Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Relationship Between Thyroid Hormones and Fat Distribution in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

Jun Yang, Chenlin Gao, Qin Wan, Yong Xu

Department of Endocrinology and Metabolism, The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China

Correspondence: Yong Xu, Department of Endocrinology and Metabolism, The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China, Tel +86 13980255895, Email xywyll@swmu.edu.cn; 254816235@qq.com

Introduction: The global prevalence of type 2 diabetes mellitus (T2DM) poses significant health and economic challenges, especially given its association with abnormal fat distribution and related metabolic complications. Thyroid hormones, key regulators of metabolism, also have been linked to variations in fat distribution. This cross-sectional study aimed to characterize the relationships between the levels of thyroid hormones, including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH), and fat distribution in T2DM patients with normal thyroid function.

Methods: Data from 2,956 T2DM patients were analysed. Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured via bioelectrical impedance analysis (BIA). Correlation and multivariate regression analyses were conducted to assess the independent effects of thyroid hormone levels on fat distribution, controlling for potential confounders.

Results: FT3 showed a significant positive correlation with both VFA (r=0.248, P<0.001) and SFA (r=0.190, *P*<0.001), while FT4 had a weak inverse correlation. TSH correlated positively with VFA and SFA but was less impactful than FT3. On multivariate regression analysis, FT3 was shown to predict increased fat distribution, while FT4 inversely affected VFA and SFA.

Conclusion: These results suggest that thyroid hormones, particularly FT3, influence fat distribution in T2DM patients. Further longitudinal studies are needed to explore thyroid hormone levels as potential biomarkers for metabolic management in T2DM.

Keywords: type 2 diabetes mellitus, thyroid hormones, visceral fat, subcutaneous fat, free triiodothyronine, FT3, free thyroxine, FT4

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, hyperglycaemia, and various metabolic abnormalities.[1] Over the past few decades, the global prevalence of T2DM has continuously increased at an alarming rate, with estimates suggesting that more than 463 million people worldwide are currently living with diabetes, the vast majority of which are T2DM cases.[2] This surge is largely driven by rising obesity rates, unhealthy lifestyles, and population aging.[3] T2DM is not only a major cause of morbidity and mortality but also places a tremendous economic burden on healthcare systems due to the frequent development of complications, including cardiovascular disease, nephropathy, and neuropathy.[4]

Among the numerous complications associated with T2DM, abnormal fat distribution plays a pivotal role in the progression of the disease and the development of insulin resistance.[5] Visceral fat is known to contribute significantly to conditions related to metabolic dysfunction, such as dyslipidaemia, hypertension, and inflammation. Subcutaneous fat, though less harmful than visceral fat, also can contribute to metabolic derangements when present in excess.[6] Given the importance of fat distribution in the pathophysiology of T2DM, understanding the factors that influence fat storage and distribution is critical for the development of effective therapeutic interventions.[7]

Thyroid hormones are well-established regulators of metabolism and energy expenditure.[8] These hormones, including free triiodothyronine (FT3) and free thyroxine (FT4), play key roles in lipid metabolism, thermogenesis, and glucose

Received: 21 May 2025
Accepted: 3 October 2025
Published: 21 October 2025

homeostasis. Thyroid-stimulating hormone (TSH), which is produced by the pituitary gland, regulates the synthesis and secretion of both FT3 and FT4.[9,10] In clinical practice, thyroid function is typically evaluated by measuring thyroid hormone levels, with deviations from normal levels indicating either hypo- or hyperthyroidism.[11,12] Interestingly, research has demonstrated that even in euthyroid individuals (those with normal thyroid function), variations in thyroid hormone levels may have significant metabolic consequences.[13,14]

Several studies[15–17] have explored the interplay between thyroid hormones and fat distribution, particularly in relation to obesity and metabolic syndrome. One study[18] found that individuals with elevated FT3 levels tend to have higher body fat percentages, particularly involving visceral fat, which is associated with greater risks of insulin resistance and cardiovascular diseases. Conversely, higher FT4 levels are linked to lower body fat and improved metabolic profiles, suggesting a protective role of FT4 in fat metabolism. These findings are consistent with the known metabolic effects of thyroid hormones, with FT3 being the more metabolically active hormone that increases the basal metabolic rate and promotes lipid oxidation.[19]

However, the relationship between thyroid hormone levels and fat distribution in T2DM patients remains poorly understood. Most studies of this relationship have focused on general populations or individuals with obesity, without specifically examining T2DM patients. Given the unique metabolic characteristics of T2DM patients, including insulin resistance and altered glucose metabolism, it is important to investigate how thyroid hormone levels influence fat distribution in this population.

The present study aimed to elucidate the relationship between thyroid hormones (FT3, FT4, and TSH) and fat distribution, specifically in terms of visceral fat area (VFA) and subcutaneous fat area (SFA), in T2DM patients with normal thyroid function. By characterizing these relationships, a goal of this study was to provide insight into the potential roles of thyroid hormones in the pathophysiology of T2DM and its complications. This information, in turn, can support the development of targeted treatments for metabolic management in T2DM patients.

Materials and Methods

Study Design and Participants

This cross-sectional study included 2,956 T2DM patients recruited from a tertiary hospital between 2021 and 2023. The initial dataset contained 10,416 entries. The inclusion criteria were: (1) age ≥18 years, (2) confirmed diagnosis of T2DM according to the World Health Organization (WHO) criteria, and (3) availability of complete data for VFA, SFA, and thyroid hormone levels (FT3, FT4, and TSH). The exclusion criteria were applied as follows: duplicate entries (6,237 cases), missing age or age <18 years (7 cases), incomplete VFA or SFA data (875 cases), unconfirmed T2DM diagnosis (31 cases), presence of thyroid disease (122 cases), and missing FT3/FT4/TSH data (188 cases). After these exclusions, 2,956 patients with complete data were included in the final analysis.

The study was approved by the Institutional Review Board of the hospital, and written informed consent was obtained from all participants prior to enrolment.

Data Collection

Demographic and Clinical Characteristics

Baseline demographic and clinical data were collected from medical records and included: age, gender, body mass index (BMI), and waist-to-hip ratio (WHR); blood pressure (systolic and diastolic); and lifestyle factors such as smoking status (never, quit, occasionally, or daily) and alcohol consumption (never, quit, occasionally, or daily).

Thyroid Hormone Measurements

Fasting blood samples were obtained in the morning from all participants for the measurement of thyroid hormone levels.[20] Serum FT3, FT4, and TSH levels were measured using enzyme-linked immunosorbent assays (ELISAs). To explore differences in fat distribution across varying levels of thyroid hormones, we stratified participants into three groups (low, normal, and high), based on serum FT3, FT4, and TSH levels. The cutoffs for these categories were defined according to standard clinical reference ranges used in routine laboratory practice and prior studies on thyroid function in euthyroid individuals: FT3 (low <1.8, normal 1.8–3.8, high >3.8 pg/mL), FT4 (low <0.78, normal

0.78–1.86, high >1.86 ng/dL), and TSH (low <0.38, normal 0.38–5.57, high >5.57 mU/L). These ranges were chosen to ensure consistency with clinical definitions and to assess potential trends across the spectrum of thyroid hormone concentrations within the euthyroid range. Quality control procedures were applied to ensure measurement accuracy, and extreme values were addressed based on statistical feedback. Specifically, values for creatinine (Cr), FT4, and TSH were adjusted as follows: Cr (151.72 μmol/L and 103.9 μmol/L), FT4 (7.71 ng/dL), and TSH (97.743 mU/L). These adjustments corrected data entry inconsistencies or biologically implausible values, improving data integrity and minimizing potential bias. Sensitivity analyses indicated these corrections did not materially alter the study's main findings.

Fat Distribution Assessment

Fat distribution was assessed by measuring VFA and SFA via bioelectrical impedance analysis (BIA)[21] using the DUALSCAN HDS-2000 instrument (Omron Healthcare, Kyoto, Japan). Measurements were taken after an overnight fast and voiding of the bladder. The device calculates body impedance through weak electrical currents passing through the body, and participant data (hospital number, height, weight, age, gender) were entered for precise calculations. The abdominal measurement unit on the device measured abdominal shape, and impedance measurements allowed for calculation of VFA and SFA according to the manufacturer's protocols.

Statistical Analysis

Descriptive Statistics

The baseline characteristics of the study population are presented as means ± standard deviations for normally distributed continuous variables, medians (interquartile ranges) for skewed variables, and as frequencies and percentages for categorical variables. Differences in baseline characteristics were assessed using the *t*-test for normally distributed continuous variables, the Mann–Whitney *U*-test for skewed variables, and the Chi-square test for categorical variables. Skewed variables (eg, triglycerides [TG], alanine transaminase [ALT]) were analyzed without log transformation. The level of statistical significance was set at $P<0.05$.

Correlation Analysis

Correlations between levels of thyroid hormones (FT3, FT4, TSH) and fat distribution measures (VFA, SFA) were analyzed via Pearson or Spearman correlation analysis based on the distribution of the data. Correlation results were evaluated at a significant level of $P<0.05$.

Multivariate Regression Analysis

Multiple linear regression models were employed to evaluate the independent effects of FT3, FT4, and TSH on VFA and SFA after adjusting for potential confounding variables, including age, gender, and BMI. Based on multicollinearity analyses, BMI and WHR were excluded from final models involving FT4 to avoid obscuring its significance in relation to fat distribution. Regression coefficients, confidence intervals, and *P*-values were reported for all predictors. All analyses were conducted using a statistical software package with significance set at $P<0.05$.

Handling of Outliers

Extreme values identified for Cr, FT4, and TSH measurements were corrected based on statistical review and clinical evaluation to enhance the robustness of the findings. A total of five values were adjusted: two for Cr (151.72 and 103.9 μmol/L), one for FT4 (7.71 ng/dL), and two for TSH (97.743 mU/L and one additional unreported outlier). These corrections addressed data entry inconsistencies or biologically implausible values, thus improving data quality and minimizing potential bias. Sensitivity analyses performed to assess the impact of these corrections showed no material changes in the direction, magnitude, or statistical significance of the associations between thyroid hormone levels and fat distribution. All statistical analyses in this study were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria), with results considered statistically significant at $P<0.05$.

Results

Baseline Characteristics of the Study Population

The baseline characteristics of the study participants (n=2,956) are summarized in Table 1, with stratification by gender. The mean age of the participants was 56.2 years, and the study population included a higher proportion of males (58.6%) than females (41.4%). Males had a significantly higher WHR and systolic blood pressure than females (both $P<0.001$). Lifestyle factors also showed gender-specific differences, with males reporting higher smoking and alcohol consumption rates than females. BMI did not differ significantly between the male and female groups ($P=0.077$).

Thyroid Hormone Levels and Fat Distribution in T2DM Patients

Table 2 presents the distribution of VFA and SFA across groups of patients with different categories of thyroid hormone levels (decreased, normal, and increased) for FT3, FT4, and TSH. Notably, patients with elevated FT3 levels (>3.8 pg/mL) show higher mean values for VFA (79.75 ± 40.12 cm²) and SFA (148.96 ± 57.06 cm²) compared to those with normal (1.8–3.8 pg/mL) or decreased (<1.8 pg/mL) FT3 levels (all $P<0.001$). Conversely, no significant variation in VFA and SFA values was observed for patients in different FT4 categories (decreased, normal, increased), suggesting a lesser

Table 1 The Basic Characteristics Stratified by Gender

Variables	Male	Female	P
Age	54.03±0.28	57.82±0.29	0.000***
BMI, kg/m2	24.79±0.09	24.56±0.10	0.077
Education			0.000***
Below high school	893	1041	
High school and above	700	316	
Job			0.023*
Blue-collar	1116	1000	
Other	481	358	
Smoke			0.000***
Never	492	1336	
Quit	258	5	
Occasionally	214	5	
Everyday	632	13	
Drink			0.000***
Never	416	1237	
Quit	318	49	
Occasionally	604	70	
Everyday	256	3	
Waist-hip ratio	0.96±0.002	0.94±0.002	0.000***
SBP, mmHg	131.68±0.48	138.21±0.60	0.000***
DBP, mmHg	79.33±0.29	78.35±0.31	0.021*
TC, mmol/L	4.81±0.06	4.95±0.04	0.679
TG, mmol/L	2.69±0.07	2.28±0.06	0.000***
HDL, mmol/L	1.08±0.01	1.25±0.01	0.000***
LDL, mmol/L	2.81±0.03	2.94±0.03	0.001**
ALT, mmol/L	33.38±1.14	25.85±0.64	0.000***
AST, mmol/L	25.16±0.62	23.31±0.52	0.025*
Cr,μmol/L	78.62±1.21	61.62±1.16	0.000***
FT3, pg/mL	2.66±0.20	2.34±0.03	0.142
FT4, ng/dL	1.20±0.01	1.20±0.01	0.612
TSH, mU/L	2.29±0.13	3.04±0.16	0.000***
VFA	83.67±1.15	77.49±1.11	0.000***
SFA	150.23±1.38	160.91±1.78	0.000***

Notes: *P<0.05; **P<0.01; ***P<0.001.

Table 2 The Basic Characteristics Stratified by Age

Variables	18-44	45-64	>65	P
Gender				0.000***
Male	267	1023	307	
Female	120	807	432	
BMI, kg/m2	25.01±4.34	24.58±3.38	24.77±3.39	0.073
Education				0.000***
Below high school	157	1182	597	
High school and above	230	648	142	
Job				0.002**
Blue-collar	252	1310	555	
Other	135	520	184	
Smoke				0.000***
Never	203	1086	539	
Quit	20	176	67	
Occasionally	54	140	25	
Everyday	110	428	107	
Drink				0.000***
Never	172	992	489	
Quit	46	228	93	
Occasionally	126	430	118	
Everyday	43	178	38	
Waist-hip ratio	0.93±0.08	0.95±0.07	0.96±0.08	0.000***
SBP, mmHg	121.88±16.37	133.5±20.10	144.29±20.51	0.000***
DBP, mmHg	74.25±12.38	79.58±11.11	79.52±11.28	0.000***
TC, mmol/L	5.07±1.70	4.9±2.22	4.69±1.29	0.006**
TG, mmol/L	3.39±3.92	2.49±2.53	2.05±1.42	0.000***
HDL, mmol/L	1.05±0.35	1.16±0.35	1.21±0.36	0.000***
LDL, mmol/L	2.94±1.10	2.88±1.08	2.8±1.00	0.095
ALT, mmol/L	39.7±35.35	29.91±41.73	24.8±21.91	0.000***
AST, mmol/L	27.25±20.83	23.95±24.29	23.65±16.71	0.020*
Cr, μmol/L	62.67±33.4	71.58±51.72	73.13±36.65	0.000
FT3, pg/mL	2.47±1.43	2.58±7.40	2.36±0.51	0.685***
FT4, ng/dL	1.25±0.56	1.19±0.36	1.19±0.25	0.007**
TSH, mU/L	2.97±9.59	2.39±3.55	3.06±6.78	0.011*
VFA	75.85±46.54	79.02±43.06	87.93±43.08	0.000***
SFA	155.35±68.62	151.07±58.04	165.10±60.19	0.000***

Notes: *P<0.05; **P<0.01; ***P<0.001.

impact of FT4 alone on fat distribution (P>0.05). Upon analysis according to the TSH categories, slightly higher values of VFA (82.39 ± 49.75 cm²) and SFA (162.44 ± 61.38 cm²) were observed in the elevated TSH group (>5.57 mU/L) compared with the decreased and normal TSH groups (all P<0.05 for both VFA and SFA).

Correlation Between Thyroid Hormone Levels and Fat Distribution in T2DM Patients

Correlation analyses revealed significant relationships between thyroid hormone levels and fat distribution parameters (Table 3). FT3 was positively correlated with both VFA (r=0.248, P<0.001) and SFA (r=0.190, P<0.001), indicating that a higher FT3 level is associated with greater fat accumulation. FT4, on the other hand, tended to show a weak inverse correlation with both VFA (r=–0.018, P=0.321) and SFA (r=–0.019, P=0.283), although these relationships were not statistically significant. TSH showed a weak but significant positive correlation with both VFA (r=0.064, P=0.001) and SFA (r=0.072, P<0.001), indicating an association with fat distribution but a weaker association than that observed between FT3 and fat distribution.

Table 3 The Distribution of VFA and SFA According to Thyroid Hormones

Variables	VFA	P	SFA	P
FT3, pg/mL		0.000***		0.000***
Decrease (<1.8)	62.45±50.85		135.35±59.73	
Normal (1.8–3.8)	82.9±42.43		157.42±60.05	
Increase (>3.8)	79.75±40.12		148.96±57.06	
FT4, ng/dL		0.965		0.884
Decrease (<0.78)	79.82±45.96		152.14±60.67	
Normal (0.78–1.86)	80.86±43.76		155.25±60.36	
Increase (>1.86)	81.75±38.33		155.91±59.17	
TSH, mU/L		0.019*		0.039*
Decrease (<0.38)	68.36±37.9		142.02±60.1	
Normal (0.38–5.57)	81.18±43.53		155.2±60.23	
Increase (>5.57)	82.39±49.75		162.44±61.38	

Notes: *P<0.05; ***P<0.001.

Correlation Between Thyroid Hormone Levels and Fat Distribution

Correlation analyses revealed significant associations between thyroid hormone levels and fat distribution parameters (Table 4). FT3 was positively correlated with both VFA ($r = 0.248$, $P < 0.001$) and SFA ($r = 0.190$, $P < 0.001$), indicating that higher FT3 levels were associated with greater visceral and subcutaneous fat accumulation. FT4 showed weak negative correlations with VFA ($r = –0.018$, $P = 0.321$) and SFA ($r = –0.019$, $P = 0.283$), but these associations were not statistically significant. TSH demonstrated weak yet significant positive correlations with both VFA ($r = 0.064$, $P = 0.001$) and SFA ($r = 0.072$, $P < 0.001$), although the strength of these relationships was less pronounced compared with FT3.

Predictive Values of Thyroid Hormones for Abnormal Fat Distribution

To further evaluate the independent effects of thyroid hormones on fat distribution, multivariate linear regression models were constructed after adjusting for potential confounding factors, including age, gender, and BMI (Table 5). FT3 remained independently and positively associated with both VFA (Coef = 8.06, 95% CI: 5.87–10.24, $P < 0.001$) and SFA (Coef = 9.71, 95% CI: 6.62–12.79, $P < 0.001$). In contrast, FT4 was inversely associated with VFA (Coef = –12.20, 95% CI: –17.36 to –7.03, $P < 0.001$) and SFA (Coef = –16.68, 95% CI: –23.98 to –9.38, $P < 0.001$), suggesting a potential protective role of FT4 against abnormal fat accumulation. TSH did not show significant associations with either VFA or SFA (all $P > 0.05$), indicating a relatively minor impact compared with FT3 and FT4.

Gender and Age-Specific Variations in Fat Distribution Among T2DM Patients

Additional analyses with patient stratification by age and gender were conducted to further elucidate the relationships between thyroid hormone levels and fat distribution in T2DM patients. As shown in Table S1, the associations between

Table 4 The Correlation Between Thyroid Hormones and VFA and SFA

Variables	FT3		FT4		TSH		FT3/FT4	
	r	P	r	P	r	P	r	P
VFA	0.248	0.000***	−0.018	0.321	0.064	0.001**	0.219	0.000***
SFA	0.190	0.000***	−0.019	0.283	0.072	0.000***	0.174	0.000***
TC	−0.11	0.010*	−0.010	0.001*	0.110	0.038*	0.01	0.978
TG	−0.01	0.625	−0.010	0.000***	0.060	0.123	0.14	0.626
HDL	−0.13	0.003**	−0.060	0.001**	1.320	0.000***	−1.25	0.563
LDL	−0.04	0.007**	−0.010	0.408	0.130	0.177	0.22	0.756

Notes: *P<0.05; **P<0.01; ***P<0.001.

Table 5 The Multivariate Linear Regression Between Thyroid Hormones and VFA and SFA

Variables	VFA			SFA		
	Coef	P	95% CI	Coef	P	95% CI
FT3	8.06	0.000***	5.87–10.24	9.71	0.000***	6.62–12.79
FT4	−12.20	0.000***	−17.36–7.03	−16.68	0.000***	−23.98–9.38
FT3/FT4	0.02	0.373	−0.02–0.05	0.05	0.038*	0.00–0.11
TSH	0.02	0.875	−0.25–0.29	0.02	0.903	−0.35–0.4
Age	0.62	0.000***	0.47–0.78	0.35	0.001**	0.13–0.57
Gender	2.78	0.224	−1.70–7.27	20.29	0.000***	13.96–26.63
Education	7.85	0.000***	4.38–11.31	9.12	0.000***	4.22–14.02
Job	−0.87	0.620	−4.32–2.58	1.49	0.549	−3.38–6.36
Smoke	−0.23	0.779	−1.85–1.39	−0.75	0.523	−3.03–1.54
Drink	3.95	0.000***	2.06–5.83	3.79	0.005**	1.13–6.45
SBP	0.25	0.000***	0.12–0.37	0.41	0.000***	0.23–0.59
DBP	0.24	0.033*	0.02–0.45	0.26	0.092	−0.04–0.57
TC	2.88	0.000***	2.15–3.62	1.94	0.000***	0.90–2.98
TG	−0.39	0.457	−1.41–0.64	−0.26	0.729	−1.70–1.19
HDL	−22.16	0.000***	−26.96–17.35	−28.66	0.000***	−35.45–21.87
LDL	2.53	0.004**	0.82–4.25	2.77	0.025*	0.35–5.20
ALT	0.18	0.000***	0.11–0.26	0.25	0.000***	0.15–0.35
AST	−0.08	0.204	−0.20–0.04	−0.08	0.380	−0.25–0.09
Cr	−0.01	0.496	−0.05–0.02	0.00	0.954	−0.05–0.05

Notes: *P<0.05; **P<0.01; ***P<0.001.

FT3 and fat distribution parameters were consistent across age groups, with younger and middle-aged adults showing similar patterns of correlation for FT3 with VFA and SFA. Among women, FT4 exhibited a more pronounced inverse relationship with VFA, and this effect was not observed in men. Gender differences were also evident in the correlation of TSH and fat distribution, with men showing a stronger association of TSH with VFA and SFA compared with women (P<0.05 for interaction).

Discussion

The present investigation of the associations between thyroid hormone levels (FT3, FT4, and TSH) and fat distribution, specifically VFA and SFA, in T2DM patients revealed the following significant associations: FT3 was positively correlated with both VFA and SFA, while FT4 was inversely associated with these fat distribution measures. TSH displayed a weak positive association that did not persist after adjustment for confounding variables. These results suggest a nuanced role for thyroid hormones in fat metabolism and distribution in T2DM patients with normal thyroid function, supporting a potential role for FT3 and FT4 as biomarkers for evaluating metabolic risk in this population.

The strong positive associations between FT3 and both VFA and SFA in our cohort align with FT3's known role as an active thyroid hormone involved in regulating metabolic rate and energy expenditure.[22] FT3's influence on lipolysis and fat accumulation may explain the observed associations, as higher FT3 levels likely stimulate greater metabolic turnover, promoting fat mobilization and deposition, particularly in visceral regions.[23] The accumulation of visceral fat is closely linked to insulin resistance, systemic inflammation, and cardiovascular complications, all of which are prevalent in T2DM patients.[24] Our findings are consistent with those of prior studies[25,26] indicating that elevated FT3 levels are associated with higher body fat percentages and greater metabolic risks, especially in populations predisposed to obesity and diabetes.

The relationship between FT3 and fat distribution also could be influenced by the unique metabolic environment of T2DM.[27] Insulin resistance, a hallmark of T2DM, is associated with altered lipid metabolism and may exacerbate FT3's effects on fat accumulation.[28] While FT3 promotes lipid oxidation and energy consumption, its effects in the context of

T2DM may be compounded by impaired glucose and lipid regulation, resulting in disproportionate fat deposition, particularly in visceral areas.[29] Thus, T2DM patients with elevated FT3 levels may be at increased risk of accumulating metabolically active visceral fat, predisposing them to worsened metabolic control and cardiovascular risk. This highlights the potential utility of FT3 as a biomarker for assessing fat-related metabolic risks in T2DM.[30]

The observed positive association between FT3 levels and fat accumulation may appear paradoxical considering the known lipolytic effects of FT3. However, previous research has suggested several mechanisms underlying this relationship in insulin-resistant states. Elevated FT3 levels in T2DM patients could reflect compensatory hypersecretion intended to overcome reduced thyroid hormone sensitivity at peripheral tissues,[30] potentially due to alterations in thyroid hormone receptor expression or signaling pathways. Additionally, impaired peripheral conversion of T4 to active T3 caused by chronic inflammation or metabolic dysfunction may lead to higher FT3 secretion from the thyroid gland to maintain metabolic homeostasis. These compensatory adjustments may paradoxically leads to the association of elevated circulating FT3 levels with greater fat accumulation, especially visceral fat, in individuals with insulin resistance and metabolic disturbances.[31]

Unlike FT3, FT4 displayed an inverse relationship with VFA and SFA, suggesting a potential protective role of FT4 in fat metabolism among T2DM patients.[32] FT4, often considered less metabolically active than FT3, appears to exert a regulatory influence on fat storage, potentially attenuating fat accumulation in both visceral and subcutaneous regions.[33] This finding aligns with the hypothesis that FT4 supports metabolic homeostasis and thereby contributes to favorable fat distribution patterns in T2DM patients. Previous studies[14,34] have shown that lower FT4 levels are linked to increased fat mass and metabolic risk, further corroborating our finding that higher FT4 levels might protect against excessive fat accumulation.

Our gender-stratified analysis suggested that the protective effect of FT4 may be more pronounced in females than in males. A potential mechanism may be related to estrogen. Estrogen has been shown to influence fat distribution by favoring subcutaneous over visceral fat storage, and this effect may interact with the influence of FT4 on metabolism.[35] In postmenopausal women, who experience shifts in both thyroid hormone levels and fat distribution, maintaining adequate FT4 levels might help mitigate visceral fat accumulation.[36] This interplay warrants further investigation to explore whether FT4 could be targeted in gender-specific interventions aimed at improving fat distribution and metabolic outcomes in T2DM patients.

TSH demonstrated a weak positive correlation with VFA and SFA, which did not remain significant after adjustment for age, gender, and BMI.[37] As a regulatory hormone, TSH primarily influences thyroid hormone synthesis and secretion rather than directly impacting metabolism or fat storage. This may explain its limited association with fat distribution in our cohort. Although previous research[38] suggested a link between higher TSH levels and obesity, our results indicate that TSH may have minimal impact on fat distribution in euthyroid individuals with normal FT3 and FT4 levels. The lack of a significant association between TSH and fat accumulation after adjustment highlights the importance of considering FT3 and FT4 independently when assessing thyroid hormone-related metabolic risks in T2DM patients.

The relatively weak and statistically nonsignificant adjusted associations observed between TSH and fat distribution parameters may be explained by the role of TSH primarily as a centrally controlled regulator of thyroid function, rather than a direct peripheral mediator of metabolic processes. TSH exerts indirect metabolic effects by influencing thyroid hormone synthesis and secretion, whereas peripheral tissues primarily respond to circulating FT3 and FT4 levels. Furthermore, existing research supports the notion that peripheral metabolic activities and fat metabolism are predominantly regulated by thyroid hormones at the tissue level, with TSH having limited direct effects outside the central axis.[39] These findings align with our observation that FT3 and FT4 showed more robust associations with fat distribution compared with TSH.

Overall, our results are consistent with previous studies[40,41] that described a positive association of FT3 with body fat and an inverse relationship of FT4 with fat accumulation. Similar findings in general populations suggest that these thyroid hormone relationships extend to T2DM patients, who exhibit distinct metabolic profiles due to insulin resistance and dyslipidemia. Studies in non-diabetic populations have linked higher FT3 levels with increased visceral and subcutaneous fat, reinforcing our observations that FT3 may predispose T2DM patients to adverse fat accumulation patterns.[42] Moreover, a study by Mele et al[36] demonstrated that FT4 levels are inversely correlated with adiposity,

suggesting that FT4 might contribute to a healthier fat distribution pattern. However, our study's focus on euthyroid T2DM patients provides novel insights and fills a gap in the literature, as few studies have exclusively examined this population.

As noted above, the significant associations between FT3 and measures of fat distribution suggest that FT3 could serve as a useful biomarker for identifying T2DM patients at risk for excessive visceral fat accumulation. Accordingly, monitoring of FT3 levels in T2DM patients may help clinicians identify individuals with heightened metabolic and cardiovascular risks linked to visceral adiposity. Moreover, our finding regarding the protective role of FT4 against abnormal fat distribution highlight the potential benefits of preserving or optimizing FT4 levels to promote a favorable fat distribution in T2DM patients. Personalized treatment approaches that consider individual thyroid hormone profiles could enhance metabolic management, potentially facilitating measures to reduce fat accumulation and improve metabolic outcomes in T2DM patients. Interventions focusing on lifestyle modification or pharmacotherapy tailored to regulate patients' FT3 and FT4 levels could provide targeted benefits.

The observed gender-specific differences in the effect of FT4 on fat distribution underscore the importance of considering gender in metabolic research. Among the women in our study, we observed a more pronounced inverse relationship between FT4 and VFA, suggesting that FT4 may offer stronger protective effects in women. Estrogen likely interacts with FT4, influencing fat distribution patterns that favour subcutaneous over visceral storage. This interaction is particularly relevant for postmenopausal women, who experience hormonal shifts that might exacerbate visceral fat accumulation. Thus, strategies to maintain adequate FT4 levels could mitigate these effects, supporting metabolic health in postmenopausal T2DM patients. Future studies should explore the existence and effects of interactions between estrogen and thyroid hormones to better understand their combined effects on fat distribution in T2DM patients.

The present study also has several limitations that should be considered. The cross-sectional design prevents us from establishing causality, leaving it unclear whether thyroid hormone changes precede or result from altered fat distribution. A longitudinal study design is required to clarify causal pathways. Additionally, the exclusion of T2DM patients with thyroid dysfunction restricts the generalizability of our findings, as the relationship between thyroid hormones and fat distribution may differ in patients with hypo- or hyperthyroidism. The used of BIA for measurement of VFA and SFA may also limit the precision of the data, compared with that produced by imaging modalities such as MRI or CT, but BIA offers the advantage of being a practical, non-invasive method for large-scale studies. Residual confounding is another limitation. Although we controlled age, gender, BMI, education, blood pressure, and lipid profiles, other clinically relevant factors were not available in our dataset. Examples include the duration of diabetes, glycemic control (HbA1c), the use of specific antidiabetic medications, smoking status, and physical activity. These factors may influence both thyroid hormone metabolism and fat distribution, and their absence from our analysis may introduce bias. Therefore, residual confounding cannot be excluded and should be considered when interpreting our findings. Future studies should aim to account for these variables to provide a more comprehensive understanding of the impacts of different thyroid hormones on fat distribution.

Finally, this study provides insight for the directions of future research. Longitudinal investigations tracking thyroid hormone levels and fat distribution over time are needed to clarify potential causal relationships in T2DM populations. Complementary mechanistic studies, including observational analyses and experimental models, may help determine whether variations in FT3 and FT4 drive fat accumulation or represent compensatory responses. Elucidating the molecular pathways linking thyroid hormones with lipid metabolism will be particularly important. In addition, examination of other thyroid hormone metabolites, such as T2 and reverse triiodothyronine (rT3), may broaden our understanding of thyroid hormone regulation of fat distribution and metabolic health.

Conclusion

In conclusion, this study highlights significant associations between thyroid hormones and fat distribution in euthyroid T2DM patients. Elevated FT3 levels were linked to increased visceral and subcutaneous fat, whereas higher FT4 levels were associated with more favourable fat distribution. These findings provide new insights into the metabolic roles of thyroid hormones and suggest that they may serve as useful indicators for identifying patients at higher metabolic risk.

Future longitudinal and mechanistic studies are warranted to validate these associations and to explore their potential relevance for personalized metabolic management in T2DM.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Institutional Review Board of the Affiliated Hospital of Southwest Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants prior to enrolment.

Acknowledgments

We thank Medjaden, Inc. for scientific editing of this paper.

Funding

The study was funded by the Youth Fund of Medical Association (No. 16213).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Hurtado MD, Vella A. What is type 2 diabetes? *Medicine*. 2019;47(1):10–15. doi:10.1016/j.mpmed.2018.10.010
2. Abdul Basith Khan M, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes — global burden of disease and forecasted trends. *J Epidemiol Global Health*. 2020;10(1):107–111. doi:10.2991/jegh.k.191028.001
3. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843. doi:10.1016/j.diabres.2019.107843
4. Zakir M, Ahuja N, Surksha MA, et al. Cardiovascular complications of diabetes: from microvascular to macrovascular pathways. *Cureus*. 2023;15(9):e45835. doi:10.7759/cureus.45835
5. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. *Int J Mol Sci*. 2024;25(3):1882. doi:10.3390/ijms25031882
6. Goswami B, Reang T, Sarkar S, Sengupta S, Bhattacharjee B. Role of body visceral fat in hypertension and dyslipidemia among the diabetic and nondiabetic ethnic population of Tripura—A comparative study. *J Family Med Primary Care*. 2020;9(6).
7. Ruze R, Liu T, Zou X, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Front Endocrinol*. 2023;14.
8. Yavuz S, Salgado Nunez Del Prado S, Celi FS. Thyroid hormone action and energy expenditure. *J Endocrine Soc*. 2019;3(7):1345–1356. doi:10.1210/js.2018-00423
9. Wang X, Wu Z, Liu Y, et al. The role of thyroid-stimulating hormone in regulating lipid metabolism: implications for body–brain communication. *Neurobiol Dis*. 2024;201:106658. doi:10.1016/j.nbd.2024.106658
10. Bansal S, Vachher M, Arora T, Kumar B, Burman A. Visceral fat: a key mediator of NAFLD development and progression. *Hum Nutr Metab*. 2023;33:200210. doi:10.1016/j.hnm.2023.200210
11. Sterenborg RBTM, Steinbrenner I, Li Y, et al. Multi-trait analysis characterizes the genetics of thyroid function and identifies causal associations with clinical implications. *Nat Commun*. 2024;15(1):888. doi:10.1038/s41467-024-44701-9
12. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. *Thyroid*. 2014;24(12):1670–1751. doi:10.1089/thy.2014.0028
13. Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. *J Clin Endocrinol Metab*. 2015;100(3):1088–1096. doi:10.1210/jc.2014-3586
14. Gokkaya N, Aydin K. Efficacy of levothyroxine monotherapy in achieving clinical euthyroidism and its impact on weight loss in women with hypothyroidism and obesity. *Scientific Reports*. 2024;14(1):27822. doi:10.1038/s41598-024-78185-w
15. Kim JM, Kim BH, Lee H, et al. The relationship between thyroid function and different obesity phenotypes in Korean euthyroid adults. *Diabetes Metab J*. 2019;43(6):867–878. doi:10.4093/dmj.2018.0130
16. Teixeira PFS, Dos Santos PB, Pazos-Moura CC. The role of thyroid hormone in metabolism and metabolic syndrome. *Therapeu Adv Endocrinol Metabo*. 2020;11:2042018820917869. doi:10.1177/2042018820917869
17. Abiri B, Ahmadi AR, Mahdavi M, Amouzegar A, Valizadeh M. Association between thyroid function and obesity phenotypes in healthy euthyroid individuals: an investigation based on Tehran Thyroid Study. *Eur J Med Res*. 2023;28(1):179. doi:10.1186/s40001-023-01135-1

18. Adamska A, Raczkowski A, Stachurska Z, et al. Body composition and serum concentration of thyroid hormones in euthyroid men and women from general population. *J Clin Med*. 2022;11(8):2118. doi:10.3390/jcm11082118
19. Hatziagelaki E, Paschou SA, Schön M, Psaltopoulou T, Roden M. NAFLD and thyroid function: pathophysiological and therapeutic considerations. *Trends Endocrinol Metab*. 2022;33(11):755–768. doi:10.1016/j.tem.2022.08.001
20. Ward CR. Chapter 69 - Thyroid Storm. In: Silverstein DC, Hopper K, editors. *Small Animal Critical Care Medicine*. 2nd ed. St. Louis: W.B. Saunders; 2015:364–367.
21. Lai C-L, Lu H-K, Huang A-C, Chu L-P, Chuang H-Y, Hsieh K-C. Bioimpedance analysis combined with sagittal abdominal diameter for abdominal subcutaneous fat measurement. *Front Nutr*. 2022;9.
22. Hoermann R, Pekker MJ, Midgley JEM, Dietrich JW. The role of supporting and disruptive mechanisms of FT3 homeostasis in regulating the hypothalamic–pituitary–thyroid axis. *Therapeu Adv Endocrinol Metabo*. 2023;14:20420188231158163. doi:10.1177/20420188231158163
23. Hu Y, Zhou F, Lei F, et al. The nonlinear relationship between thyroid function parameters and metabolic dysfunction-associated fatty liver disease. *Front Endocrinol*. 2023;14.
24. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity*. 2022;55(1):31–55. doi:10.1016/j.immuni.2021.12.013
25. Sun X, Chen L, Wu R, Zhang D, He Y. Association of thyroid hormone with body fat content and lipid metabolism in euthyroid male patients with type 2 diabetes mellitus: a cross-sectional study. *BMC Endocr Disord*. 2021;21(1):241. doi:10.1186/s12902-021-00903-6
26. Yu L, Liu Y, Wang Y, et al. Increased thyroid hormone sensitivity is correlated with visceral obesity in patients with type 2 diabetes. *Lipids health Dis*. 2024;23(1):337. doi:10.1186/s12944-024-02320-9
27. Bouazza A, Favier R, Fontaine E, Leverve X, Koceir E-A. Potential applications of thyroid hormone derivatives in obesity and type 2 diabetes: focus on 3,5-diiodothyronine (3,5-T2) in psammomys obesus (fat sand rat) model. *Nutrients*. 2022;14(15):3044. doi:10.3390/nu14153044
28. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia*. 2010;53(7):1270–1287. doi:10.1007/s00125-010-1684-1
29. Emiroğlu C, Özdemir Ç, Görpelioğlu S, Aypak C. The relationship between thyroid hormones, metabolic syndrome and HOMA-IR in people with obesity or overweight. *Clin Diabetol*. 2022;11(5):333–339. doi:10.5603/DK.a2022.0043
30. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocrin Rev*. 2019;40(3):789–824. doi:10.1210/er.2018-00163
31. Holtorf K. Peripheral thyroid hormone conversion and its impact on TSH and metabolic activity. *J Restorat Med*. 2014;3(1):30–52. doi:10.14200/jrm.2014.3.0103
32. Cao B, Li K, Ke J, Zhao D. Impaired sensitivity to thyroid hormones is associated with the change of abdominal fat in euthyroid type 2 diabetes patients: a retrospective cohort study. *J Diabe Res*. 2024;2024(1):8462987. doi:10.1155/2024/8462987
33. Freedland ES. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. *Nutr Metab*. 2004;1(1):12.
34. Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: an intriguing link. *Indian J Endocrinol Metab*. 2016;20(4):554–557. doi:10.4103/2230-8210.183454
35. Mazza E, Troiano E, Ferro Y, et al. Obesity, dietary patterns, and hormonal balance modulation: gender-specific impacts. *Nutrients*. 2024;16(11):1629. doi:10.3390/nu16111629
36. Mele C, Mai S, Cena T, et al. The pattern of TSH and fT4 levels across different BMI ranges in a large cohort of euthyroid patients with obesity. *Front Endocrinol*. 2022;13.
37. Shaoba A, Basu S, Mantis S, Minutti C. Serum thyroid-stimulating hormone levels and body mass index percentiles in children with primary hypothyroidism on levothyroxine replacement. *J Clin Res Pediatr Endocrinol*. 2017;9(4):337–343. doi:10.4274/jcrpe.3661
38. Witte T, Völzke H, Lerch MM, et al. Association between serum thyroid-stimulating hormone levels and visceral adipose tissue: a population-based study in Northeast Germany. *Euro Thyroid J*. 2017;6(1):12–19. doi:10.1159/000450977
39. McAninch EA, Bianco AC. Thyroid hormone signaling in energy homeostasis and energy metabolism. *Ann N Y Acad Sci*. 2014;1311:77–87. doi:10.1111/nyas.12374
40. Biondi B. Thyroid and obesity: an intriguing relationship. *J Clin Endocrinol Metab*. 2010;95(8):3614–3617. doi:10.1210/jc.2010-1245
41. Mullur R, Liu -Y-Y, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev*. 2014;94(2):355–382. doi:10.1152/physrev.00030.2013
42. Tacke F, Horn P, Wai-Sun Wong V, et al. EASL–EASD–EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81(3):492–542.