−0.06±0.26	0.06±0.34	−0.03±0.27	**0.046**	0.00±0.37	−0.05±0.34	−0.09±0.35	−0.04±0.35	0.278
TFQIFT3	0.31±0.32	0.00±0.41	0.03±0.41	0.029±0.36	**0.036**	0.00±0.38	0.24±0.38	−0.09±0.36	0.01±0.38	0.237
TSHI	1.84±0.58	1.93±0.59	2.10±0.81	1.89±0.61	0.094	1.99±0.67	1.97±0.61	1.84±0.64	1.95±0.63	0.415
TT4RI	18.94±11.94	17.98±11.93	25.72±18.24	19.90±12.56	**0.017**	21.20±13.95	20.61±14.01	18.48±12.12	20.38±13.6	0.534
TT3RI	7.64±5.15	7.48±4.89	9.96±7.78	7.91±5.25	**0.021**	8.35±5.69	8.53±6.34	7.44±5.99	8.25±6.06	0.572
TG (mmol/L)	1.90±1.17	1.45±0.76	2.07±1.19	1.94±1.17	**0.044**	2.06±0.94	1.85±1.39	3.43±10.93	2.47±6.37	0.255
HDL (mmol/L)	1.02±0.34	1.07±0.38	0.94±0.20	0.99±0.29	**0.037**	1.11±0.26	1.09±0.27	1.12±0.26	1.11±0.26	0.808
LDL (mmol/L)	2.55±0.98	2.21±0.79	2.62±0.96	2.56±0.96	0.151	2.76±0.89	2.47±0.88	2.61±0.87	2.65±0.89	0.134
TC (mmol/L)	4.58±1.26	4.25±1.19	4.79±1.31	4.65±1.28	0.093	5.00±1.32	4.67±1.27	4.92±1.53	4.90±1.38	0.359
Fasting blood glucose (mmol/L)	8.89±4.37	8.07±3.08	7.83±3.33	8.40±3.91	**0.047**	8.35±3.58	8.34±3.16	7.65±2.95	8.12±3.30	0.302
ALT (U/L)	27.24±20.92	22.79±12.93	41.70±37.26	32.93±29.42	**< 0.001**	29.09±38.18	20.00±14.36	36.63±62.73	29.71±45.18	0.122
AST (U/L)	25.89±18.51	24.92±16.83	33.63±25.38	29.03±21.83	**0.004**	25.93±23.6	23.4±11.44	31.56±28.2	27.27±23.53	0.112
Creatinine (umol/L)	86.63±68.49	91.36±80.9	84.54±35.59	86.08±58.1	0.854	62.52±24.93	66.84±41.56	66.39±24.39	64.7±28.94	0.558
Hemoglobin A1c (%)	9.19±2.27	9.06±2.39	9.29±2.54	9.22±2.38	0.879	8.46±2.04	9.46±2.44	8.41±2.16	8.65±2.2	**0.012**
Age	57.76±11.41	57.50±9.20	54.59±16.94	56.43±13.91	0.111	63.12±12.96	63.21±12.14	65.39±13.25	63.89±12.88	0.446
BMI	25.82±1.44	25.14±1.18	27.80±2.74	26.59±2.31	**< 0.001**	26.47±1.66	25.71±1.72	28.81±3.06	27.09±2.55	**< 0.001**

Upper limb fat ratio	19.93±3.53	13.00±4.57	27.60±5.25	22.64±6.29	**< 0.001**	38.94±5.69	34.48±4.77	45.32±4.08	40.13±6.42	**< 0.001**
Lower limb fat ratio	19.27±3.55	13.85±4.41	26.32±4.73	21.82±5.76	**< 0.001**	33.81±4.59	27.92±5.23	39.25±5.02	34.4±6.34	**< 0.001**
Trunk fat ratio	31.4±3.03	17.69±5.37	39.81±3.13	33.96±6.80	**< 0.001**	41.45±2.38	33.98±3.63	47.35±2.15	41.86±5.46	**< 0.001**
Android fat ratio	36.06±3.14	21.56±5.92	44.57±3.25	38.60±7.04	**< 0.001**	47.45±2.28	40.18±3.84	52.84±2.36	47.73±5.28	**< 0.001**
Gynoid fat ratio	25.21±3.53	18.62±5.23	31.48±4.39	27.36±5.55	**< 0.001**	38.97±4.18	33.43±4.19	43.61±4.07	39.36±5.52	**< 0.001**
Total fat ratio	24.91±2.54	15.39±4.1	32.54±3.12	27.42±5.69	**< 0.001**	37.45±2.24	31.02±2.86	43.12±2.49	38.00±5.00	**< 0.001**
ASMI	8.58±0.75	8.72±0.90	8.35±1.00	8.49±0.88	**0.025**	6.95±0.78	7.02±1.04	6.96±0.83	6.97±0.86	0.883
SMI	17.03±5.03	17.57±1.13	16.20±1.50	16.72±3.78	0.070	14.28±1.09	14.69±1.46	14.3±1.46	14.37±1.31	0.158

Notes: The moderate group included those with a moderate BMI, android fat, and ASMI. Patients in the HMLA group had the lowest BMI and android fat ratio, and the highest ASMI. Patients in the HALM group had the highest BMI and android fat ratio and lowest ASMI. $P < 0.05$ considered statistically significant.

Abbreviations: FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; $TFQI_{FT4}$, Thyroid feedback quantile index of FT4; $TFQI_{FT3}$, Thyroid feedback quantile index of FT3; TT4RI, thyrotropin T4 resistance Index; TT3RI, thyrotropin T3 resistance index; TSHI, TSH index; TG, Triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; TC, Total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, Hemoglobin; BMI, body mass index; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index; Data are presented as the mean ± SD.

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Table 5 The Correlation Between Thyroid Hormones and Body Composition in Overweight and Obese Men

	FT4 (pmol/L)		FT3 (pmol/L)		TSH (mIU/L)	
	r	*p*	*r*	*p*	*r*	*p*
Upper limb fat ratio	0.137	**0.010**	0.056	0.292	0.013	0.804
ASMI	0.043	0.420	0.118	**0.027**	-0.017	0.753
SMI	-0.009	0.870	0.047	0.378	-0.053	0.319
Lower limb fat ratio	0.118	**0.026**	0.014	0.797	0.060	0.257
Trunk fat ratio	0.132	**0.013**	0.094	0.077	0.033	0.533
Android fat ratio	0.105	**0.048**	0.124	**0.019**	0.012	0.827
Android fat/Android muscle	0.108	**0.042**	0.130	**0.014**	0.006	0.912
Android fat / Gynoid fat	-0.012	0.822	0.100	0.061	-0.069	0.197
Gynoid fat ratio	0.108	**0.042**	0.013	0.802	0.056	0.292
Total fat ratio	0.126	**0.018**	0.061	0.249	0.049	0.358

Notes: P < 0.05 considered statistically significant. R is a positive number for positive correlation.
Abbreviations: FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index.

Table 6 The Correlation Between Thyroid-Associated Variables and Body Composition in Overweight and Obese Men

	$TFQI_{FT4}$		$TFQI_{FT3}$		TSHI		TT4RI		TT3RI	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Upper limb fat ratio	0.106	**0.046**	0.074	0.165	0.093	0.079	0.072	0.174	0.056	0.290
ASMI	-0.023	0.663	0.246	**<0.001**	-0.025	0.637	-0.006	0.903	0.125	**0.018**
SMI	-0.087	0.102	-0.016	0.760	-0.094	0.077	-0.061	0.253	-0.043	0.440
Lower limb fat ratio	0.121	**0.022**	0.033	0.534	0.125	**0.018**	0.081	0.129	0.052	0.330
Trunk fat ratio	0.067	0.206	0.094	0.076	0.064	0.227	0.029	0.581	0.034	0.527
Android fat ratio	0.045	0.396	0.111	**0.037**	0.043	0.418	0.016	0.761	0.030	0.578
Android fat / Gynoid fat	-0.075	0.158	0.131	**0.014**	-0.082	0.125	-0.074	0.167	-0.133	**0.012**
Gynoid fat ratio	0.119	**0.025**	0.046	0.386	0.119	**0.025**	0.082	0.121	0.050	0.347
Total fat ratio	0.096	0.070	0.072	0.174	0.094	0.078	0.054	0.307	0.044	0.410

Notes: P < 0.05 considered statistically significant. R is a positive number for positive correlation.
Abbreviations: $TFQI_{FT4}$, Thyroid feedback quantile index of FT4; $TFQI_{FT3}$, Thyroid feedback quantile index of FT3; TT4RI, thyrotropin T4 resistance Index; TT3RI, thyrotropin T3 resistance index; TSHI, TSH index; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index.

negatively correlated with the lumbar skeletal muscle area but positively correlated with total adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue. Therefore, impaired TH sensitivity appears to influence the distribution of adipose tissue and muscles. Interestingly, we also found that $TFQI_{FT3}$ was positively associated with the ASMI, contrary to the results reported by Fang et al.

The hypothalamic–pituitary–thyroid (HPT) axis is a significant neuroendocrine system that controls the secretion and regulation of TH. RTH β is a clinical syndrome characterized by reduced sensitivity to THs. It is caused by mutations in the TH receptor beta (THRB) gene, which negatively regulates the HPT axis.[35] The main feature of RTH[34] is an increase

Table 7 Logistic Regression Analysis in Overweight and Obese Men. Compared with HMLA Group

		B	Std. Error	Wald	df	*p*	Exp (B)	95% Confidence Interval for Exp (B)	
								Lower Bound	Upper Bound
	TFQIFT4	7.258	4.274	2.883	1	0.089	14.390	0.326	61.542
	TFQIFT3	−2.909	2.758	1.113	1	0.291	0.055	0	12.126
	TT4RI	0.033	0.113	0.084	1	0.771	1.033	0.828	1.289
Moderates	**TT3RI**	−0.302	0.318	0.906	1	0.341	0.739	0.396	1.378
	FT3 (pmol/L)	0.839	1.278	0.431	1	0.512	2.313	0.189	28.295
	TSH (mIU/L)	1.873	1.661	1.272	1	0.259	3.511	0.251	36.842
	TSHI	−2.853	1.645	3.009	1	0.083	0.058	0.002	1.448
	FT4 (pmol/L)	−0.234	0.317	0.543	1	0.461	0.791	0.425	1.474
	Age	−0.011	0.018	0.365	1	0.546	0.989	0.955	1.024
	TFQIFT4	0.230	2.409	0.009	1	0.924	1.258	0.011	14.441
	TFQIFT3	2.666	1.129	5.572	1	**0.018**	3.380	1.572	11.540
HALM	**TT4RI**	−0.016	0.076	0.045	1	0.831	0.984	0.848	1.142
	TT3RI	0.526	0.211	6.222	1	**0.013**	1.693	1.119	2.559
	FT3 (pmol/L)	1.695	0.766	4.902	1	**0.027**	2.446	1.215	9.416
	TSH (mIU/L)	−1.357	1.462	0.861	1	0.354	0.257	0.015	4.525
	TSHI	0.244	0.887	0.076	1	0.783	1.276	0.225	7.255
	FT4 (pmol/L)	−0.137	0.178	0.597	1	0.440	0.872	0.615	1.235
	Age	0.015	0.009	2.718	1	0.099	1.015	0.997	1.033

Notes: The moderate group included those with a moderate BMI, android fat, and ASMI. Patients in the HMLA group had the lowest BMI and android fat ratio, and the highest ASMI. Patients in the HALM group had the highest BMI and android fat ratio and lowest ASMI. We conducted logistic regression after adjusting age for confounding factors. P < 0.05 considered statistically significant.

Abbreviations: FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TFQIFT4, Thyroid feedback quantile index of FT4; TFQIFT3, Thyroid feedback quantile index of FT3; TT4RI, thyrotropin T4 resistance Index; TT3RI, thyrotropin T3 resistance index; TSHI, TSH index; ASMI, appendicular skeletal muscle mass index; SMI, skeletal muscle index.

in TH levels in the blood without inhibiting TSH, resulting in symptoms of thyroid toxicity in tissues that primarily express TRα1, such as the heart, bones, muscles, and adipose tissue, leading to various metabolic disorders.[36,37]

Leptin, a hormone primarily secreted by adipose tissue, plays a role in regulating caloric intake and energy storage by acting on the hypothalamic appetite center. Studies have reported that variations in leptin levels are associated with thyroid dysfunction in both animal models and humans. Changes in central TH sensitivity may affect leptin secretion, influencing feeding behavior and causing changes in adiposity and glucose metabolism. Low leptin levels inhibit the secretion of hypothalamic neurons.[38] Moreover, an increase in leptin derived from adipose tissue accumulation, particularly central adiposity, may activate the thyroid axis.

We studied the expression of genes related to TH action in adipose tissue and skeletal muscle in subjects with different degrees of insulin sensitivity and explored their regulation through insulin and free fatty acids (FFAs).[39] These findings indicate that alterations in adipose tissue and skeletal muscle expression of TH-related genes suggest decreased tissue TH activity in obesity. The failure to increase TH-related gene expression in obesity and during FFA oversupply may aggravate lipotoxicity.[39] Further evidence from basic research shows that type 1 iodothyronine deiodinase catalyzes

the conversion of FT4 to FT3 in white adipose tissue and that its expression and activity are increased in obese individuals.[40] Some studies have demonstrated a positive correlation between serum TSH and indicators of insulin resistance. Insulin resistance in obesity seems to reduce the activity of type 2 iodothyronine deiodinase in thyroid cells, resulting in reduced thyroid function and a subsequent increase in TSH synthesis. Additionally, several studies have shown that TSH and FT3 levels decrease significantly after weight loss through diet or bariatric surgery.[41–43] The changes in plasma TSH and FT3 levels in obese individuals may be a consequence of hypertrophic changes in adiposity. Nevertheless, the mechanisms underlying TH sensitivity, fat distribution, and muscle mass are not yet fully understood.

Individuals with a high BMI, high abdominal fat ratio, and low ASMI have an increased risk of developing metabolic disorders. Therefore, a cluster analysis was conducted on all participants with a BMI ≥24 kg/m^2 on the basis of these three indicators. After regrouping the overweight and obese participants, the FT3 level in the HMLA group (which had the highest muscle composition and the lowest android fat composition) was lower than the FT3 levels in the Moderates and HALM groups (participants with overweight and obesity, characterized by the highest android fat composition and the lowest muscle composition). Higher TT3RI and $TFQI_{FT3}$ levels were associated with greater android fat and lower muscle composition. In this study, we found a positive correlation between FT3 and $TFQI_{FT3}$ levels and between android fat content and the ASMI. However, $TFQI_{FT3}$, TT3RI, and FT3 levels were highest in the cluster with overweight and obese participants who had high android fat composition and low muscle composition. We speculated that central fat accumulation plays a more prominent role in TH activity and TH sensitivity than appendicular skeletal muscle mass does in overweight and obese individuals. However, this conclusion cannot be generalized to women, as we did not observe any differences in the serum levels of TSH, FT3, or FT4 between overweight and obese women in this study. The difference between men and women may be attributed to estrogen levels. Men have high insulin resistance due to the lack of a potential protective effect of estrogen, which may enhance the influence of FT4 and FT3.[44] Prospective longitudinal and interventional studies are needed in the future.

These findings revealed a high level of FT3 and impaired central TH sensitivity, which are associated with central obesity and low muscle mass in overweight and obese men with T2DM. This finding highlights the increased risk faced by these individuals and underscores how thyroid function not only affects metabolic health but also affects body composition, particularly in those who are already prone to metabolic complications.

Further research is needed to explore the observed sex differences and the underlying mechanisms driving these associations.

Our study has several limitations. Given its cross-sectional design, this study could only establish associations between THs and body composition and not causal associations. Additional prospective studies are necessary to clarify this causal association. Moreover, all participants in our study were of Han Chinese ethnicity; therefore, the results cannot be extrapolated to other ethnicities.

Conclusion

THs and central TH sensitivity are associated with the fat ratio and muscle mass in euthyroid T2DM patients, and high levels of TT3RI and $TFQI_{FT3}$ are associated with central obesity and low muscle mass in T2DM men with overweight and obesity.

Abbreviations

T2DM, type 2 diabetes mellitus; TFQI, Thyroid Feedback Quartile-Based index; TT3RI, thyrotroph T3 resistance index; TT4RI, thyrotroph T4 resistance index; TSHI, thyroid stimulating hormone index; ASM, appendicular skeletal muscle mass; TFQIFT4, Thyroid feedback quantile index of FT4; TFQIFT3, thyroid feedback quantile index of FT3; FT3, Free triiodothyronine; SMI, skeletal muscle mass index; THs, Thyroid hormones; FT4; free thyroxine; TSH, thyroid-stimulating hormone; HOMA-IR, homeostasis model assessment for insulin resistance; BMI, body mass index; ASMI, appendicular skeletal muscle mass index; DXA, Dual-energy X-ray absorptiometry; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate transaminase; HMLA, Patients with the lowest BMI, android fat ratio, and highest ASMI; HALM, Patients with the highest BMI, android fat ratio, and lowest ASMI; OR, odds ratios; CI, confidence interval; FFAs, free fatty acids.

Disclosure

The authors report no conflicts of interest in this work.

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