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Original Article

Associations between thyroid axis changes and glycemic improvement after weight loss in type 2 diabetes: a mediation analysis

Peng Li[1], Jingjing Zhang[1], Mei Li[2]

[1]Department of Geriatrics, The First People's Hospital of Xianyang, No. 10, Biyuan West Road, Qindu District, Xianyang 712000, Shaanxi, China; [2]Department of Endocrinology, Baoji People's Hospital, No. 24, Xinhua Lane, Jing'er Road, Weibin District, Baoji 721000, Shaanxi, China

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Abstract: Objective: To explore whether the favorable association between weight loss and glycemic improvement in patients with obesity and type 2 diabetes mellitus (T2DM) is partially mediated by weight loss-induced changes in the hypothalamic-pituitary-thyroid (HPT) axis, including alterations in thyroid-stimulating hormone (ΔTSH), free triiodothyronine (ΔFT3), and free thyroxine (ΔFT4). Methods: A total of 364 patients with obesity and T2DM who underwent bariatric surgery, glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy, or standardized lifestyle intervention were enrolled in this retrospective real-world cohort study. Anthropometric, glycemic, and thyroid function indicators were measured at baseline and after a median follow-up of approximately 12 months. Results: Weight loss interventions led to significant reductions in body weight, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and homeostatic model assessment for insulin resistance (HOMA-IR), as well as a significant increase in homeostatic model assessment for β-cell function (HOMA-β) (all $P < 0.001$). Serum TSH and FT3 levels decreased markedly after intervention (both $P < 0.001$), whereas FT4 levels remained stable ($P = 0.542$). Changes in TSH and FT3 were significantly correlated with changes in HbA1c (ΔTSH: $r = 0.319$, $P < 0.001$; ΔFT3: $r = 0.135$, $P = 0.010$). The HPT axis exerted a significant total indirect mediating effect of 10.7% on the association between weight loss and HbA1c improvement ($P = 0.032$), with ΔTSH contributing 5.5% and ΔFT3 contributing 5.2% of the total effect. Subgroup analysis showed that the indirect mediating effect was more prominent in patients with higher baseline TSH levels. Conclusion: Changes in thyroid axis markers, specifically reductions in TSH and FT3, significantly and indirectly mediate the improvement in glycemic control following weight loss interventions in T2DM patients. Although this mediating effect is modest in overall magnitude, it is augmented in individuals with elevated baseline TSH levels. These findings suggest a novel auxiliary mechanism underlying the metabolic benefits of weight loss mediated by HPT axis remodeling.

Keywords: Weight-loss treatment, type 2 diabetes mellitus, thyroid axis, thyroid-stimulating hormone, free triiodothyronine, glycated hemoglobin, mediation effect, structural equation modeling, real-world study

Introduction

Globally, the disease burden of chronic metabolic disorders attributable to obesity and type 2 diabetes mellitus (T2DM) has reached an unprecedented level. Latest epidemiological data demonstrate that the prevalence of adult obesity has increased continuously over the past three decades, serving as a pivotal risk factor for cardiovascular diseases, T2DM, and multiple metabolic complications [1]. In China, rapid urbanization, unhealthy lifestyle transitions, and population aging have further driven the rising prevalence of obesity and T2DM [2]. The therapeutic paradigm for obesity complicated with T2DM has undergone a fundamental shift. Traditional passive weight management has been replaced by proactive weight-loss interventions that substantially improve glycemic profiles, lipid metabolism, and pancreatic islet function. Current mainstream weight-loss strategies include bariatric metabolic surgery, glucagon-like peptide-1 receptor agonist (GLP-1RA) pharmacotherapy, and standardized life-

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style intervention consisting of regular physical activity and healthy dietary regulation [3-5]. Accumulating clinical evidence based on large patient cohorts has confirmed that these interventions not only reduce body weight effectively but also lower HbA1c levels, enhance insulin sensitivity, and mitigate cardiovascular disease risks [6, 7].

The interaction between obesity and the thyroid axis is intricate and bidirectional. Clinically, obese individuals without overt thyroid dysfunction typically present with mildly elevated TSH and relatively high FT3 levels, while FT4 concentrations remain within the normal reference range. This characteristic thyroid phenotype is recognized as an adaptive feedback response to excessive energy accumulation in the body [8]. Large-scale cohort studies have validated this phenomenon: weight gain is strongly correlated with elevated circulating TSH and FT3 levels and a slight reduction in FT4 levels. This correlation indicates that adipose tissue accumulation can modulate the activity of the hypothalamic-pituitary-thyroid (HPT) axis; conversely, thyroid axis alterations may regulate systemic energy metabolism via hypothalamic leptin signaling and other feedback pathways [9]. Moreover, chronic immune-inflammatory activation induced by obesity, visceral fat deposition, and altered iodothyronine deiodinase activity can trigger additional endocrine adaptive changes [10]. However, it remains unclear whether these obesity-related thyroid functional alterations act as mediators of metabolic improvements after weight loss. To date, no systematic path analysis has been conducted to clarify this scientific question.

Mechanistically, thyroid hormones are critical regulators of glucose metabolism, lipid metabolism, and pancreatic islet function. They modulate hepatic gluconeogenesis, peripheral muscular glucose uptake, and adipose tissue glucose oxidation, thereby participating in multiple core metabolic pathways [8]. Even in individuals with clinically normal thyroid function, subtle fluctuations in TSH and FT3 levels in the context of obesity or T2DM are closely associated with insulin resistance, dyslipidemia, and increased risk of metabolic syndrome [11]. Existing studies have indicated that thyroid axis dysregulation is not merely a passive consequence of abnormal body weight status but actively participates in the regulatory network of glucose metabolism and insulin action. In this context, exploring whether the normalization of thyroid markers after weight loss is biologically linked to improved glycemic control is of great clinical significance.

Although previous studies have observed postoperative thyroid function changes following bariatric surgery, most findings are derived from short-term observational studies and fail to elaborate the systematic mechanistic role of thyroid axis indicators in metabolic improvement [12]. Recent systematic reviews and meta-analyses have confirmed that bariatric surgery induces significant reductions in TSH, T3, and FT3 levels with no remarkable change in FT4 levels, suggesting that weight loss can reshape thyroid hormone feedback regulation [13]. In addition, existing studies report inconsistent correlations between postoperative ΔTSH and changes in body fat or metabolic markers, implying that the HPT axis response to weight loss is modulated by patients' baseline characteristics and intervention modalities [14]. As a first-line pharmacological weight-loss treatment, GLP-1RAs have well-documented weight-reducing and hypoglycemic benefits, while their effects on thyroid function remain controversial, representing an unresolved research gap in this field [15].

Multiple critical gaps exist in current research. First, most studies only describe phenotypic changes in thyroid function after weight loss, without establishing a structural equation model (SEM) incorporating ΔTSH, ΔFT3, and ΔFT4 as parallel mediators to quantify their independent contributions to the "weight loss - HbA1c improvement" pathway. Second, large real-world cohort studies are lacking to systematically compare the differential thyroid axis responses and corresponding metabolic regulatory effects among patients with different baseline TSH levels. Third, most previous studies have limited sample sizes and only focused on a single weight-loss intervention, which cannot reflect the real-world scenario where multiple intervention strategies are commonly applied. Finally, few studies have adopted mediation analysis or equivalent statistical methods to integrate thyroid axis indicators into a multivariable mediating framework for mechanistic exploration.

Accordingly, this retrospective real-world cohort study enrolled patients receiving three mainstream weight-loss interventions (bariatric metabolic surgery, GLP-1RA therapy, and standardized lifestyle intervention) to address the following research objectives: to analyze the pre- and post-intervention differences in metabolic and thyroid function indicators across different baseline TSH strata; to clarify the independent contribution of thyroid axis changes to HbA1c improvement via hierarchical multiple regression analysis; to construct a parallel mediation SEM to quantify the mediating effects of ΔTSH, ΔFT3, and ΔFT4 on the association between weight loss and HbA1c reduction; and to verify the modifying effect of baseline TSH levels on the above mediating pathways through multigroup and subgroup analyses. We hypothesized that weight loss-induced reductions in thyroid axis indicators (predominantly decreased TSH) partially mediate the improvement in glycemic control, and this mediating effect is more pronounced in T2DM patients with higher baseline TSH levels.

Materials and methods

Sample size calculation

The sample size of this study was determined based on the prevalence of elevated TSH/subclinical hypothyroidism in obese populations and the statistical power requirements for mediation effect testing. Previous systematic reviews and meta-analyses reported that the pooled prevalence of subclinical hypothyroidism in obese populations was 14.6% (95% CI: 9.2-20.9%) [16]. Large obesity cohort studies further demonstrated that approximately 25% of obese individuals present with mild to moderate TSH elevation (< 10 mIU/L) [9]. Therefore, a conservative expected prevalence (P = 0.25) of TSH elevation in obese T2DM patients was adopted for sample size estimation.

Based on the cross-sectional proportion formula: $N = Z^2 \times [P(1-P)]/E^2$, where Z = 1.96 (two-sided $\alpha = 0.05$), P = 0.25, and E = 0.05 (allowable error), the minimum required sample size was calculated as 289 cases. In addition, according to the sample size simulation criteria for mediation effects proposed by Fritz and MacKinnon, a sample of 462 (bias-corrected bootstrap) or 558 (percentile bootstrap) cases is required to achieve 80% statistical power for detecting small mediating effects (path coefficients = 0.14). For small-to-medium effect sizes (0.26), the required sample size ranges from 368 to 412 cases [17]. The final sample of 364 patients in this study met the minimum sample size requirement for proportion estimation and was close to the standard for detecting small-to-medium mediation effects.

General information

This study was designed as a retrospective real-world cohort study based on electronic health record (EHR) data. Clinical data of patients with T2DM who received standardized weight-loss treatment from February 2019 to March 2023 were extracted from the EHR database of the First People's Hospital of Xianyang. A total of 364 eligible patients were included, with a median follow-up duration of 12 months (interquartile range [IQR]: 9-15 months). The study protocol was approved by the Medical Ethics Committee of The First People's Hospital of Xianyang. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Inclusion criteria: (1) age ranging from 18 to 70 years; (2) newly diagnosed or previously confirmed T2DM in accordance with World Health Organization diagnostic criteria; (3) body mass index (BMI) ≥ 28 kg/m^2, or BMI ≥ 27.5 kg/m^2 combined with at least one metabolic comorbidity; (4) receipt of one of the three standardized weight-loss interventions: bariatric metabolic surgery, GLP-1RA pharmacotherapy, or structured lifestyle intervention; (5) complete baseline and follow-up laboratory data of thyroid function and glycemic indicators.

Exclusion criteria: (1) prior history of thyroid diseases (hyperthyroidism, clinical hypothyroidism, Hashimoto's thyroiditis, thyroid cancer) or ongoing treatment with thyroid hormone replacement or antithyroid drugs; (2) baseline TSH > 10 mU/L or FT4 levels outside the normal reference range (to exclude clinically significant thyroid dysfunction); (3) pregnancy or lactation status; (4) severe hepatic or renal impairment (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] > 3 times the upper limit of normal, or estimated glomerular filtration rate < 30 mL/min/1.73 m^2); (5) long-term use of drugs affecting thyroid function (amiodarone, lithium, glucocorticoids); (6)

active malignant tumors or severe psychiatric disorders; (7) incomplete clinical data affecting statistical analysis.

Clinical data

Collected clinical data included the following categories: (1) Baseline demographic characteristics: age, sex, smoking history, hypertension history, and diabetes duration. (2) Weight-loss intervention modalities: bariatric metabolic surgery (sleeve gastrectomy, gastric bypass), GLP-1RA pharmacotherapy, and structured lifestyle intervention. (3) Hypoglycemic medication usage: metformin, sulfonylureas, sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP-4i), alpha-glucosidase inhibitors, and insulin. (4) Anthropometric indicators: pre- and post-intervention body weight (kg), BMI (kg/m^2), and waist circumference (cm). The percentage of weight loss was calculated as [(baseline weight - follow-up weight)/baseline weight] × 100%. (5) Glycemic metabolic indicators: HbA1c, FPG, fasting insulin (FINS), and fasting C-peptide. HOMA-IR was calculated as FPG (mmol/L) × FINS (μU/mL)/22.5; HOMA-β was calculated as 20 × FINS (μU/mL)/[FPG (mmol/L) - 3.5]. (6) Thyroid function indicators: TSH (mU/L), FT3 (pmol/L), FT4 (pmol/L), and the calculated FT3/FT4 ratio. (7) Lipid indicators: total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). (8) Hepatic function indicators: alanine aminotransferase (ALT) (U/L) and aspartate aminotransferase (AST) (U/L).

All enrolled patients were stratified into two subgroups based on a baseline TSH cutoff value of 3.5 mU/L: the low TSH group (TSH < 3.5 mU/L, n = 220) and the high TSH group (TSH ≥ 3.5 mU/L, n = 144). This cutoff was selected based on previous studies confirming the correlation between upper-normal TSH levels and elevated metabolic risk in obese populations [18, 19], while ensuring balanced sample sizes between the two groups.

Laboratory methods

All venous blood samples were collected after an overnight fast (≥ 8 hours) in the morning for uniform laboratory detection. HbA1c was measured via high-performance liquid chromatography (HPLC) using a Bio-Rad D-10 hemoglobin analyzer and supporting reagent kits (Bio-Rad Laboratories Inc., USA). FPG, TC, TG, LDL-C, HDL-C, ALT, and AST were detected using a fully automatic biochemical analyzer (Hitachi/Roche cobas c702, Japan) with standardized enzymatic assay kits (Roche Diagnostics GmbH, Switzerland). Specifically, FPG was tested via the hexokinase method, TC via the cholesterol oxidase method, TG via the glycerol phosphate oxidase method, LDL-C and HDL-C via direct homogeneous enzymatic assays, and ALT/AST via the IFCC-recommended rate method. FINS and fasting C-peptide were measured by electrochemiluminescence immunoassay (ECLIA) using a Roche cobas e801 automatic immunoassay analyzer and matching Elecsys reagent kits (Roche Diagnostics GmbH, Switzerland). Thyroid function indicators (TSH, FT3, FT4) were also detected via ECLIA on the same cobas e801 platform with dedicated reagent kits.

The laboratory's normal reference ranges were TSH 0.27-4.20 mU/L, FT3 3.10-6.80 pmol/L, and FT4 12.00-22.00 pmol/L. All detections were completed in a clinical laboratory certified by the National Center for Clinical Laboratories for external quality assessment, with strict implementation of internal quality control standards.

Anthropometric measurements were performed with standardized protocols. Body weight was measured by a calibrated electronic scale (accuracy: 0.1 kg) with patients in light clothing and barefoot; height was measured by a fixed stadiometer (accuracy: 0.1 cm) for BMI calculation; waist circumference was measured at the midpoint between the lower costal margin and iliac crest with an inelastic tape during gentle expiration (accuracy: 0.1 cm).

Outcome measures

Primary outcome: Changes in HbA1c levels before and after intervention (ΔHbA1c = post-intervention HbA1c - baseline HbA1c), reflecting the improvement of long-term glycemic control after weight-loss treatment.

Secondary outcomes: (1) Changes in FPG (ΔFPG); (2) Changes in insulin resistance (ΔHOMA-IR); (3) Changes in pancreatic beta-cell function (ΔHOMA-β); (4) Changes in thyroid function indicators (ΔTSH, ΔFT3, ΔFT4, and

ΔFT3/FT4 ratio); (5) Changes in anthropometric indices (body weight, BMI, waist circumference, and weight loss percentage); (6) Changes in lipid profiles (ΔTC, ΔTG, ΔLDL-C, ΔHDL-C) and hepatic function markers (ΔALT, ΔAST).

Statistical analysis

All statistical analyses were performed using R 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 27.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to verify the normality of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation, with independent-samples t-test for inter-group comparison and paired t-test for intra-group pre-post comparison. Non-normally distributed continuous variables were expressed as median (interquartile range) [M (Q1, Q3)], with Mann-Whitney U test for inter-group comparison and Wilcoxon signed-rank test for intra-group comparison. Categorical variables were described as case number (percentage) [n (%)] and compared via chi-squared test or Fisher's exact test as appropriate.

Spearman rank correlation analysis was used to assess the correlation between changes in metabolic and thyroid indicators. Hierarchical multiple linear regression was constructed to explore the independent determinants of ΔHbA1c. Model 1 only included weight loss percentage; Model 2 adjusted for age, sex, diabetes duration, baseline HbA1c, and baseline BMI on the basis of Model 1; Model 3 further incorporated ΔTSH; Model 4 finally added ΔFT3 and ΔFT4. The F-change test was used to compare the fitting efficiency of different models. Standardized regression coefficients (β) and 95% confidence intervals (CI) were reported. The variance inflation factor (VIF) was used to evaluate multicollinearity (VIF > 5 indicated potential collinearity, VIF > 10 indicated severe collinearity). Residual normality, autocorrelation, and heteroscedasticity were assessed via the Shapiro-Wilk test, Durbin-Watson test, and Breusch-Pagan test, respectively.

A parallel mediation SEM was established with weight loss percentage as the independent variable, ΔHbA1c/ΔFPG as the dependent variable, and ΔTSH, ΔFT3, ΔFT4 as parallel mediating variables. Non-parametric bootstrap analysis (5000 resamples) was performed to calculate indirect effects and total indirect effects with 95% CIs; a 95% CI excluding zero indicated a statistically significant mediating effect. The mediation proportion (PM) of each pathway was calculated. Model fitness was evaluated based on standard criteria: comparative fit index (CFI) ≥ 0.95, Tucker-Lewis index (TLI) ≥ 0.95, root mean square error of approximation (RMSEA) ≤ 0.05, and standardized root mean square residual (SRMR) ≤ 0.05. Multi-group analysis with delta-chi-squared test was conducted to compare pathway coefficient differences between baseline TSH subgroups. The Sobel test was used to verify the robustness of mediation effects.

Sensitivity analyses were performed to validate the stability of mediating effects, including exclusion of patients with baseline TSH > 4.5 mU/L, additional adjustment for intervention modalities and baseline lipid levels, and exclusion of patients with excessive weight loss (> 20%). Subgroup analyses were stratified by intervention modality, sex, age (< 60 vs ≥ 60 years), baseline BMI (< 28 vs ≥ 28 kg/m^2), baseline TSH (< 3.5 vs ≥ 3.5 mU/L), diabetes duration (< 10 vs ≥ 10 years), and baseline HbA1c (< 8% vs ≥ 8%). All subgroup regression models were adjusted for age, sex, diabetes duration, baseline HbA1c, and baseline BMI. Interaction terms were tested to identify effect modification. All statistical tests were two-tailed, and $P < 0.05$ was defined as statistically significant. Core R packages used for analysis included lavaan (SEM and mediation analysis), mediation (sensitivity analysis and Sobel test), car (regression diagnosis), and lmtest (heteroscedasticity test).

Results

Comparison of baseline characteristics

A total of 364 patients with T2DM receiving weight-loss interventions were enrolled in the present study and stratified into two subgroups according to baseline TSH levels: the high baseline TSH group (TSH ≥ 3.5 mU/L, n = 144) and the low baseline TSH group (TSH < 3.5 mU/L, n = 220). The two groups were comparable in terms of weight-loss intervention modalities, sex distribution, smoking history, hypertension prevalence, age, and hypoglycemic medication usage (all $P > 0.05$). Patients

Table 1. Comparison of baseline characteristics between TSH < 3.5 and TSH ≥ 3.5 groups

Variable	Total	TSH < 3.5 group (n = 220)	TSH ≥ 3.5 group (n = 144)	Statistic	*P* value
Weight-loss modality				0.230	0.892
Metabolic surgery	142 (39.01%)	88 (40.00%)	54 (37.50%)		
GLP-1RA	131 (35.99%)	78 (35.45%)	53 (36.81%)		
Lifestyle intervention	91 (25.00%)	54 (24.55%)	37 (25.69%)		
Sex				0.554	0.457
Male	168 (46.15%)	105 (47.73%)	63 (43.75%)		
Female	196 (53.85%)	115 (52.27%)	81 (56.25%)		
Smoking history				0.369	0.543
Yes	87 (23.90%)	55 (25.00%)	32 (22.22%)		
No	277 (76.10%)	165 (75.00%)	112 (77.78%)		
Hypertension				0.507	0.477
Yes	156 (42.86%)	91 (41.36%)	65 (45.14%)		
No	208 (57.14%)	129 (58.64%)	79 (54.86%)		
Metformin				0.277	0.599
Yes	298 (81.87%)	182 (82.73%)	116 (80.56%)		
No	66 (18.13%)	38 (17.27%)	28 (19.44%)		
Sulfonylureas				0.200	0.655
Yes	89 (24.45%)	52 (23.64%)	37 (25.69%)		
No	275 (75.55%)	168 (76.36%)	107 (74.31%)		
SGLT2i				0.297	0.586
Yes	76 (20.88%)	48 (21.82%)	28 (19.44%)		
No	288 (79.12%)	172 (78.18%)	116 (80.56%)		
DPP-4i				0.190	0.663
Yes	62 (17.03%)	39 (17.73%)	23 (15.97%)		
No	302 (82.97%)	181 (82.27%)	121 (84.03%)		
Alpha-glucosidase inhibitors				0.099	0.754
Yes	53 (14.56%)	31 (14.09%)	22 (15.28%)		
No	311 (85.44%)	189 (85.91%)	122 (84.72%)		
Insulin				0.696	0.404
Yes	95 (26.10%)	54 (24.55%)	41 (28.47%)		
No	269 (73.90%)	166 (75.45%)	103 (71.53%)		
Age (years)	51.61±10.87	51.60±10.78	51.63±11.04	0.031	0.975
Diabetes duration (years)	6.00 [4.00, 9.00]	6.00 [4.00, 8.00]	7.00 [4.00, 10.00]	2.281	0.023
BMI (kg/m^2)	32.26±4.85	31.66±4.62	33.17±5.04	2.944	0.003
Waist circumference (cm)	103.87±11.57	102.12±10.29	106.54±12.88	3.630	< 0.001

Note: TSH, thyroid-stimulating hormone; BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor.

with high baseline TSH exhibited a more severe baseline metabolic burden (**Table 1**).

Comparison of pre- and post-treatment changes in metabolic and thyroid function parameters

In the overall cohort, weight-loss interventions yielded significant reductions in body weight, BMI, and relative weight loss percentage (all P < 0.001). Glycemic indicators were markedly improved after treatment, with significant decreases in HbA1c FPG, fasting insulin, fasting C-peptide, and HOMA-IR, as well as a significant increase in HOMA-β (all P < 0.001). For thyroid function, serum TSH, FT3, and FT3/FT4 ratio were significantly reduced following intervention, whereas FT4 levels remained

Table 2. Comparison of clinical indicators before and after weight-loss treatment in all patients

Parameter	Pre-treatment	Post-treatment	Difference	Statistic	*P* value
Body weight (kg)	93.2±14.5	81.4±12.8	-11.8±10.1	Z = 14.562	< 0.001
BMI (kg/m^2)	32.3±4.8	28.3±5.1	-4±3.6	Z = 14.449	< 0.001
Percent weight loss (%)	-	-	-12.1±10.3	t = -22.409	< 0.001
HbA1c (%)	8.73±0.94	7.78±0.86	-0.95±1.27	t = 14.210	< 0.001
FPG (mmol/L)	9.19±2.25	7.55±1.86	-1.64±2.88	t = 10.866	< 0.001
Fasting insulin (microU/mL)	18.9±8.8	13.7±6.5	-5.3±10.6	t = 9.466	< 0.001
Fasting C-peptide (ng/mL)	3.22±1.12	2.64±0.94	-0.58±1.44	t = 7.671	< 0.001
HOMA-IR	7.62±3.77	4.5±2.69	-3.12±4.65	t = 12.781	< 0.001
HOMA-beta	45.3±21	52.4±23.8	+7.1±33	t = -4.135	< 0.001
TSH (mU/L)	3.82±1.8	2.86±1.18	-0.96±1.38	Z = 11.774	< 0.001
FT3 (pmol/L)	5.17±0.8	4.78±0.68	-0.39±1.02	t = 7.351	< 0.001
FT4 (pmol/L)	16.49±2.36	16.59±2.14	+0.1±3.02	t = -0.611	0.542
FT3/FT4 ratio	0.32±0.069	0.293±0.059	-0.027±0.09	Z = 5.787	< 0.001
TC (mmol/L)	5.16±1.08	4.77±0.99	-0.4±1.46	t = 5.164	< 0.001
TG (mmol/L)	2.3±1.26	1.58±0.89	-0.72±1.61	Z = 7.417	< 0.001
LDL-C (mmol/L)	3.24±0.9	2.89±0.82	-0.35±1.17	t = 5.697	< 0.001
HDL-C (mmol/L)	1.07±0.28	1.18±0.29	+0.11±0.39	t = -5.556	< 0.001
ALT (U/L)	37±17	26±12	-12±21	t = 10.648	< 0.001
AST (U/L)	29±11	24±9	-5±15	t = 6.886	< 0.001

Note: BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

unchanged. In addition, lipid and hepatic function parameters were substantially improved: TC, TG, LDL-C, ALT, and AST were significantly decreased, while HDL-C was significantly increased after weight-loss treatment (**Table 2**).

Comparison of pre- and post-treatment changes in anthropometric measurements

Both the high and low baseline TSH groups demonstrated significant reductions in body weight and BMI after weight-loss interventions. No significant intergroup differences were observed in absolute weight loss, BMI reduction, or relative weight loss percentage, indicating comparable weight-loss efficacy regardless of baseline TSH levels (all P > 0.05, **Figure 1**).

Comparison of pre- and post-treatment changes in glycemic parameters

All glycemic indicators were significantly improved in both groups after treatment, with significant reductions in HbA1c, FPG, fasting insulin, fasting C-peptide, and HOMA-IR, as well as increased HOMA-β. Subgroup comparison revealed that the reduction in HbA1c was significantly greater in the TSH ≥ 3.5 mU/L group than that in the TSH < 3.5 mU/L group. Although the FPG reduction followed a similar trend, the intergroup difference did not reach statistical significance (ΔP = 0.058). No significant intergroup differences were found in changes of fasting C-peptide, HOMA-IR, or HOMA-β (**Figure 2**, all P > 0.05).

Comparison of pre- and post-treatment changes in thyroid function parameters

Both groups exhibited significant postoperative reductions in TSH levels, with a substantially greater TSH decline observed in the TSH ≥ 3.5 mU/L group (ΔP < 0.001). Consistently, FT3 levels and the FT3/FT4 ratio were significantly decreased in both groups, while FT4 levels remained stable before and after treatment across all participants. No significant intergroup differences were detected in the changes of FT3, FT4, or FT3/FT4 ratio (all P > 0.05, **Figure 3**).

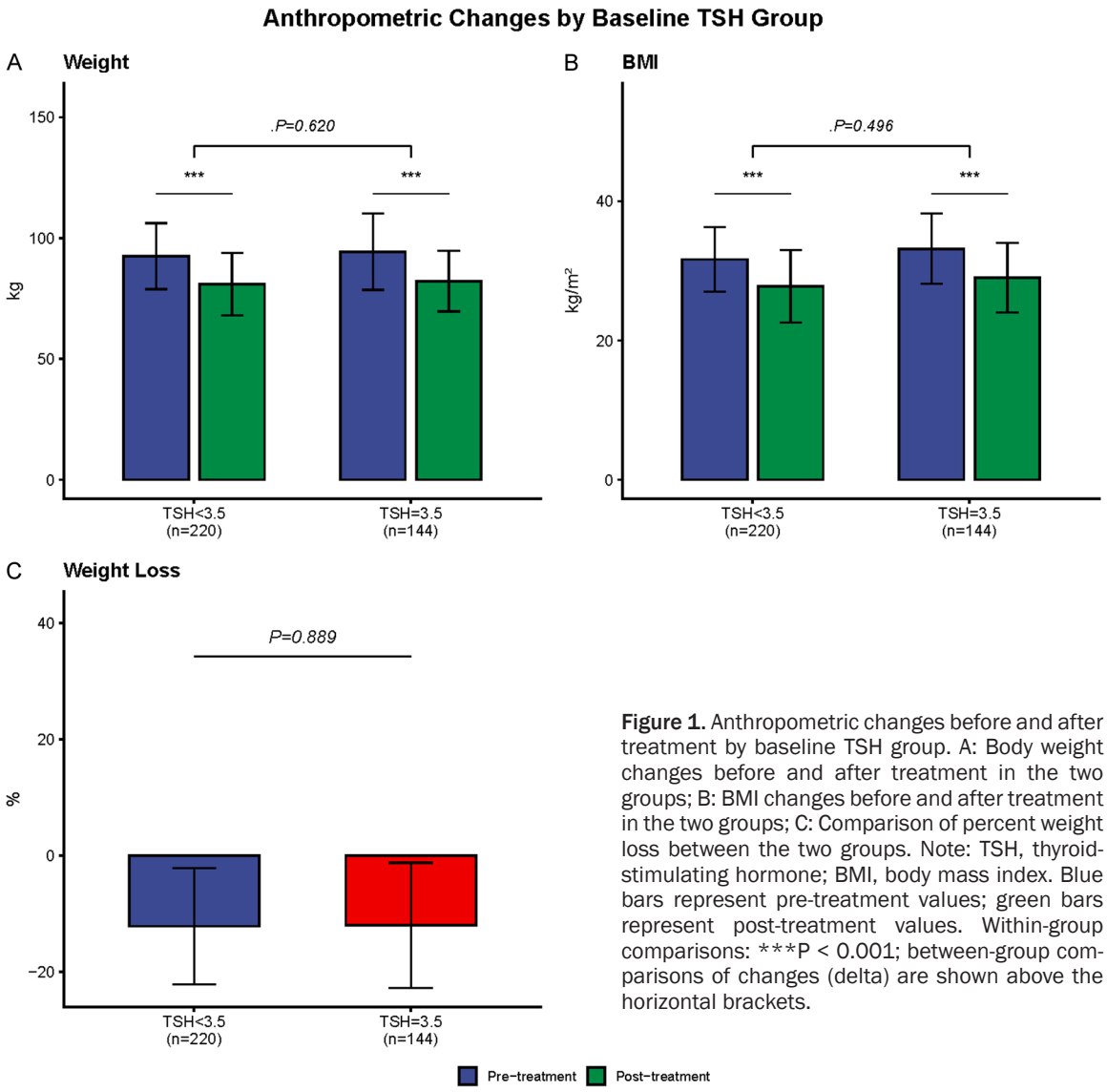

Figure 1. Anthropometric changes before and after treatment by baseline TSH group. A: Body weight changes before and after treatment in the two groups; B: BMI changes before and after treatment in the two groups; C: Comparison of percent weight loss between the two groups. Note: TSH, thyroid-stimulating hormone; BMI, body mass index. Blue bars represent pre-treatment values; green bars represent post-treatment values. Within-group comparisons: ***P < 0.001; between-group comparisons of changes (delta) are shown above the horizontal brackets.

Comparison of pre- and post-treatment changes in lipid and liver function parameters

Weight-loss interventions significantly improved lipid profiles and hepatic function in both groups. Specifically, the TSH ≥ 3.5 mU/L group showed a significantly greater reduction in LDL-C levels than the TSH < 3.5 mU/L group (ΔP = 0.022). No significant intergroup differences were observed in the changes of TC, TG, HDL-C, ALT, or AST levels (all P > 0.05, **Figure 4**).

Spearman correlation analysis among changed parameters

Spearman correlation analysis was performed to evaluate the correlations between treatment-induced changes in core metabolic and thyroid parameters. ΔTSH was positively correlated with ΔHbA1c (r = 0.319), ΔFPG (r = 0.190), ΔHOMA-IR (r = 0.203), and weight loss percentage (r = 0.216) (all P < 0.001). Since all delta values were calculated as post-treatment levels minus baseline levels, these positive correlations indicated that greater reductions in TSH were accompanied by more favorable improvements in glycemic control, insulin resistance, and body weight. Additionally, ΔFT3 was positively correlated with weight loss percentage (r = 0.208, P < 0.001) and ΔHbA1c (r = 0.135, P = 0.010), whereas ΔFT4 showed no significant correlation with any metabolic parameter. Among all glycemic indicators, ΔHbA1c

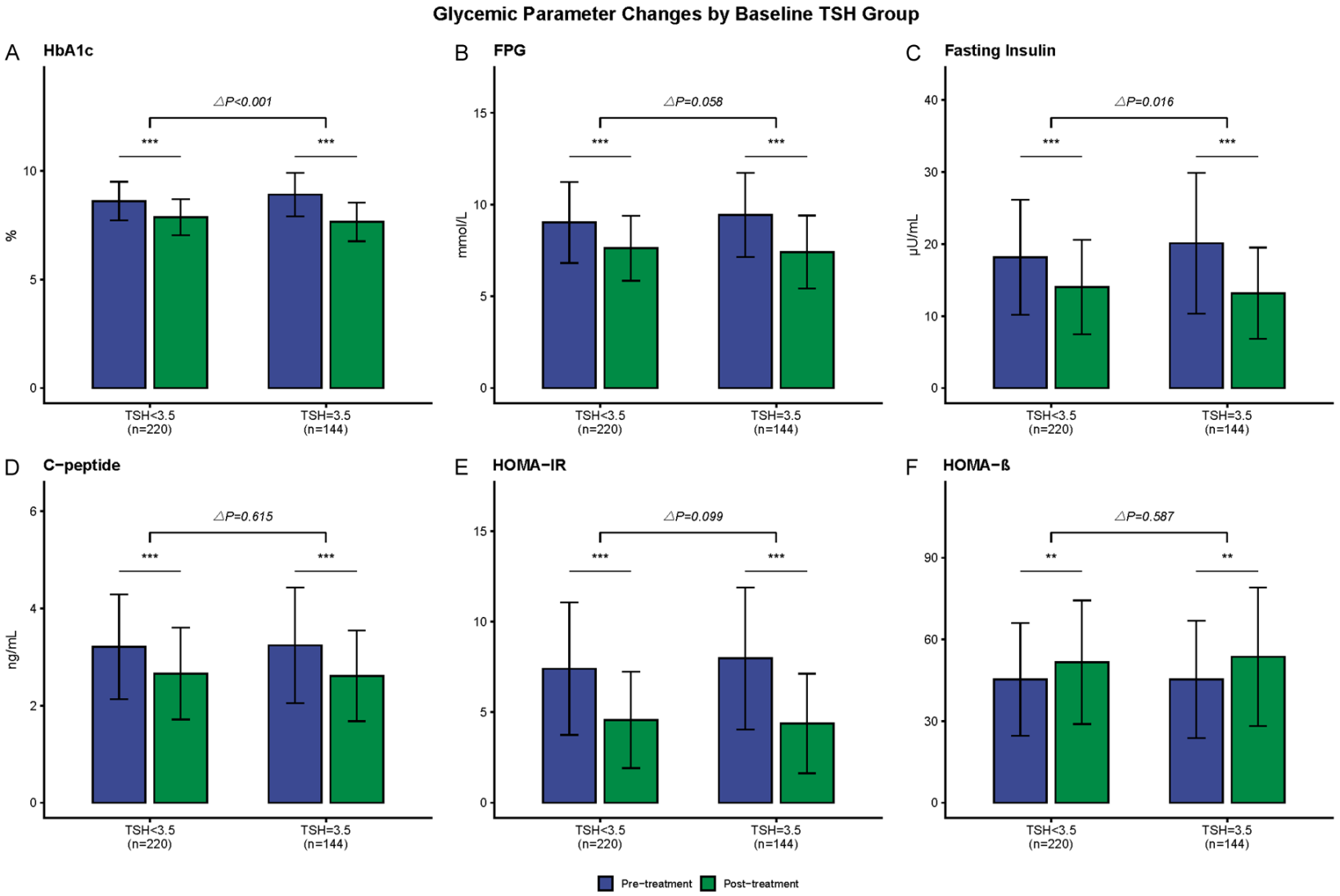

Figure 2. Glycemic parameter changes before and after treatment by baseline TSH group. A: HbA1c changes; B: FPG changes; C: Fasting insulin changes; D: C-peptide changes; E: HOMA-IR changes; F: HOMA-beta changes. Note: TSH, thyroid-stimulating hormone; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-beta, homeostasis model assessment of beta-cell function. Blue bars represent pre-treatment values; green bars represent post-treatment values. Within-group comparisons: **P < 0.01, ***P < 0.001; between-group comparisons of changes (delta) are shown above the horizontal brackets.

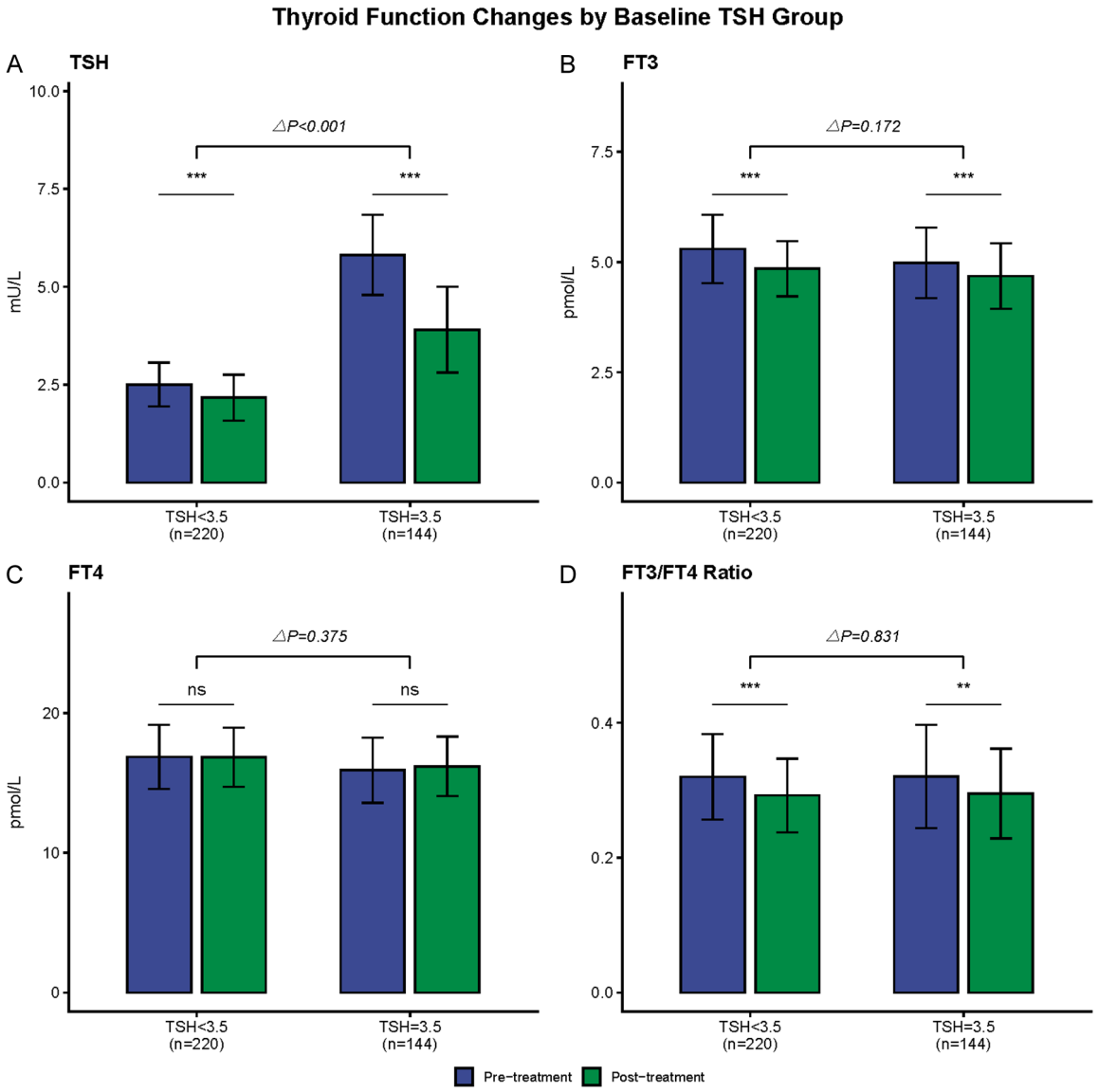

Figure 3. Thyroid function changes before and after treatment by baseline TSH group. A: TSH changes; B: FT3 changes; C: FT4 changes; D: FT3/FT4 ratio changes. Note: TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine. Blue bars represent pre-treatment values; green bars represent post-treatment values. Within-group comparisons: **P < 0.01, ***P < 0.001, ns: not significant; between-group comparisons of changes (delta) are shown above the horizontal brackets.

exhibited the strongest correlation with ΔFPG ($r = 0.565$, $P < 0.001$). Both ΔHbA1c and ΔHOMA-IR were significantly correlated with weight loss percentage. Other weak correlations are summarized in **Figure 5**.

Hierarchical multiple linear regression for factors associated with ΔHbA1c

Hierarchical multiple linear regression analysis was conducted to explore the independent contributions of thyroid axis changes to ΔHbA1c. In Model 1, weight loss percentage was significantly associated with ΔHbA1c, though the model demonstrated low explanatory power. After adjusting for age, sex, diabetes duration, baseline HbA1c, and baseline BMI in Model 2, weight loss percentage remained an independent predictor, with baseline HbA1c serving as the strongest predictive factor for ΔHbA1c. Model fitting was substantially improved after the inclusion of ΔTSH in Model 3, and ΔTSH was identified as an independent positive predictor of ΔHbA1c ($\beta = 0.113$, $P < 0.001$). The

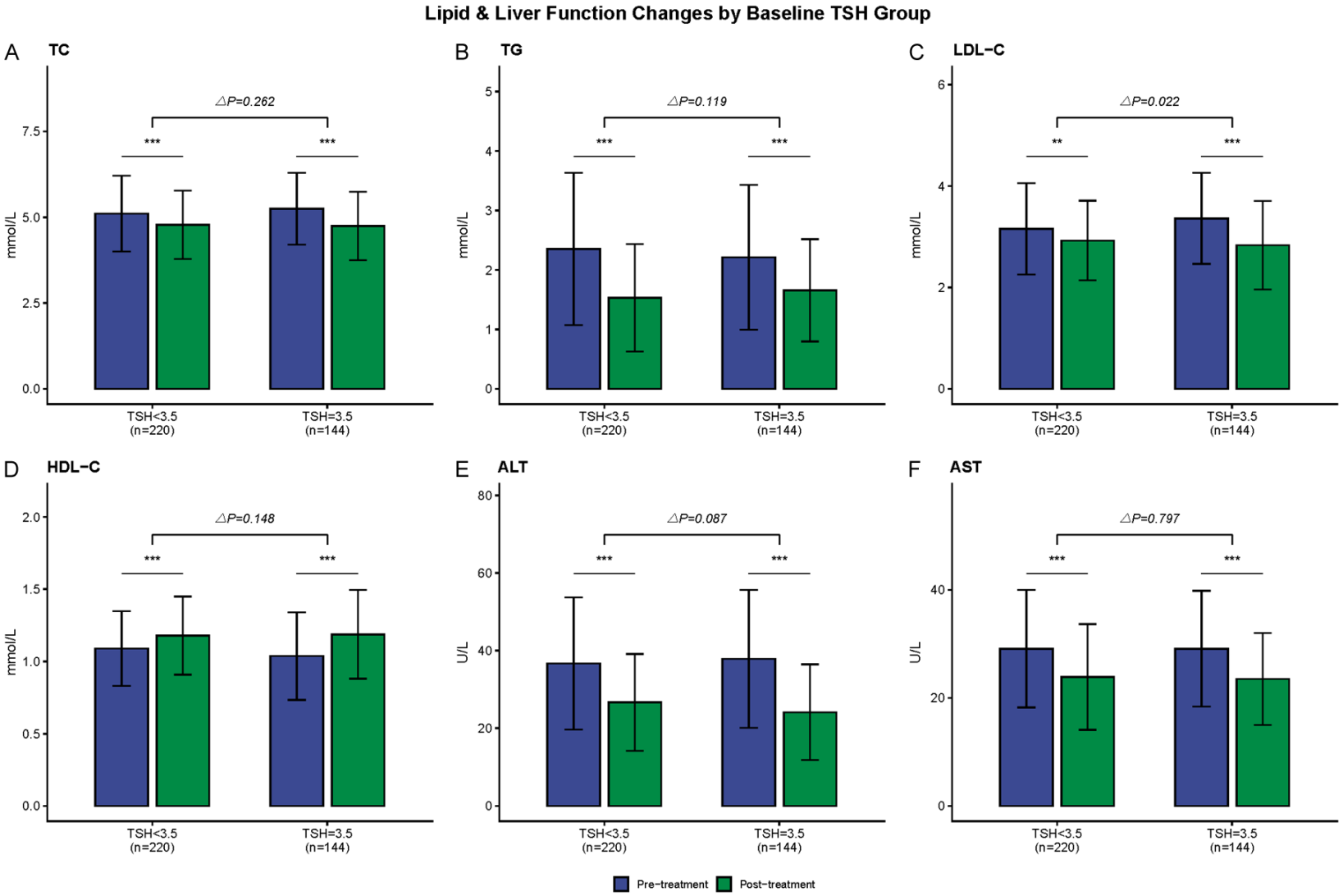

Figure 4. Lipid profile and liver function changes before and after treatment by baseline TSH group. A: TC changes; B: TG changes; C: LDL-C changes; D: HDL-C changes; E: ALT changes; F: AST changes. Note: TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase. Blue bars represent pre-treatment values; green bars represent post-treatment values. Within-group comparisons: **P < 0.01, ***P < 0.001; between-group comparisons of changes (delta) are shown above the horizontal brackets.

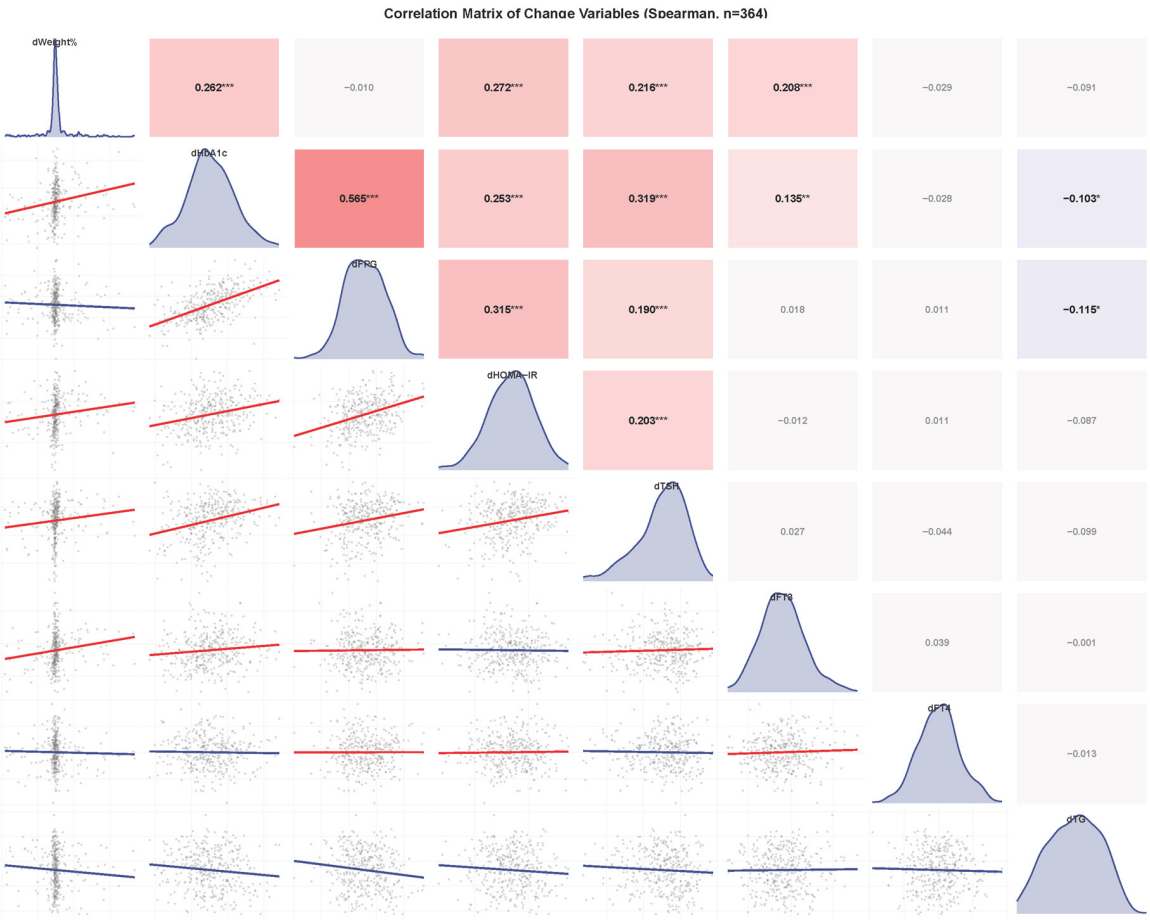

Figure 5. Spearman correlation scatter matrix of change variables. The upper triangle displays Spearman correlation coefficients with significance annotations, with background color intensity reflecting correlation strength (red for positive correlations, blue for negative correlations). The diagonal shows density distribution curves for each variable. The lower triangle shows scatter plots with fitted trend lines (red lines for positive correlations, blue lines for negative correlations). Note: dWeight%, percentage of weight change; dHbA1c, change in glycated hemoglobin; dFPG, change in fasting plasma glucose; dHOMA-IR, change in homeostasis model assessment of insulin resistance; dTSH, change in thyroid-stimulating hormone; dFT3, change in free triiodothyronine; dFT4, change in free thyroxine; dTG, change in triglycerides. *P < 0.05, **P < 0.01, ***P < 0.001.

standardized regression coefficient of weight loss percentage decreased from 0.201 to 0.189 after incorporating ΔTSH. In Model 4, ΔFT3 was also independently associated with ΔHbA1c (β = 0.069, P = 0.036), while ΔFT4 showed no significant association. The cumulative attenuation of the standardized coefficient for weight loss from Model 2 to Model 4 was 10.7%, indicating that changes in the thyroid axis (primarily ΔTSH and ΔFT3) partially explained the association between weight loss and glycemic improvement. Regression diagnostics confirmed that the final model was free of multicollinearity, residual non-normality, autocorrelation, and heteroscedasticity (**Figure 6**).

Parallel mediation analysis: thyroid axis as a mediator between weight loss and ΔHbA1c

A parallel mediation SEM was constructed with weight loss percentage as the independent variable, ΔHbA1c as the dependent variable, and ΔTSH, ΔFT3, and ΔFT4 as parallel mediating variables. The model achieved excellent fitting indices (CFI = 1.000, TLI = 1.048, RMSEA = 0.000, SRMR = 0.007). Weight loss percentage significantly predicted reductions in ΔTSH and ΔFT3 but had no significant effect on ΔFT4. Decreases in TSH and FT3 were significantly associated with reduced HbA1c levels. Weight loss retained a significant direct effect on ΔHbA1c after adjusting for thyroid mediators.

Figure. Hierarchical Regression Analysis for .HbA1c

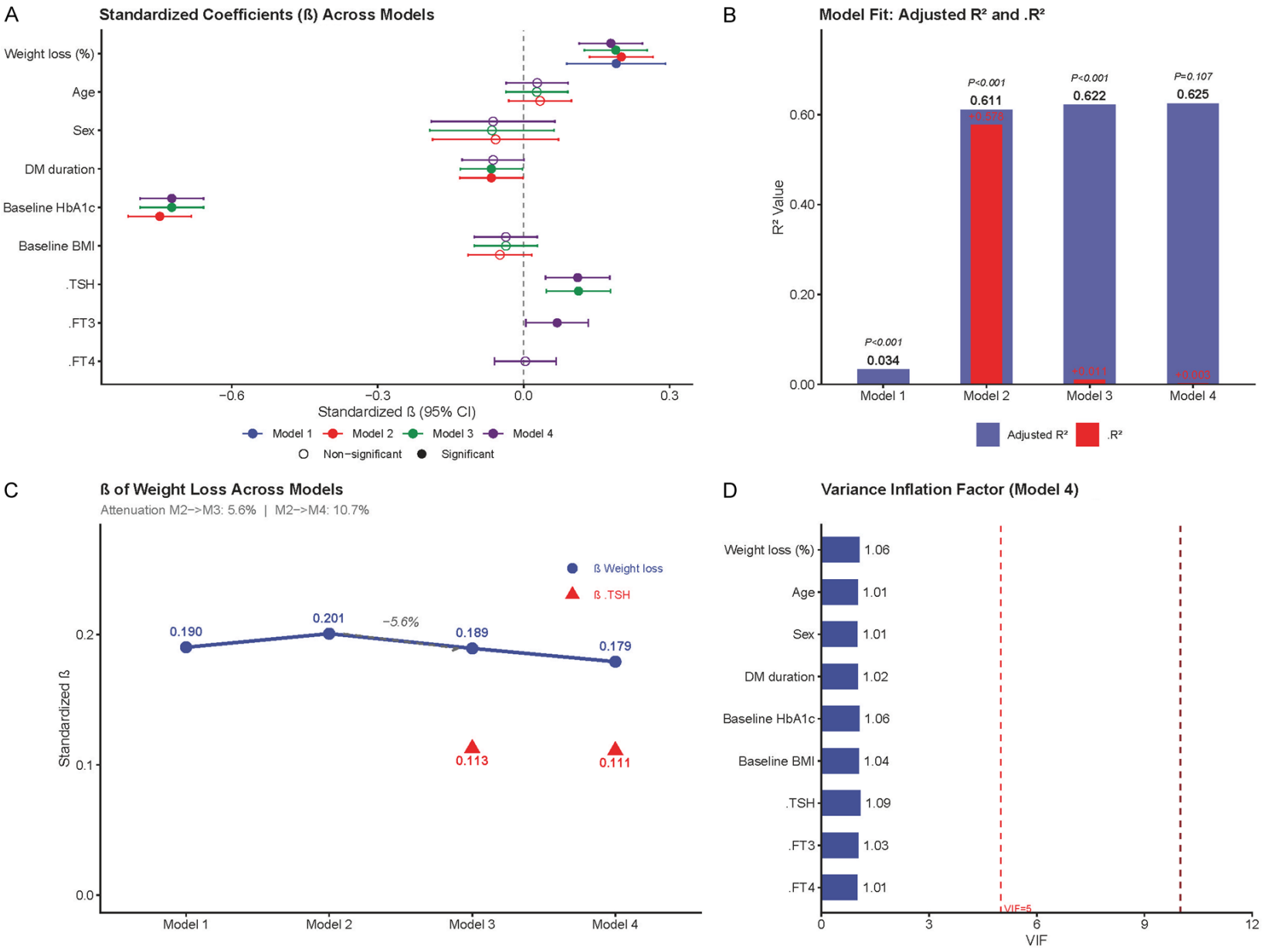

Figure 6. Visualization of hierarchical regression analysis for delta-HbA1c. (A) Forest plot showing the standardized regression coefficients (beta) with 95% confidence intervals for each independent variable across the four models; (B) Comparison of adjusted R-squared and delta-R-squared across models; (C) Trends in standardized coefficients for percent weight loss and delta-TSH across successive models; (D) Variance inflation factors (VIF) for all variables in the final model (Model 4). Note: delta-HbA1c, change in glycated hemoglobin; delta-TSH, change in thyroid-stimulating hormone; delta-FT3, change in free triiodothyronine; delta-FT4, change in free thyroxine; BMI, body mass index; DM, diabetes mellitus; VIF, variance inflation factor. The dashed arrow in (C) indicates attenuation of the weight loss beta coefficient after adjustment for thyroid axis changes.

Individual indirect effects of ΔTSH and ΔFT3 were marginally significant, while the total indirect mediating effect of the thyroid axis was statistically significant (P = 0.032), with a total mediated proportion of 10.7%. Specifically, ΔTSH contributed 5.5% and ΔFT3 contributed 5.2% to the total mediating effect, whereas ΔFT4 exerted a negligible effect. Multi-group analysis revealed no significant global intergroup difference in the overall mediation model. However, the mediating pathways were stronger in the TSH ≥ 3.5 mU/L group, particularly the pathways from weight loss to ΔTSH and from ΔFT3 to ΔHbA1c (all P > 0.05, **Figure 7**).

Parallel mediation analysis: thyroid axis as a mediator between weight loss and ΔFPG

The parallel mediation model for ΔFPG also exhibited good model fitness. Consistent with the ΔHbA1c model, the total and direct effects of weight loss percentage on ΔFPG were not statistically significant. The total indirect mediating effect and corresponding mediated proportion of the thyroid axis on ΔFPG were also non-significant. Multi-group analysis detected no global intergroup differences. In subgroup analysis, ΔTSH was significantly associated with ΔFPG in the TSH ≥ 3.5 mU/L group but not in the TSH < 3.5 mU/L group. These findings indicated that thyroid axis remodeling is more strongly linked to long-term glycemic improvement reflected by HbA1c than short-term fasting glucose changes (**Figure 8**).

Subgroup analysis of weight loss effects on ΔHbA1c

Stratified subgroup analyses were performed based on intervention modality, sex, age, baseline BMI, baseline TSH, diabetes duration, and baseline HbA1c, with adjustments for age, sex, diabetes duration, baseline HbA1c, and baseline BMI. The association between weight loss percentage and ΔHbA1c remained statistically significant across most subgroups. No significant modification was observed for sex, age, baseline BMI, diabetes duration, or baseline HbA1c. Notably, borderline interactive trends were detected for baseline TSH and intervention modality (both P for interaction = 0.054). The regression coefficient of weight loss percentage for ΔHbA1c was higher in the TSH ≥ 3.5 mU/L group than that in the TSH < 3.5 mU/L group, suggesting a potentially greater glycemic benefit of weight loss in patients with elevated baseline TSH. These subgroup findings are exploratory and require further validation, as the interaction effects did not reach the conventional statistical threshold (**Figure 9**).

Sensitivity analysis of mediation effects

Multiple sensitivity analyses were conducted to verify the robustness of the thyroid axis-mediated effects. The primary analysis showed that ΔTSH mediated 5.6% of the association between weight loss and ΔHbA1c (95% CI: 0.7-12.8%, P = 0.019). Further adjustments for intervention modalities and baseline lipid levels, as well as exclusion of patients with excessive weight loss (> 20%), did not alter the magnitude or significance of the ΔTSH mediating effect. However, the mediating proportion became non-significant after excluding patients with baseline TSH > 4.5 mU/L, which was consistent with the multi-group analysis results and confirmed that the overall thyroid mediating effect was primarily driven by patients with higher baseline TSH levels. Collectively, sensitivity analyses demonstrated stable and consistent mediating effects, with the ΔTSH-mediated proportion ranging from 5.1% to 7.4% across most baseline scenarios (**Table 3**).

Discussion

Based on real-world clinical data from 364 obese patients with T2DM receiving standardized weight-loss interventions, this study systematically explored the mediating role of thyroid axis remodeling in weight loss-induced

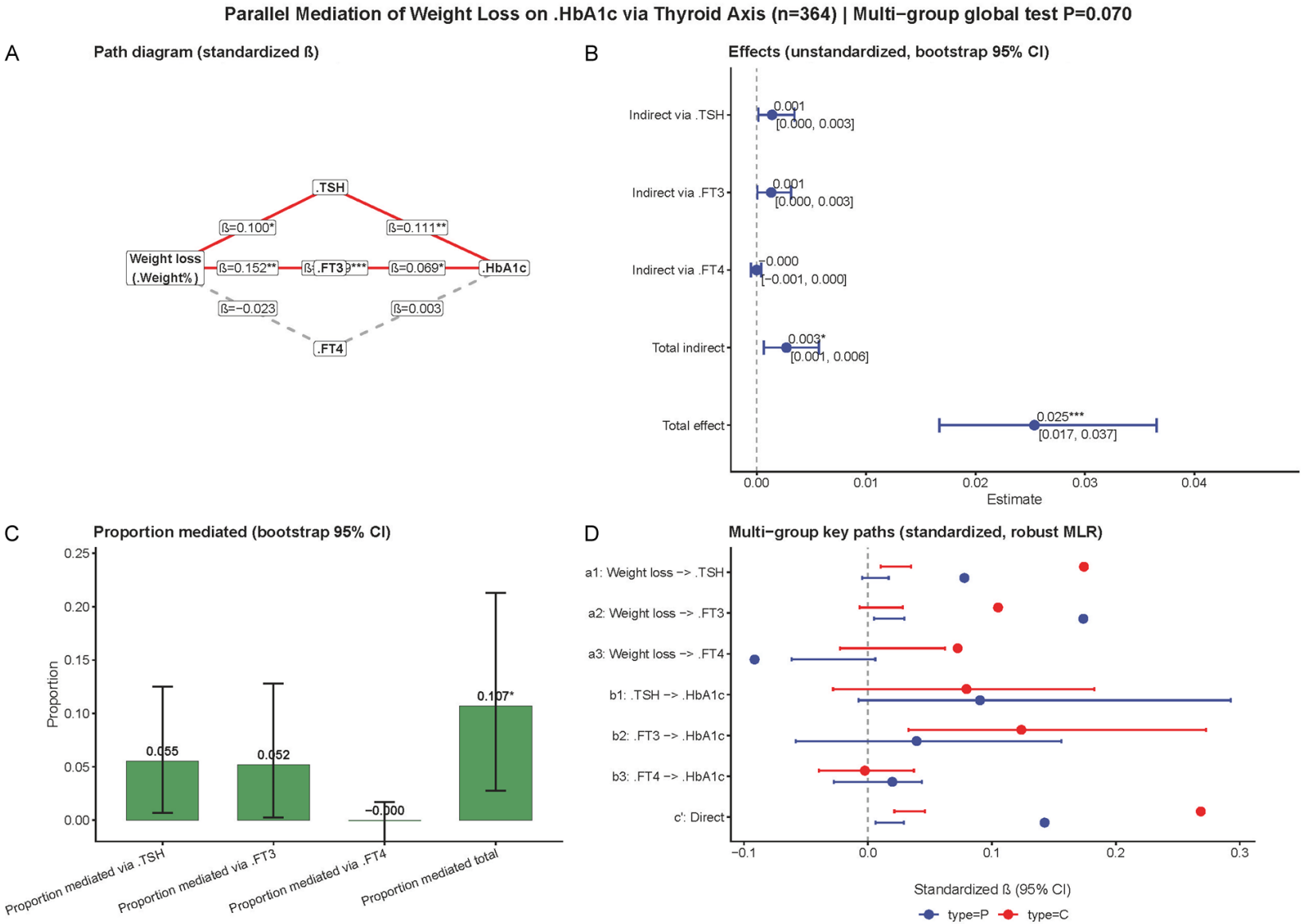

Figure 7. Parallel mediation of weight loss on delta-HbA1c via thyroid axis changes. (A) Standardized path coefficient diagram; (B) Forest plot of unstandardized estimates with bootstrap 95% confidence intervals for each direct effect, indirect effect, and total effect; (C) Bootstrap 95% confidence intervals for each mediation pathway and the total mediated proportion; (D) Comparison of standardized coefficients for key pathways across the two groups in multi-group analysis. Note:

delta-HbA1c, change in glycated hemoglobin; delta-TSH, change in thyroid-stimulating hormone; delta-FT3, change in free triiodothyronine; delta-FT4, change in free thyroxine. Bootstrap 95% confidence intervals based on 5000 resamples. In (D), type P: TSH < 3.5 group; type C: TSH ≥ 3.5 group. *P < 0.05, **P < 0.01, ***P < 0.001.

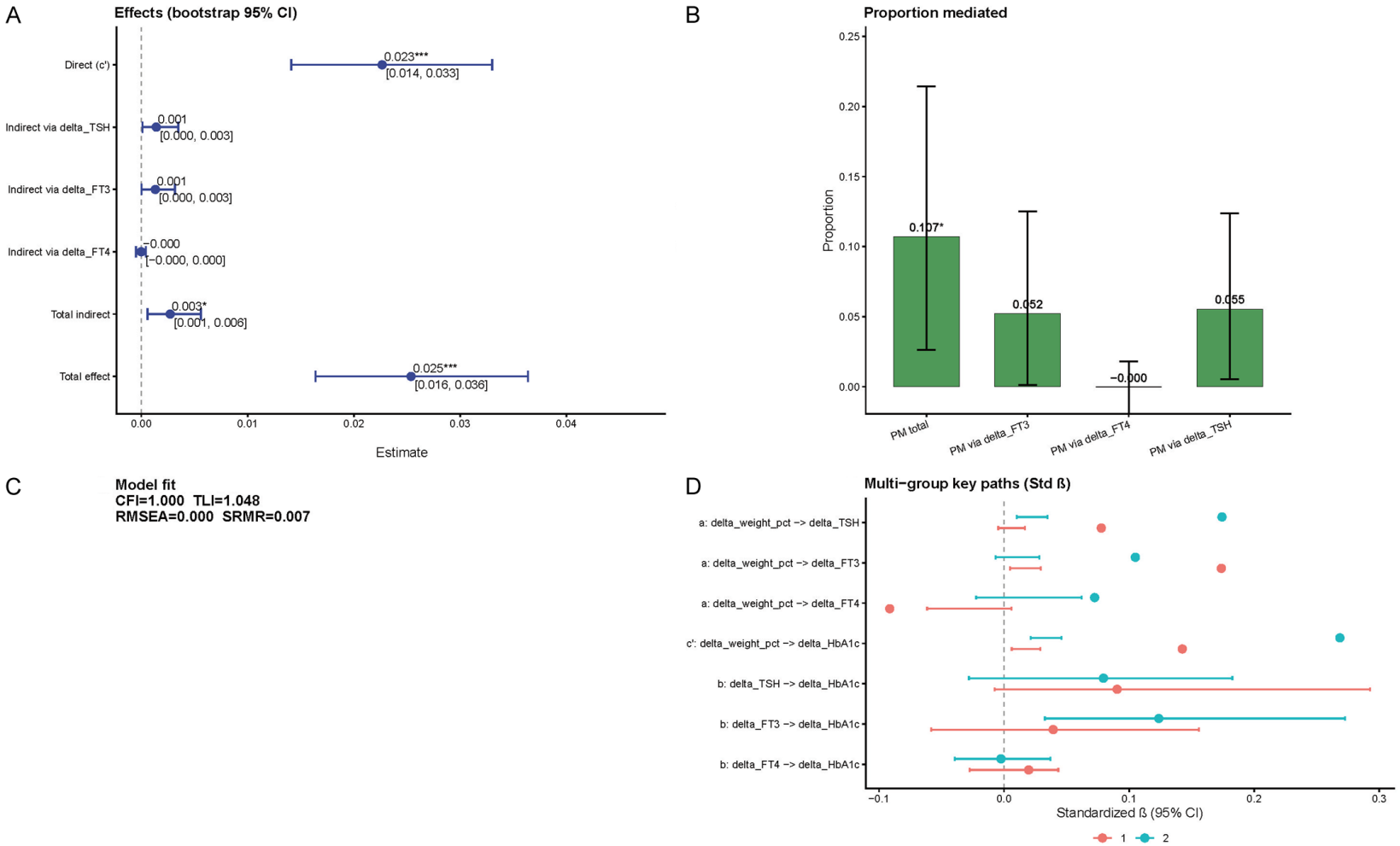

Figure 8. Parallel mediation of weight loss on delta-FPG via thyroid axis changes. (A) Forest plot of unstandardized estimates with bootstrap 95% confidence intervals for each direct effect, indirect effect, and total effect; (B) Bootstrap 95% confidence intervals for each mediation pathway and the total mediated proportion; (C) Model fit indices; (D) Comparison of standardized coefficients for key pathways across the two groups in multi-group analysis. Note: delta-FPG, change in fasting plasma glucose; delta-TSH, change in thyroid-stimulating hormone; delta-FT3, change in free triiodothyronine; delta-FT4, change in free thyroxine. Bootstrap 95% confidence intervals based on 5000 resamples. In (D), group 1: TSH < 3.5 group; group 2: TSH ≥ 3.5 group. *P < 0.05, ***P < 0.001.

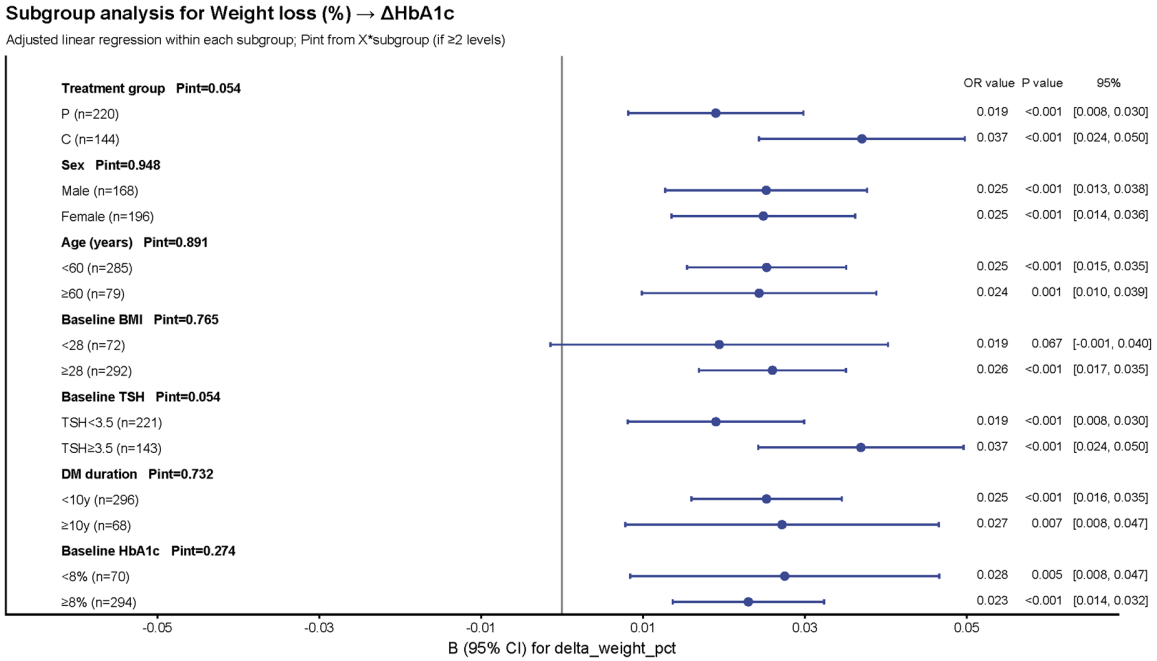

Figure 9. Forest plot of subgroup analysis for the association between weight loss percentage and delta-HbA1c. Note: delta-HbA1c, change in glycated hemoglobin; TSH, thyroid-stimulating hormone; BMI, body mass index; DM, diabetes mellitus. Each estimate represents the unstandardized regression coefficient (B) with 95% confidence interval, adjusted for age, sex, DM duration, baseline HbA1c, and baseline BMI. P_int: *P* value for interaction between weight loss percentage and the subgroup variable. *P < 0.05, **P < 0.01, ***P < 0.001.

metabolic improvement. The core findings are summarized as follows: weight-loss interventions significantly reduced body weight and improved glycemic control and thyroid function; patients with higher baseline TSH levels achieved greater HbA1c reduction after treatment; hierarchical regression analysis confirmed that both ΔTSH and ΔFT3 were independent protective predictors of ΔHbA1c; the inclusion of thyroid axis indicators reduced the standardized weight loss coefficient by 10.7%; parallel mediation SEM verified that thyroid axis changes (predominantly ΔTSH and ΔFT3) mediated 10.7% of the association between weight loss and HbA1c improvement, with a more pronounced mediating effect in patients with elevated baseline TSH. These results indicate that weight loss-induced thyroid axis remodeling partially contributes to glycemic amelioration, though this effect is modest in magnitude and serves as an auxiliary rather than a dominant metabolic regulatory pathway.

The significant reductions in TSH and FT3 with stable FT4 levels after weight loss reflect adaptive HPT axis regulation in obese individuals, which can be explained by multiple biological mechanisms. As summarized in a systematic review by Costa-E-Sousa and Brooks [20], the leptin-HPT axis pathway plays a core regulatory role. Obesity-induced hyperleptinemia enhances leptin signaling from the hypothalamic arcuate nucleus to the paraventricular nucleus, upregulating thyrotropin-releasing hormone (TRH) expression and subsequently increasing TSH secretion and HPT axis activity. Weight loss reduces circulating leptin levels and weakens central TRH stimulation, thereby lowering TSH levels and normalizing HPT axis function. A large cohort study of 5009 obese individuals by Mele et al. validated that leptin is an independent positive predictor of TSH after confounding adjustment, providing clinical evidence for this regulatory mechanism [9]. In addition, obesity upregulates adipose type 2 deiodinase activity, which promotes peripheral conversion of FT4 to FT3 and results in elevated circulating FT3 levels. Reduced adipose mass and decreased deiodinase activity following weight loss further drive FT3 reduction. Biondi [21] also demonstrated that altered adipose TSH receptor expression and modified deiodinase activity are key pathological bases of obesity-related adaptive thyroid changes.

Table 3. Sensitivity analyses for the mediation effect of ΔTSH

Strategy	N	Proportion mediated (%)	95% CI (%)	*P* value	Sobel Z	Sobel P	Note
Main analysis (full sample)	364	5.6%	0.7%-12.8%	0.019	-1.69	0.092	
Exclude baseline TSH > 4.5 mU/L	232	4.6%	-2.6%-17.8%	0.274	-1.10	0.270	
Exclude antidiabetic medication change during follow-up	364	5.6%	0.8%-12.7%	0.019	-1.69	0.092	Applied only if a medication-change indicator column exists (not found - > NOT applied)
Additionally adjust for weight-loss treatment modality	364	5.6%	0.7%-12.9%	0.015	-1.68	0.092	
Additionally adjust for baseline lipids	364	5.1%	0.3%-12.0%	0.032	-1.53	0.126	
Exclude extreme weight loss (> 20%)	334	7.4%	0.8%-19.9%	0.020	-1.63	0.103	
Include follow-up ≥ 12 months only	364	5.6%	0.7%-12.9%	0.020	-1.69	0.092	Applied only if follow-up duration column exists (not found - > NOT applied)

Note: ΔTSH, change in thyroid-stimulating hormone; ΔHbA1c, change in glycated hemoglobin; BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Mediation proportion and 95% confidence intervals estimated via nonparametric bootstrap with 5000 resamples. Sobel test provides a parametric check of the indirect effect. All models adjusted for age, sex, diabetes mellitus duration, baseline HbA1c, and baseline BMI unless otherwise specified.

The stable FT4 levels observed in this study are consistent with the adaptive regulation theory and existing literature, confirming that obesity-associated thyroid axis alterations mainly occur at the central TSH regulatory and peripheral T3 conversion levels, rather than affecting pituitary FT4 secretion.

Changes in TSH and FT3 were significantly correlated with glycemic improvement in this study, which may be explained by multiple metabolic pathways, although the two-timepoint study design precludes definitive causal inference. ΔTSH showed a weak-to-moderate positive correlation with ΔHbA1c. Given that all delta values were calculated as post-treatment minus baseline levels, this positive correlation indicates that greater TSH reduction corresponds to more substantial HbA1c improvement. Notably, ΔTSH remained an independent predictor of ΔHbA1c after adjusting for weight loss and other confounding factors ($\beta = 0.113$, $P < 0.001$). Mechanistically, Zhang et al. [22] clarified that elevated TSH exacerbates insulin resistance by promoting macrophage M1 polarization, increasing pro-inflammatory cytokine secretion, and activating the EGR1/LCN2/SOCS3 pathway, which enhances hepatic gluconeogenesis and impairs peripheral glucose uptake. This biological pathway explains the observed ΔTSH-ΔHbA1c association, while the weak effect size suggests that thyroid regulation is only one of multiple pathways mediating weight loss-related glycemic improvement. Epidemiological studies further support the link between thyroid hormone metabolism and glucose homeostasis. Jin et al. [23] found that elevated FT3 and FT3/FT4 ratios were positively associated with metabolic syndrome and dyslipidemia in euthyroid populations. The ELSA-Brasil prospective cohort study (8.2-year follow-up, n = 7948) reported that a higher FT3/FT4 ratio predicted increased diabetes risk, particularly in overweight and obese individuals [24]. These longitudinal findings confirm the close association between peripheral thyroid hormone conversion and systemic glucose metabolism. The weak correlation between ΔTSH and ΔHOMA-IR in our study further suggests that insulin sensitivity improvement is only a partial intermediate pathway linking thyroid remodeling and glycemic regulation. Bidirectional interactions between thyroid function and metabolic status cannot be excluded, and prospective longitudinal studies with dynamic multi-timepoint monitoring are required to clarify the temporal causal sequence.

The thyroid function change pattern identified in this study is highly consistent with published meta-analyses. Two large-scale meta-analyses including over 8000 bariatric surgery patients confirmed significant postoperative reductions in TSH and FT3 with unchanged FT4 levels [13, 25]. Existing studies also reported that 87% of patients with obesity-related subclinical hypothyroidism achieved postoperative remission, with baseline thyroid function explaining most inter-study heterogeneity [12], which supports the modulatory effect of baseline TSH observed in our research. Notably, most previous studies focused solely on bariatric surgery, while Nayak et al. [26] confirmed that both surgical and dietary weight-loss interventions reduce TSH and FT3 levels. Our study further expands this conclusion, demonstrating that thyroid axis remodeling and its glycemic regulatory effects are universal across multiple mainstream weight-loss modalities, rather than being merely a secondary effect of surgical gastrointestinal anatomical changes. Different weight-loss strategies possess distinct metabolic regulatory mechanisms; for example, GLP-1RAs improve glycemia independently via enhancing incretin secretion, delaying gastric emptying, and regulating central appetite. Future stratified analyses are warranted to explore potential differences in thyroid-mediated metabolic benefits across different intervention modalities. Methodologically, this study has several innovative strengths: it is the first study to incorporate ΔTSH, ΔFT3, and ΔFT4 as parallel mediators in a unified SEM model to quantify their independent contributions; it systematically quantifies both total and pathway-specific thyroid mediating proportions; and it adopts multi-group analysis to reveal baseline TSH-driven population heterogeneity in mediation effects.

Multi-group and subgroup analyses verified that baseline TSH levels modulate the magnitude of thyroid-mediated glycemic benefits. The weight loss-to-ΔTSH pathway was statistically significant in the TSH ≥ 3.5 mU/L group but not in the TSH < 3.5 mU/L group, indicating that patients with higher baseline TSH have greater potential for thyroid axis remodeling following weight loss. A large-scale meta-analysis by Roa

Duenas et al. [27] confirmed a positive dose-response relationship between TSH and BMI at the population level, which further supports our findings. Subgroup analysis showed that the predictive effect size of weight loss on ΔHbA1c was nearly twofold higher in the high baseline TSH group, with a borderline significant interaction. The 3.5 mU/L TSH cutoff adopted in this study is a validated upper-normal threshold for metabolic risk stratification in obese populations. However, the TSH-glycemic benefit relationship may be non-linear. Future studies should validate optimal TSH cutoffs and explore continuous TSH dose-response patterns. Baseline TSH has the potential to serve as a novel auxiliary biomarker for predicting weight-loss-induced glycemic improvement in obese T2DM patients, pending further prospective validation.

Comprehensive sensitivity analyses confirmed the robustness of our mediation model. The thyroid-mediated effect remained stable after adjusting for intervention types and baseline lipid levels and after excluding extreme weight-loss cases, with a consistent mediating proportion of 5.1-7.4%. The loss of statistical significance after excluding patients with baseline TSH > 4.5 mU/L further confirms that high baseline TSH is the key population characteristic driving the thyroid-mediated metabolic benefit. As highlighted in methodological guidelines for mediation analysis [28], unmeasured confounding is a major limitation of cross-sectional mediation models. Our multi-dimensional sensitivity analyses minimized potential bias from assumption violations. The 10.7% thyroid-mediated proportion observed in this study is comparable to previously reported anthropometric indicator-mediated effects in metabolic regulation [29], representing a reasonable and biologically meaningful effect size in the complex multi-pathway metabolic regulatory network. All bootstrap analyses were performed with 5000 resamples. Regression diagnostics confirmed no multicollinearity, normal residual distribution and homoscedasticity, ensuring reliable statistical inference.

These findings carry important clinical implications. Weight-loss interventions improve glycemic status not only via mechanical fat reduction but also through adaptive endocrine remodeling of the thyroid axis, which exerts a modest adjunctive metabolic benefit. Accumulating evidence has confirmed the close interplay between thyroid hormone sensitivity, adipose insulin resistance, and metabolically unhealthy obesity [11, 30]. Combined with our results, baseline thyroid function assessment can be integrated into pre-intervention evaluation systems to stratify patient responses to weight-loss treatment. Obese T2DM patients with upper-normal baseline TSH levels may achieve superior glycemic benefits from weight-loss interventions, supporting the feasibility of individualized precision weight management. It is critical to emphasize that the 10.7% mediating effect is modest; thyroid axis remodeling acts as a secondary regulatory pathway rather than the core driver of glycemic improvement. Its clinical translational value should be interpreted prudently in combination with other metabolic regulatory networks, including insulin signaling, gut hormone secretion, and inflammatory responses.

This study possesses multiple strengths. The real-world EHR-based cohort design with a moderate sample size of 364 patients ensures high external validity. The inclusion of three mainstream weight-loss modalities enhances the generalizability of findings. The analytical framework, including hierarchical regression, parallel mediation SEM, multi-group stratification, subgroup analysis, and systematic sensitivity testing, ensures rigorous and comprehensive statistical inference.

Several limitations of this study should be acknowledged. First, the retrospective two-timepoint design cannot establish the strict temporal and causal sequence of weight loss, thyroid axis changes, and glycemic improvement. All observed mediating effects represent statistical associations rather than definitive causal relationships. Second, the single-center data source may limit nationwide generalizability. Third, key upstream regulatory factors (e.g., leptin, TRH) and adipose deiodinase activity were not measured, restricting the exploration of underlying molecular mechanisms. Fourth, although the sample size met the basic requirements for detecting small-to-moderate mediation effects, it may still be underpowered for identifying subtle indirect pathways, and the modest effect size requires cautious interpretation. Future research should adopt multicenter,

prospective, multi-timepoint dynamic monitoring designs, incorporate multi-omics technologies, and detect key endocrine and enzymatic indicators to further validate and refine the findings of this study.

Conclusion

In conclusion, this real-world retrospective cohort study with mediation analysis preliminarily validates the "obesity-thyroid axis-glucose metabolism" regulatory hypothesis. Weight-loss treatment-induced reductions in TSH and FT3 partially and indirectly mediate glycemic improvement in obese T2DM patients. This thyroid-mediated metabolic benefit is more prominent in individuals with higher baseline TSH levels within the normal reference range. Baseline TSH has the potential to serve as a predictive biomarker for stratifying glycemic responses to weight-loss interventions. Nevertheless, prospective multi-timepoint studies are required to clarify the causal temporal sequence and further verify the clinical translational value of thyroid axis remodeling in metabolic regulation.

Disclosure of conflict of interest

None.

Address correspondence to: Mei Li, Department of Endocrinology, Baoji People's Hospital, No. 24, Xinhua Lane, Jing'er Road, Weibin District, Baoji 721000, Shaanxi, China. E-mail: Limei1979@126.com

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