

Visceral Fat Area and Subcutaneous Fat Area Increase in Hyperthyroidism Patients After Treatment—A Single-Group Repeated-Measures Trial

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Purpose: There is evidence that long-term vascular risk remains increased in patients with hyperthyroidism even after normalization of thyroid function, and the mechanisms that regulate this risk are unclear. The aim of this study was to assess how visceral fat area and subcutaneous fat area change after hyperthyroidism treatment, and to further explore the relationship between thyroid hormones, abdominal fat area (visceral fat area and subcutaneous fat area), and lipids.

Patients and Methods: 50 patients with newly diagnosed Graves' disease were selected. Anthropometric parameters (weight, height, body mass index, waist circumference, neck circumference), laboratory parameters (thyroid hormones, lipid metabolism indices), abdominal fat area (visceral fat area and subcutaneous fat area), and drug dose were collected. Measurements were made at baseline, 6 and 12 months after treatment. We used linear mixed-effects models for analysis.

Results: The results showed that the following indexes changed significantly at different time points: visceral fat area, subcutaneous fat area, free triiodothyronine, free thyroxine, thyroid stimulating hormone, total cholesterol, high-density lipoprotein, low-density lipoprotein, body weight, neck circumference, body mass index, waist circumference, and drug dose (All $P < 0.001$). We found that free triiodothyronine and free thyroxine were significantly negatively associated with abdominal fat area ($P < 0.01$). There was no significant correlation between drug dose and abdominal fat area ($P > 0.05$). Total cholesterol and low-density lipoprotein were significantly positively associated with abdominal fat area ($P < 0.01$). However, high-density lipoprotein ($P = 0.06$) was not correlated with abdominal fat area. Moreover, the results showed a significant negative correlation between thyroid hormones and lipids ($P < 0.001$).

Conclusion: After anti-thyroid medicine treatment, patients had elevated visceral fat area and subcutaneous fat area and altered lipid profiles. These changes may be one of the reasons why metabolic and cardiovascular diseases remain increased after thyroid function is restored.

Keywords: visceral fat area, subcutaneous fat area, thyroid hormones, lipids, Graves' disease

Introduction

The incidence of hyperthyroidism is on the rise, and the age of onset is gradually advancing. Graves' disease (GD) is the most common type of hyperthyroidism, and its pathogenesis is complex. The thyroid stimulating hormone (TSH) receptor antibody is the ultimate cause of GD. These antibodies bind to TSH receptors on the surface of thyroid follicular cells, resulting in excessive secretion of thyroid hormones (THs) and increased multisystem excitability and

hypermetabolism.¹ The typical manifestation of hyperthyroidism is palpitation, shaking hands, fatigue, a strong appetite but weight loss, and other symptoms. For patients with hyperthyroidism, anti-thyroid drugs (especially methimazole) are the main choice of treatment at present.² Most of the above symptoms will be relieved after treatment of hyperthyroidism.

Studies have clearly shown a significant increase in cardiovascular morbidity and mortality in patients with hyperthyroidism because thyroid receptors are also present on cardiomyocytes and vascular endothelial cells and are sensitive to changes in the concentration of THs.³ Overproduction of THs can lead to increased heart rate, a hyperdynamic state of circulation, and even cardiovascular disease (CVD) such as atrial fibrillation.⁴ These changes are reversible with regular treatment. However, there is evidence that long-term vascular risk remains increased even after normalization of thyroid function.⁵ A study evaluating the rate of hospitalizations and mortality due to CVD in patients with hyperthyroidism after surgery showed that all hospitalizations due to CVD, hypertension, heart failure, valvular disease, and cardiomyopathy remained more common 10 years after thyroidectomy^{6,7} and could persist up to 20 years after effective surgical treatment. Similarly, compared with the general population, patients with hyperthyroidism treated with radioactive iodine or with antithyroid drugs continue to have increased cardiovascular morbidity and CVD mortality for decades, even if their final THs levels return to normal.^{8–11} These evidences suggest that regardless of treatment, the risk of CVD remains high even after thyroid function modification. The mechanisms mediating this risk are not yet clear.

Previous studies have shown that the weight gain after treatment of hyperthyroidism is mainly the increase of muscle content,¹² but recent studies have suggested that the weight gain may be related to the increase of visceral and subcutaneous fat.¹³ A study have further pointed out that THs has some effect on abdominal visceral fat and subcutaneous fat.¹⁴ Visceral fat is an important risk factor for CVD. The increased visceral fat can lead to insulin resistance and hyperinsulinemia.¹⁵ In addition to being associated with glucose metabolism, the visceral fat area (VFA) is positively associated with hypertension and dyslipidemia.⁵ Some experiments have demonstrated that the ratio of VFA to body fat mass is a better predictor of coronary heart disease.¹⁶ In contrast, the increase in subcutaneous fat is more likely to cause diabetes, because subcutaneous fat releases free fatty acids into the circulation, and elevated levels of free fatty acids are associated with insulin resistance.^{17,18}

Therefore, we hypothesized that the increased incidence of CVD after treatment of hyperthyroidism would be associated with increased VFA or subcutaneous fat area (SFA). We collected abdominal fat area parameters, laboratory parameters, and anthropometric parameters in patients with GD at baseline, and 6 and 12 months of follow-up, respectively. The aim of this study was to investigate the changes of these parameters over time and to further investigate the correlation between serum lipids, THs and abdominal fat area.

Materials and Methods

The present study was performed as a single group pre-test–posttest semi-experimental design.

Subjects

50 patients with newly diagnosed GD who attended the Department of Endocrinology of the First Hospital of Shanxi Medical University in July 2022 were selected. The diagnosis of GD was based on the presence of thyrotoxicosis with positive thyrotropin (TSH) receptor antibodies with or without thyroid enlargement.¹⁹ All patients were treated with methimazole for 1 year. Dose adjustments of methimazole were performed by each patient's physician. Exclusion criteria included age <18 or >75 years; transient thyrotoxicosis due to destructive thyroiditis; athletes, fitness trainers; suffering from diseases affecting the indexes of the study investigations, such as Cushing's syndrome, malignant neoplasms, nephrotic syndrome, etc; taking medications affecting lipids and thyroid function, such as glucocorticoids, amiodarone, lipid-lowering medications, weight-loss medications, etc; suffering from severe cardiac, hepatic, renal, brain and other chronic diseases; being in the active stage of chronic diseases, surgery, trauma and other stressful situations; the existence of mental illness diagnosis or physical disability, who can not cooperate with the examination.

Anthropometric and Laboratory Parameters

General information of all subjects was collected, including age, sex, height, weight, waist circumference, neck circumference. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of height (m²). After fasting for at least 8 hours, venous blood was drawn from the anterior elbow early the next morning to measure free triiodothyronine (FT3), free thyroxine (FT4), TSH, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG). FT3, FT4 and TSH were measured by chemiluminescence immunoassay (Abbott I2000, Abbott Reagent).

Abdominal Fat Area Parameters

In this study, we applied Bioelectrical impedance analysis (BIA) to evaluate the distribution of abdominal adipose tissue in hyperthyroid patients. BIA is easy to perform, saves time, and has no risk of radiation exposure. Several studies have demonstrated significant correlation between BIA measurements and CT and MRI.^{20,21} The abdominal SFA and VFA were measured by dual BIA using the visceral fat detection device DUALSCAN HDS-2000 (Omron, Japan). The subjects were fasted for at least 8 hours before the examination, and the abdomen was exposed while lying on the examination bed. Breath-holding was required during the measurement. First, the overall cross-sectional area of the abdomen was measured using the abdominal detection unit, then the electrode belt and limb electrode clips were installed, and the subjects were instructed to hold their breath again, and the abdominal SFA and VFA were measured in cm².

Statistical Analysis

SPSS27.0 software was used to analyze the data. Kurtosis and skewness tests were used to test the normal distribution of the data. Data conforming to normal distribution were described by mean and standard deviation (SD). Non-normal distribution was described by median and quartile [q25, q75]. We used linear mixed-effects models to compare means for repeated measures (before the intervention and at 6 and 12 months after the intervention). Bonferroni corrections were used for post hoc comparisons when significant interactions were found in linear mixed effects models. Furthermore, we used this model to investigate the effects of THs and lipids on SFA and VFA in hyperthyroidism patients during treatment. Similarly, we also explored the effect of THs on lipids. In all models, sex and age were controlled. $p < 0.05$ was considered significant.

Results

50 patients completed 6 - and 12-month follow-up. The mean age was 39.02 years (13.27) and the age range was 19–74. Of the 50 patients, 45 (90%) were female. The mean waist circumference of the 50 patients was 80.78 cm (9.94), the mean neck circumference was 33.57 cm (3.20), the weight was 59.02 kg (11.11), and the height was 162c m (0.07). The average initial dose of methimazole is 16.90mg (5.04). There were no reports of abnormal or spontaneous adverse events in this study. Baseline demographic and clinical characteristics are shown in [Table 1](#).

For the abdominal fat area parameters, the results of the linear mixed-effects model showed an increase in both SFA ($F = 21.38$, $p < 0.001$) ([Figure 1A](#)) and VFA ($F = 23.45$, $p < 0.001$) ([Figure 1B](#)) after treatment for hyperthyroidism. The results of the Bonferroni post hoc test showed that the values at 6 and 12 months after treatment were all significantly higher than the values before treatment ($T1 < T2, T1 < T3$, All $P < 0.001$), but there were no statistically significant differences between 6 months and 12 months after intervention ($T2$ and $T3$) (All $P > 0.05$) ([Table 2](#)) ([Figure 1](#)).

For laboratory parameters, the results of linear mixed-effects modeling showed that after treatment of hyperthyroidism, both FT3 ($F = 121.60$, $p < 0.001$) ([Figure 2A](#)) and FT4 ($F = 124.63$, $p < 0.001$) ([Figure 2B](#)) decreased, while TSH ($F = 14.96$, $P < 0.001$) ([Figure 2C](#)) was increased. TC ($F = 27.96$, $p < 0.001$) ([Figure 3A](#)), HDL ($F = 6.70$, $p < 0.001$) ([Figure 3B](#)), and LDL ($F = 23.00$, $p < 0.01$) ([Figure 3C](#)) were increased. However, the change in TG ($F = 0.85$, $p = 0.43$) ([Figure 3D](#)) was not significant ($p > 0.05$) across time points. Bonferroni post hoc test results of the above parameters with significant changes showed that there were statistically significant differences between pre-intervention and 6 months after intervention ($T1$ and $T2$) and between pre-intervention and 12 months after intervention ($T1$ and $T3$) (All

Table 1 Baseline Demographic and Clinical Characteristics (n = 50)

Variable	M (SD)
Female (N, %)	45(90%)
Age (Years)	39.02(13.27)
Neck circumference(cm)	33.57(3.20)
Waist circumference(cm)	80.78(9.94)
Height (cm)	162(0.07)
Body weight (kg)	59.02(11.11)
BMI (kg/m ²)	22.44(3.12)
Visceral fat area (cm ²)	48.04(24.19)
Subcutaneous fat area (cm ²)	168.38(70.95)
FT3 (pmol/L)	27.20(13.65)
FT4 (pmol/L)	59.67(25.70)
TSH (uIU/mL)	0.02(0.04)
TC (mmol/L)	3.62(1.06)
TG (mmol/L)	1.35(0.58)
LDL (mmol/L)	1.95(0.64)
HDL (mmol/L)	1.30(0.31)
Methimazole (mg)	16.90(5.04)

Abbreviations: M, mean; SD, standard deviation.

$P < 0.05$). However, the difference was not statistically significant ($p > 0.05$) when comparing 6 and 12 months after the intervention (T2 and T3) (Table 2) (Figures 2 and 3).

For anthropometric parameters, the results of linear mixed-effects modeling showed increases in body weight ($F = 19.82$, $p < 0.001$) (Figure 4A), neck circumference ($F = 13.76$, $p < 0.001$) (Figure 4B), BMI ($F = 21.44$, $p < 0.001$) (Figure 4C) and waist circumference ($F = 14.44$, $p < 0.001$) (Figure 4D) after treatment. The results of the Bonferroni post hoc test showed that the values at 6 and 12 months after treatment were all significantly higher than the values before treatment ($T1 < T2, T1 < T3$, All $P < 0.001$), but there were no significant differences between 6 months and 12 months after intervention (T2 and T3) (All $P > 0.05$) (Table 2)(Figure 4).

For the dose of methimazole, the linear mixed effects model showed that the dose was reduced after hyperthyroidism. The results of the Bonferroni post hoc test showed that the dose is gradually reduced over time ($T1 > T2 > T3$) (All $P < 0.001$) (Table 2) (Figure 5).

We investigated the effects of THs on SFA and VFA in patients with hyperthyroidism, and found that for SFA, the results of the linear mixed effects model showed that FT3 (Estimate= -2.12 , $P < 0.001$) and FT4 (Estimate= -1.02 , $P < 0.001$) were significantly negatively correlated with SFA. We also find that FT3 plays a bigger role than FT4. TSH (Estimate= 3.62 , $P = 0.001$) was positively correlated with SFA. Also for VFA, the results of the linear mixed effects model

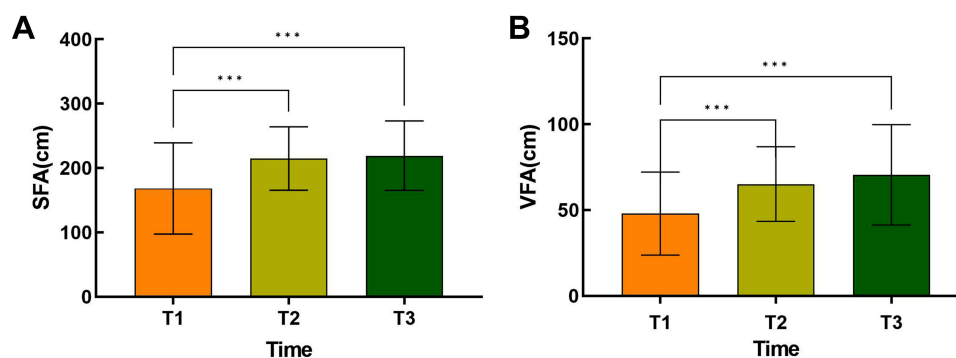


Figure 1 (A) Comparison of SFA at different time points. *** $P < 0.001$ (B) Comparison of VFA at different time points. *** $P < 0.001$.

Table 2 Comparison of the Following Parameters at Different Time Points

Variable	Before Treatment (T1)	6 Months After Treatment (T2)	12 Months After Treatment (T3)	Reference Range	F	P-value*	P-value** (Pairwise Comparison)
Abdominal fat area parameters							
Visceral fat area (cm ²)	48.04(24.19)	65.22(21.77)	70.56(29.27)	-	23.45	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
Subcutaneous fat area (cm ²)	168.38(70.95)	214.82(49.34)	219.16(53.85)	-	23.38	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
Laboratory parameters							
FT3 (pmol/L)	27.20(13.65)	4.82(1.75)	7.16(4.69)	3.1–6.8	121.60	<0.001	T1>T2(P<0.001) T1>T3(P<0.001)
FT4 (pmol/L)	59.67(25.70)	13.52(4.47)	20.97(11.55)	12–22	124.63	<0.001	T1>T2(P<0.001) T1>T3(P<0.001)
TSH (uIU/mL)	0.02(0.04)	5.92(9.20)	3.28(3.00)	0.27–4.2	14.96	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
TC(mmol/L)	3.62(1.06)	5.07(1.03)	4.58(1.14)	2.86–5.988	27.96	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
TG(mmol/L)	1.35(0.58)	1.29(0.75)	1.43(0.71)	0.56–1.7	0.85	0.43	-
LDL(mmol/L)	1.95(0.64)	2.89(0.74)	2.76(0.94)	2.07–3.12	23.00	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
HDL(mmol/L)	1.30(0.31)	1.47(0.32)	1.49(0.41)	0.94–2.0	6.70	0.002	T1<T2(P<0.05) T1<T3(P<0.001)
Anthropometric parameters							
Neck circumference(cm)	33.57(3.20)	35.38(3.19)	35.53(2.64)	-	13.76	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
Waist circumference(cm)	80.78(9.94)	86.60(8.45)	86.53(8.37)	-	14.44	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
Body weight (kg)	59.02(11.11)	64.29(9.70)	65.78(9.51)	-	19.82	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
BMI (kg/m ²)	22.44(3.12)	24.53(3.09)	25.08(2.78)	-	21.44	<0.001	T1<T2(P<0.001) T1<T3(P<0.001)
Antithyroid drug							
Methimazole(mg)	16.90(5.04)	9.33(4.34)	5.28(3.89)	-	126.27	<0.001	T1>T2>T3 (All P<0.001)

Notes: * Linear mixed-effects model; **Bonferroni posthoc test.

showed that FT3 (Estimate=-0.71, P<0.001) and FT4 (Estimate=-0.35, P<0.001) were significantly negatively correlated with VFA. We also find that FT3 has a greater effect than FT4. TSH (Estimate=1.97, P=0.002) was positively correlated with VFA. In addition, according to the results in the table, we find that THs has a greater impact on SFA than on VFA (Table 3).

We explored the effect of lipid metabolism parameters on SFA and VFA in hyperthyroidism patients during treatment, and found that TC (Estimate=12.94, P<0.001) and LDL (Estimate=18.74, P<0.001) were positively correlated with SFA, and the effect of LDL was greater. However, HDL (Estimate=25.98, P=0.06) was not significantly associated with SFA. Also for VFA, the results showed that TC (Estimate=4.75, P=0.002) and LDL (Estimate=9.30, P<0.001) were significantly positively correlated with VFA, and the effect of LDL was greater. However, HDL (Estimate=0.80, P=0.89) was not significantly correlated with VFA. In addition, according to the results in the table, we found that lipid metabolism indicators had a greater impact on SFA (Table 3).

We investigated the effect of methimazole dose on VFA and SFA during anti-thyroid treatment. The results showed that there was no significant correlation between the dose of methimazole and abdominal fat area (both VFA and SFA) (Both P>0.05) (Table 4).

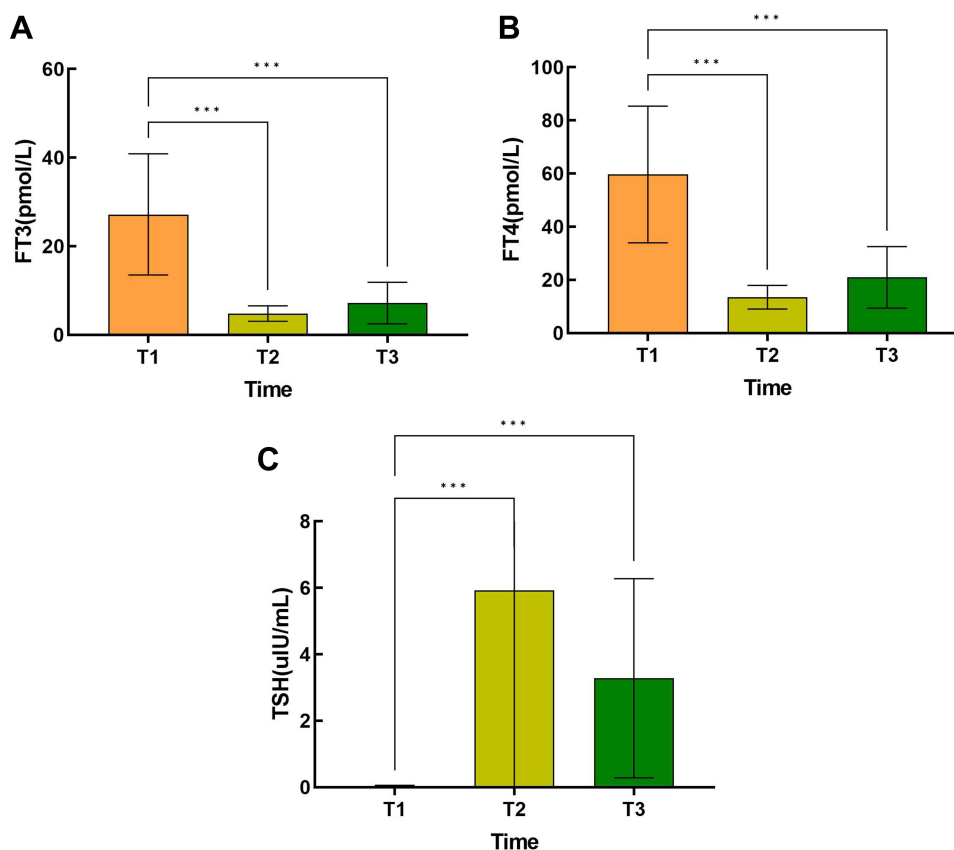


Figure 2 (A) Comparison of FT3 at different time points. *** $P < 0.001$ (B) Comparison of FT4 at different time points. *** $P < 0.001$ (C) Comparison of TSH at different time points. *** $P < 0.001$.

The linear mixed effect model showed that FT3 and FT4 were negatively correlated with TC, LDL and HDL (All $P < 0.001$). Compared with FT4, FT3 had a greater effect on each index of lipid metabolism. FT3 and FT4 had the greatest effect on TC compared with LDL and HDL. For TSH, our results showed that TSH was only positively correlated with TC ($P < 0.05$), and had no significant correlation with LDL and HDL (Both $P > 0.05$) (Table 5).

Discussion

In this study, we prospectively evaluated the dynamic changes in abdominal fat area parameters, laboratory parameters, and anthropometric parameters in patients with hyperthyroid hormone during 12 months of drug therapy. The inter-relationships between THs, lipids, and abdominal fat area were further investigated. At 6- and 12- months follow-up we found that VFA and SFA increased after treatment. THs basically returned to normal levels. Blood lipids were in the normal range before treatment, and TC, HDL and LDL were elevated after treatment, but still within the normal reference range. However, there was no significant change in TG before and after treatment.

The results of this experiment showed that FT3 and FT4 were negatively correlated with SFA and VFA. There was no significant correlation between the dose of methimazole and abdominal fat area. This suggests that THs directly regulates abdominal fat area during hyperthyroidism treatment, and drug dose has no significant effect in this process. The main mechanisms related to the enhancement of lipolysis in adipose tissue induced by THs are as follows: 1. THs can up-regulate the number of β_2 adrenergic receptors and reduce the activity of phosphodiesterase, and indirectly promote lipolysis through the effect of catecholamine.^{22,23} 2. THs can promote the transformation of white adipose tissue into brown adipose tissue, and increase heat production by inducing uncoupling protein-1.²⁴⁻²⁶ 3. FT3 promotes mRNA expression of liver fibroblast growth factor 21 (FGF21), and FGF21 can induce brown adipose tissue to stimulate thermogenesis.^{27,28} Previous studies have shown that the content of FGF21 in patients with hyperthyroidism increases

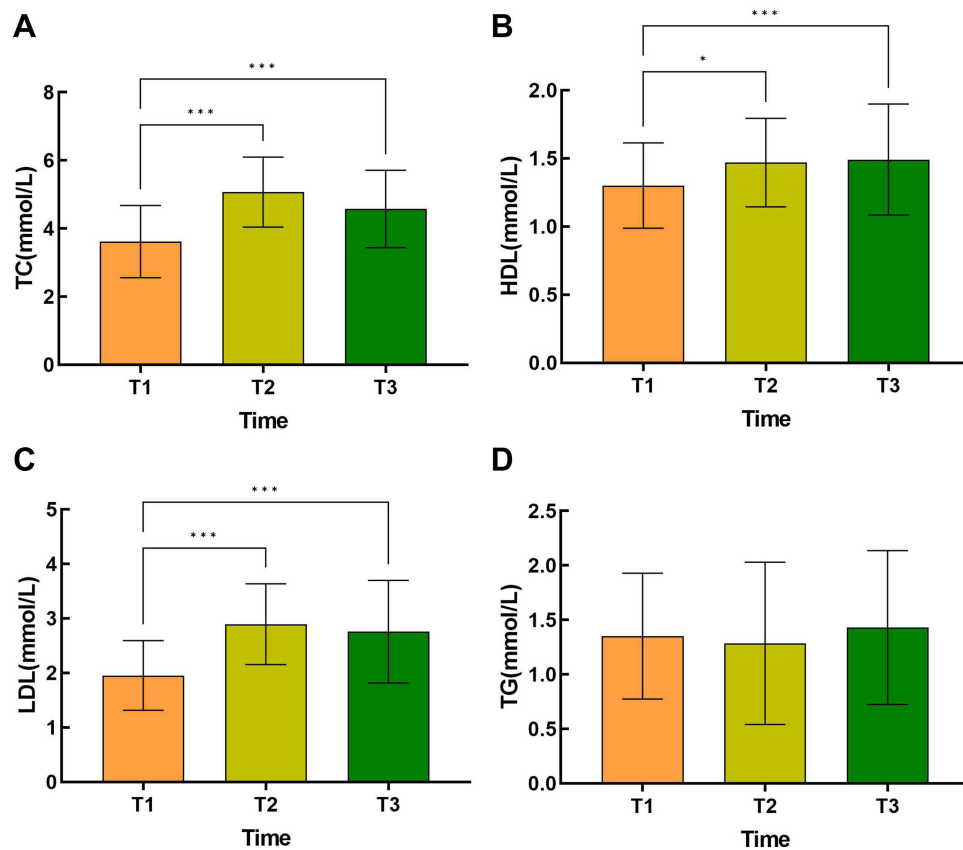


Figure 3 (A) Comparison of TC at different time points. ***P<0.001 (B) Comparison of HDL at different time points. ***P<0.001 *P<0.05 (C) Comparison of LDL at different time points. ***P<0.001 (D) Comparison of TG at different time points. P>0.05.

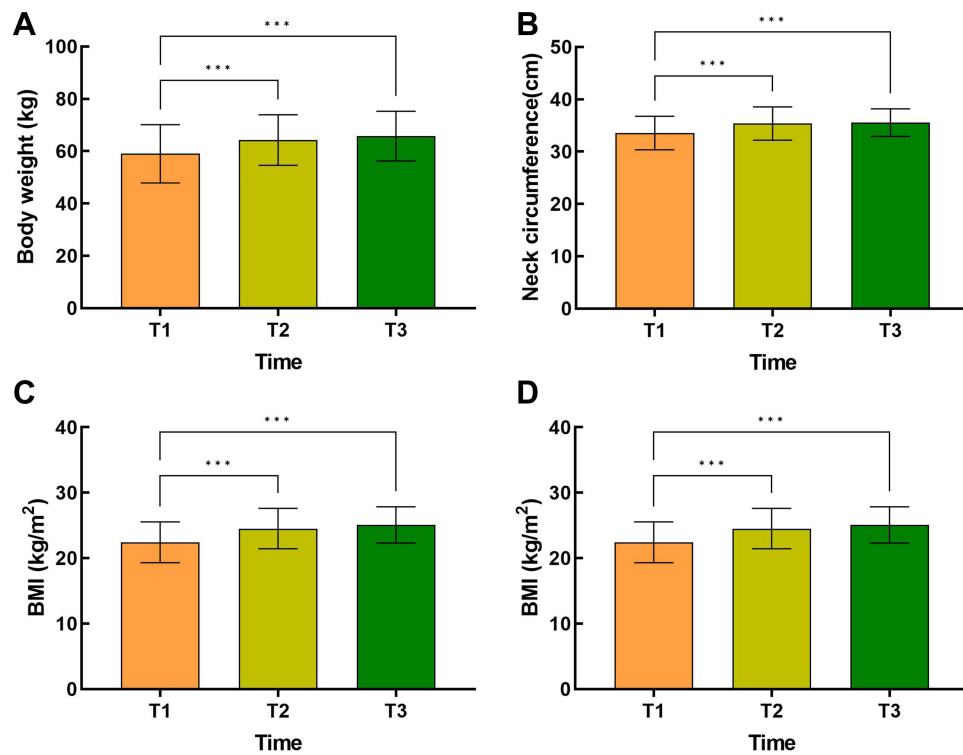


Figure 4 (A) Comparison of body weight at different time points. ***P<0.001 (B) Comparison of neck circumference at different time points. ***P<0.001 (C) Comparison of BMI at different time points. ***P<0.001 (D) Comparison of waist circumference at different time points. ***P<0.001.

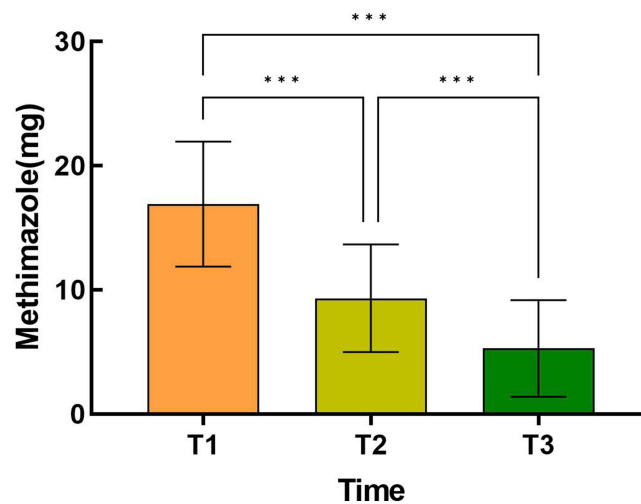


Figure 5 Comparison of methimazole dose at different time points. *** $P < 0.001$.

and is negatively correlated with body fat percentage.²⁹ Our study showed an increase in abdominal fat area during the treatment of hyperthyroidism. This is possible because decreased THs concentrations during treatment increase abdominal fat area by down-regulating the aforementioned mechanisms. Clinical manifestations were an increase in body weight, abdominal fat area, and waist circumference compared to pre-treatment.

We found that TC and LDL were positively correlated with SFA and VFA during the treatment, however, HDL was not correlated with SFA and VFA. It suggests that lipids somehow affect the abdominal fat area. The increase in abdominal fat area in patients with hyperthyroidism after treatment may be due in part to the increase in LDL and TC. Several previous studies have shown that LDL is positively associated with VFA and independently predicts cardiovascular events.^{30–32} In a study of Canadian, Lemieux et al³³ found that CT-measured VFA was positively associated with LDL levels. A one-year lifestyle intervention study of 107 non-diabetic white men with abdominal obesity found that

Table 3 The Effects of Thyroid Hormones and Lipids on VFA and SFA Were Summarized by a Linear Mixed-Effect Model

Variable	VFA			SFA		
	Estimate (SE)	95% CI	P-value	Estimate (SE)	95% CI	P-value
FT3 (pmol/L)	-0.71(0.12)	(-0.95, -0.47)	<0.001	-2.12(0.38)	(-2.90, -1.34)	<0.001
FT4 (pmol/L)	-0.35(0.06)	(-0.47, -0.23)	<0.001	-1.02(0.18)	(-1.39, -0.65)	<0.001
TSH (uIU/mL)	1.97(0.55)	(0.82, 3.13)	0.002	3.62(0.99)	(1.57, 5.68)	0.001
TC (mmol/L)	4.75(1.52)	(1.75, 7.75)	0.002	12.94(3.59)	(5.83, 20.04)	<0.001
LDL (mmol/L)	9.30(2.00)	(5.34, 13.26)	<0.001	18.74(4.88)	(9.08, 28.39)	<0.001
HDL (mmol/L)	0.80(5.87)	(-10.80, 12.40)	0.89	25.98(13.69)	(-1.08, 53.04)	0.06

Notes: Variable: Parameters that were statistically significant at different time points were included; Estimate: Maximum Likelihood Estimation; Gender/sex and age were controlled in the model.

Abbreviation: SE, Standard error.

Table 4 The Effects of Methimazole Dose on VFA and SFA Were Summarized by a Linear Mixed-Effect Model

Variable	VFA			SFA		
	Estimate (SE)	95% CI	P-value	Estimate (SE)	95% CI	P-value
Methimazole(mg)	-1.31(0.26)	(-1.81, 0.80)	0.06	-3.58(3.37)	(-10.19, 3.04)	0.29

Notes: Estimate: Maximum Likelihood Estimation; Gender/sex and age were controlled in the model.

Abbreviation: SE, Standard error.

Table 5 The Effects of Thyroid Hormones on Blood Lipids Were Summarized by a Linear Mixed-Effect Model

Variable	TC (mmol/L)			LDL (mmol/L)			HDL (mmol/L)		
	Estimate (SE)	95% CI	P-value	Estimate (SE)	95% CI	P-value	Estimate (SE)	95% CI	P-value
FT3(pmol/L)	-0.46(0.01)	(-0.06, -0.03)	<0.001	-0.03(0.005)	(-0.04, -0.02)	<0.001	-0.007(0.002)	(-0.011, -0.004)	<0.001
FT4(pmol/L)	-0.02(0.003)	(-0.03, -0.02)	<0.001	-0.02(0.003)	(-0.02, -0.01)	<0.001	-0.003(0.0009)	(-0.005, -0.002)	<0.001
TSH (uIU/mL)	0.07(0.02)	(0.02, 0.12)	0.007	0.02(0.01)	(-0.01,0.04)	0.188	0.005(0.005)	(-0.03,0.03)	0.46

Notes: Variable: Parameters that were statistically significant at different time points were included; Estimate: Maximum Likelihood Estimation; Gender/sex and age were controlled in the model.

Abbreviation: SE, Standard error.

a reduction in LDL was accompanied by a significant reduction in VFA.³⁴ A study of 157 subjects with a high prevalence of metabolic syndrome (34%) found that LDL levels were independently associated with VFA in men, but not in women.³⁵ Therefore, the current treatment target is LDL. Consistent with our study some larger studies have shown a significant positive correlation between TC and VFA.^{35,36} In addition, the relationship between HDL and changes in abdominal fat area has also been demonstrated in many studies. One study evaluated whether the accumulation of abdominal fat measured by CT over a 5-year period was correlated with baseline HDL concentration and found that HDL concentration and future abdominal fat accumulation were negatively correlated, indicating that in this population, the accumulation of abdominal fat was greater in subjects with lower baseline HDL concentration.³⁷ Hye-Rin Park et al further illustrated that the TG/HDL ratio was associated with visceral fat but not with SFA.³⁸ Song et al found that baseline plasma HDL concentration independently predicted intra-abdominal adiposity after performing a 5-year follow-up.³⁷ However, the relationship between HDL and abdominal fat area was not found in our study.

During the transition phase from hyperthyroidism to normal thyroid function, FT3 and FT4 were negatively correlated with TC, LDL, and HDL. It indicates that THs do regulate lipids during the treatment of hyperthyroid patients. Decrease in THs increases lipid levels. It has been shown that THs stimulate the expression of the LDL receptor mRNA gene on the hepatocyte membrane, leading to an increase in the number and activity of LDL receptors. Ultimately, the ability to remove LDL via the LDL receptor pathway increases, resulting in lower LDL levels.^{39,40} Elevated LDL eventually leads to elevated TC.^{41,42} In addition, reduced THs levels decrease hepatic cholesterol 7 α -hydroxylase activity, contributing to decreased cholesterol metabolism, which can also lead to elevated TC levels during hyperthyroidism treatment.⁴³ It has been shown that a decrease in THs levels decreases the activity of lipoprotein lipase, the enzyme responsible for the removal of TG-rich lipoproteins, which leads to an increase in serum TG levels.⁴⁴ However, in our study we found no significant change in TG during follow-up. For changes in HDL, the effect of changes in THs levels on HDL cholesterol levels has produced conflicting results as reported in the existing literature.^{45–47} In our study, we found a significant increase in HDL cholesterol levels after treatment of hyperthyroidism.

Existing studies have shown that VFA measured at the umbilicus is independently associated with the development of coronary artery disease and that VFA is a better predictor of cardiovascular risk factors than BMI.^{48–50} In contrast, there are no consistent findings regarding the relationship between SFA and CVD risk.⁴⁸ In this study, we focused on treatment-induced changes in abdominal fat area in patients. The results showed that both VFA and SFA increased after GD treatment. In addition to this, we also focused on the changes in lipid profile during hyperthyroidism treatment. The results showed that in addition to TG, LDL, HDL and TC were elevated and we found that LDL levels were significantly elevated leading to an increase in the LDL to HDL ratio. It has been shown that the ratio of LDL to HDL is considered a prognostic marker for CVD, and an elevated LDL to HDL ratio suggests an increased risk of cardiac exercise.⁵¹ Taken together with the above available evidence and our results, we speculate that increased abdominal fat area as well as altered lipid profiles are potential causes of metabolic disorder and CVD in hyperthyroid patients after treatment.

Although this study generated some new knowledge about the above-measured parameters in patients with hyperthyroidism, there are still some limitations. First, this was a single-center study, whereas the results of a multicenter study that recruited more participants may be more reliable. Second, this was a single-group repeated measures design study. Studies with control groups (eg, randomized controlled trials) are needed to assess changes in the above parameters and

their interrelationships after hyperthyroidism treatment. Third, we had only a 12-month follow-up, and a longer-term study is needed to assess long-term effects.

Conclusion

In conclusion, our results suggest that the reason why metabolic disorder and CVD remain increased after thyroid function is restored may somehow be related to the increase in abdominal fat area as well as the altered lipid profile. Therefore, during the diagnosis and treatment of hyperthyroidism, it is recommended to monitor the distribution of abdominal fat and lipid metabolism indicators in order to find the abnormal situation of adipose tissue and lipid metabolism in time.

Abbreviations

FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; Graves' disease, GD; thyroid hormones, THs; CVD, cardiovascular disease; THs, thyroid hormones.

Ethics Approval and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Ethics Committee of the First Hospital of Shanxi Medical University/ Date of approval: March 13, 2018 / Approval number: 2018K002) and with the Helsinki Declaration of 1964 and later versions. Informed consent for it was obtained from all patients for being included in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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