

Received: 2020.07.14

Accepted: 2020.10.08

Available online: 2020.10.27

Published: 2021.01.02

Association Between Thyroid Function and Body Composition in Type 2 Diabetes Mellitus (T2DM) Patients: Does Sex Have a Role?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF G 1,2 **Lu Chen**
BCF 2 **Min Zhang**
BCF 1 **Shoukui Xiang**
BCD 1 **Xiaohong Jiang**
CF 2 **Hongliu Gu**
CD 2 **Qi Sha**
D 2 **Meidi Qu**
AEG 3 **Ting Xu**

1 Department of Endocrinology and Metabolism, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, P.R. China
2 Department of Clinical Nutrition, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, P.R. China
3 Department of Rheumatology and Immunology, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, P.R. China

Corresponding Authors: Ting Xu, e-mail: daisy_tingting@163.com, Lu Chen, e-mail: cl2324@czfph.com

Source of support: This work was supported by the Applied and Basic Research Program of Changzhou Scientific and Technological Project (Grant No. CJ20190103) and the Major Scientific and Technological Project of Changzhou City Commission of Health and Family Planning of China (No. ZD201707)

Background: The relationship between thyroid hormones and body anthropometric measures in type 2 diabetes mellitus (T2DM) patients with normal thyroid function is unclear. The purpose of this study was to evaluate the association between thyroid hormones and body composition in euthyroid T2DM patients in men and women.

Material/Methods: This was a cross-sectional study that included 561 euthyroid T2DM patients. Fasting venous blood was collected to test laboratory indexes. Bioelectric impedance analysis (BIA) was used to measure body composition. Propensity score matching (PSM) was used to enroll patients with similar baseline characteristics. The least absolute shrinkage and selection operator (LASSO) algorithm was used to establish a linear regression model of thyroid hormone and body composition. PSM was performed to match 159 men and 159 women.

Results: The LASSO regression analysis suggested that thyroid-stimulating hormone (TSH) level was not correlated with body composition parameters in females. In females, free triiodothyronine (FT3) level was positively correlated with body mass index (BMI), fat-free mass index (FFMI), and skeletal muscle index (SMI), and was negatively correlated with extracellular water fraction (EWF). In males, FT3 level was positively correlated with waist circumference (WC) and SMI and negatively correlated with EWF. Free thyroxine (FT4) level in both women and men was positively correlated with body fat mass (BFM) and left lower-limb muscle mass (LLLMM). Moreover, in males, FT4 level was correlated with more body composition parameters. In euthyroid T2DM patients, FT3 level was positively correlated with SMI and negatively correlated with EWF, while FT4 level was positively correlated with BFM and LLLMM.

Conclusions: Thyroid function can affect body composition in euthyroid T2DM patients. Thyroid function is more likely to affect the fat and muscle distribution of males than females.

MeSH Keywords: **Body Composition • Body Water • Diabetes Mellitus, Type 2 • Muscle, Skeletal • Thyroid Hormones • Thyrotropin**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/927440>

 2734

 2

 4

 35



Background

Thyroid hormones play a key role in controlling energy homeostasis, thermogenesis, oxygen consumption, and lipid and glucose metabolism, thus affecting body composition [1]. Skeletal muscle is the main target of thyroid hormone signal transduction [2]. Skeletal muscles contain type 2 (DIO2) and type 3 (DIO3) iodothyronine deiodinases [3]. Triiodothyronine (T3) can be produced by thyroxine under the action of DIO2 and can be inactivated under the action of DIO3. T3 binds to the thyroid hormone nuclear receptor to regulate gene transcription and protein expression to achieve the development, homeostasis, and regeneration of skeletal muscles [4]. Both fat synthesis and lipolysis are reported to be closely related to thyroid hormones. The main reason for that is the upregulation of metabolic pathways relevant to resting energy expenditure (REE). Thyroid hormones are reported to affect the uncoupling of cellular metabolism from adenosine triphosphate synthesis and can change the efficiency of metabolic processes downstream from the mitochondria [5,6]. To sum up, thyroid hormones can affect both skeletal and fat distribution.

Over the past decades, much research has focused on the association between thyroid function and anthropometric measurements in euthyroid subjects. Positive associations between serum thyroid-stimulating hormone (TSH) levels and fat parameters, including body mass index (BMI), body weight, waist circumference (WC), waist-to-hip ratio (WHR), subcutaneous fat, and preperitoneal fat, were found in euthyroid subjects [7–9]. BMI, WC, hip circumference (HC), WHR, and percentage of body fat (PBF) were found to increase with the elevation of free triiodothyronine (FT3) levels in euthyroid subjects [10,11]. Free thyroxine (FT4) was reported to be positively correlated with body fat mass (BFM), abdominal subcutaneous fat, and cross-sectional muscle area in a euthyroid population [12,13].

Body composition and pattern of distribution of body fat and muscle are both risk factors for and the cause of type 2 diabetes mellitus (T2DM) [14]. People with T2DM have more ectopic fat at the expense of skeletal muscle, both quantitatively and qualitatively [15]. A population-based prospective cohort study, which included 8452 participants, reported a higher risk for T2DM in patients with higher TSH levels in the normal range [16]. In euthyroid adults, diabetes was found to be associated with an increased FT4/FT3 ratio [17]. Thus, the association between thyroid function and anthropometric measurements in euthyroid T2DM patients is different from that in euthyroid subjects without T2DM.

However, to the best of our knowledge, few studies have investigated the relationship between thyroid hormones and body composition in T2DM patients with normal thyroid function. Moreover, most previous studies on thyroid hormones and

anthropometric measurements were focused on simple obesity parameters, including BMI, WC, HC, and WHR [7–11,13], and only a few studies measured parameters of body fat and body muscle [12]. Simple parameters cannot provide an accurate measurement of an individual's specific body composition.

Therefore, in this study, we analyzed the association between thyroid hormones and 26 body composition parameters in T2DM patients with normal thyroid function.

Material and Methods

Research subjects

This was a cross-sectional study. We enrolled 561 T2DM patients hospitalized in the Department of Endocrinology and Metabolism of Changzhou First People's Hospital from February 2016 to August 2018, including 331 men and 230 women. The diagnosis of T2DM was based on: (1) Fasting blood glucose ≥ 7.0 mmol/L; (2) Random blood glucose ≥ 11.1 mmol/L, or stimulated glucose level of above 11.1 mmol/L following a standard oral glucose tolerance test (OGTT); and (3) Hemoglobin A1c (HbA1c) greater than 6.5%. We excluded people with the following conditions: T1DM (positive auto-antibodies and/or persisting insulin requirement from diagnosis), monogenic diabetes, diabetes developing in a person with a known diabetes-associated syndrome such as Prader-Willi or Bardet-Biedl syndromes, diagnosis of diabetes while on medical therapy with a known diabetogenic medication, pancreatic failure, or cystic fibrosis-related diabetes [18]. We also excluded people with the following: (1) TSH level outside the normal range (0.3–5.5 μ IU/ml); (2) history of hyperthyroidism, hypothyroidism, thyroid surgery, and family history of thyroid disease; (3) took thyroid hormone medicines or antithyroid medicines; (4) took medicines that affect thyroid function (e.g., contraceptives, estrogen, amiodarone, and other iodine-containing drugs, and lithium agents); (5) malignant tumors; and (6) pregnant women. This study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Changzhou First People's Hospital. Written informed consent was obtained from all enrolled patients.

Research methods

Age and disease course of the patients were recorded. Height, body weight, WC, and HC were measured. BMI was calculated as the ratio of body weight (kg) and squared height (m^2). WHR was calculated as the ratio of WC (cm) and HC (cm). Blood pressure was measured. Fasting venous blood was collected early in the morning to detect fasting blood glucose, uric acid, total cholesterol, triacylglycerol, high-density lipoprotein, and low-density lipoprotein (AU5831 automatic biochemical analyzer,

Table 1. Comparison of general data between male and female groups before propensity score matching.

Group	Female group N=230	Male group N=331	P value
Age (years)	59.2±12.3	56.4±12.3	0.009
Height (cm)	159.2±4.8	171.1±5.4	<0.001
Weight (kg)	62.1±11.5	72.5±11.3	<0.001
BMI (kg/m ²)	24.4±3.9	24.7±3.6	0.354
Systolic pressure (mmHg)	138.7±18.7	135.4±16.6	0.029
Diastolic pressure (mmHg)	82.4±9.6	84.3±10.8	0.033
Disease course (years)	9.0±7.7	7.3±6.4	0.003
Fasting blood glucose (mmol/L)	8.5±2.5	8.6±2.5	0.834
Fasting C-peptide (pmol/L)	1.9±1.1	2.0±1.2	0.412
Modified HOMA-IR	3.4±1.1	3.5±1.3	0.302
Modified HOMA-islet	43.7±38.7	47.2±47.5	0.371
HbA1c (%)	9.6±2.4	9.9±4.3	0.349
Uric acid (μmol/L)	270.8±87.8	316.6±91.4	<0.001
Total cholesterol (mmol/L)	4.7±1.1	4.5±1.2	0.031
Triacylglycerol (mmol/L)	2.2±1.9	2.5±2.6	0.237
High-density lipoprotein (mmol/L)	1.1±0.3	1.0±0.2	<0.001
Low-density lipoprotein (mmol/L)	2.5±0.7	2.3±0.8	0.010

Results in the table: Mean±SD/N (%).BMI – body mass index; HOMA-IR – homeostasis model assessment for insulin resistance; HOMA-islet – homeostasis model assessment for islet beta-cell function; HbA1c – hemoglobin A1c.

Beckman Coulter Life Sciences, USA). HbA1c was determined by high-performance liquid chromatography (HPLC) (D-10 system, Bio-Rad, USA) and was expressed in National Glycohemoglobin Standardization Program (NGSP) units (%). The fasting C-peptide, TSH, FT4, and FT3 were determined using electrochemiluminescence immunoassay (ECLIA). The modified formula used to evaluate insulin resistance and islet function with C-peptide was as follows. The modified HOMA-IR (homeostasis model assessment for insulin resistance) was calculated according to the following formula: $1.5 \times \text{fasting blood glucose (mmol/L)} \times \text{fasting C-peptide (pmol/L)} / 2800$. The modified HOMA-islet (homeostasis model assessment for islet beta-cell function) was calculated according to the following formula: $0.27 \times \text{fasting C-peptide (pmol/L)} / [\text{fasting blood glucose (mmol/L)} - 3.5]$ [19].

All patients fasted for at least 8 h, and body composition was measured using BIA (Inbody 770 body composition analyzer, BioSpace, Seoul, Korea) [20]. All BIAs were performed by the same nutritionist. Measurements included extracellular water (EW), BFM, fat-free mass (FFM), total body muscle mass (TBMM), lean body mass (LBM), skeletal muscle mass (SMM),

PBF, X50HZ phase angle, basal metabolic rate (BMR), right upper-limb muscle mass (RULMM), left upper-limb muscle mass (LULMM), trunk muscle mass (TMM), right lower-limb muscle mass (RLLMM), left lower-limb muscle mass (LLLMM), extracellular water fraction (EWF), visceral fat area (VFA), body cell mass (BCM), and total body water (TBW). The fat-free mass index (FFMI) was calculated as $\text{FFM} / \text{body height}^2$ (kg/m²). The percentage of fat-free mass (PFFM) was calculated by $\text{FFM} / \text{body weight}$. The skeletal muscle index (SMI) was calculated by $\text{SMM} / \text{body height}^2$ (kg/m²). The percentage of skeletal muscle mass (PSMM) was calculated as $\text{SMM} / \text{body weight}$. The fat mass index (FMI) was calculated by $\text{BFM} / \text{body height}^2$ (kg/m²). X50HZ phase angle is a parameter of overall nutritional status; it has been shown to reflect disease-related outcomes, including hospitalization and mortality, and it was treated as a continuous variable in statistical analysis [21].

Statistical analysis

Considering the difference of baseline characteristics between the 2 groups (Table 1), propensity score matching (PSM) was

used to form a group of patients with similar baseline characteristics. The propensity score is the conditional probability of having a specific exposure given a set of covariates measured at baseline. The propensity score was estimated using a non-parsimonious multivariate logistic regression model, with sex as a grouping variable and all baseline features listed in **Table 1** as covariates. The greedy-matching algorithm was used to generate one-to-one matched pairings without replacement, and the difference of the propensity score between the 2 groups was allowed to be within 0.1 [22].

Continuous variables were expressed as the mean \pm SD or the median (Q1–Q3), while categorical variables were expressed as frequency (%). The independent samples *t* test or Mann-Whitney U test was used to compare continuous variables, while the chi-square test was used to compare categorical variables. The categorical variables were tested using the Pearson chi-square test and Fisher exact test. Spearman's rank correlation analysis was used to construct the correlation heat map among body composition parameters.

We used the least absolute shrinkage and selection operator (LASSO) algorithm to select the best prediction feature among the 18 selected indexes [23]. The LASSO algorithm added L1 regularization to the least-squares algorithm to avoid over-fitting. The linear regression model between the thyroid function index and the body composition was established using logistic regression.

All analyses were performed using software R, version 3.4.3 (<http://www.R-project.org>). $P < 0.05$ was considered statistically significant. Patients with missing key variables were excluded from the analysis, and their data were not estimated.

Results

Before PSM, there were differences between the 2 groups in baseline variables (**Table 1**). PSM was performed to match the 159 men and 159 women, after which, there were no significant differences in age, disease course, blood pressure, fasting blood glucose, fasting C-peptide, modified HOMA-IR, modified HOMA-islet, HbA1c, uric acid, total cholesterol, triacylglycerol, high-density lipoprotein and low-density lipoprotein between the 2 groups ($P > 0.1$) (**Table 2**).

Comparison of thyroid function between the 2 groups after matching

The levels of TSH, FT3, and FT4, were different between the 2 groups ($P < 0.05$). The mean serum TSH level was 2.50 ± 1.24 μ IU/ml in women and 2.22 ± 1.05 μ IU/ml in men. The mean FT3 level was 4.10 ± 0.53 pmol/L in women and 4.37 ± 0.67 pmol/L

in men. The mean FT4 level was 16.05 ± 2.19 pmol/L in women and 16.94 ± 2.34 pmol/L in men (**Table 2**).

Comparison of body composition parameters between the 2 groups after matching

There was no difference in BMI and WC between the 2 groups ($P > 0.05$), but there were significant differences in HC and WHR ($P < 0.05$). There were significant differences between men and women in EW, BFM, TBMM, LBM, SMM, PBF, FFMI, PFFM, SMI, PSMM, FMI, X50HZ phase angle, BMR, RULMM, LULMM, TMM, RLLMM, LLLMM, EWF, VFA, BCM, and TBW ($P < 0.05$) (**Table 2**).

Heat map analysis of the correlation between human body compositions in the 2 groups

The heat map showed that the body composition parameters of men and women were mostly positively correlated with each other (**Figure 1**).

Correlation analysis of thyroid function and body composition in the 2 groups

Correlation analysis of TSH and body composition in the 2 groups

The results of LASSO regression analysis showed that in T2DM women, TSH was not correlated with BMI, WC, HC, WHR, EW, BFM, TBMM, LBM, SMM, PBF, FFMI, PFFM, SMI, PSMM, FMI, X50HZ phase angle, BMR, RULMM, LULMM, TMM, RLLMM, LLLMM, EWF, VFA, BCM, and TBW. TSH level in men with T2DM was positively correlated with BMI, PBF, and EWF, and negatively correlated with WHR (**Figure 2**).

Correlation analysis of FT3 level and body composition in the 2 groups

The results of LASSO regression analysis suggested that the level of FT3 in women was positively correlated with BMI, FFMI, and SMI, but negatively correlated with EWF. FT3 level in men was positively correlated with the WC and SMI and negatively correlated with EWF (**Figure 3**).

Correlation analysis between FT4 level and body composition in the 2 groups

LASSO regression analysis results showed that FT4 level in women was positively correlated with BFM and LLLMM. FT4 level in men was positively correlated with WHR, BFM, PBF, PFFM, SMI, RLLMM, LLLMM, VFA, and BCM, but negatively correlated with EW, X50HZ phase angle, RULMM, TMM, and EWF (**Figure 4**).

Table 2. Comparison of general data and body composition parameters between male and female groups after propensity score matching.

Group	Female group N=159	Male group N=159	P value
Age (years)	57.63±12.12	56.98±12.99	0.6460
Disease course (years)	8.23±6.18	7.67±6.39	0.4250
Systolic pressure (mmHg)	136.52±16.71	135.31±16.22	0.5115
Diastolic pressure (mmHg)	82.65±8.69	82.72±10.76	0.9497
Fasting blood glucose (mmol/L)	8.53±2.44	8.36±2.32	0.5272
Fasting C-peptide (pmol/L)	1.94±1.11	1.92±1.31	0.8773
Modified HOMA-IR	3.43±1.09	3.41±1.41	0.9093
Modified HOMA-islet	45.29±38.05	45.02±36.32	0.9483
HbA1c (%)	9.59±2.39	9.71±2.80	0.6767
Uric acid (μmol/L)	281.71±89.81	296.92±79.32	0.1105
Total cholesterol (mmol/L)	4.53±0.99	4.40±1.25	0.3296
Triacylglycerol (mmol/L)	2.28±1.67	2.26±2.79	0.9621
High-density lipoprotein (mmol/L)	1.08±0.24	1.03±0.25	0.1173
Low-density lipoprotein (mmol/L)	2.43±0.71	2.35±0.83	0.3612
BMI (kg/m ²)	24.34±3.71	24.31±3.41	0.9423
WC (cm)	86.54±9.97	88.71±10.02	0.0531
HC (cm)	93.76±6.04	96.52±5.70	<0.0001
WHR	0.92±0.06	0.92±0.06	0.6329
EW (kg)	11.65±1.39	14.86±1.68	<0.0001
BFM (kg)	21.17±7.31	18.31±6.58	0.0003
TBMM (kg)	38.62±4.63	49.79±5.94	<0.0001
LBM (kg)	41.00±4.89	52.72±6.31	<0.0001
SMM (kg)	22.12±2.91	29.23±3.85	<0.0001
PBF	33.30±5.83	25.22±6.14	<0.0001
FFMI (kg/m ²)	16.06±1.43	18.02±1.71	<0.0001
PFFM	0.67±0.06	0.75±0.06	<0.0001
SMI (kg/m ²)	6.36±0.70	7.59±0.73	<0.0001
PSMM	0.36±0.03	0.41±0.03	<0.0001
FMI (kg/m ²)	8.28±2.68	6.28±2.26	<0.0001
X50HZ phase angle	4.84±0.54	5.35±0.72	<0.0001
BMR (kcal/day)	1255.52±105.57	1508.74±136.38	<0.0001
RULMM (kg)	2.12±0.40	2.98±0.48	<0.0001
LULMM (kg)	2.08±0.39	2.90±0.48	<0.0001

Table 2 continued. Comparison of general data and body composition parameters between male and female groups after propensity score matching.

Group	Female group N=159	Male group N=159	P value
TMM (kg)	18.75±2.40	23.94±2.83	<0.0001
RLLMM (kg)	6.05±0.86	8.19±1.04	<0.0001
LLLMM (kg)	6.02±0.86	8.14±1.02	<0.0001
EWf	0.39±0.01	0.38±0.01	0.0001
VFA (cm ²)	105.58±40.53	84.55±31.91	<0.0001
BCM (kg)	26.49±3.20	34.30±4.22	<0.0001
TBW (kg)	30.14±3.61	38.81±4.59	<0.0001
TSH (μIU/ml)	2.50±1.24	2.22±1.05	0.0342
FT3 (pmol/l)	4.10±0.53	4.37±0.67	0.0002
FT4 (pmol/l)	16.05 ± 2.19	16.94 ± 2.34	0.0008

Results in the table: Mean±SD/N (%). HbA1c – hemoglobin A1c; HOMA-IR – homeostasis model assessment for insulin resistance; HOMA-islet – homeostasis model assessment for islet beta-cell function; BMI – body mass index; WC – waist circumference; HC – hip circumference; WHR – waist-to-hip ratio; EW – extracellular water; BFM – body fat mass; TBMM – total body muscle mass; LBM – lean body mass; SMM – skeletal muscle mass; PBF – percentage of body fat; FFMI – fat-free mass index; PFFM – percentage of fat-free mass; SMI – skeletal muscle index; PSMM – percentage of skeletal muscle mass; FMI – fat mass index; BMR – basal metabolic rate; RULMM – right upper-limb muscle mass; LULMM – left upper-limb muscle mass; TMM – trunk muscle mass; RLLMM – right lower-limb muscle mass; LLLMM – left lower-limb muscle mass; EWf – extracellular water fraction; VFA – visceral fat area; BCM – body cell mass; TBW – total body water; TSH – thyrotropin; FT4 – free thyroxine; FT3 – free triiodothyronine.

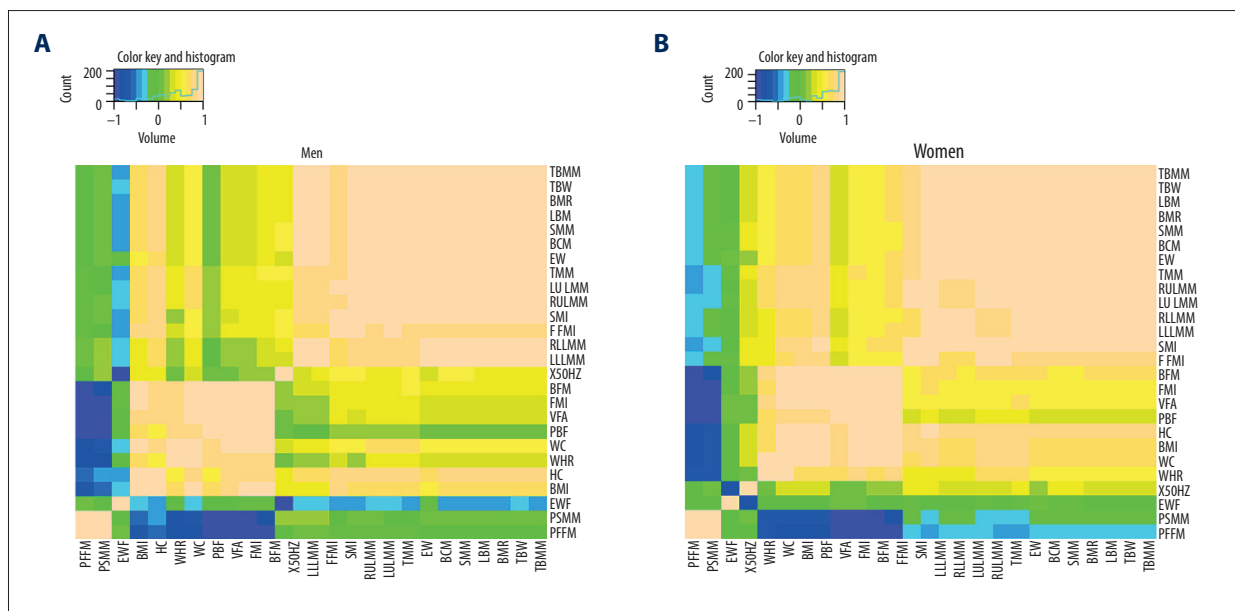


Figure 1. (A, B) The correlation heat map among body composition parameters established by the Spearman's rank correlation analysis. The color key and histogram bar in the upper left corner indicated the correlation between each body composition parameters. A correlation equal to 0 indicated the best independence in the corresponding body composition parameters, while a correlation equal to 1 or -1 indicated a complete correlation.

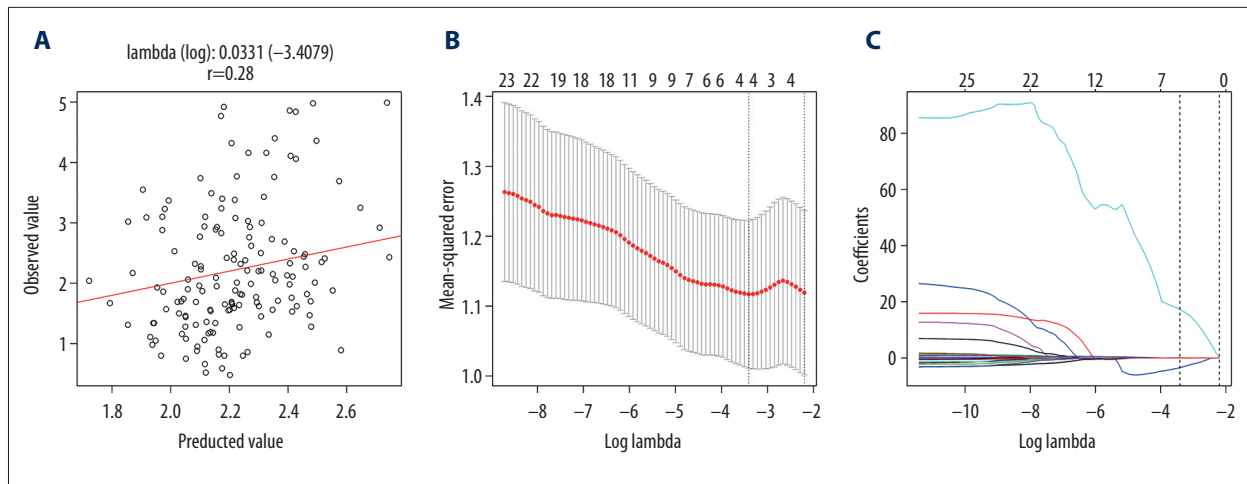


Figure 2. The LASSO algorithm and 10-fold cross-validation were used to extract the best subset of body composition parameters related to male TSH. **(A)** Scatterplot of the predicted and observed values ($r=0.28$). **(B)** The best body composition parameters selected based on regression coefficients. **(C)** LASSO coefficient curve of 26 body composition parameters. LASSO – least absolute shrinkage and selection operator; TSH – thyroid-stimulating hormone.

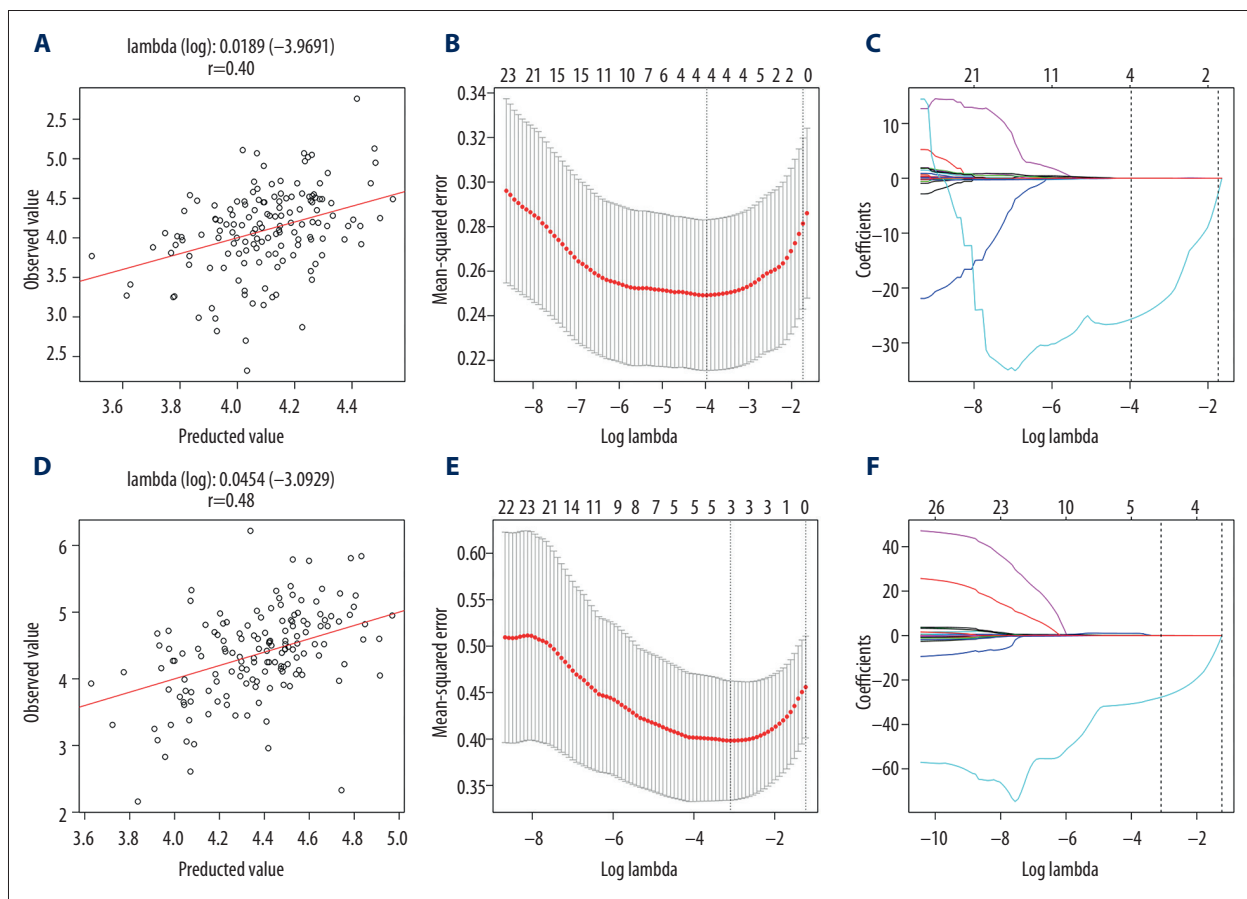


Figure 3. The LASSO algorithm and 10-fold cross-validation were used to extract the best subsets of body composition parameters related to female and male FT3. **(A)** Scatterplot of predicted and observed values in female group ($r=0.40$). **(B)** The best body composition parameters selected based on regression coefficients in female group. **(C)** LASSO coefficient curve in female group. **(D)** Scatterplot in male group ($r=0.48$). **(E)** The best body composition parameters selected in male group. **(F)** LASSO coefficient curve in male group. LASSO – least absolute shrinkage and selection operator; FT3 – free triiodothyronine.

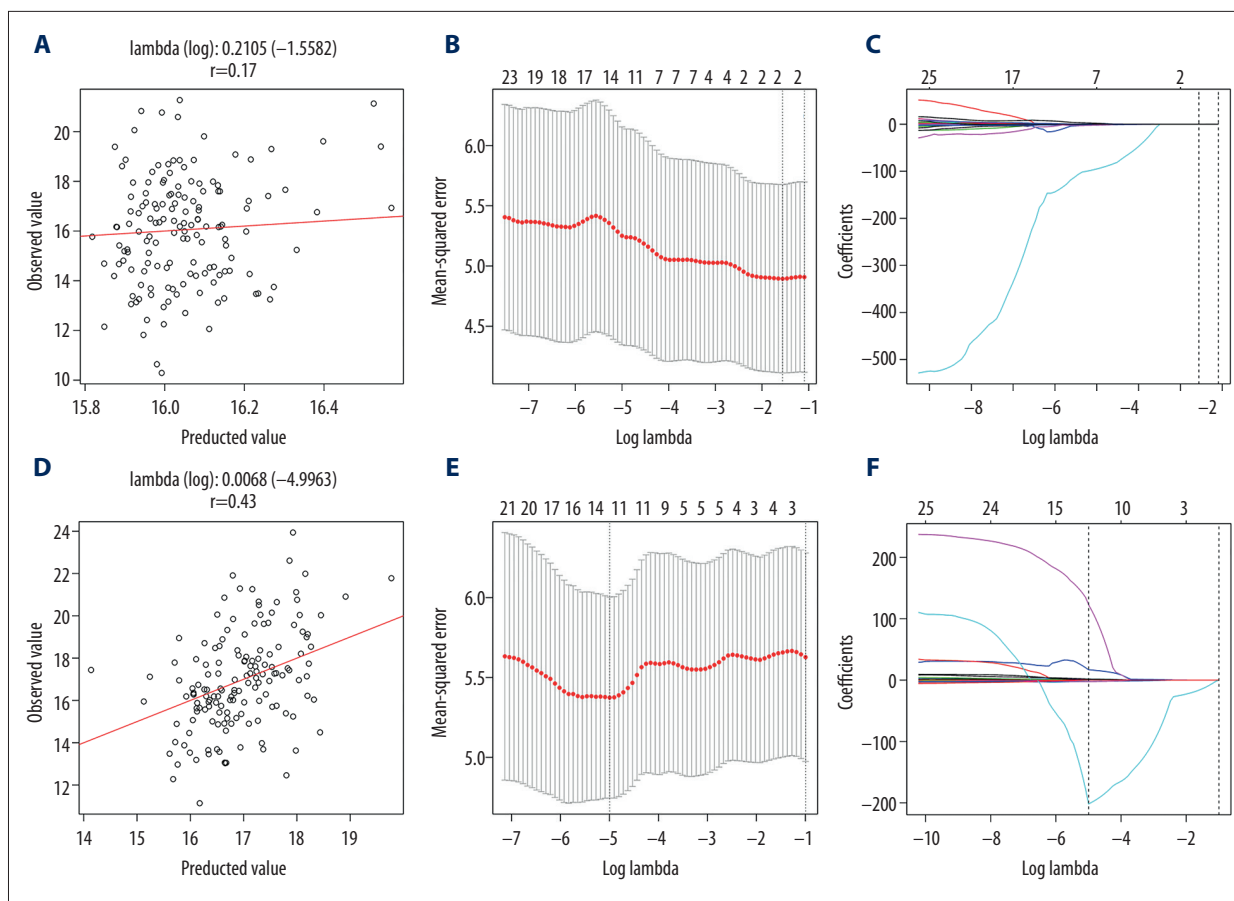


Figure 4. The LASSO algorithm and 10-fold cross-validation were used to extract the best subsets of body composition parameters related to female and male FT4. **(A)** Scatterplot of predicted and observed values in female group ($r=0.17$). **(B)** The best body composition parameters selected based on regression coefficients in female group. **(C)** LASSO coefficient curve of 26 body composition parameters in female group. **(D)** Scatterplot in male group ($r=0.43$). **(E)** The best body composition parameters selected in male group. **(F)** LASSO coefficient curve in male group. LASSO – least absolute shrinkage and selection operator; FT4 – free thyroxine.

Discussion

In the current study, we demonstrated that thyroid function is associated with body composition parameters in euthyroid T2DM patients. We observe strong associations between thyroid hormones and body anthropometric measures in male patients. We found that higher FT3 levels are associated with healthier body composition (with higher muscle mass and lower fat) in female euthyroid T2DM patients.

A retrospective cross-sectional study of 36 655 people with normal thyroid function found that the FT3 level was negatively correlated with SMI and BMI in both men and women [24]. A cross-sectional study in 941 healthy men suggested that muscle mass (whole-body lean mass and cross-sectional muscle area at the level of the radius and the tibia) were inversely correlated with thyroid hormones [12]. These previous reports are inconsistent with our results. The possible

reasons are as follows. First of all, the included populations in our study were different. We investigated T2DM patients, but not healthy people. Diabetes patients have a long-term absolute or relative deficiency of insulin, which leads to a decrease of thyroid iodine uptake and the destruction of thyroid function and structure [25]. Body composition indicators of WHR, BFP, and visceral fat area are crucial factors associated with the incidence of T2DM [26]. T2DM patients have complicated physiological characteristics, and it is inappropriate to apply the results of healthy people to T2DM patients. Secondly, the average age of the patients included in our study was higher than that of the participants in the above 2 trials. The average age of female and male patients in the study by Kwon et al. was 34.7 ± 7.5 years and 38.1 ± 7.7 years, respectively [24]. The patients included in the study by Roef et al. were all males age 25–45 years [12]. With the increase of age, the quality and strength of skeletal muscle consistently change. It is reported that over age 50 years, the quality of skeletal muscle

decreases by 1–2% per year and muscle strength decreases by 1.5% per year, and after age 60 years, it decreases by 3% per year [27]. Older age was also found to affect the thyroid function through intra-thyroidal chemical elements and thyrotropin receptor antibodies [28,29]. The combined effect of age on body composition and thyroid function might partly explain the difference.

To the best of our knowledge, the present study is the first to assess EWF and thyroid function in T2DM patients. EWF is an index of body fluid retention. In a physiological state, the osmotic pressure gradient is the main force driving the diffusion of water molecules in and out of cells [30,31]. We found that for both male and female T2DM patients with normal thyroid function, FT3 level was negatively correlated with EWF. T3 affects many organs and tissues throughout the body, and can increase metabolic rate and protein synthesis [32]. More research is needed to explore whether protein synthesis is related to colloidal osmotic pressure, and whether it leads to a decrease of EWF.

Our results suggest that FT4 content is positively correlated with BFM and LLLMM in euthyroid T2DM patients of both sexes. In 2009, a cross-sectional study with 303 healthy individuals showed that FT4 was a predictor of subcutaneous fat, independent of age, sex, and smoking [13]. In 2012, Roef et al. reported that the BFM was positively correlated with FT4 in healthy men [12], in agreement with the present results.

Notably, some of our results regarding the correlation between thyroid hormones and anthropometric markers were inconsistent between men and women. Our results showed higher T3 levels are associated with more favorable body composition (with higher muscle mass and lower fat) in female T2DM patients with normal thyroid function. Our results also suggested that thyroid function is more likely to affect the fat and muscle distribution of male patients. Several potential mechanisms may explain this sex-related difference. It was reported that the sex steroids modulate thyrocyte proliferation and growth indices in a sex-specific way. Androgens influence the growth and differentiation of thyrocytes through augmented expression of androgen receptor (AR), while estrogen imparts

the sex difference through a manner beyond estrogen receptors [33]. It was reported that oxidative processes might also be responsible for sexual dimorphism [34]. Further research is needed to better understand the exact mechanism of sex differences in the relationship between thyroid function and body composition in euthyroid T2DM patients.

Our study has some limitations. Firstly, the blood glucose control in T2DM patients was not very good. The HbA1c levels in women and men included in the study were $9.59 \pm 2.39\%$ and $9.71 \pm 2.80\%$, respectively. Recent fluctuations of blood glucose may have affected the test results. Secondly, we did not evaluate the use of medicines in T2DM patients. As is well known, some T2DM medicines can affect body composition [35]. Also, our study was observational. More research was needed in the future to explore the potential mechanism involved. Finally, although BIA is a safe, inexpensive, and reliable technique for human body composition analysis, it has shortcomings compared with other methods; for example, compared with dual-energy X-ray absorptiometry, BIA tends to overestimate muscle mass [20].

Conclusions

In conclusion, thyroid hormones have pleiotropic effects on body composition parameters in euthyroid T2DM patients, and sex differences may affect the association. Thyroid function is more likely to affect the fat and muscle distribution of males than females, and higher T3 levels are associated with healthier body composition (with higher muscle mass and lower fat) in female T2DM patients with normal thyroid function.

Data availability statement

Raw data can be obtained upon request from the corresponding author.

Conflict of interest

None.

References:

- Brent GA: Mechanisms of thyroid hormone action. *J Clin Invest*, 2012; 122: 3035–43
- Mullur R, Liu Y-Y, Brent GA: Thyroid hormone regulation of metabolism. *Physiol Rev*, 2014; 94: 355–82
- Schweizer U, Steegborn C: New insights into the structure and mechanism of iodothyronine deiodinases. *J Mol Endocrinol*, 2015; 55: R37–52
- Yen PM: Physiological and molecular basis of thyroid hormone action. *Physiol Rev*, 2001; 81: 1097–142
- Reinehr T: Obesity and thyroid function. *Mol Cell Endocrinol*, 2010; 316: 165–71
- Martínez-Sánchez N, Moreno-Navarrete JM, Contreras C et al: Thyroid hormones induce browning of white fat. *J Endocrinol*, 2017; 232: 351–62
- de Moura Souza A, Sichieri R: Association between serum TSH concentration within the normal range and adiposity. *Eur J Endocrinol*, 2011; 165: 11–15
- Tiller D, Ittermann T, Greiser KH et al: Association of serum thyrotropin with anthropometric markers of obesity in the general population. *Thyroid*, 2016; 26: 1205–14.
- Lambrinoudaki I, Armeni E, Rizos D et al: Indices of adiposity and thyroid hormones in euthyroid postmenopausal women. *Eur J Endocrinol*, 2015; 173: 237–45
- Ren R, Jiang X, Zhang X et al: Association between thyroid hormones and body fat in euthyroid subjects. *Clin Endocrinol (Oxf)*, 2014; 80: 585–90
- Kitahara CM, Platz EA, Ladenson PW et al: Body fatness and markers of thyroid function among U.S. men and women. *PLoS One*, 2012; 7: e34979
- Roef G, Lapauw B, Goemaere S et al: Body composition and metabolic parameters are associated with variation in thyroid hormone levels among euthyroid young men. *Eur J Endocrinol*, 2012; 167: 719–26
- Alevizaki M, Saltiki K, Voidonikola P et al: Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals. *Eur J Endocrinol*, 2009; 161: 459–65
- Heshka S, Ruggiero A, Bray GA et al: Altered body composition in type 2 diabetes mellitus. *Int J Obes (Lond)*, 2008; 32: 780–87
- Solanki JD, Makwana AH, Mehta HB et al: Body composition in type 2 diabetes: Change in quality and not just quantity that matters. *Int J Prev Med*, 2015; 6: 122
- Chaker L, Ligthart S, Korevaar TI et al: Thyroid function and risk of type 2 diabetes: A population-based prospective cohort study. *BMC Med*, 2016; 14: 150
- Qin K, Zhang F, Wu Q et al: Thyroid hormone changes in euthyroid patients with diabetes. *Diabetes Metab Syndr Obes*, 2020; 13: 2533–40
- Zheng Y, Ley SH, Hu FB: Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*, 2018; 14: 88–98
- Matthews DR, Hosker JP, Rudenski AS et al: Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, 1985; 28: 412–19
- Beaudart C, Bruyere O, Geerinck A et al: Equation models developed with bioelectric impedance analysis tools to assess muscle mass: A systematic review. *Clin Nutr ESPEN*, 2020; 35: 47–62
- Jøker-Jensen H, Mathiasen AS, Køhler M, Rasmussen HH et al: Micronutrient deficits in patients with chronic pancreatitis: Prevalence, risk factors and pitfalls. *Eur J Gastroenterol Hepatol*, 2020; 32: 1328–34
- Patino CM, Ferreira JC: Propensity scores: A tool to help quantify treatment effects in observational studies. *J Bras Pneumol*, 2017; 43: 86
- McNeish DM: Using lasso for predictor selection and to assuage overfitting: A method long overlooked in behavioral sciences. *Multivariate Behav Res*, 2015; 50: 471–84
- Kwon H, Cho JH, Lee DY et al: Association between thyroid hormone levels, body composition and insulin resistance in euthyroid subjects with normal thyroid ultrasound: The Kangbuk Samsung Health Study. *Clin Endocrinol (Oxf)*, 2018; 89: 649–55
- Kalra S, Aggarwal S, Khandelwal D: Thyroid dysfunction and type 2 diabetes mellitus: Screening strategies and implications for management. *Diabetes Ther*, 2019; 10: 2035–44
- Chen Y, He D, Yang T et al: Relationship between body composition indicators and risk of type 2 diabetes mellitus in Chinese adults. *BMC Public Health*, 2020; 20: 452
- von Haehling S, Morley JE, Anker SD: An overview of sarcopenia: facts and numbers on prevalence and clinical impact. *J Cachexia Sarcopenia Muscle*, 2010; 1: 129–33
- Bano A, Gan E, Addison C et al: Age may influence the impact of TRAbs on thyroid function and relapse-risk in patients with Graves disease. *J Clin Endocrinol Metab*, 2019; 104: 1378–85
- Zaichick V, Zaichick S: Associations between age and 50 trace element contents and relationships in intact thyroid of males. *Aging Clin Exp Res*, 2018; 30: 1059–70
- Visconti L, Cernaro V, Calimeri S et al: The myth of water and salt: From aquaretics to tenapanor. *J Ren Nutr*, 2018; 28: 73–82
- Masuda T, Murakami T, Igarashi Y et al: Dual impact of tolvaptan on intracellular and extracellular water in chronic kidney disease patients with fluid retention. *Intern Med*, 2016; 55: 2759–64
- Armstrong M, Asuka E, Fingeret A: Physiology, Thyroid function. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020
- Stanley JA, Aruldas MM, Yuvaraju PB et al: Is gender difference in post-natal thyroid growth associated with specific expression patterns of androgen and estrogen receptors? *Steroids*, 2010; 75: 1058–66
- Stepniak J, Lewinski A, Karbownik-Lewinska M: Sexual dimorphism of NADPH Oxidase/H₂O₂ system in rat thyroid cells; Effect of exogenous 17β-estradiol. *Int J Mol Sci*, 2018; 19: 4063
- Kamei S, Iwamoto M, Kameyama M et al: Effect of tofogliflozin on body composition and glycemic control in Japanese subjects with type 2 diabetes mellitus. *J Diabetes Res*, 2018; 2018: 6470137