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Original Article

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The Effects of Anti-thyroid Drugs on Lipoproteins and Insulin Resistance in Graves' Disease: A Randomized Clinical Trial

Wismandari Wisnu [1,2] **Idrus Alwi** [3] **Nafrialdi Nafrialdi** [4] **Tjokorda Gde Dalem Pemayun** [5] **Nico Iswanto Pantoro** [2] **Calysta Nadya Wijaya** [2] **Dicky Levenus Tahapary** [1,2] **Tri Juli Edi Tarigan** [1,2] **Imam Subekti** [1,2]

[1]Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia
[2]Metabolic Disorder, Cardiovascular and Aging Research Center, Indonesian Medical Education and Research Institute, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
[3]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia
[4]Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
[5]Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Faculty of Medicine Diponegoro University, Dr. Kariadi General Hospital, Semarang, Indonesia

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Correspondence to
Imam Subekti
Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo National Referral Hospital, Diponegoro 71 Street, Central Jakarta 10430, Indonesia.
Email: imam.subekti@ui.ac.id

ORCID iDs
Wismandari Wisnu
https://orcid.org/0000-0002-2172-6703
Idrus Alwi
https://orcid.org/0000-0001-5662-8743
Nafrialdi Nafrialdi
https://orcid.org/0000-0001-8912-7259
Tjokorda Gde Dalem Pemayun
https://orcid.org/0000-0002-5718-2605
Nico Iswanto Pantoro
https://orcid.org/0000-0002-4983-2225
Calysta Nadya Wijaya
https://orcid.org/0009-0007-6854-3430
Dicky Levenus Tahapary
https://orcid.org/0000-0002-4048-5159

ABSTRACT

Objective: Graves' disease (GD) is characterized by thyroid overactivity. Anti-thyroid drugs (ATDs), such as propylthiouracil (PTU) and methimazole (MMI), are commonly used for GD treatment, and studies have suggested a link between these drugs and elevated lipoprotein levels. However, data on their effects on lipoproteins, insulin resistance, or low-density lipoprotein receptor (LDL-R) levels are lacking, both in Indonesia and in other countries. This study investigated changes in lipoproteins, LDL-R, and insulin resistance markers with ATD treatment.
Methods: This study is a secondary analysis of a randomized clinical trial entitled "The Differential Effects of Propylthiouracil and Methimazole as Graves' Disease Treatment on Vascular Atherosclerosis Markers" conducted in Jakarta, Indonesia. Thirty-seven newly diagnosed GD patients received MMI or PTU for 3 months.
Results: After 3 months of ATD treatment, LDL-R levels significantly decreased compared to baseline (197 vs. 144 ng/mL, $p<0.001$), while most lipoproteins, including TC, LDL-C, HDL-C, non-HDL-C, the cholesterol ratio, and the LDL-C/HDL-C ratio, increased. Unexpectedly, neither the PTU nor MMI groups showed an increased dyslipidemia prevalence. Although body mass index increased significantly and fasting plasma glucose decreased slightly, no significant post-treatment change in insulin resistance was observed. The study received ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (ref KET-784/UN.2.F1/ETIK/PPM.00.02/2019) and was registered on clinicaltrials.gov (NCT05118542).
Conclusion: ATD treatment for GD led to a significant increase in total cholesterol, LDL-cholesterol, and high-density lipoprotein-cholesterol levels, along with a reduction in LDL-R levels. Both PTU and MMI showed similar effects. These findings provide valuable insights into the effects of ATDs on lipoproteins and insulin resistance in GD patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT05118542

Keywords: Graves disease; Methimazole; Propylthiouracil; Lipoproteins; Insulin resistance

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Tri Juli Edi Tarigan
https://orcid.org/0000-0001-6086-700X
Imam Subekti
https://orcid.org/0000-0002-1740-6512

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Conflict of Interest
The authors have no conflicts of interest to declare.

Data Availability Statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions
Conceptualization: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Tahapary DL, Tarigan TJE, Subekti I; Data curation: Wisnu W, Pantoro NI, Wijaya CN, Tahapary DL, Subekti I; Formal analysis: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Pantoro NI, Wijaya CN, Tahapary DL, Tarigan TJE, Subekti I; Funding acquisition: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Tahapary DL, Tarigan TJE, Subekti I; Investigation: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Pantoro NI, Wijaya CN, Tahapary DL, Tarigan TJE, Subekti I; Methodology: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Pantoro NI, Wijaya CN, Tahapary DL, Tarigan TJE, Subekti I; Project administration: Wisnu W, Pantoro NI, Wijaya CN, Tahapary DL, Tarigan TJE, Subekti I; Resources: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Tahapary DL, Tarigan TJE, Subekti I; Software: Wisnu W, Pantoro NI, Wijaya CN, Subekti I; Supervision: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Tahapary DL, Tarigan TJE, Subekti I; Validation: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Tahapary DL, Tarigan TJE, Subekti I; Visualization: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Tahapary DL, Tarigan TJE, Subekti I; Writing - original draft: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Pantoro NI, Wijaya CN, Tahapary DL, Tarigan TJE, Subekti I; Writing - review & editing: Wisnu W, Alwi I, Nafrialdi N, Pemayun TGD, Pantoro NI, Wijaya CN, Tahapary DL, Subekti I.

INTRODUCTION

Graves' disease (GD) is an autoimmune disease that causes thyroid gland overactivity. With a yearly incidence of 20–50 cases per 100,000 persons, GD is the most common cause of hyperthyroidism, accounting for 60%–80% of cases.[1,2] Thyroid hormones play a crucial role in metabolism, including the metabolism of lipids and glucose.[3] Therefore, understanding the relationship between GD, its treatment, and the management of dyslipidemia and insulin resistance is vital for managing the risk of atherosclerotic cardiovascular disease.[4,5]

Low-density lipoprotein receptor (LDL-R) is a crucial transmembrane glycoprotein that plays a key role in the uptake and internalization of LDL-cholesterol (LDL-C) and other apolipoprotein-containing lipoproteins.[6-8] Thyroid hormones have both positive and negative effects on dyslipidemia. They regulate hepatic cholesterol metabolism through various mechanisms,[9-11] including the induction of 3-hydroxy-3-methylglutaryl coenzyme A reductase for fatty acid synthesis and the upregulation of lipid mobilization and degradation, primarily via LDL-R.[6,12,13] Additionally, thyroid hormones increase the activity of cholesteryl ester transfer protein (CETP), which results in lower high-density lipoprotein-cholesterol (HDL-C) levels.[14]

Insulin resistance is the primary pathophysiological mechanism underlying type 2 diabetes, which is the third leading cause of death, accounting for an estimated 1.5 million deaths globally.[15] Previous studies have documented cases of insulin resistance associated with GD.[10,11]

Excess thyroid hormone levels can cause insulin resistance through various mechanisms.[16-18] However, there are currently no guidelines for assessing insulin resistance in GD. In the liver, thyroid hormones elevate key enzymes involved in gluconeogenesis and glycogenolysis. Excess thyroid hormones lead to beta cell dysfunction and peripheral insulin resistance by enhancing glucose utilization and stimulating the production of proinflammatory cytokines.[17] Thyroid hormones also increase intestinal glucose absorption.[18]

Treatment modalities for GD include anti-thyroid drugs (ATDs), radioactive iodine, and surgery.[19-22] These treatments aim to restore thyroid hormones to the euthyroid state, thereby normalizing lipid and glucose metabolism. However, there are limited data on the relationship between GD, its treatment, and the effects on lipid and glucose metabolism.

Propylthiouracil (PTU) and methimazole (MMI) are the most commonly used ATDs. Lakshmana Perumal et al.,[3] in their observational study, reported that glucose resistance improved in some patients after 5 months of treatment with ATDs, although it persisted in others. Meanwhile, a meta-analysis by Tan et al.[23] reported a superior effect of MMI in treating hypothyroidism. Other studies have reported that PTU has anti-atherogenic effects independent of its impact on hypothyroidism.[24,25]

Given the limited data from experimental studies on this topic, this study aimed to compare lipoprotein parameters, LDL-R levels, lipid parameters, and markers of insulin resistance before and after treatment with ATDs PTU and MMI in patients with GD.

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MATERIALS AND METHODS

1. Study design

This study is a secondary analysis of the randomized clinical trial titled "The Differential Effects of Propylthiouracil and Methimazole as Graves' Disease Treatment on Vascular Atherosclerosis Markers,"[25] conducted at Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. The trial included 36 newly diagnosed GD patients who were treated with either MMI or PTU for 3 months. The assignment of ATDs was carried out using true simple randomization, facilitated by the randomization software randomizer.org. During enrollment, the research assistant conducted the randomization, communicated the results to the principal investigator, and coordinated with the hospital pharmacy to provide the medications. Additionally, the research assistant supported pharmacovigilance efforts. All participants provided written informed consent before engaging in any study activities. Further details on the study's methodology are available in the previous publication.[25] This manuscript has been prepared in accordance with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations) and the CONSORT (Consolidated Standards of Reporting Trials) statement.

2. Study population

Study participants were patients with a clinical suspicion of GD, characterized by hyperthyroidism accompanied by diffuse goiter and/or ophthalmopathy. These individuals were subsequently tested for thyroid-stimulating hormone (TSH) receptor antibody levels to confirm a GD diagnosis. The exclusion criteria included pregnant women, patients currently on immunosuppressive drugs, those with a history of coronary heart disease or known malignancy, and patients who experienced severe side effects from ATDs, including allergic reactions.

Patients who met the eligibility criteria were randomly assigned to either the PTU or MMI groups and received the appropriate medication for 3 months. Participants were monitored monthly for side effects, and thyroid hormone levels were used to assess the efficacy of the treatment. Based on these levels, the patient's endocrinologist adjusted the dosage accordingly. Only participants who achieved euthyroid status after 3 months of treatment will be included in the final analysis to reduce the proinflammatory effects of hyperthyroidism.

3. Outcome measurement

The primary outcome of the study was to observe changes in lipoproteins following 3 months of anti-thyroid treatment. Venous blood samples were collected after an overnight fast at both the baseline and after 3 months of treatment to measure lipoproteins, including total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TGs). We also calculated the cholesterol ratio and the LDL-C/HDL-C ratio. Additionally, LDL-R levels were measured to investigate their association with lipoprotein changes in GD patients. Subjects were categorized as having dyslipidemia if they met any of the following criteria: TG >150 mg/dL, LDL-C >130 mg/dL, HDL-C <40 mg/dL for males or <50 mg/dL for females, or TC >200 mg/dL, based on the American Heart Association and National Cholesterol Education Program Adult Treatment Panel III guidelines.[26,27]

The secondary outcomes of the study included changes in parameters related to insulin resistance, such as fasting plasma glucose (FPG), fasting insulin levels, and the homeostasis model assessment of insulin resistance (HOMA-IR) index. The HOMA-IR index was calculated by multiplying the fasting insulin level by the FPG level. Additionally, study

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subjects were classified as having prediabetes if their fasting blood glucose levels were between 100 mg/dL and 125 mg/dL.[28]

Thyroid hormone levels were measured using electro-chemiluminescence immunoassay (ECLIA) methods (Abbott) to quantify TSH, free thyroxine (fT4), and total triiodothyronine (T3) levels. Similarly, glucose and insulin levels were determined using ECLIA methods (Abbott), while lipoproteins were measured using the enzymatic calorimetry method. LDL-R levels were quantified using the enzyme-linked immunosorbent assay method (R&D Systems). Another outcome measured in this study was body mass index (BMI), which was calculated by dividing weight in kilograms (kg) by the square of height in meters (m). Subjects were then classified based on their BMI into categories including overweight (BMI ≥23–24.9 kg/m^2) and obesity (BMI ≥25 kg/m^2).[29] Furthermore, we investigated potential factors affecting alterations in lipid profiles and insulin resistance following 3 months of ATD treatment. The factors examined included sex, age (≥60 years old), hypertension, smoking history, and overweight.

4. Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics version 26.0 (IBM). The results were presented as proportions (percentages) for categorical variables and as means (with standard deviations) or medians (with interquartile ranges) for continuous variables, depending on the normality of the data. The Shapiro-Wilk test was used to assess data normality. Graphical representations were created with GraphPad Prism version 9.0 (GraphPad Software). Based on the distribution of the data, changes in thyroid hormones, lipoproteins, and insulin resistance markers were analyzed using either the paired *t*-test or the Wilcoxon test. Differences in the effects between the MMI and PTU groups were examined using either the independent *t*-test or the Mann-Whitney test, depending on the distribution of the mean differences. Additionally, the McNemar test was employed to analyze changes in the prevalence of dyslipidemia before and after treatment. Multiple linear regression was used to identify factors influencing changes in lipid profiles and insulin resistance following 3 months of ATD treatment.

RESULTS

Of the 36 patients with GD, only 24 met the inclusion criteria and achieved euthyroid status after 3 months of ATD treatment (**Table 1**) and were included in the final analysis. During the observation period, 9 participants dropped out: 4 due to the coronavirus disease 2019 (COVID-19) pandemic, one due to pregnancy, one due to poor adherence to therapy, and 2 due to allergic reactions. Additionally, 3 individuals did not achieve euthyroid status after 3 months of treatment. Only euthyroid participants were considered for further study since hyperthyroidism indicates chronic inflammation. Thirteen subjects received PTU, while the other 11 received MMI. The mean age of the participants was 39.6 years, and the FPG levels were within the normal range. However, even after randomization, a smoking history was more common in participants who received MMI treatment (p=0.01). Although statistically

Table 1. Thyroid hormone changes in Graves' disease patients after 3 months of anti-thyroid drug treatment

Research parameter	Baseline	After 3 mo of treatment	*p*-value
TSH (μIU/mL)	0.003 (0.003–0.003)	0.003 (0.003–0.742)	0.001*
Total T3 (ng/dL)	3.810 (1.470)	1.000 (0.840–1.320)	<0.001*
fT4 (ng/dL)	2.950 (2.105–4.427)	0.910 (0.715–1.195)	<0.001*

TSH, thyroid stimulating hormone; Total T3, total triiodothyronine; fT4, free thyroxine.
Wilcoxon test; *p<0.05.

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Table 2. Baseline characteristics of study participants

Variables	All participants (n=24)	PTU (n=13)	MMI (n=11)
Age (yr)	39.6±11.9	38.9±14.0	40.5±9.4
Female	15 (62.5)	10 (76.9)	5 (45.5)
History of hypertension	5 (20.8)	4 (30.8)	1 (9.1)
Family history of thyroid disease	10 (41.7)	5 (38.5)	5 (45.5)
Smoking history	10 (41.7)	2 (15.4)	8 (72.7)
History of psychological stress	8 (33.3)	5 (38.5)	3 (27.3)
Body mass index (kg/m^2)	22.33±2.91	22.63±1.64	21.97±4.00
Neck circumference (cm)	33.8±2.6	33.3±2.6	34.2±2.8
TRAb, IU/L	13.1 (5.2–26.2)	11.1 (5.3–32.9)	16.8 (4.8–25.8)
Fasting plasma glucose (mg/dL)	95 (91–101)	94 (85–104)	96 (94–100)
Fasting serum insulin (μIU/mL)	6.8 (5.4–11.2)	7.5 (3.1)	9.1 (4.0)
LDL-R (ng/mL)	197 (129–363)	228.0 (143.9)	289.3 (214.2)
Total cholesterol (mg/dL)	148 (128–185)	143.8 (42.3)	168.6 (39.7)
LDL-C (mg/dL)	87 (65–106)	77.0 (29.4)	103.5 (38.9)
HDL-C (mg/dL)	43 (39–49)	45 (39–53)	42 (39–47)
Triglycerides (mg/dL)	92 (70–134)	84.5 (35.5)	121.4 (44.1)
Comorbidities			
Overweight	8 (33.3)	5 (38.5)	3 (27.3)
Obese	3 (12.5)	0 (0.0)	3 (27.3)
Prediabetes	5 (20.8)	2 (15.4)	3 (27.3)
Dyslipidemia	20 (83.3)	11 (84.6)	9 (81.8)
Medication			
Statin	0 (0.0)	0 (0.0)	0 (0.0)
Metformin	0 (0.0)	0 (0.0)	0 (0.0)
Thiazolidinedione	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as mean ± standard deviation, number (%) or number (range).
HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LDL-R, low-density lipoprotein receptor; MMI, methimazole; PTU, propylthiouracil; TRAb, thyroid stimulating hormone receptor antibodies.

non-significant, TC, LDL-C, and TG levels were slightly higher, while HDL-C levels were lower in the MMI group than in the PTU group. Furthermore, comorbidities were evident in the participants, with a higher proportion of overweight individuals in the PTU group (38.5%) compared to those in the MMI group (27.3%). There was a higher prevalence of obesity in the MMI group (27.3%) than in the PTU group (0.0%). In contrast, a higher prevalence of dyslipidemia was found in the PTU group (84.6%) than in the MMI group (81.8%). Notably, both groups reported no medication use for diabetes and dyslipidemia at baseline (**Table 2**).

After 3 months of ATD treatment, we observed a significant reduction in LDL-R levels along with an increase in most lipoproteins, including TC, LDL-C, HDL-C, non-HDL-C, the cholesterol ratio, and the LDL-C/HDL-C ratio (**Table 3**). Interestingly, these increases in lipoproteins did not lead to a higher overall prevalence of dyslipidemia, either in the PTU group or the MMI group (**Fig. 1**). Subsequently, our investigation focused on the lipoproteins contributing to dyslipidemia at baseline and after 3 months of ATD treatment. Initially, HDL-C was the primary contributor to dyslipidemia (62.5%), followed by TC and LDL-C (each at 20.8%). After 3 months of ATD treatment, we noted an increased contribution to dyslipidemia from TC (58.3%) and LDL-C (41.7%), along with a decrease in the contribution from HDL-C (25%). However, the contributions of TC and LDL-C to dyslipidemia after 3 months of ATD treatment were still lower than the contribution of HDL-C to dyslipidemia at baseline. This resulted in a decreased proportion of dyslipidemia after 3 months of ATD treatment (**Table 4**).

In our analysis of the differential effects of PTU and MMI treatments, we observed significant increases in LDL-C (p<0.001), the cholesterol ratio (p=0.03), and the LDL-C/HDL-C ratio

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Table 3. Lipoproteins change in Graves' disease patients after 3 months of anti-thyroid drug treatment

Research parameter	All subjects (n=24)	PTU (n=13)	Methimazole (n=11)	*p*-value (overall)
LDL-R (ng/mL)				0.62‖
Baseline	197 (129–363)	228.0 (143.9)	289.3 (214.2)	
After 3 mo of treatment	144 (82–294)	146.4 (92.5)	223.3 (176.6)	
p-value	<0.001*†	0.005*‡	0.004*‡	
Total cholesterol (mg/dL)				0.74‖
Baseline	148 (128–185)	138 (1.4)	166 (1.3)	
After 3 mo of treatment	206 (181–242)	195 (1.2)	240 (1.3)	
p-value	<0.001*†	<0.001*‡	0.003*‡	
LDL-C (mg/dL)				0.67‖
Baseline	87 (65–106)	77.0 (29.4)	103.5 (38.9)	
After 3 mo of treatment	124 (108–157)	118.1 (18.8)	154.4 (64.4)	
p-value	0.002*†	< 0.001*‡	0.058‡	
HDL-C (mg/dL)				0.99§
Baseline	43 (39–49)	46.9 (40.5–54.4)	43.1 (38.7–47.8)	
After 3 mo of treatment	56 (48–66)	57.6 (48.6–68.2)	52.8 (45.9–60.8)	
p-value	0.001*†	0.007*†	0.025*†	
Triglyceride (mg/dL)				0.80‖
Baseline	92 (70–134)	84.5 (35.5)	116 (42.5)	
After 3 mo of treatment	94 (62–117)	77.5 (29.1)	112.4 (52.4)	
p-value	0.726†	0.51‡	0.61‡	
Cholesterol ratio (mg/dL)				0.72§
Baseline	3.28 (2.81–4.27)	2.95 (2.54–3.41)	3.82 (3.25–4.49)	
After 3 mo of treatment	3.52 (3.07–4.36)	3.38 (3.01–3.78)	4.54 (3.38–6.10)	
p-value	0.004*†	0.03*†	0.07†	
LDL-C/HDL-C ratio (mg/dL)				0.93‖
Baseline	1.94 (1.30–2.76)	1.65 (0.19)	2.41 (0.27)	
After 3 mo of treatment	2.08 (1.74–2.97)	2.12 (0.19)	2.91 (0.39)	
p-value	0.007*†	0.004*‡	0.21*‡	
Non-HDL (mg/dL)				0.18‖
Baseline	102 (83–139)	95.38 (9.34)	125.09 (11.6)	
After 3 mo of treatment	148 (123–177)	137.23 (6.29)	195.64 (24.68)	
p-value	<0.001*†	<0.001*‡	0.007*‡	

PTU, propylthiouracil; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LDL-R, low-density lipoprotein receptor; HDL, high-density lipoprotein.
*$p<0.05$; †Wilcoxon test; ‡Paired *t*-test; §Mann-Whitney test; ‖Independent *t*-test.

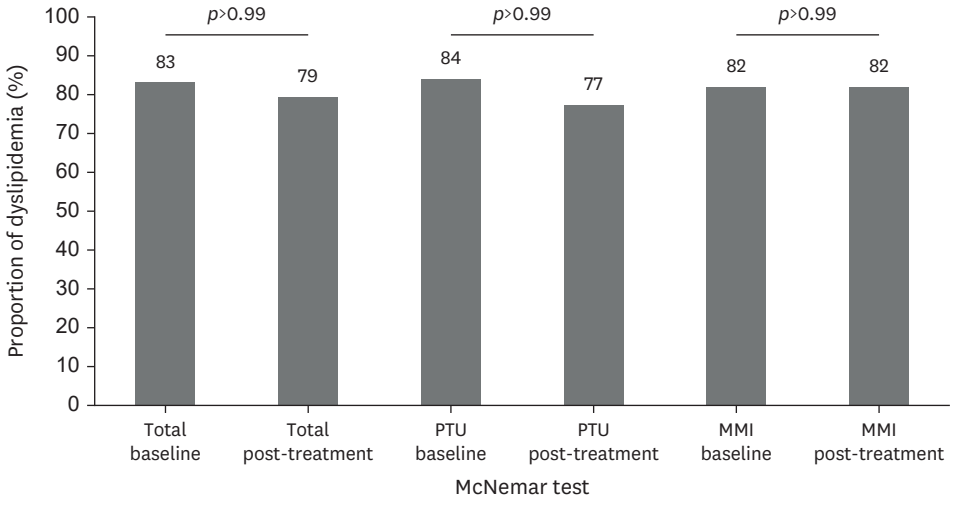

Fig. 1. The proportion of Graves' disease patients with dyslipidemia before and after anti-thyroid drug treatment. PTU, propylthiouracil; MMI, methimazole.

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Table 4. Contributions of different lipoproteins to dyslipidemia at baseline and after 3 months of anti-thyroid drug treatment

Variables	Dyslipidemia (n=24)	
	Baseline	After 3 months of treatment
Total cholesterol	5 (20.8)	14 (58.3)
LDL-C	5 (20.8)	10 (41.7)
HDL-C	15 (62.5)	6 (25.0)
Triglycerides	3 (12.5)	3 (12.5)

Values are presented as number (%).
HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Table 5. Changes in insulin resistance in Graves' disease patients after 3 months of anti-thyroid drug treatment

Parameter	All subjects (n=24)	PTU (n=13)	MMI (n=11)	*p*-value
HOMA-IR				0.12§
Baseline	1.81 (1.29–2.63)	1.66 (1.29–2.62)	2.00 (1.29–2.96)	
After 3 mo of treatment	1.80 (1.42–3.50)	1.76 (1.36–1.94)	3.09 (1.48–4.72)	
p-value	0.39†	0.60†	0.21†	
Fasting serum insulin (μIU/mL)				0.19§
Baseline	6.8 (5.4–11.2)	6.6 (5.1–10.4)	8.6 (5.6–12.5)	
After 3 mo of treatment	8.6 (6.0–14.2)	7.7 (5.6–8.6)	13.9 (6.1–19.5)	
p-value	0.13†	0.68†	0.19†	
Fasting plasma glucose (mg/dL)				0.28§
Baseline	95 (91–101)	94 (85–104)	96 (94–100)	
After 3 mo of treatment	92 (86–102)	88 (84.5–100.5)	95 (87–103)	
p-value	0.024*†	0.04*†	0.39†	
Body mass index (kg/m^2)				0.59‖
Baseline	22.3 (2.9)	22.6 (1.6)	22.0 (4.0)	
After 3 mo of treatment	23.8 (2.9)	24.3 (2.3)	23.3 (3.5)	
p-value	<0.001*‡	0.001*‡	0.005*‡	

PTU, propylthiouracil; MMI, methimazole; HOMA-IR, homeostasis model assessment of insulin resistance.
*p<0.05; †Wilcoxon test; ‡Paired t-test; §Mann-Whitney test; ‖Independent t-test.

(p=0.004) in the PTU group, but not in the MMI group. However, no significant differences were found when comparing the changes between the 2 groups (**Table 3**).

Regarding the markers of insulin resistance, we observed no change in HOMA-IR levels after treatment, despite a significant increase in BMI and a slight, though not clinically significant, reduction in FPG levels (**Table 5**).

Upon analyzing the individual effects of PTU and MMI, we observed a significant reduction in FPG in the PTU group, which resulted in improved HOMA-IR parameters. Additionally, although not statistically significant, patients in the MMI group exhibited a slight increase in the HOMA-IR index (**Table 5**). Furthermore, we found that obesity status was the only statistically significant factor influencing changes in LDL-C (p<0.001), TC (p<0.001), and TG (p=0.007) following 3 months of ATD treatment (**Table 6**).

Table 6. Factors affecting lipid profiles and insulin resistance changes after 3 months of anti-thyroid drug treatment

Variables	*p*-value				
	Δ LDL-C	Δ HDL-C	Δ TC	Δ Triglyceride	Δ HOMA-IR
Sex	0.867	0.353	0.802	0.204	0.704
Age (≥60 years old)	0.632	0.149	0.238	0.682	0.867
Hypertension	0.125	0.774	0.073	0.630	0.510
Smoking history	0.368	0.525	0.442	0.767	0.769
Obesity	<0.001*	0.392	<0.001*	0.007*	0.906

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HOMA-IR, homeostasis model assessment insulin resistance.
Multiple linear regression, *p<0.05.

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DISCUSSION

Our study is the first to investigate the comprehensive effects of hyperthyroidism and its treatment on lipoproteins and insulin resistance. Our results confirmed that transitioning from a hyperthyroid to a euthyroid state increased levels of various lipoproteins, including TC, HDL-C, LDL-C, cholesterol ratio, non-HDL-C, and the LDL-C/HDL-C ratio. Despite these increases, the prevalence of dyslipidemia did not rise. We propose that elevating lipoprotein levels in GD patients following treatment with ATD enhances lipid metabolism. Additionally, we observed that both PTU and MMI treatments had comparable effects on lipid and glucose metabolism.

We observed increases in TC, LDL-C, and HDL-C in GD patients after the normalization of thyroid hormone levels via ATD treatment. Thyroid hormones are primary regulators of lipid mobilization, degradation, and synthesis. In a hyperthyroid state, cholesterol excretion and turnover are elevated, which leads to decreased levels of TC and LDL-C. Additionally, increased activity of CETP, which converts HDL-C into very LDLs, may reduce HDL-C levels. As thyroid hormone levels normalize, lipid metabolism gradually stabilizes, resulting in increased levels of TC, LDL-C, and HDL-C. Multiple studies have demonstrated a correlation between thyroid function and lipid profile concentrations. Xiao et al.[30] examined lipoprotein levels in 41 hyperthyroid patients before and 3 months after initiating ATD therapy and found a statistically significant increase in TC, LDL-C, and HDL-C but not in TG. In another study, serum levels of HDL-C and LDL-C were significantly lower in patients with hyperthyroidism compared to the average population.[31] Thyroid hormones have been shown to increase the cellular uptake and catabolism of LDL particles by stimulating LDL-R.[10,32]

A distinguishing feature of hyperthyroidism is the increased synthesis of endogenous plasma TG. This leads to a modest rise in plasma TG concentration, which is offset by increased TG elimination efficiency.[33] The activation of adenyl cyclase and concomitant stimulation[34] of lipolysis in adipose tissue by thyroid hormones significantly increase the turnover rate and plasma concentration of free fatty acids (FFAs)[35-38] and glycerol.[39,40]

In the present study, both the PTU and MMI groups exhibited significant changes in most lipoprotein parameters. In addition, our findings show that PTU and MMI had comparable effects on lipoproteins. Wu et al.[41] reported elevated lipoprotein levels and atherosclerosis risk in GD patients receiving PTU or MMI treatment. Luo et al.[42] found that PTU and MMI led to similar increases in lipoprotein levels. Another study by Wu et al.[41] found that PTU and MMI treatment, alongside the decrease in thyroid hormones, significantly reduced the gene expression of LDL-R-related protein 1 and hepatic lipase. Treatment with ATDs has been associated with reduced clearance of circulating remnant lipoproteins, potentially leading to an unfavorable blood lipid profile.[41]

The observed changes in lipid profiles in GD patients receiving ATD treatment highlight the complex interaction between these medications and thyroid hormones. This underscores the inherent complexity in the relationship between thyroid function and lipid metabolism, offering valuable insights into the intricate dynamics involved in ATD interventions in GD.

Our study found a significant decrease in LDL-R levels after 3 months of ATD treatment (**Table 3**). These results may be linked to the hypocholesterolemic effects of thyroid hormones, which are thought to be due to the induction of specific enzymes and LDL-R in the liver, the key organ for cholesterol homeostasis.[43,44] T3 rapidly increased hepatic LDL-R

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mRNA and immunoreactive protein levels at low doses.[6] A study by Ness et al.[6] in mice found that thyroid hormones increased the expression of hepatic LDL-R at the transcriptional level. A reduction in LDL-R expression can also be replicated in cultured hepatic cells following ATD treatment, indicating that the effects of thyroid hormone on LDL-R expression are direct and not secondary to non-hepatic actions of the hormone. T3 and T4 are naturally occurring hormones and are potent hypocholesterolemic agents.[45]

Intriguingly, despite elevated lipoprotein levels, the incidence of dyslipidemia remained the same or even decreased following ATD treatment. To the best of our knowledge, no previous studies have explored the prevalence of dyslipidemia in patients with GD. HDL-C levels are reduced in hyperthyroidism due to increased CETP activity, whereas Tan et al.[23] observed an increase in HDL-C levels post-treatment. However, since we did not measure CETP levels, we were not able to thoroughly investigate its role.

We observed similar levels of HOMA-IR 3 months after treatment with ATDs. However, other studies have reported inconsistent results. Chng et al.[46] found that HOMA-IR levels remained stable after therapy with ATDs. In contrast to those studies, Tene et al.[47] and Kiani et al.[48] observed reduced HOMA-IR levels after the study participants achieved a euthyroid state. GD patients frequently show impaired glucose tolerance due to increased FFA concentrations and elevated peripheral glucose transport and utilization.[49] Additionally, despite the anticipated resistance to insulin's inhibitory effect on gluconeogenesis, it has been observed that the transcription of several enzymes involved in lipid synthesis or metabolism is increased in hyperinsulinemic, insulin-resistant mice.[50] Furthermore, it has been previously reported that T3 induces lipogenesis through the transcriptional activation of the malic enzyme, which is involved in fatty acid synthesis.[51] Thus, the induction of lipogenic enzymes by T3 could potentially exacerbate the dysregulation of liver glucose and lipid metabolism typically seen in IR.[49] Consequently, the relationship between GD and insulin resistance warrants further investigation.

Previous meta-analyses on this subject have reported inconsistent results. Luo et al.[42] reported that the levels of 2-hour plasma glucose and FPG were significantly lower after treatment (p<0.05). In our study, FPG decreased significantly after PTU treatment, but not after MMI treatment. However, no significant differences were observed between both groups.

Additionally, we found that obesity can affect changes in LDL-C, TC, and TG after 3 months of ATD treatment. A study by Wang et al.[52] identified a positive correlation between fT3 and TC as well as LDL-C levels in overweight and obese patients. This suggests that body weight may influence the impact of thyroid hormones on the lipid profile. Disturbed thyroid hormone levels have been observed in individuals with a BMI ≥25 kg/m^2. Obesity is closely linked to dyslipidemia and an increase in FFA fluxes to the liver, adipose tissue, and skeletal muscle. This, in turn, alters the expression of lipoprotein lipase activity, impairs lipolysis, and interferes with TG accumulation and transport, ultimately resulting in dyslipidemia.[53] The precise mechanism through which BMI modulates the effects of thyroid hormones on the lipid profile remains unclear. It is possible that certain adipokines, such as leptin, play a role through the hypothalamic-pituitary-thyroid axis.[54,55]

Our study was the first clinical trial to investigate the effects of ATDs on lipoproteins and insulin resistance in patients with GD. We found significant increases in lipoproteins and decreases in LDL-R, but the proportion of patients with dyslipidemia remained similar after 3 months of treatment. However, this study faced several limitations. High dropout

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rates occurred due to adverse drug reactions and the COVID-19 pandemic. Additionally, attempts to resume recruitment between February 2020 and August 2020 were unsuccessful as potential participants declined to join due to concerns about the pandemic, thereby diminishing the statistical power of our study. Furthermore, we did not measure apolipoproteins and CETP levels, nor did we employ the hyperinsulinemic-euglycemic clamp examination, the gold standard for assessing insulin resistance.

In conclusion, we observed significant increases in TC, HDL-C, and LDL-C, but not in TG, along with a reduction in LDL-R 3 months after ATD treatment in GD patients. Additionally, we found no changes in HOMA-IR after 3 months of ATD treatment. There were no significant differences in the effects of PTU and MMI treatment on either lipoprotein levels or insulin resistance in GD patients.

Our results emphasize the importance of re-evaluating lipoprotein levels following hyperthyroidism resolution to reduce cardiovascular risk. Furthermore, clinicians should be aware that hyperthyroidism treatment may reveal underlying dyslipidemia, implying that a lipid evaluation should be repeated when the patient achieves a euthyroid state. Further studies are required to explore the changes in lipoproteins and insulin resistance until remission is achieved.

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