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Original Article

Elevated thyroid-stimulating hormone correlates with insulin resistance and β-cell dysfunction in type 2 diabetes with subclinical hypothyroidism

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Abstract: Objective: To investigate the correlation between thyroid-stimulating hormone (TSH) levels and insulin function indices, including the homeostatic model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-ISLET), in patients with type 2 diabetes mellitus (T2DM) complicated by subclinical hypothyroidism (SCH), and to evaluate their diagnostic value for identifying elevated TSH states. Methods: A total of 384 T2DM patients treated between April 2022 and November 2024 were retrospectively analyzed. Among them, 184 patients with SCH comprised the combined group, and 200 patients with T2DM alone comprised the diabetes group. Demographic data, fasting plasma glucose (FPG), fasting insulin (FINS), and TSH were collected to calculate HOMA-IR and HOMA-ISLET. Inter-group comparisons, correlation analyses, and receiver operating characteristic (ROC) curve analyses were performed. Results: Compared to the diabetes group, the combined group showed significantly higher TSH, HOMA-IR, and HOMA-ISLET (all $P < 0.001$). TSH correlated positively with HOMA-IR and negatively with HOMA-ISLET (combined group: $r = 0.587$ and -0.464; diabetes group: $r = 0.334$ and -0.545; all $P < 0.001$). ROC analysis demonstrated favorable diagnostic performance for HOMA-IR (AUC = 0.720 for SCH; 0.892 for elevated TSH) and HOMA-ISLET (AUC = 0.711 for SCH; 0.878 for elevated TSH). HOMA-IR showed stronger discriminative ability than HOMA-ISLET in distinguishing diabetes-only from high TSH states (AUC = 0.928 vs. 0.709). Conclusions: Elevated TSH levels are closely associated with increased insulin resistance and impaired β-cell function in T2DM. Both HOMA-IR and HOMA-ISLET are valuable diagnostic tools, with HOMA-IR demonstrating superior clinical applicability for detecting T2DM with SCH and elevated TSH states.

Keywords: Type 2 diabetes mellitus, subclinical hypothyroidism, thyroid-stimulating hormone, homeostatic model assessment of insulin resistance, homeostatic model assessment of islet β-cell function

Introduction

Type 2 diabetes mellitus (T2DM) represents a metabolic disorder characterized by chronic hyperglycemia, with its global prevalence continuing to rise, establishing itself as a major public health concern threatening human health worldwide [1, 2]. The pathogenesis primarily involves two core pathologic processes, insulin resistance and β-cell dysfunction [3, 4]. In clinical practice, these two components can be quantitatively assessed through the homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of islet β-cell function (HOMA-ISLET), providing crucial evidence for diabetes diagnosis and treatment [5, 6].

Subclinical hypothyroidism (SCH) refers to a concealed state where serum thyroid-stimulating hormone (TSH) levels are elevated while free thyroxine (FT4) remains within normal ranges, and is commonly observed in middle-aged and elderly populations, particularly among female patients [7]. A systematic review indicated that SCH significantly exacerbates glucose and lipid metabolism abnormalities in PCOS patients, particularly HOMA-IR and dyslip-

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idemia [8], supporting that abnormal TSH levels exert widespread effects on metabolic homeostasis. Furthermore, epidemiologic data demonstrate [9] that the incidence of SCH among T2DM patients is higher than that of the general population, indicating potential shared pathophysiologic mechanisms.

On one hand, thyroid hormones indirectly influence insulin sensitivity through regulation of basal metabolic rate, hepatic glucose output, and lipid metabolism. On the other hand, TSH itself may exacerbate insulin resistance and β-cell stress through promotion of inflammatory responses and regulation of adipocyte factor release [10, 11]. Evidence from the literature [12] shows that SCH significantly affects insulin resistance across various metabolic diseases; for instance, in polycystic ovary syndrome patients, SCH markedly elevates both insulin resistance and insulin levels.

Although some studies have sought to explore the relationship between TSH levels and insulin metabolism, most focus on general populations or non-diabetic individuals. Systematic data on metabolic characteristics and correlation analysis for the specific population of T2DM patients with SCH is still scarce. Additionally, it remains unclear whether insulin function indicators possess diagnostic value in identifying abnormal TSH levels in T2DM patients, particularly in subclinical states. Therefore, comprehensive research is necessary to clarify the metabolic significance of TSH levels in T2DM patients and explore the feasibility of using these indicators as auxiliary diagnostic tools.

This study, based on large-sample retrospective data, systematically compared T2DM patients with subclinical hypothyroidism versus those with T2DM alone regarding insulin resistance, β-cell function, and TSH levels. We further explored correlations between TSH and insulin function indicators and employed receiver operating characteristic (ROC) curve methodology to evaluate the diagnostic efficacy of HOMA-IR and HOMA-ISLET in identifying elevated TSH states, particularly for distinguishing between high TSH and normal/low TSH conditions.

The study results not only enhance clinical awareness of thyroid dysfunction in T2DM patients and promote coordinated management of diabetes and thyroid disorders, but also provide clinicians with a feasible strategy for identifying thyroid dysfunction using simple, economical metabolic indicators (such as HOMA models), particularly suitable for primary care screening needs. More importantly, the research suggests that elevated TSH levels may not merely reflect endocrine abnormalities, but may serve as an early signal of glucose metabolism disorders, providing additional clinical application value in T2DM metabolic status assessment.

Materials and methods

Sample size calculation

HOMA-IR was selected as the primary outcome indicator for sample size calculation. In Yang's research [13], the HOMA-IR in T2DM patients with SCH was 3.96 (2.55, 6.28), while in those with T2DM alone was 3.93 (2.55, 6.05). Based on clinical significance, we hypothesized that a difference of 0.3 in HOMA-IR between groups would be clinically meaningful, with an estimated standard deviation of 2.5 based on literature data. Using a two-sided test with $\alpha = 0.05$ and power $1-\beta = 0.80$, the following formula was applied for sample size calculation: $n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{\delta^2}$. $Z_{\alpha/2} = 1.96$, $Z_{\beta} = 0.84$, $\sigma = 2.5$, $\delta = 0.3$. The calculation indicated that 180 samples per group were needed, with a total of 360 samples required.

Patient information

This retrospective study included 184 patients diagnosed with T2DM and concurrent SCH at Kangbashi Branch of Ordos City Central Hospital from April 2022 to November 2024 as the combined group. Additionally, 200 T2DM patients treated during the same period were selected as the diabetes group. This study was approved by the medical ethics committee of Kangbashi Branch of Ordos City Central Hospital.

Inclusion and exclusion criteria

General inclusion criteria (applied to all participants): Age ≥ 18 years, regardless of gender. Meeting the World Health Organization (WHO)

or American Diabetes Association (ADA) diagnostic criteria for T2DM. Complete clinical and laboratory data available. No treatment with insulin sensitizers, thyroid-related drugs, or medications that may interfere with insulin secretion/TSH levels during the study period.

Additional inclusion criteria for the combined group (T2DM + SCH): In addition to the general criteria, patients must also meet the diagnostic criteria for SCH: elevated serum TSH levels with normal free thyroxine (FT4) levels.

Additional inclusion criteria for the diabetes group: Patients meeting only the diagnostic criteria for T2DM and not fulfilling the diagnostic criteria for SCH (normal TSH and FT4 levels).

Exclusion criteria (applied to all participants): Other types of diabetes (e.g., type 1 diabetes, gestational diabetes, or specific types of secondary diabetes). Diagnosed hyperthyroidism or clinical hypothyroidism (abnormal FT4). Severe hepatic or renal dysfunction, acute or chronic infection, malignancy, or other severe systemic diseases. Current treatment with insulin, glucocorticoids, statins, or other medications that significantly interfere with insulin or thyroid function. Pregnancy.

Laboratory value testing

In this study, all subjects underwent fasting venous blood collection of 5-6 mL in the early morning, performed by professional medical personnel and immediately sent to the laboratory for testing. Fasting plasma glucose (FPG, mmol/L) was measured using an automated biochemical analyzer (Hitachi 7600, Hitachi High-Technologies, Tokyo, Japan). Fasting insulin (FINS, μIU/mL) was determined by chemiluminescence immunoassay (Cobas e601, Roche Diagnostics, Mannheim, Germany). Serum thyroid-stimulating hormone (TSH, μIU/mL) was measured by electrochemiluminescence immunoassay (Abbott Architect i2000SR, Abbott Laboratories, Chicago, IL, USA). Based on these results, HOMA-IR and HOMA-ISLET were calculated using the following formulas: HOMA-IR = [fasting glucose concentration (mmol/L) × fasting insulin concentration (mU/L)] ÷ 22.5 [16]. HOMA-ISLET = 20 × fasting insulin concentration (μIU/mL) ÷ [fasting glucose concentration (mmol/L) - 3.5] [17]. All sample testing was completed in the same laboratory using standardized equipment and trained personnel to ensure accuracy and consistency.

Clinical data collection

This study collected basic demographic information, medical history, and relevant laboratory indicators for all included subjects. All clinical data were organized in standardized format to ensure data completeness and comparability. All information was obtained through electronic medical records and outpatient follow-up records.

Outcome measurements

Primary outcome measurements: Analysis of correlations between TSH levels and HOMA-IR, HOMA-ISLET to evaluate the impact of TSH on insulin resistance and β-cell function; ROC curve analysis of HOMA-IR and HOMA-ISLET diagnostic efficacy to assess their clinical application value in identifying T2DM with subclinical hypothyroidism and elevated TSH states.

Secondary outcome measurements: Collection and statistical analysis of patients' basic clinical data; subgroup stratification of diabetic patients by TSH levels (low TSH, medium TSH, and high TSH groups) with comparison of metabolic parameter differences among subgroups; analysis of correlations between HOMA-IR, HOMA-ISLET, and TSH in different TSH level subgroups to clarify their trend changes under different functional states; further evaluation through ROC curves of HOMA-IR and HOMA-ISLET discriminative ability in distinguishing high TSH group from low TSH group, and between high TSH group and T2DM patients.

Statistical analysis

All statistical analyses in this study were completed using R software (version 4.3.3). Categorical variables were presented as frequencies and percentages, with inter-group comparisons using Pearson chi-square test, continuity correction chi-square test, or Fisher's exact test as appropriate. Continuous variables tested for normality via the Kolmogorov-Smirnov (K-S) testing. Those normal distribution data were presented as mean ± standard deviation ($\bar{x}$ ± sd) and inter-group comparisons were analyzed using independent samples t-test or one-way analysis of variance (ANOVA). Non-normally

distributed variables were presented as median and interquartile range [M (P25, P75)] and analyzed using rank-sum test (Mann-Whitney U test) or Kruskal-Wallis H test for multiple group comparisons. Variable correlations were assessed using Pearson correlation analysis. Diagnostic efficacy was evaluated using ROC curve analysis, with the area under the curve (AUC), cutoff values, sensitivity, specificity, and Youden index parameters reported. All tests were two-sided, and $P < 0.05$ was considered significant.

Results

Comparison of baseline characteristics

No significant differences were observed in terms of age ($P = 0.571$), gender ($P = 0.414$), BMI ($P = 0.253$), disease duration ($P = 0.608$), hypertension history ($P = 0.559$), coronary artery disease history ($P = 0.217$), hyperlipidemia history ($P = 0.169$), smoking history ($P = 0.678$), alcohol consumption history ($P = 0.326$), marital status ($P = 0.182$), or educational level ($P = 0.236$) (**Table 1**).

Comparison of insulin-related values

The combined group demonstrated significantly higher TSH, and HOMA-IR levels than the diabetes group (both $P < 0.001$). Additionally, the combined group showed significantly superior islet function compared to the diabetes group, with higher HOMA-ISLET levels ($P < 0.001$) (**Table 2**).

Correlation analysis results between insulin-related values and TSH

In the combined group, HOMA-IR was positively correlated with TSH ($r = 0.587$, $P < 0.001$; **Figure 1A**), while HOMA-ISLET was negatively correlated with TSH ($r = -0.464$, $P < 0.001$; **Figure 1B**). In the diabetes group, similar positive correlation between HOMA-IR and TSH ($r = 0.334$, $P < 0.001$; **Figure 1C**) and negative correlation between HOMA-ISLET and TSH ($r = -0.545$, $P < 0.001$; **Figure 1D**) were observed.

Diagnostic value of insulin-related values in combined patients

In combined patients, HOMA-IR achieved an ROC AUC of 0.720 (95% CI: 0.669-0.771; **Figure 2A**), with 64.13% sensitivity and 69.50% specificity. At a cutoff value of 3.73, the Youden index reached 33.63%, with overall accuracy of 66.93% and precision of 64.13%. HOMA-ISLET achieved an AUC of 0.711 (95% CI: 0.657-0.766; **Figure 2B**), with 50.54% sensitivity and 90.50% specificity. At a cutoff value of 54.435, the Youden index was 41.04%, with overall accuracy of 71.35%, precision of 50.54%, and F1 score of 62.84%. These results suggest that both HOMA-IR and HOMA-ISLET hold diagnostic value for distinguishing combined patients, with HOMA-IR demonstrating superior balance between sensitivity and specificity, while HOMA-ISLET is characterized by high specificity.

Comparison of baseline characteristics among TSH level subgroups

Comparison of baseline characteristics among different TSH level subgroups within the diabetes group (low, medium, high TSH groups) revealed no significant differences in age ($P = 0.561$), gender ($P = 0.303$), BMI ($P = 0.203$), disease duration ($P = 0.828$), hypertension history ($P = 0.888$), coronary artery disease history ($P = 0.533$), hyperlipidemia history ($P = 0.125$), smoking history ($P = 0.678$), alcohol consumption history ($P = 0.567$), marital status ($P = 0.320$), or educational level ($P = 0.178$) (**Table 3**).

Comparison of metabolic characteristics among TSH level subgroups

HOMA-IR levels differed significantly among TSH level subgroups ($P < 0.001$). Both medium and high TSH groups showed significantly higher HOMA-IR levels than the diabetes and low TSH groups ($P < 0.05$) with the high TSH group significantly exceeding the medium TSH group ($P < 0.05$), suggesting elevated TSH levels correlate with enhanced insulin resistance. HOMA-ISLET levels also differed significantly among groups ($P < 0.001$), with both low and medium TSH groups demonstrating significantly superior islet function compared to the diabetes and high TSH groups, and the high TSH group significantly lower than the medium TSH group ($P < 0.05$). This indicates higher TSH levels may be associated with decreased islet function, while moderate TSH levels may reflect better islet functional status (**Table 4**).

Table 1. Comparison of baseline characteristics between diabetes and combined groups

Variable	Total	Combined Group (n = 184)	Diabetes Group (n = 200)	t/Z/χ^2	*P*-value
Age	59.58±5.24	59.74±4.97	59.44±5.49	-0.568	0.571
Gender					
Male	192 (50.00%)	88 (47.83%)	104 (52.00%)	0.668	0.414
Female	192 (50.00%)	96 (52.17%)	96 (48.00%)		
BMI	22.89±3.04	23.08±3.17	22.72±2.91	-1.146	0.253
Disease Duration	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.513	0.608
Hypertension History					
Yes	65 (16.93%)	29 (15.76%)	36 (18.00%)	0.342	0.559
No	319 (83.07%)	155 (84.24%)	164 (82.00%)		
Coronary Artery Disease History					
Yes	25 (6.51%)	9 (4.89%)	16 (8.00%)	1.522	0.217
No	359 (93.49%)	175 (95.11%)	184 (92.00%)		
Hyperlipidemia History					
Yes	21 (5.47%)	7 (3.80%)	14 (7.00%)	1.893	0.169
No	363 (94.53%)	177 (96.20%)	186 (93.00%)		
Smoking History					
Yes	215 (55.99%)	101 (54.89%)	114 (57.00%)	0.173	0.678
No	169 (44.01%)	83 (45.11%)	86 (43.00%)		
Alcohol Consumption History					
Yes	66 (17.19%)	28 (15.22%)	38 (19.00%)	0.963	0.326
No	318 (82.81%)	156 (84.78%)	162 (81.00%)		
Marital Status					
Married	350 (91.15%)	164 (89.13%)	186 (93.00%)	1.778	0.182
Other	34 (8.85%)	20 (10.87%)	14 (7.00%)		
Educational Level					
≥ High School	158 (41.15%)	70 (38.04%)	88 (44.00%)	1.404	0.236
< High School	226 (58.85%)	114 (61.96%)	112 (56.00%)		

Note: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function, TSH: Thyroid Stimulating Hormone.

Table 2. Comparison of insulin-related values between diabetes and combined groups

Variable	Total	Combined Group (n = 184)	Diabetes Group (n = 200)	t/Z	*P*-value
TSH	4.08 [1.79, 6.92]	6.99 [5.70, 8.55]	1.91 [1.03, 3.44]	16.934	< 0.001
HOMA-IR	3.56 [2.79, 4.46]	4.09 [3.24, 5.02]	3.12 [2.54, 3.97]	7.459	< 0.001
HOMA-ISLET	48.63 [42.08, 56.00]	54.49 [44.20, 63.47]	45.98 [41.24, 50.16]	7.151	< 0.001

Note: TSH: Thyroid Stimulating Hormone, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function.

Correlation of metabolic measurements among TSH level subgroups

Among different TSH level subgroups, HOMA-IR demonstrated positive correlation trends with TSH. In the high TSH group, HOMA-IR and TSH showed positive correlation (r = 0.303, P = 0.141) but did not reach statistical significance (**Figure 3A**). In the medium and low TSH groups, this correlation was significant, with r values of 0.318 (P = 0.001) and 0.315 (P = 0.018), respectively (**Figure 3B** and **3C**), suggesting that insulin resistance maintains a stable and significant positive relationship with TSH levels under low - medium TSH conditions.

For HOMA-ISLET correlation analysis with TSH, the high TSH group showed no apparent corre-

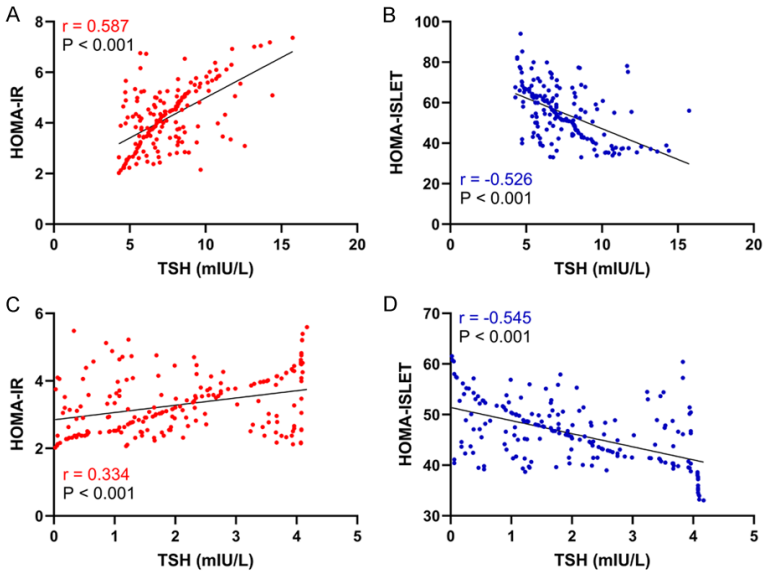

Figure 1. Correlation analysis of insulin-related values and TSH in combined and diabetes groups. A. Correlation analysis between HOMA-IR and TSH in the combined group. B. Correlation analysis between HOMA-ISLET and TSH in the combined group. C. Correlation analysis between HOMA-IR and TSH in the diabetes group. D. Correlation analysis between HOMA-ISLET and TSH in the diabetes group. Note: TSH: Thyroid Stimulating Hormone, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function.

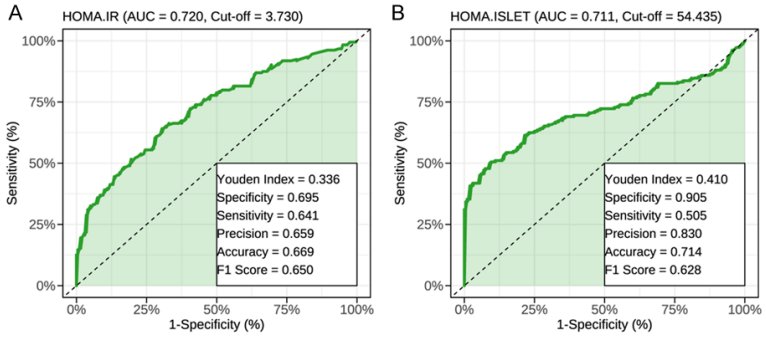

Figure 2. Receiver Operating Characteristic (ROC) curve analysis of HOMA-IR and HOMA-ISLET in combined group. A. ROC curve analysis of HOMA-IR. B. ROC curve analysis of HOMA-ISLET. Note: AUC: Area Under the Curve, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function.

lation (r = 0.051, P = 0.806, **Figure 3D**), while in low and medium TSH groups, HOMA-ISLET demonstrated significant negative correlation with TSH, with r values of -0.352 and -0.498, respectively (both P < 0.001) (**Figure 3E** and **3F**).

Efficacy analysis of HOMA-IR and HOMA-ISLET in diagnosing elevated TSH

To further evaluate the value of insulin-related values in diagnosing elevated TSH levels, ROC curve analysis was performed between low and high TSH groups. It was shown that HOMA-IR achieved an AUC of 0.892 (95% CI: 0.818-0.967) for diagnosing elevated TSH states. At a cutoff value of 5.025, sensitivity was 80.00% and specificity was 87.50%, with corresponding Youden index of 0.675, accuracy of 85.19%, precision of 80.00%, and F1 score of 76.92% (**Figure 4A**).

HOMA-ISLET achieved an AUC of 0.878 (95% CI: 0.776-0.980), with 72.00% sensitivity and exceptionally high 100.00% specificity at a cutoff value of 39.050, Youden index of 0.720, accuracy of 91.40%, precision of 100.00%, and F1 score of 83.70% (**Figure 4B**). Both measures demonstrated favorable diagnostic efficacy, with HOMA-IR showing better balance between sensitivity and specificity, while HOMA-ISLET demonstrated significant advantages in specificity and precision, suggesting potentially high clinical reference value for identifying patients with significantly elevated TSH.

Comparison of HOMA-IR and HOMA-ISLET discriminative ability between diabetes and high TSH groups

ROC curve analysis was performed to compare T2DM patients alone versus those with high TSH, aiming to further explore the diagnostic efficacy of HOMA-IR and HOMA-ISLET for distinguishing between the two groups. Analysis results showed that HOMA-IR achieved an AUC of 0.928 (95% CI: 0.867-0.988). At a cutoff value of 4.970, sensitivity was 80.00% and specificity reached 96.50%, with Youden index of 0.765, accuracy of 94.67%, precision of 80.00%, and F1 score of 76.92%, demonstrating excellent diagnostic capability (**Figure 5A**).

Table 3. Comparison of baseline characteristics among TSH level subgroups

Variable	Diabetes Group (n = 200)	Low TSH Group	Medium TSH Group	High TSH Group	Statistical Value	*P*-value
Age	59.44±5.49	60.50±5.00	59.36±4.75	59.60±5.74	0.686	0.561
Gender						
Male	104 (52.00%)	32 (57.14%)	46 (44.66%)	10 (40.00%)	3.638	0.303
Female	96 (48.00%)	24 (42.86%)	57 (55.34%)	15 (60.00%)		
BMI	22.72±2.91	22.99±3.36	22.88±3.12	24.10±2.83	1.544	0.203
Disease Duration	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.889	0.828
Hypertension History						
Yes	36 (18.00%)	9 (16.07%)	17 (16.50%)	3 (12.00%)	0.638	0.888
No	164 (82.00%)	47 (83.93%)	86 (83.50%)	22 (88.00%)		
Coronary Artery Disease History						
Yes	16 (8.00%)	4 (7.14%)	4 (3.88%)	1 (4.00%)	2.193	0.533
No	184 (92.00%)	52 (92.86%)	99 (96.12%)	24 (96.00%)		
Hyperlipidemia History						
Yes	14 (7.00%)	1 (1.79%)	3 (2.91%)	3 (12.00%)	5.741	0.125
No	186 (93.00%)	55 (98.21%)	100 (97.09%)	22 (88.00%)		
Smoking History						
Yes	114 (57.00%)	34 (60.71%)	55 (53.40%)	12 (48.00%)	1.519	0.678
No	86 (43.00%)	22 (39.29%)	48 (46.60%)	13 (52.00%)		
Alcohol Consumption History						
Yes	38 (19.00%)	9 (16.07%)	17 (16.50%)	2 (8.00%)	2.027	0.567
No	162 (81.00%)	47 (83.93%)	86 (83.50%)	23 (92.00%)		
Marital Status						
Married	186 (93.00%)	49 (87.50%)	91 (88.35%)	24 (96.00%)	3.502	0.32
Other	14 (7.00%)	7 (12.50%)	12 (11.65%)	1 (4.00%)		
Educational Level						
≥ High School	88 (44.00%)	27 (48.21%)	34 (33.01%)	9 (36.00%)	4.917	0.178
< High School	112 (56.00%)	29 (51.79%)	69 (66.99%)	16 (64.00%)		

Note: TSH: Thyroid Stimulating Hormone.

Table 4. Comparison of metabolic characteristics among TSH level subgroups

Variable	Diabetes Group (n = 200)	Low TSH Group	Medium TSH Group	High TSH Group	Statistical Value	*P*-value
HOMA-IR	3.12 [2.54, 3.97]	3.17 [2.63, 4.23]	4.23 [3.62, 4.84][a,b]	5.83 [5.09, 6.30][a,b,c]	95.958	< 0.001
HOMA-ISLET	45.98 [41.24, 50.16][a]	63.48 [54.33, 68.86]	52.22 [46.56, 60.30][a,b]	37.42 [35.48, 44.21][a,b,c]	105.637	< 0.001

Note: a: P < 0.05 vs. Diabetes group. b: P < 0.05 vs. Low TSH group. c: P < 0.05 vs. Medium TSH group. TSH: Thyroid Stimulating Hormone.

In contrast, HOMA-ISLET achieved an AUC of 0.709 (95% CI: 0.553-0.864). At a cutoff value of 38.915, sensitivity was 72.00% and specificity was 88.50%, with Youden index of 0.605. Although accuracy reached 86.70%, precision was only 28.00% with F1 score of 0.545, indicating relatively weaker diagnostic efficacy (**Figure 5B**). Overall, HOMA-IR demonstrated stronger discriminative efficacy in distinguishing between T2DM patients and those with high TSH, with higher clinical application value.

Discussion

T2DM and thyroid dysfunction frequently coexist, with SCH affecting approximately 10-15% of diabetic patients. The complex interplay between thyroid hormones and glucose metabolism has been increasingly recognized, yet the specific metabolic characteristics of T2DM patients with concurrent SCH remain incompletely understood. Understanding these relationships is crucial for optimizing clinical management and preventing cardiovascular complications in this high-risk population.

Our study demonstrated that T2DM patients with SCH exhibited significantly elevated TSH, HOMA-IR, and HOMA-ISLET levels compared to patients with T2DM alone, indicating more severe insulin resistance and altered pancreatic β-cell function. The correlation analysis

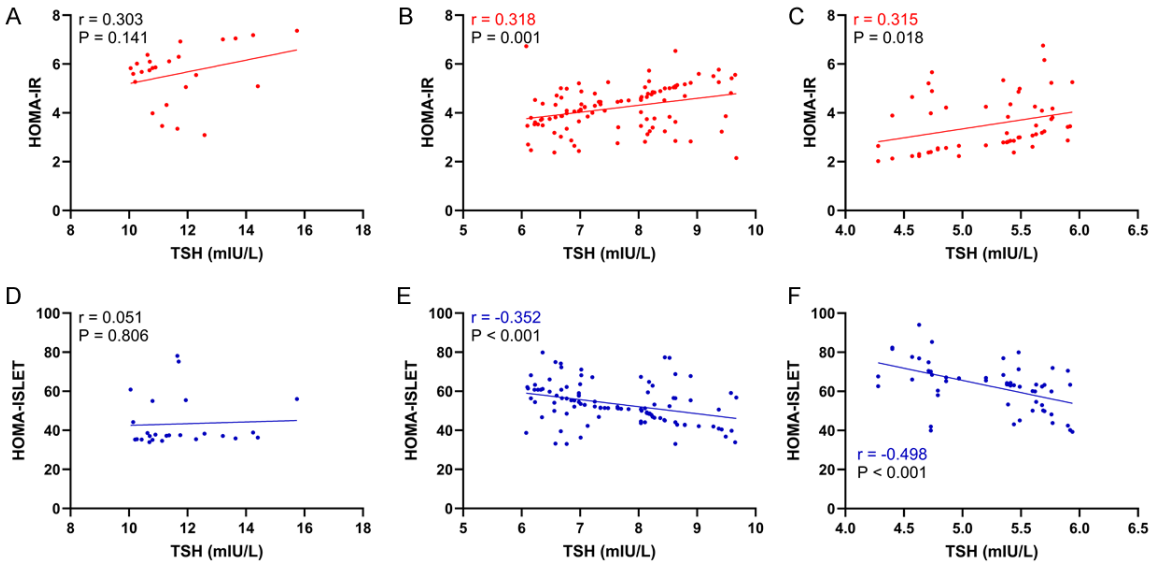

Figure 3. Correlation analysis of HOMA-IR and HOMA-ISLET with TSH in TSH level subgroups. A. Correlation analysis between HOMA-IR and TSH in high TSH group. B. Correlation analysis between HOMA-IR and TSH in medium TSH group. C. Correlation analysis between HOMA-IR and TSH in low TSH group. D. Correlation analysis between HOMA-ISLET and TSH in high TSH group. E. Correlation analysis between HOMA-ISLET and TSH in medium TSH group. F. Correlation analysis between HOMA-ISLET and TSH in low TSH group. Note: TSH: Thyroid Stimulating Hormone, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function.

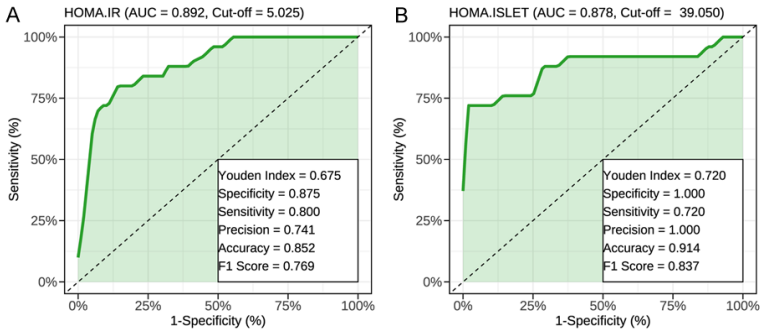

Figure 4. Diagnostic efficacy analysis of HOMA-IR and HOMA-ISLET for high TSH status (low TSH group vs. high TSH group). A. ROC curve of HOMA-IR. B. ROC curve of HOMA-ISLET. Note: TSH: Thyroid Stimulating Hormone, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function.

revealed significant positive correlation between TSH and HOMA-IR and negative correlation with HOMA-ISLET, with this pattern remaining consistent across different TSH level subgroups. These findings align with previous research demonstrating the metabolic impact of subclinical thyroid dysfunction. Literature supports that although TSH did not significantly affect HOMA-IR in established T2DM patients, SCH caused obvious insulin resistance in normoglycemic populations [13-15], indicating that TSH may serve as an early signal of metabolic disorders, particularly showing greater predictive value in compensated states. Collectively, these results establish TSH elevation as a key biomarker for metabolic deterioration in diabetic patients.

Nemtsova et al. [18] indicated that the comorbid state of T2DM and SCH exacerbates metabolic disorders, potentially serving as a basis for high cardiovascular complication rates. Similarly, studies in women with SCH showed that both HOMA-IR and HOMA-B were significantly elevated and positively correlated with TSH [19], supporting our observed association between TSH elevation and insulin resistance. Allam et al. [20] observed that in T2DM patients with diabetic peripheral neuropathy, SCH significantly elevated insulin resistance levels while exacerbating complication severity. This convergent evidence from multiple populations confirms that the TSH-insulin resistance relationship represents

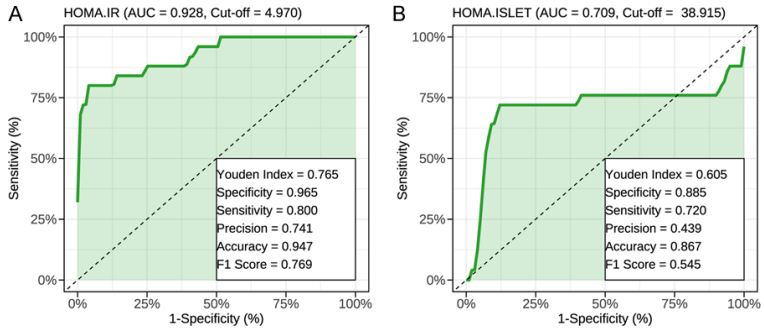

Figure 5. ROC curve analysis of HOMA-IR and HOMA-ISLET between the diabetes group and high TSH group. A. ROC curve of HOMA-IR. B. ROC curve of HOMA-ISLET. Note: TSH: Thyroid Stimulating Hormone, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HOMA-ISLET: Homeostasis Model Assessment of Islet Function.

a consistent pathophysiologic mechanism across diverse clinical contexts.

The mechanistic basis for these relationships has been elucidated by Fan et al. [21], who demonstrated through animal and cellular models that TSH can exacerbate insulin resistance and peripheral nerve damage by activating pro-inflammatory signals and oxidative stress pathways. This provides biological support for our clinical observations and suggests that TSH elevation is not merely a biomarker but may actively participate in metabolic deterioration. The elevated HOMA-ISLET levels in our combined group, despite negative correlation with TSH, likely reflects compensatory hypersecretion rather than improved pancreatic function. Our TSH stratification analysis supported this interpretation, showing that medium TSH levels were associated with slight HOMA-ISLET elevation (suggesting preserved compensatory capacity), while high TSH levels demonstrated obvious β-cell functional decline. These mechanistic insights reveal that TSH actively drives metabolic dysfunction through inflammatory pathways while simultaneously triggering compensatory pancreatic responses.

This biphasic pattern is consistent with the natural history of β-cell dysfunction, where initial compensatory hyperinsulinemia eventually transitions to functional exhaustion. The predictive value of thyroid abnormalities is further supported by Krishnamurthy et al. [22], who demonstrated that anti-TPO antibody levels were elevated before insulin resistance manifestation, suggesting that thyroid-related abnormalities may precede glucose metabolic disorders. This temporal relationship indicates that TSH may serve as an early metabolic signal, particularly valuable in compensated states [23]. The progressive nature of this relationship suggests that thyroid monitoring could provide crucial early warning signals for metabolic decline in diabetic patients.

Our findings have direct relevance to diabetic complications. Similarly, El-Sehrawy et al. [24] found that in DR patients, TSH elevation significantly correlated with HOMA-IR and vascular endothelial growth factor, suggesting that TSH may participate in microvascular pathology development through multiple pathways. Our ROC analysis revealed that both HOMA-IR and HOMA-ISLET possessed favorable ability to identify high TSH states. HOMA-IR demonstrated balanced performance between sensitivity and specificity, while HOMA-ISLET showed superior specificity. When comparing high TSH with T2DM alone groups, HOMA-IR's AUC increased to 0.928, superior to HOMA-ISLET's 0.709, suggesting greater suitability for identifying T2DM patients with concurrent endocrine disorders. These diagnostic capabilities establish HOMA-IR as a practical screening tool for identifying patients at risk for thyroid-related metabolic complications.

These diagnostic capabilities are clinically relevant given that SCH patients demonstrate different coronary microcirculatory responses under identical metabolic risk factors [25], and that TSH abnormalities may alter metabolic system sensitivity. This study provides several important clinical insights. First, it establishes that routine TSH monitoring should be incorporated into metabolic assessments for T2DM patients, as elevated TSH may serve as an early signal of worsening metabolic status. Second, the strong diagnostic performance of HOMA-IR provides a practical tool for identifying patients at risk for thyroid-related metabolic complications. The clinical utility is enhanced by the fact that TSH, HOMA-IR, and HOMA-ISLET are all routine clinical testing values,

making our findings immediately applicable in clinical practice. Patients with significantly elevated HOMA-IR (≥ 4.9) or markedly decreased HOMA-ISLET warrant vigilance for high metabolic risk status and may benefit from more intensive monitoring and intervention. These practical applications demonstrate how our findings can be immediately integrated into routine clinical practice to improve patient risk stratification and management.

Furthermore, our findings suggest therapeutic implications. El-Sehrawy et al. [24] also proposed that TSH elevation can exacerbate insulin resistance and synergistically act with VEGF, suggesting that thyroid hormone replacement therapy might improve metabolic outcomes in selected patients. Marushchak et al. [10] found T2DM patients with SCH exhibited significantly increased lipid abnormalities and macrovascular complication risks, supporting the use of HOMA-related indicators for early risk assessment. The study also contributes to risk stratification strategies. The consistent TSH-HOMA correlations across different subgroups provide confidence that these relationships are robust and can inform clinical decision-making. The comprehensive evaluation combining TSH with HOMA parameters offers a more nuanced approach to metabolic assessment than either measure alone. These therapeutic and risk stratification insights open new avenues for personalized treatment approaches in diabetic patients with concurrent thyroid dysfunction.

Several limitations should be acknowledged. First, the single-center retrospective design may involve selection bias, and the extended data collection timeframe introduces potential heterogeneity. Second, more comprehensive thyroid function indicators such as FT3, FT4, and thyroid antibodies were not included, which may affect accurate SCH classification and mechanistic interpretation. Third, the lack of long-term tracking of TSH dynamic changes limits our ability to establish definitive causal relationships between thyroid dysfunction and metabolic data. Additionally, our ROC analysis results require validation in external datasets through multi-center studies to confirm robustness and broader clinical applicability. The cross-sectional design also prevents assessment of whether the observed relationships change over time or with therapeutic interventions. While these limitations constrain the current study's scope, they also highlight critical areas where future research can build upon our foundational findings.

Future research should address these limitations through several approaches. Prospective cohort studies are needed to dynamically assess long-term effects of TSH changes on insulin sensitivity and β-cell function. Incorporating comprehensive thyroid function panels, inflammatory markers, and cardiovascular risk factors would enable construction of predictive models based on multiple values with improved accuracy and clinical utility. Intervention studies exploring the metabolic impact of levothyroxine therapy in T2DM patients with SCH represent another important research direction. Such studies could establish whether thyroid hormone replacement improves insulin sensitivity and reduces cardiovascular risk, potentially expanding therapeutic options for this patient population. Finally, mechanistic studies investigating the molecular pathways linking TSH elevation to insulin resistance and β-cell dysfunction would provide deeper understanding of disease pathogenesis and identify novel therapeutic targets. Integration of genomic, proteomic, and metabolomic approaches could reveal biomarkers for personalized treatment strategies in T2DM patients with thyroid dysfunction. These comprehensive research directions will transform our current observational insights into actionable therapeutic strategies for improving outcomes in this complex patient population.

Conclusion

This study confirmed that elevated TSH levels are closely associated with enhanced insulin resistance and decreased β-cell function in T2DM patients. Both HOMA-IR and HOMA-ISLET hold diagnostic value for identifying high TSH states, with HOMA-IR demonstrating greater clinical application potential. The research results provide insight for identification and management of T2DM patients with SCH.

Disclosure of conflict of interest

None.

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