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Predictive factors for metabolic profile alterations following radioactive iodine treatment in hyperthyroidism

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Keywords: iodine radioisotopes, Graves' disease, toxic adenoma, insulin resistance, leptin, HOMA-IR, TyG index, metabolic predictors, TSH suppression.

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Radioactive iodine (RAI) therapy is an effective treatment for hyperthyroidism, particularly Graves' disease and toxic adenoma. Although its efficacy in normalizing thyroid hormone levels is well-established, predictive biomarkers for long-term metabolic effects remain underexplored.

Aim. To examine post-RAI metabolic changes and assess the predictive value of baseline TSH and metabolic indices for metabolic risk in patients with Graves' disease and toxic adenoma.

Materials and methods. This prospective study included 83 patients (Graves' disease, n = 62; toxic adenoma, n = 21), aged 25–65 years, who underwent RAI therapy. Participants were stratified by pre-treatment TSH levels: Group A (≤0.01 mIU/L) and Group B (>0.01 mIU/L). Metabolic parameters (glucose, insulin, HOMA-IR, leptin, TyG index, lipid profile, and BMI) were assessed before and 12 months after treatment. Statistical analyses included Mann–Whitney U and Wilcoxon signed-rank test, and ROC curve analysis.

Results. Group A, with suppressed baseline TSH, exhibited significantly higher post-treatment insulin resistance (HOMA-IR: 4.77 vs. 3.09, $p < 0.001$), fasting insulin ($p < 0.001$), TyG index ($p = 0.005$), and fasting glucose ($p = 0.006$), despite comparable BMI between groups. Leptin levels were higher in Group A but not statistically significant. Wilcoxon tests revealed significant improvements in hormonal and metabolic parameters in both groups. ROC analysis identified LDL (AUC = 0.662, $p = 0.027$) and HDL (AUC = 0.665, $p = 0.024$) as significant predictors of metabolic outcomes, while leptin showed borderline significance (AUC = 0.631, $p = 0.074$).

Conclusions. RAI treatment in hyperthyroid patients is associated with substantial metabolic changes, particularly in those with suppressed pre-treatment TSH levels. Insulin resistance and adipokine dysregulation are more pronounced in this subgroup, with LDL and HDL values identified as significant post-RAI metabolic predictors. These findings underscore the need for metabolic risk stratification and targeted follow-up in patients undergoing RAI therapy.

Ключові слова: радіоактивний йод, хвороба Грейвса, токсична аденома, інсулінорезистентність, лептин, HOMA-IR, індекс TyG, метаболічні предиктори, ТТГ.

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Фактори прогнозування змін метаболічного профілю після лікування радіоактивним йодом при гіпертиреозі

А. Е. Маммадова

Радіойодтерапія – ефективний метод лікування гіпертиреозу, зокрема при хворобі Грейвса та токсичній аденомі. Хоча її ефективність у нормалізації рівнів тиреоїдних гормонів підтверджено, прогностичні біомаркери тривалих метаболічних ефектів досі вивчено недостатньо.

Мета роботи – дослідити метаболічні зміни після радіойодтерапії, оцінити прогностичне значення вихідного рівня тиреотропного гормона (ТТГ) та метаболічних індексів щодо метаболічного ризику у пацієнтів із хворобою Грейвса та токсичною аденомою.

Матеріали і методи. До проспективного дослідження залучено 83 пацієнти (62 особи з хворобою Грейвса, 21 хворий із токсичною аденомою) віком 25–65 років, які отримували радіойодтерапію. Учасників стратифікували за рівнем ТТГ до лікування: група А (≤0,01 мМО/л) і група В (>0,01 мМО/л). Метаболічні показники (глюкоза, інсулін, HOMA-IR, лептин, тригліцеридно-глюкозний індекс, ліпідний профіль та індекс маси тіла) вивчали до та через 12 місяців після лікування. Для статистичного аналізу використано критерії Манна–Вітні та Вілкоксона, виконано ROC-аналіз.

Результати. У групі А (зі зниженим вихідним рівнем ТТГ) після лікування встановлено достовірне посилення інсулінорезистентності (HOMA-IR – 4,77 проти 3,09, $p < 0,001$), підвищення рівня інсуліну натще ($p < 0,001$), тригліцеридно-глюкозного індексу ($p = 0,005$) та рівня глюкози натще ($p = 0,006$), попри зіставні значення індексу маси тіла в обох групах. Рівень лептину вищий у групі А, але різниця не досягла рівня статистичної значущості. За тестом Вілкоксона в обох групах встановлено значуще покращення гормональних і метаболічних показників. У результаті ROC-аналізу рівні ліпопротеїнів низької щільності (AUC = 0,662, $p = 0,027$) і ліпопротеїнів високої щільності (AUC = 0,665, $p = 0,024$) оцінено як значущі предиктори метаболічних наслідків, а рівень лептину мав граничну значущість (AUC = 0,631, $p = 0,074$).

Висновки. Радіойодтерапія у пацієнтів із гіпертиреозом характеризується вираженими метаболічними змінами, особливо коли рівень ТТГ до лікування знижений. У цій підгрупі більш виражені інсулінорезистентність і дисрегуляція адипокінів, а рівні ліпопротеїнів низької щільності і ліпопротеїнів високої щільності є значущими прогностичними маркерами метаболічних наслідків після радіойодтерапії. Результати дослідження підтверджують необхідність стратифікації метаболічного ризику та цільового спостереження в пацієнтів, які отримують радіойодтерапію.

The two most common causes of hyperthyroidism are Graves' disease, characterized by autoimmune activation of the thyroid gland, and toxic adenoma, distinguished by autonomously functioning nodules. For both conditions, radioactive iodine (RAI) therapy continues to be a popular, successful, and economical therapeutic option, especially when definitive therapy is needed to achieve stable thyroid function or induce hypothyroidism [1].

The long-term metabolic effects of RAI therapy, particularly with regard to insulin sensitivity, adipokine dynamics, and glucose and lipid metabolism, have drawn increasing interest in addition to the achievement of euthyroidism. Basal metabolic rate, thermogenesis, lipid and carbohydrate metabolism, and body weight homeostasis are primarily regulated by thyroid hormones [2]. These pathways can therefore be disrupted by hyperthyroidism and its treatment, resulting in a variety of metabolic abnormalities.

One study has shown that treatment-induced euthyroidism or hypothyroidism might lead to insulin resistance, dyslipidemia, and weight gain, particularly in individuals with markedly suppressed pre-treatment TSH levels or underlying metabolic disturbances, despite the transient improvement in insulin sensitivity observed during the hyperthyroid state due to elevated energy expenditure and enhanced lipolysis [3].

Thyroid health and leptin, a crucial adipokine involved in appetite control and energy expenditure, are strongly related. While euthyroidism restoration may result in a rebound effect and perhaps contribute to post-RAI metabolic alterations, hyperthyroidism has been shown to reduce blood leptin concentrations [4]. Indicators like the triglyceride-glucose (TyG) index and the homeostasis model assessment of insulin resistance (HOMA-IR) have proven useful in identifying minimal alterations in metabolic risk for patients with thyroid dysfunction [5].

Despite these realizations, there is still a lack of comprehensive data comparing the metabolic impacts of RAI in toxic adenoma and Graves' disease. Moreover, the predictive role of baseline TSH suppression and associated biomarkers (such as leptin, TyG, and HOMA-IR) in predicting long-term metabolic consequences is not well understood.

This study intends to fill an existing knowledge gap by providing deeper insight into the systemic outcomes of RAI therapy, facilitating individualized follow-up care and therapeutic planning for patients after definitive management of hyperthyroidism.

Aim

This study aimed to evaluate metabolic changes, including insulin resistance, lipid profile, leptin levels, and BMI, and to determine the predictive value of baseline TSH and metabolic indices for post-RAI metabolic risk in patients with Graves' disease and toxic adenoma.

Materials and methods

This prospective study included 83 patients diagnosed with Graves' disease (n = 62) and toxic adenoma (n = 21), who underwent RAI treatment at the Nuclear Medicine Department of the National Oncology Center between 2023–2025. Participants were categorized into two pre-treatment groups: Group A (TSH ≤0.01 mIU/L) – n = 54; and Group B (TSH >0.01 mIU/L) – n = 29. Patients in the Graves' disease group had a mean age of 45.69 ± 11.75 years, while those in the toxic adenoma group had a mean age of 49.48 ± 9.30 years. The overall age range for participants was 25–65 years.

Fasting blood samples were collected in the morning between 08:00 and 09:00 a. m. following an overnight fast of at least 10 hours. Serum glucose, total cholesterol, HDL-C, LDL-C, and triglycerides were measured using an enzymatic colorimetric method on a Roche Cobas 6000 analyzer (Roche Diagnostics, Mannheim, Germany). Insulin levels were determined via chemiluminescent immunoassay (CLIA) using the ADVIA Centaur XP system (Siemens Healthcare Diagnostics, USA). Serum leptin concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits (BioVendor, Czech Republic) according to the manufacturer's protocol. TSH, free T4 (FT4), and free T3 (FT3) were measured using electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany).

Derived indices included the HOMA-IR were calculated as [fasting glucose (mmol/L) × fasting insulin (μIU/mL)] / 22.5, and the triglyceride-glucose (TyG) index was calculated as ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2].

Parameters including glucose, insulin, leptin, lipid profile components (e. g., total cholesterol, HDL-C, LDL-C, and triglycerides), HOMA-IR, TyG index, and BMI were assessed before treatment and 12 months post-treatment.

All statistical analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Prior to analysis, the distribution of continuous variables was assessed using the Shapiro–Wilk test to determine the appropriate statistical methods. Variables not meeting the assumption of normality were analyzed using non-parametric tests.

Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range, Q1–Q3) for non-normally distributed variables. Categorical variables were reported as frequencies and percentages. The Mann–Whitney U test was used to compare independent non-normally distributed continuous variables between Group A and Group B (stratified by baseline TSH levels). The Wilcoxon signed-rank test was applied for paired comparisons of pre- and post-treatment variables within each group to assess the effect of RAI therapy on metabolic and hormonal parameters. The Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic and prognostic utility of baseline metabolic markers (e. g., LDL, HDL, leptin) in predicting post-treatment metabolic risk. The area under the curve (AUC) was calculated, along with 95 % confidence intervals, to determine discriminative power. Statistical significance was set at a p-value of <0.05 in all analyses.

Inclusion criteria: diagnosis of Graves' disease or toxic adenoma, patients aged between 25-65 years, patients scheduled for RAI therapy.

Exclusion criteria: pregnancy or breastfeeding, history of thyroid surgery or previous RAI therapy, presence of other significant endocrine or metabolic diseases, chronic kidney or liver disease.

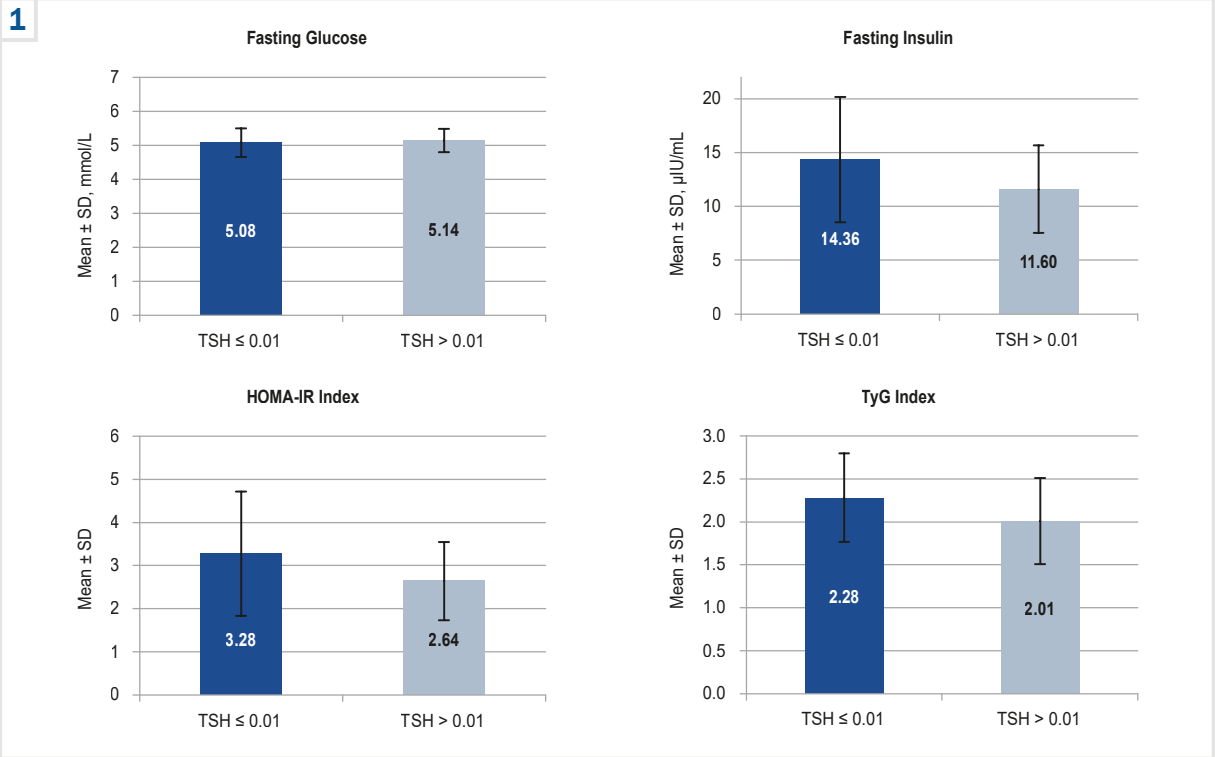

Fig. 1. Metabolic parameters stratified by pre-RAI TSH levels: glucose, insulin, HOMA-IR, and TyG index.

Table 1. Mann–Whitney analysis outcomes

Parameter, units of measurement	Mann–Whitney U	Group A, TSN ≤0.01	Group B, TSH >0.01	p-value
Free thyroxine (FT4), ng/dL	476.5	1.32 (1.07; 1.71)	1.08 (0.96; 1.36)	0.003
Free triiodothyronine (FT3), ng/dL	33.5	6.23 (4.40; 8.87)	3.07 (2.73; 3.73)	<0.001
FT4/FT3 ratio	55.0	0.27 (0.20; 0.43)	0.56 (0.40; 0.69)	0.003
Fasting insulin, mIU/L	567.5	18.5 (14.2; 22.1)	13.2 (10.2; 14.6)	<0.001
Fasting glucose, mmol/L	496,5	5.8 (5.3; 6.3)	5.4 (5.2; 5.6)	0.006
HOMA-IR	359.0	4.40 (3.30;6.00)	3.10 (2.50; 3.50)	<0.001
TyG index	469.0	2.79 (2.21; 3.07)	2.36 (2.03; 2.58)	0.003

Results

Comparison of baseline characteristics by TSH level. Patients were categorized into two groups based on baseline TSH values: Group A (TSH ≤0.01 mIU/L) and Group B (TSH >0.01 mIU/L). Group A received significantly higher doses of methimazole at baseline compared to Group B (24.5 mg vs. 18.7 mg, p = 0.007), consistent with a more pronounced thyrotoxic state. TSH levels were markedly suppressed in Group A (0.007 mIU/L vs. 0.321 mIU/L, p < 0.001), with correspondingly elevated FT3 levels (8.33 ng/dL vs. 3.37 ng/dL, p = 0.013) and a reduced FT4/FT3 ratio (p = 0.004), indicating a predominance of T3 toxicosis *(Fig. 1)*.

Post-treatment hormonal and metabolic outcomes. Following RAI therapy, patients in Group A exhibited significantly higher post-treatment TSH (2.25 mIU/L vs. 1.96 mIU/L, p = 0.041) and FT4 levels (1.40 ng/dL vs. 1.18 ng/dL, p = 0.005) as compared to Group B.

Metabolic assessments have revealed that Group A had worse insulin resistance profiles post-treatment. Fasting insulin levels were elevated in Group A (17.6 µU/mL vs. 12.8 µU/mL, p < 0.001), as well as HOMA-IR scores (4.77 vs. 3.09, p < 0.001) and TyG indices (2.67 vs. 2.33, p = 0.005), despite similar BMI values between groups. Although leptin levels did not reach statistical significance, a higher mean leptin value was observed in Group A (27.4 ng/mL vs. 25.3 ng/mL), supporting a trend toward greater post-treatment metabolic burden in those with more severe thyrotoxicosis.

The Mann–Whitney U test has demonstrated significant differences between groups A and B after treatment in several metabolic and hormonal variables *(Table 1)*.

Notably, FT3 (p < 0.001), FT4 (p = 0.003), and the FT4/FT3 ratio (p = 0.003) differed markedly between groups, reflecting the degree of thyroid hormone excess. Additionally, fasting insulin (p < 0.001), fasting glucose (p = 0.006), HOMA-IR (p < 0.001), and TyG-related indices (p = 0.003) were significantly higher in the TSH ≤0.01 group, further substantiating greater metabolic dysregulation among patients with suppressed TSH.

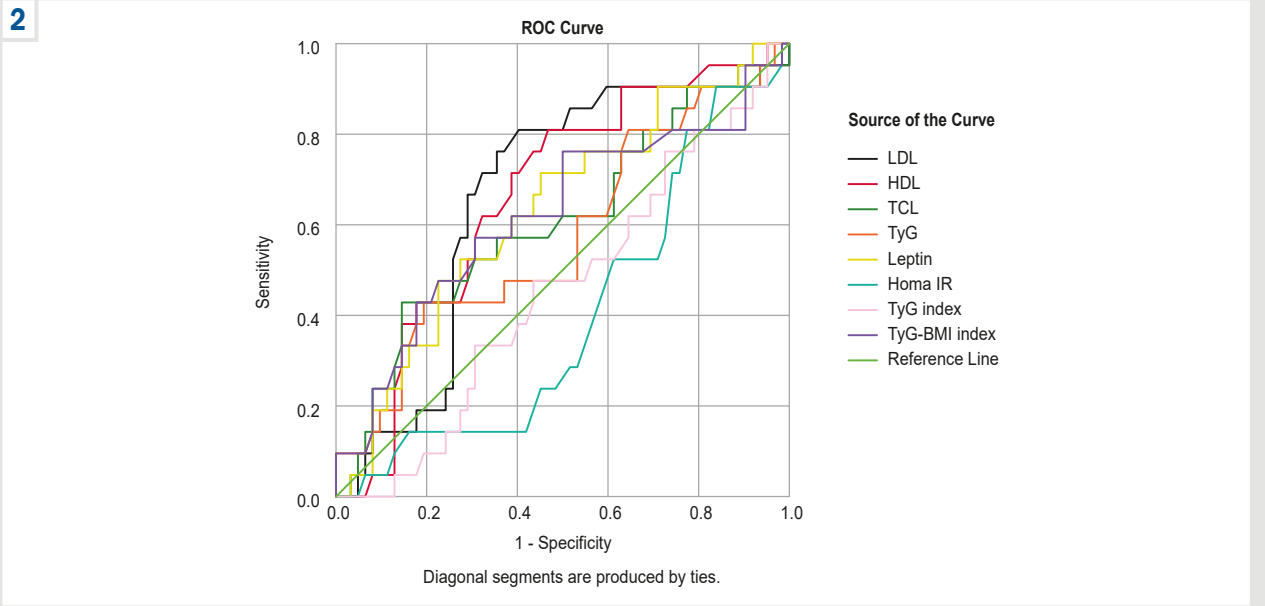

Fig. 2. ROC curves for predictive factors (LDL, HDL, and leptin).

Wilcoxon signed-rank tests have indicated statistically significant changes in nearly all evaluated parameters post-treatment in both TSH groups, including changes in thyroid hormones (FT3, FT4), metabolic markers (insulin, leptin, HOMA-IR, TyG indices), lipid profile components (LDL, HDL, TCL), and BMI *(Table 2)*.

ROC curve analysis has identified LDL (AUC = 0.662, p = 0.027) and HDL (AUC = 0.665, p = 0.024) as significant predictors of metabolic outcomes following RAI therapy *(Table 3)*. Although leptin had a borderline significant p-value (p = 0.074), its moderate AUC (0.631) supported its inclusion due to known biological relevance in thyroid and fat metabolism. The TyG-BMI index has demonstrated moderate predictive ability (AUC = 0.621, p = 0.099), indicating the need for further validation in studies with larger populations *(Fig. 2)*.

Table 2. Wilcoxon test outcomes

Group	Significant changes	p-value
TSN ≤0.01	FT4, FT3, insulin, leptin, LDL, HDL, TCL, HOMA-IR, BMI, TyG, TyG-BMI	<0.001
TSH >0.01	FT4, FT3, insulin, leptin, LDL, HDL, TCL, HOMA-IR, BMI, TyG, TyG-BMI	<0.001

Table 3. ROC analysis identifying predictive factors

Parameter	AUC	p-value	95 % CI
LDL	0.662	0.027	0.531–0.794
HDL	0.665	0.024	0.537–0.793
Leptin	0.631	0.074*	0.494–0.768
TyG-BMI index	0.621	0.099	0.471–0.771

*: borderline statistical significance; included due to clinical relevance and moderate predictive potential.

Discussion

The prognostic significance of baseline TSH suppression in predicting post-RAI metabolic outcomes in hyperthyroid individuals is highlighted in this study. In line with T3-dominant thyroid hormone profiles, patients with severely suppressed TSH levels (≤0.01 mIU/L) have shown more severe biochemical thyrotoxicosis, characterized by higher FT3 levels and lower FT4/FT3 ratios. This trait has been associated with increased metabolic burden, cardiovascular disease, and metabolic stress in the past [6,7].

Thyroid hormone levels returned to normal after the therapy in both groups, but insulin resistance profiles (higher fasting insulin, HOMA-IR, and TyG index) were noticeably worse in the group with low TSH levels. These results are in line with recent research indicating that the degree of hyperthyroidism before RAI therapy may influence metabolic outcomes after treatment, possibly through long-lasting changes in insulin signaling pathways and adipose tissue functions [8,9].

While there was no significant difference in serum leptin levels between the groups, but there was a tendency toward higher levels in the group with low TSH levels. Previous research has demonstrated dysregulation of the leptin-thyroid axis following correction of thyroid dysfunction, which may indicate adipose tissue response or subclinical inflammation after RAI therapy [10].

Crucially, LDL-C and HDL-C have been found to be statistically significant predictors of post-RAI metabolic dysfunction via ROC analysis. These conventional lipid indicators are still useful for identifying patients who are at risk at an early stage, especially when combined with novel indices such as leptin or TyG-BMI. Although larger trials are required to prove its clinical relevance, the moderate AUC for leptin (0.631, p = 0.074) further supports its potential predictive value in metabolic surveillance following RAI therapy.

To sum up, the baseline TSH suppression level serves as both a predictor of post-RAI metabolic abnormalities and an indicator of disease severity. To mitigate the risk of insulin resistance and dyslipidemia, patients with suppressed TSH at

baseline may benefit from more thorough metabolic monitoring and personalized lifestyle or pharmacological interventions.

Conclusions

1. This study demonstrates significant metabolic alterations following RAI treatment for hyperthyroidism, which are significantly associated with baseline TSH levels. Notably, insulin resistance and leptin levels emerged as pivotal indicators influencing metabolic outcomes post-treatment.

2. LDL, HDL, and leptin show notably high predictive potential, highlighting their clinical relevance in risk stratification and therapeutic planning post-RAI.

Prospects for further research. Further research should validate the predictive value of TyG, leptin, and TyG-BMI indices in larger, long-term cohorts. Studies integrating immunological and inflammatory markers may clarify metabolic variability, especially in Graves' disease. Comparative research on RAI, surgery, and antithyroid drug therapy is needed to evaluate differences in metabolic and quality-of-life outcomes. Additionally, interventional trials targeting post-RAI metabolic risk through nutritional or pharmacologic strategies are warranted.

Ethical approval
The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Local Ethics Committee of Azerbaijan Medical University (Protocol No. 03, dated 12.06.2024). Informed written consent was obtained from all participants.

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References

1. Elliyanti A. Radioiodine for Graves' Disease Therapy. IntechOpen; 2021. doi: 10.5772/INTECHOPEN.96949
2. Guo Y, Huang D, Sun J, Zhai Z, Xiao H, Hao W, et al. Radioactive iodine-131 therapy reduced the risk of major adverse cardiovascular events and all-cause mortality in elderly patients with hyperthyroidism combined with type 2 diabetes. Int J Gen Med. 2024;17:4281-95. doi: 10.2147/IJGM.S484910
3. Safari F, Nabavizadeh A, Vardanjani HM. The association between thyroid function and insulin resistance as measured by the metabolic score for insulin resistance (METS-IR): insights from NHANES 2007-2012. BMC Endocr Disord. 2024;24(1):267. doi: 10.1186/s12902-024-01779-y
4. Cheng H, Hu Y, Zhao H, Zhou G, Wang G, Ma C, et al. Exploring the association between triglyceride-glucose index and thyroid function. Eur J Med Res. 2023;28(1):508. doi: 10.1186/s40001-023-01501-z. Erratum in: Eur J Med Res. 2024;29(1):77. doi: 10.1186/s40001-024-01658-1
5. Li L, Cai G, Lu W, Li F, Yu L, Xiao J. Interaction between triglyceride-glucose index and thyroid hormones on coronary artery disease risk in patient with euthyroid. Front Endocrinol (Lausanne). 2023;14:1255656. doi: 10.3389/fendo.2023.1255656
6. Wang H, Liu J, Feng Y, Ma A, Wang T. The burden of cardiovascular diseases attributable to metabolic risk factors and its change from 1990 to 2019: a systematic analysis and prediction. Front Epidemiol. 2023;3:1048515. doi: 10.3389/fepid.2023.1048515
7. Kim HJ. Long-term management of Graves disease: a narrative review. J Yeungnam Med Sci. 2023;40(1):12-22. doi: 10.12701/jyms.2022.00444
8. Devi B, Bala C, Naidu C, Devi L, Kiranmai C. Association of leptin with insulin resistance in type 2 diabetes mellitus. Int J Health Sci (Qassim). 2022;6(S2):8057. doi: 10.53730/ijhs.v6ns2.8057
9. Lee SY, Pearce EN. Hyperthyroidism: A Review. JAMA. 2023;330(15):1472-83. doi: 10.1001/jama.2023.19052
10. Zhao X, An X, Yang C, Sun W, Ji H, Lian F. The crucial role and mechanism of insulin resistance in metabolic disease. Front Endocrinol (Lausanne). 2023;14:1149239. doi: 10.3389/fendo.2023.1149239