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Associations between sensitivity to thyroid hormones and insulin resistance in euthyroid adults with obesity

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Background: Impaired sensitivity to thyroid hormones (TH) was associated with metabolic syndrome. The study aimed to explore the association between central TH sensitivity indices and insulin resistance (IR) in euthyroid adults with obesity.

Methods: This cross-sectional study enrolled 293 euthyroid outpatients with obesity in Beijing Chao-Yang Hospital. We used the thyroid feedback quantile-based index (TFQI), thyroid stimulating hormone index (TSHI), and thyrotrophic T4 resistance index (TT4RI) to indicate central TH sensitivity. IR was assessed by homeostasis model assessment of insulin resistance (HOMA-IR), hepatic insulin resistance index (hepatic-IR), the Matsuda index, and the adipose tissue insulin resistance index (Adipo-IR). Participants were categorized according to tertiles of TH sensitivity indices. We used multiple linear regressions to explore the associations.

Results: There was a significant stepwise increase in HOMA-IR and Adipo-IR from the lowest to the highest tertiles of TH sensitivity indices (all $P<0.05$). After adjustment for age, sex, body mass index, hypertension, hyperlipidemia, and diabetes, only Adipo-IR was significantly associated with TH sensitivity indices. On average, each unit increased in TFQI, TSHI, and TT4RI was associated with 1.19 ($P=0.053$), 1.16 ($P=0.04$), and 1.01 ($P=0.03$) units increased in Adipo-IR, respectively. There was no significant association between TH sensitivity indices and HOMA-IR, hepatic-IR, and the Matsuda index after adjustment for other risk factors.

Conclusions: Reduced central TH sensitivity was associated with increased adipose tissue insulin resistance in euthyroid adults with obesity. The results further confirmed the importance of TH sensitivity on metabolic diseases.

KEYWORDS

thyroid hormone sensitivity, insulin resistance, adipose tissue, obesity, metabolic diseases

1 Introduction

Evidence for the association between thyroid hormones (THs) and glucose metabolism appeared for a long time. THs have an insulin-antagonistic effect on the liver, leading to increased hepatic glucose output by enhancing the rate of gluconeogenesis and glycogenolysis (1). Thyroid stimulating hormone (TSH) and THs correlate with multiple cardiometabolic risk factors, including insulin resistance (IR) (2). Subjects with hyperthyroidism or hypothyroidism can also show impaired glucose tolerance and IR (1). Dysregulation of carbohydrate metabolism and thyroid dysfunction are closely linked. TH can regulate insulin secretion by both direct and indirect pathways, which may involve diminishing the secretion triggered by glucose or attenuating the sensitivity of pancreatic β cells (3). However, studies addressing the association between THs and IR have been controversial. Jose's study indicated that both serum TSH and free thyroxine (FT4)*TSH product were positively associated with IR in healthy euthyroid subjects without diabetes (4). Another study of 940 euthyroid participants suggested that high free tri-iodothyronine (FT3) levels within the normal range are associated with IR measured by the insulin clamp technique both cross-sectionally and longitudinally (5). Data from two independent epidemiological studies also confirmed a consistent association between FT3 and IR (6). Ambrosi's study of 581 euthyroid subjects with obesity showed a positive association between TSH and IR but a negative association between FT4 and IR [IR was calculated by homeostasis model assessment of insulin resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI)] (7). However, a Mendelian randomization study by Maxime found no evidence for a causal association between circulatory levels of TSH and FT4 with IR (8), so did another study from the sixth Korean National Health and Nutrition Examination Survey, suggesting no association between TSH, FT4, and HOMA-IR (9). In a euthyroid population with 1275 participants of obesity, TSH has no association with IR indicated by HOMA-IR, and the positive relationship between FT3 and IR lost its significance after adjustment for other confounders (10). Amouzegar's cross-sectional study of 2758 euthyroid subjects free of thyroid disorders and diabetes found the association between THs and IR differed by sex, with no association between FT4 or TSH and HOMA-IR among women, but a positive association between FT4 and HOMA-IR among men (11). It is reasonable to assume that the discrepancies in these findings may stem from variable TH sensitivity among different populations.

The hypothalamic-pituitary-thyroid axis maintains the equilibrium of TH levels. Central sensitivity to THs reflects the pituitary responsiveness to them. Recently, researchers proposed several indices assessed by measuring circulating FT4 values and TSH values and representing the central sensitivity of TH. These indexes include thyroid feedback quantile-based index (TFQI), TSH index (TSHI), and thyrotrophic T4 resistance index (TT4RI) (12, 13). Previous studies indicated that impaired sensitivity to TH was associated with metabolic syndrome, diabetes, diabetes-related mortality, hyperuricemia, hyperhomocysteinemia, high remnant cholesterol levels, hypertension, and cardiovascular disease risk score (12, 14–17), suggesting that decreased sensitivity to THs can contribute to metabolic disorders. However, little is known about the association between the sensitivity of TH and IR, which is also a hallmark of the metabolic syndrome (18), with only one study of 80 prepubertal euthyroid children with obesity from three Italian pediatric endocrinology centers revealing that TFQI was negatively associated with the Matsuda-index (19).

THs exert bidirectional effects on insulin signaling, agonistic in muscle tissue and antagonistic in the liver. Hyperthyroidism disrupts this equilibrium, precipitating hepatic insulin resistance and glucose intolerance. Hypothyroidism induces more nuanced insulin resistance, primarily in peripheral tissues. This resistance could stem from impaired mitochondrial oxidative phosphorylation and reduced blood perfusion in muscular and adipose tissues (1). Multiple methods and indices have been refined to evaluate IR in different tissues, reflecting both static measures and dynamic testing. The intricate interplay of glucose and insulin metabolism is driven by diverse stimuli in several tissues. HOMA-IR is a simple, minimally invasive and widely used method for IR (20). The hepatic insulin resistance (hepatic-IR) index coming from the measurement of plasma glucose and insulin concentrations during an oral glucose tolerance test (OGTT) is presented for quantitation of hepatic insulin sensitivity (21). The Matsuda index is used to measure the composite whole-body insulin sensitivity including both hepatic and peripheral tissue insulin sensitivity (22). The adipose tissue insulin resistance index (Adipo-IR index) is calculated as the product of the fasting insulin and free fatty acid (FFA) concentration and is useful in large-scale clinical practice (23).

Considering the complex effect of THs on glucose metabolism and metabolic disorders, we aimed to explore the relationship between sensitivity to TH and IR in euthyroid adults with obesity. We used the following indices to assess insulin resistance of different tissues, including HOMA-IR, hepatic-IR, Adipo-IR, and the Matsuda index for whole-body insulin sensitivity.

2 Materials and methods

2.1 Study population

This cross-sectional study enrolled outpatients with obesity counseling weight loss in the Department of Endocrinology, Beijing Chao-Yang Hospital between April 2017 and August 2021. The inclusion criteria were: (1) age ≥ 18 years old; (2) obesity which is defined as a body mass index (BMI) of 28kg/m^2 or higher in the Chinese population (24); (3) normal blood levels of TSH, FT4 and FT3 (the laboratory normality reference ranges were 0.55 - 4.78 μIU/mL for TSH, 11.45 - 22.65 pmol/L for FT4, and 2.0-4.4pg/ml for FT3); (4) receiving a 75-g OGTT. Subjects who met the following criteria were excluded: (1) missing data in FT4, FT3, TSH, FFA, or OGTT results; (2) previous history of thyroid diseases; (3) antithyroid therapy or thyroid hormone replacement treatment; (4) Elevated levels of anti-thyroid peroxidase (anti-TPO) or anti-thyroglobulin (anti-TG) antibodies (anti-TPO ≥ 60U/ml or anti-TG ≥ 60U/ml); (5) taking hypoglycemic or lipid-lowering

medications; (6) severe renal or liver dysfunction (denoting as estimated glomerular filtration rate (eGFR)< 60 ml/min/1.73m2, alanine transaminase (ALT) or aspartate transaminase (AST) more than three times the upper limit of normal range). At last, the study enrolled 293 participants in the analysis. Referring to the results of previous research enrolling 80 participants and studying the association between TH sensitivity and IR (19), we assume that a sample size of approximately 300 individuals has sufficient power to detect differences. The study was in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board at Beijing Chao-Yang Hospital, Capital Medical University (Approval number: 2022-Science-517). We got informed consent from all subjects.

2.2 Measurement of clinical information

Qualified physicians regularly collected the medical information of all participants, including age, sex, weight, height, and medical history. Venous blood samples were collected from the participants in the morning after more than 10 hours of overnight fasting, then sent to the standard clinical laboratories of Beijing Chao-Yang Hospital. We use the glucose oxidase method to measure blood glucose, the chemiluminescence method for blood insulin, and the colorimetric enzymatic method for ALT, AST, creatinine, lipids, and FFA (Siemens Healthcare Diagnostics). TSH, FT4, and FT3 were measured by electrochemiluminescence immunoassay, and anti-TPO and anti-TG were measured by chemiluminescent immunoassay, using an Abbott Architect i2000 (Abbott Diagnostics). At 8:00 A.M., after a more than 10-hour overnight fast, subjects received OGTT. Blood samples were taken at 0, 60, and 120 minutes for the measurement of blood glucose and insulin concentrations. Blood samples at 30 minutes during OGTT were also collected from 152 patients (111 patients without diabetes and 41 patients with diabetes).

2.3 Definition of variables

BMI is calculated by a person's weight in kilograms divided by the square of height in meters. Dyslipidemia was defined as total cholesterol (TC) ≥ 5.2mmol/L, or triglyceride (TG) ≥ 1.7mmol/L, or low-density lipoprotein cholesterol (LDL-C) ≥ 3.4mmol/L, or high-density lipoprotein cholesterol (HDL-C)< 1.0mmol/L, or non-high-density lipoprotein cholesterol (non-HDL-C) ≥ 4.1mmol/L (25). The criteria for the diagnosis of diabetes were: fasting blood glucose (FBG) ≥ 7.0 mmol/L or hemoglobin A1C (HbA1c) ≥ 6.5% (48 mmol/mol) or random plasma glucose ≥11.1 mmol/L with classic symptoms of hyperglycemia, or taking glucose-lowering drugs (26). TFQI was calculated as cumulative distribution function (cdf) (FT4) - [1 – cdf (TSH)], i.e., the difference between the FT4 quantile and the reversed TSH quantile. This index ranges between -1 and 1, with negative values indicating higher sensitivity to FT4, and positive values indicating lower sensitivity to FT4 (12). TSHI was calculated as ln TSH (mIU/L) + 0.1345 * FT4(pmol/L) (13). TT4RI was calculated as FT4 (pmol/L) * TSH (mIU/L) (12). Higher TSHI or TT4RI represented lower central sensitivity to thyroid hormones. HOMA-IR, which has been used widely as an indirect method for quantifying insulin resistance, is defined as [FBG (mmol/L) × fasting insulin (uIU/ml))/22.5] (20). The hepatic-IR index was defined as the product of the total area under curve (AUC) for glucose and insulin during the first 30 min of the OGTT ($glucose_{0-30}$[AUC] * $insulin_{0-30}$[AUC]) (21). The whole-body insulin sensitivity was estimated by the Matsuda index derived from the OGTT (22):

$$\frac{10000}{\sqrt{(fasting\ glucose * fasting\ insulin) * (mean\ glucose * mean\ insulin\ during\ OGTT)}}$$

Adipo-IR index was calculated as the product of the fasting insulin and FFA concentration [Adipo-IR index = fasting insulin (μIU/mL) × fasting FFA (mmol/L)] (23).

2.4 Statistical analysis

We described continuous variables that fit normal distribution as mean ± standard deviation (SD), and those that didn't conform to a normal distribution as median (quartiles), and categorical variables as count (percentage). Non-normally distributed variables were log-transformed when put into linear regression models (e.g., age, BMI, HOMA-IR, hepatic-IR, the Matsuda index, and Adipo-IR). We categorized TFQI, TSHI, and TT4RI into three groups according to tertiles (Supplementary Table 1), using the lowest tertile range (Q1) as the reference group. We used one-way analysis of variance (ANOVA) to compare the distributions of insulin resistance indices (after log-transformed) across tertiles of TH sensitivity indices in the crude analysis. We used multiple linear regression models to explore the association between TH sensitivity indices and insulin resistance indices after adjustment for potential confounders (e.g., age, sex, BMI, hypertension, hyperlipidemia, diabetes, eGFR). $P< 0.05$ was considered statistically significant. Analyses were carried out using R version 4.1.2.

3 Results

3.1 Baseline information

In total, there were 293 participants enrolled in the study. The median age of the total subjects was 31 years old, and the median BMI was 38.4 kg/m^2. Most of the participants were female (71.7%), without hypertension (70.6%), without diabetes (75.1%) and with hyperlipidemia (71.3%). Results of other laboratory tests, TH sensitivity indices, and insulin resistance indices are shown in Table 1.

3.2 Univariate analysis between TH sensitivity indices and IR

As Figure 1, Supplementary Table 2 showed, there was a significant stepwise increase in HOMA-IR and Adipo-IR from the lowest to the highest tertiles of TH sensitivity indices (all P<0.05).

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TABLE 1 Baseline information of the total subjects.

	Male (n=83)	Female (n=210)	Overall (n=293)
Age (years)	32 [27.5, 37.5]	31 [26, 36.8]	31 [27, 37]
BMI (kg/m^2)	42.9 [36.8, 48.6]	36.8 [33.5, 42.2]	38.4 [34.1, 44.8]
Hypertension, n (%)	35 (42.2%)	51 (24.3%)	86 (29.4%)
Hyperlipidemia, n (%)	72 (86.7%)	137 (65.2%)	209 (71.3%)
Diabetes, n (%)	24 (28.9%)	49 (23.3%)	73 (24.9%)
FFA (mmol/L)	0.68 [0.54, 0.84]	0.63 [0.48, 0.78]	0.64 [0.49, 0.80]
FT4 (pmol/L)	16.09 [14.29, 17.12]	15.70 [14.29, 16.86]	15.83 [14.29, 16.99]
FT3 (pg/ml)	3.50 [3.18, 3.71]	3.19 [2.97, 3.41]	3.26 [3.02, 3.56]
TSH (μIU/mL)	2.41 [1.67, 3.13]	2.43 [1.99, 3.14]	2.42 [1.90, 3.14]
TFQI	-0.05 [-0.31, 0.38]	0.02 [-0.28, 0.31]	0.02 [-0.29, 0.33]
TSHI	2.92 [2.61, 3.32]	3.00 [2.72, 3.33]	2.98 [2.70, 3.33]
TT4RI	39.7 (16.6)	39.6 (14.5)	39.7 (15.1)
Fasting glucose (mmol/L)	5.65 [5.30, 6.56]	5.62 [4.98, 6.34]	5.63 [5.10, 6.40]
0.5-hour glucose (mmol/L)	10.12 [9.22, 11.42]	10.05 [8.58, 11.59]	10.08 [8.71, 11.57]
1-hour glucose (mmol/L)	10.32 [8.40, 13.04]	10.26 [8.77, 13.26]	10.27 [8.71, 13.17]
2-hour glucose (mmol/L)	7.87 [5.88, 10.18]	7.81 [6.52, 10.30]	7.82 [6.32, 10.27]
Fasting insulin (uIU/ml)	31.35 [22.96, 44.65]	25.14 [18.44, 37.64]	26.94 [18.89, 38.84]
0.5-hour insulin (uIU/ml)	132.2 [96.6, 193.3]	113.3 [72.3, 182.5]	117.9 [73.3, 182.9]
1-hour insulin (uIU/ml)	149.2 [96.5, 251.7]	133.6 [80.3, 201.9]	138.0 [82.4, 216.7]
2-hour insulin (uIU/ml)	108.9 [48.0, 180.7]	111.3 [64.1, 181.5]	110.7 [57.3, 182.3]
HOMA-IR	8.64 [6.02, 13.45]	6.42 [4.18, 10.33]	6.87 [4.36, 10.95]
Hepatic-IR	158.6 [126.1, 254.3]	149.3 [100.6, 206.9]	150.1 [102.6, 209.1]
Matsuda index	25.7 [17.4, 37.1]	29.2 [20.1, 42.9]	27.6 [19.0, 42.2]
Adipo-IR	21.4 [12.9, 32.6]	15.7 [9.9, 25.1]	17.5 [10.6, 27.3]

BMI, body mass index; FFA, free fatty acid; FT4, free thyroxine; FT3, free tri-iodothyronine; TSH, thyroid stimulating hormone; TFQI, Thyroid Feedback Quantile-based Index; TSHI, TSH index; TT4RI, thyrotrophic T4 resistance index; HOMA-IR, homeostasis model assessment of insulin resistance; Hepatic-IR, hepatic insulin resistance index; Adipo-IR, adipose tissue insulin resistance index.

There were 141 (48.1%) missing data in 0.5-hour glucose, 0.5-hour insulin levels, as well as in Hepatic-IR. Hepatic-IR also increased across tertiles of TT4RI (P=0.04). There was no significant difference in the hepatic-IR index across tertiles of TFQI and TSHI, and the Matsuda index across tertiles of all three TH sensitivity indices (all P>0.05).

3.3 Multiple regression analysis between TH sensitivity indices and IR

As Table 2 displayed, after adjustment for age, sex, BMI, hypertension, hyperlipidemia, and diabetes, only Adipo-IR was significantly associated with TH sensitivity indices. Subjects in the highest tertile of TFQI had 0.20 units increased in log Adipo-IR ($e^{0.20}$ = 1.22) compared with subjects in the lowest tertile of TFQI (P=0.03). Subjects in the highest tertile of TSHI had 0.18 units increased in log Adipo-IR ($e^{0.18}$ = 1.20) compared with subjects in the lowest tertile of TSHI (P=0.04). Subjects in the highest tertile of TT4RI had 0.22 units increased in log Adipo-IR ($e^{0.22}$ = 1.25) compared with subjects in the lowest tertile of TT4RI (P=0.02). On average, each unit increased in TFQI, TSHI, and TT4RI was associated with 1.19 ($e^{0.17}$=1.19, P=0.053), 1.16 ($e^{0.15}$=1.16, P=0.04), and 1.01 ($e^{0.005}$=1.01, P=0.03) units increased in Adipo-IR, respectively. Generally, there was no significant association between TH sensitivity indices and HOMA-IR, hepatic-IR, and the Matsuda index after adjustment for other risk factors.

4 Discussion

In this study of euthyroid individuals with obesity, we observed a positive but weak correlation between TH sensitivity indices and IR calculated by HOMA-IR, which lost its significance after adjustment for age, sex, BMI, hypertension, hyperlipidemia, and diabetes. We also first found that reduced central TH sensitivity was significantly associated with adipose IR after adjustment for other potential confounders. Our study further confirmed the association between decreased TH sensitivity and metabolic disorders in people with obesity.

TH could regulate some genes involved in gluconeogenesis, glycogen metabolism, and insulin signaling (1). In animal studies, it was observed that the induction of hyperthyroidism or hypothyroidism in mice resulted in corresponding increases or decreases in the hepatocyte membrane glucose transporter (GLUT2) content, highlighting the regulatory role of TH on GLUT2 expression on hepatocyte membranes. TH up-regulates hepatic GLUT2 mRNA and protein expression, increasing hepatic glucose output (27). TH could also modulate hepatic glucose metabolism by a central pathway. Stimulation of TH-sensitive neurons in the paraventricular nucleus in the euthyroid condition increases endogenous glucose production via sympathetic projections to the liver, independently of circulating glucoregulatory hormone concentrations (28). Similarly, thyroid functions also affect GLUT2 expression in pancreatic islets β cells (29). However, although we observed a positive but weak correlation between TH sensitivity indices and IR calculated by HOMA-IR and hepatic-IR (Figure 1), the associations lost their significance after adjustment for age, sex, BMI, hypertension, hyperlipidemia, and diabetes, and we didn't find a significant association between TH sensitivity indices and the Matsuda index. Conversely, one previous study of 80 prepubertal euthyroid

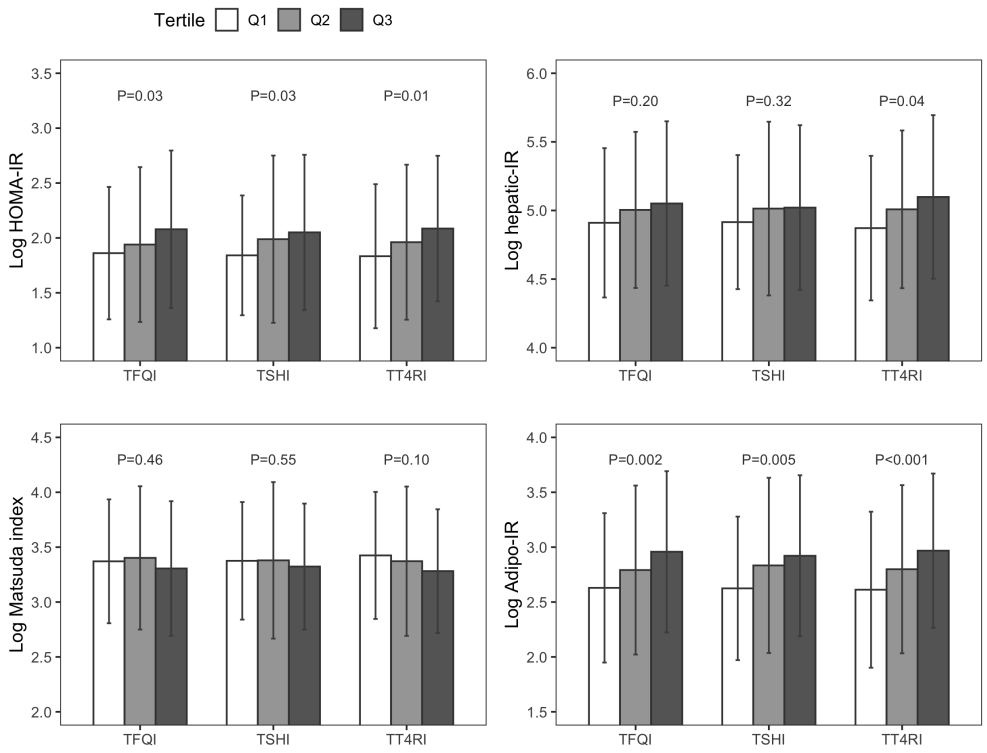

FIGURE 1
Insulin resistance indices across tertiles of thyroid hormone sensitivity indices. TFQI, Thyroid Feedback Quantile-based Index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotrophic T4 resistance index; HOMA-IR, homeostasis model assessment of insulin resistance; Hepatic-IR, hepatic insulin resistance index; Adipo-IR, adipose tissue insulin resistance index.

children with obesity revealed that TFQI was negatively associated with the Matsuda-index, demonstrating an association between decreased central sensitivity to THs and decreased whole-body insulin sensitivity (19). The populations in that study were Caucasian and it excluded children with impaired fasting blood glucose or impaired glucose tolerance; Our study enrolled Asian adults instead of Caucasian children and was adjusted for different confounding factors, including age, sex, BMI, hypertension, hyperlipidemia, and diabetes. We further conducted stratified analyses and found that sex, hypertension, hyperlipidemia, and diabetes were not significant modifiers in the associations between TH sensitivity and IR. The associations between central TH sensitivity and hepatic and whole-body insulin sensitivity need to be explored in future studies with larger samples and more general populations than just people with obesity.

Our study demonstrated a negative association between central TH sensitivity and adipose IR in people with obesity. TH regulates lipogenesis and lipolysis primarily by modulating adrenergic activity. Reduced sensitivity of TH may lead to a marked reduction in catecholamine-stimulated lipolysis, increased visceral adiposity, and decreased insulin sensitivity (30). The intricate relationship between TH and adipose tissue has always been a hot topic for researchers. T3 induction of lipogenic enzymes which are involved in fatty acid synthesis and lipogenesis could aggravate the dysregulation of liver glucose and lipid metabolism, a characteristic of IR (1). An inactivating mutation in the human type 2 deiodinase (D2) gene could lead to decreased intracellular availability of active thyroid hormone, which in turn, would decrease the transcription of GLUT4 in insulin-sensitive tissues, such as skeletal muscle and adipose tissue, contributing to IR (31). The negative association between central TH sensitivity and adipose IR might also be due to some cytokines. In hyperthyroidism, subcutaneous adipose tissue releases interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which could then act as an endocrine mediator of IR in lipolysis (32). Research has shown that TNF-α and IL, specifically IL-1 and IL-6, can suppress the mRNA expression of the sodium/iodide symporter, which is a critical component in the synthesis of THs. In addition to this, proinflammatory cytokines have been linked to the inhibition of type 1 deiodinase (D1) and the stimulation of type 3 deiodinase (D3) in the human hepatocarcinoma cell line (33–35). Another potential mechanism is leptin. Mild hypothyroidism is also characterized by decreased insulin responsiveness in skeletal muscle and adipose tissue, which is in part due to lowered plasma leptin levels and the overexpression of resistin in adipose tissue, and this insulin resistance is partly alleviated by intracerebroventricular leptin administration (36). According to the authors of this study, the dysregulation of leptin action at the hypothalamus acts partly roles in the development of IR. Leptin receptors have been found in the anterior pituitary and thyroid gland. Studies suggest that in the rat pituitary, leptin may act as an autocrine/paracrine inhibitor of TSH release, and also suppresses TSH-induced thyroid function (37, 38). Furthermore, the metabolism of THs can be influenced by leptin. The administration of exogenous leptin has been shown to

TABLE 2 Multiple linear regression between thyroid hormone sensitivity indices and insulin resistance.

	Tertiles	TFQI		TSHI		TT4RI	
		β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
HOMA-IR							
TH indices categorized	Q1	Ref	–	Ref	–	Ref	–
	Q2	0.05 (0.08)	0.57	0.14 (0.08)	0.08	0.09 (0.25)	0.25
	Q3	0.10 (0.08)	0.21	0.11 (0.08)	0.19	0.17 (0.08)	0.03*
TH indices continuous	–	0.09 (0.08)	0.24	0.10 (0.07)	0.14	0.004 (0.002)	0.10
Hepatic-IR							
TH indices categorized	Q1	Ref	–	Ref	–	Ref	–
	Q2	0.05 (0.10)	0.61	0.04 (0.11)	0.71	-0.01 (0.11)	0.91
	Q3	0.06 (0.11)	0.58	0.03 (0.11)	0.78	0.12 (0.11)	0.28
TH indices continuous	–	0.08 (0.11)	0.46	0.08 (0.09)	0.41	0.004 (0.003)	0.17
Matsuda index							
TH indices categorized	Q1	Ref	–	Ref	–	Ref	–
	Q2	0.07 (0.08)	0.37	0.03 (0.08)	0.74	-0.002 (0.08)	0.98
	Q3	0.03 (0.08)	0.69	0.04 (0.08)	0.62	-0.07 (0.08)	0.34
TH indices continuous	–	0.05 (0.07)	0.53	0.03 (0.06)	0.69	-0.0005 (0.002)	0.80
Adipo-IR							
TH indices categorized	Q1	Ref	–	Ref	–	Ref	–
	Q2	0.15 (0.09)	0.09	0.18 (0.09)	0.04*	0.10 (0.09)	0.26
	Q3	0.20 (0.09)	0.03*	0.18 (0.09)	0.04*	0.22 (0.09)	0.02*
TH indices continuous	–	0.17 (0.09)	0.053	0.15 (0.08)	0.04*	0.005 (0.002)	0.03*

Adjustment for age, sex, body mass index, hypertension, hyperlipidemia, and diabetes.
TH, thyroid hormone; TFQI, Thyroid Feedback Quantile-based Index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotrophic T4 resistance index; HOMA-IR, homeostasis model assessment of insulin resistance; Hepatic-IR, hepatic insulin resistance index; Adipo-IR, adipose tissue insulin resistance index; SE, standard error; Ref, reference.
*P<0.05.
-, Not applicable.

increase the activity of D1 in the liver and pituitary gland, while concurrently leading to a decrease in the activity of D2 in the hypothalamus and brown adipose tissue (33).

Interestingly, we further did mediation analysis and found that the blood lipids, especially TG levels, mediated the correlation between TH sensitivity indices and adipose IR. The effects of TH sensitivity indices on Adipo-IR were alleviated when conditioning on TG levels. Results of the mediation analysis showed that 6.1% (*P*=0.055) of the effect of TFQI, 6.2% (*P*=0.025) of the effect of TSHI, and 2% (*P*=0.001) of the effect of TT4RI on Adipo-IR could be explained by TG levels. Previous study indicated that plasma TH concentration is associated with hepatic TG content (39). T3 is also capable of modulating the expression of lipogenic enzyme and augments the accumulation of TG in adipocytes (40). The interaction between TH and adiposity is reciprocal. TH exerts significant regulatory effects on the central nervous system. Administering T3 centrally leads to an increase in body temperature, a decrease in hypothalamic AMP-activated protein kinase (AMPK) levels and an enhanced activity in the sympathetic nerves, and upregulates thermogenic markers in brown adipose tissue. The hypothalamic AMPK and fatty-acid metabolism are integral to TH's regulation of energy balance (41). In primary human differentiated adipocytes, TSH triggers lipolysis and impedes insulin signaling via the inhibition of phosphorylation on protein kinase B (Akt) (42). This mechanism could potentially contribute to the development of IR. However, another study in differentiated adipocytes showed that TSH could directly induce the activity of glycerol-3-phosphate-acyltransferase 3, the rate-limiting enzyme in TG synthesis, leading to an increase in TG synthesis. THs in the liver promote lipogenesis from glucose metabolism and the re-esterification of FFAs into TG by upregulating lipogenic gene transcription. THs also concurrently increase hepatic lipase activity, lipophagy, and mitochondrial fatty acid oxidation—the main mechanisms the liver employs to mitigate steatosis (43). THs increase lipoprotein lipase activity, affecting very low-density lipoprotein (VLDL) levels in the liver and serum, potentially leading to increased serum TG, as the primary lipid component of VLDL is TG (33). In addition, Adipo-IR correlates with TG levels. Adipose tissue dysfunction and insulin resistance escalate lipolysis and FFA release, leading to decreased lipoprotein lipase activity and increased cholesteryl ester transfer protein expression. This dysregulation enhances hepatic TG-rich VLDL production and reduces TG hydrolysis, resulting in hypertriglyceridemia and lipid metabolic disorders (44).

THs display a dual role of both imitating and countering insulin's actions across varying organs, such as insulin agonistic in muscle or antagonistic in the liver (1). Nevertheless, this interaction maintains a delicate equilibrium, crucial for normal glucose metabolism. An imbalance, either deficiency or surplus of THs, can disrupt this equilibrium, resulting in changes in carbohydrate metabolism. Furthermore, impaired sensitivity to TH was also associated with metabolic disorders, even in the euthyroid population (12, 14–17). In conclusion, our study indicated that impaired central sensitivity to TH was associated with adipose IR in euthyroid people with obesity, and further confirmed the importance of decreased TH sensitivity in metabolic diseases. Our study provides new evidence for the role of reduced central TH sensitivity on glucose and lipid metabolism, laying a foundation for future research on the relationship between THs and consequent cardiovascular metabolic risks.

The present study has some limitations. First, its cross-sectional design does not provide a causal explanation of the relationships. Second, this is a single-center study of subjects with obesity, limiting the generalizability to people with normal weight and people from other countries. Thirdly, the participants in our study were outpatients with obesity who counseled weight loss in the hospital instead of ordinary persons with obesity, which might cause a selection bias. Finally, we didn't collect data on some potential confounding factors, such as diet, physical activity, and other hormonal influences, which might leave some residual confounding. Future research taking these factors into account and with larger samples and more general populations is needed.

Data availability statement

The raw data supporting the conclusions of this article will not be made publicly available because the ethical approval obtained for this study prevents the human data being shared publicly to protect patients' privacy. Requests to access the datasets should be directed to GW, wangguang@bjcyh.com.

Ethics statement

The studies involving humans were approved by Ethical Review Board of Beijing Chao-Yang Hospital, Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YW: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. XL: Conceptualization, Methodology, Writing – original draft. RC: Writing – original draft. JL: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. GW: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1366830/full#supplementary-material.

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