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Correlation of triglyceride-glucose index, complement C5, and lipoprotein(a) with carotid intima-media thickness in thyroid dysfunction: A cross-sectional study

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Objective. Thyroid dysfunction is associated with metabolic disturbances and an increased risk of atherosclerosis. This cross-sectional study investigated the relationships between the triglyceride-glucose index (TyG index), complement C5, lipoprotein(a) (Lp(a)), and carotid intima-media thickness (cIMT).

Methods. Clinical data were collected, blood samples analyzed, and cIMT measured using high-resolution ultrasound in 54 participants with thyroid dysfunction (27 with hypothyroidism and 27 with hyperthyroidism).

Results. The study found a significant positive correlation between the TyG index and cIMT in both hypothyroid and hyperthyroid patients. Complement C5 levels were also positively correlated with cIMT. No significant association was found between Lp(a) and cIMT.

Discussion. These findings highlight the complex interplay between thyroid dysfunction, metabolic dysregulation, and vascular health emphasizing the need for comprehensive cardiovascular risk assessment and management in patients with thyroid disorders.

Keywords: atherosclerosis, carotid intima-media thickness, complement C5, hyperthyroidism, hypothyroidism, lipoprotein(a), triglyceride-glucose index

Atherosclerosis is a chronic and progressive condition that poses a significant threat to cardiovascular health marked by endothelial dysfunction, inflammation, and lipid accumulation within arterial walls (Xu et al. 2023). This disease is a primary contributor to various cardiovascular issues including coronary artery disease and stroke, which collectively account for over 15 million deaths annually worldwide (Tsao et al. 2023). Despite substantial advancements in understanding the risk factors and secondary prevention strategies for cardiovascular diseases, ongoing research continues to investigate additional mediators that may initiate or exacerbate these conditions (Jabbar et al. 2017).

Thyroid hormones are crucial in regulating metabolic processes influencing lipid production, clearance, and release. Hypothyroidism is associated with hyperlipidemia, a significant risk factor for atherosclerosis and correlates with an increased prevalence of ischemic heart disease (Delitala et al. 2017). Conversely, hyperthyroidism can disrupt insulin signaling and glucose metabolism often leading to glucose intolerance. Elevated glucose levels can exacerbate atherosclerosis through mechanisms

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like increased oxidative stress and vascular structure alterations (Poznyak et al. 2022). The gradual progression of atherosclerosis in the carotid arteries often begins with asymptomatic changes, such as thickening of the intima and media layers, quantifiable using carotid intima-media thickness (cIMT) assessments. Although a connection between thyroid function and atherosclerosis is acknowledged, the precise mechanisms by which thyroid hormones influence this process remain inadequately understood (Saric et al. 2022).

The triglyceride-glucose index (TyG), introduced in 2008, has become a practical marker for estimating insulin resistance, combining lipid and glucose-related factors to assess cardiovascular risk (Simental-Mendia et al. 2008; Sanchez-Garcia et al. 2020). Insulin resistance, a key risk factor for cardiovascular disease, is reliably reflected by the TyG index, as demonstrated in recent studies involving both the general population and individuals with diabetes (Tao et al. 2022).

Lipoprotein(a) (Lp(a)), a variant of low-density lipoprotein (LDL) with an attached apolipoprotein(a), has been recognized as a coronary artery disease risk factor for decades. Genetically determined, Lp(a) exhibits pro-atherosclerotic, pro-thrombotic, and pro-inflammatory roles contributing to its relevance in atherosclerosis (Rehberger Likozar et al. 2020).

The complement system, a crucial component of innate immunity, also influences atherosclerosis development. Activation of specific complement components, particularly complement C5, promotes inflammatory processes linked to plaque formation. Martinez-Lopez et al. (2020) have identified C5 as a potential biomarker for assessing atherosclerosis severity, even at subclinical stages, emphasizing its dual role in inflammation and atherosclerotic progression.

Epidemiological research has identified that hypothyroidism is associated with accelerated coronary atherosclerosis, primarily due to contributing factors such as hypercholesterolemia, hypertension, and endothelial dysfunction (Ichiki 2010). Conversely, hyperthyroidism, particularly in patients with Graves' disease (GD), has been linked to atherosclerosis through mechanisms involving autoimmune inflammation and the effects of excess thyroid hormones (Wisnu et al. 2021).

Despite these insights, a gap remains in understanding the specific roles of the TyG index, complement C5, and Lp(a) in atherosclerosis among patients with thyroid dysfunction. This study aims to evaluate the relationships between these markers and cIMT in patients with both hyperthyroidism and hypothyroidism. The findings will contribute to developing preventive strategies and improving cardiovascular risk management in this population.

Materials and Methods

Study participants. This cross-sectional study was conducted from January to October 2024 at a Central General Hospital in Semarang. A total of 54 participants were included, consisting of 27 patients with primary hypothyroidism and 27 with primary hyperthyroidism, all aged 18 years or older. Diagnoses were confirmed by an endocrinologist and all participants were receiving regular follow-up care at the hospital's endocrinology outpatient clinic. Patients with severe comorbid conditions, a history of ischemic stroke or coronary artery disease or those with GD who had undergone radioactive iodine therapy or total thyroidectomy were excluded from the study.

Clinical data collection and analysis. The study was approved by the Research Ethics Board of Kariadi Hospital (No.16176/EC/KEPK-RSDK/2024), and informed consent was obtained from all participants. The clinical features of hypothyroidism documented in this study included symptoms such as malaise, weight gain, constipation, excessive sleepiness, hoarseness, dry skin, decreased sweating, periorbital edema, and thyroid enlargement. Diagnosis duration was categorized into two groups: less than six months and more than six months. Levothyroxine and statin use were evaluated. Common comorbidities included diabetes mellitus, hypertension, dyslipidemia, other autoimmune conditions, and a history of smoking.

Hyperthyroidism manifestations included weight loss, diarrhea, insomnia, excessive sweating with heat intolerance, palpitations, dyspnea on exertion, increased appetite, tremors, exophthalmos, and thyroid enlargement. Diagnosis duration was similarly categorized. Therapies included propylthiouracil (PTU) and methimazole with an evaluation of statin use. Comorbidities observed were diabetes mellitus, hypertension, dyslipidemia, other autoimmune conditions, and smoking history.

Patient information was collected via a structured questionnaire after obtaining written informed consent. Blood samples were drawn from the antecubital vein after overnight fasting. Initial laboratory analyses including triglycerides and fasting glucose were conducted at the certified central laboratory of Kariadi Hospital, Semarang. The TyG index was calculated by the following formula (Simental-Mendia et al. 2008):

TyG index = Ln [fasting glucose (mg/dL) × triglycerides (mg/dL)/2].

Blood samples for complement C5 and Lp(a) analysis were processed immediately after collection. Serum was separated by centrifugation at 3500 rpm for 8 min and stored at -80°C until analysis. These tests were conducted at the certified central laboratory of Diponegoro University, Semarang. Complement C5 levels were measured using the Human Complement Component C5 ELISA kit (Catalog No. E0347Hu, BT Lab, Shanghai, China), and Lp(a) levels were measured using the Human LPA (Lipoprotein a) ELISA Kit (Catalog No. EH0660, Finetest, US). Initial laboratory parameters, including thyroid-stimulating hormone (TSH), free thyroxine (FT4), thyroid peroxidase (TPO) antibodies (TPOAb), and TSH receptor antibodies (TRAb) were obtained from medical records.

cIMT assessment. cIMT was assessed by a single experienced radiologist blinded to the participants' clinical data. A high-resolution B-mode ultrasound system (Logiq S7, GE Healthcare) equipped with a 12 MHz linear array transducer was used. Images were acquired from the far wall of both the right and left common carotid arteries, 1–2 cm proximal to the carotid bulb, ensuring the absence of atherosclerotic plaques in the region of interest. Three cIMT measurements were obtained at each site: at the thickest point, 1 cm proximal, and 1 cm distal to the thickest point. The mean and maximum cIMT values were calculated for each carotid artery.

Statistical analysis. Data were recorded in Microsoft Excel and analyzed using IBM SPSS Statistics (version 29). Descriptive statistics, including means, standard deviations, and percentages were computed. The Shapiro-Wilks test was used to assess data normality. Associations between variables were analyzed using the Spearman correlation coefficient for non-normally distributed data. Group comparisons were performed using the Mann-Whitney U test for two independent samples and the Kruskal-Wallis test for multiple groups, as appropriate for non-parametric data. For normally distributed data, two-sample t-tests were employed to compare numerical measurements between groups. Statistical significance was determined at a 95% confidence level with $p<0.05$ considered significant.

Results

After conducting research between January 2024 and October 2024 using consecutive sampling on patients attending the Internal Medicine outpatient clinic at Dr. Kariadi General Hospital, Semarang, a total of 446 patients with hypothyroidism and hyperthyroidism were identified. Of these, 54 patients met the inclusion and exclusion criteria.

Characteristics of study participants. The study included 54 participants, with a higher proportion of females (n=43, 79.6%) than males (n=11, 20.4%). The mean age was 41.27±14.41 years, ranging from 19 to 67 years. Participants were categorized into three age

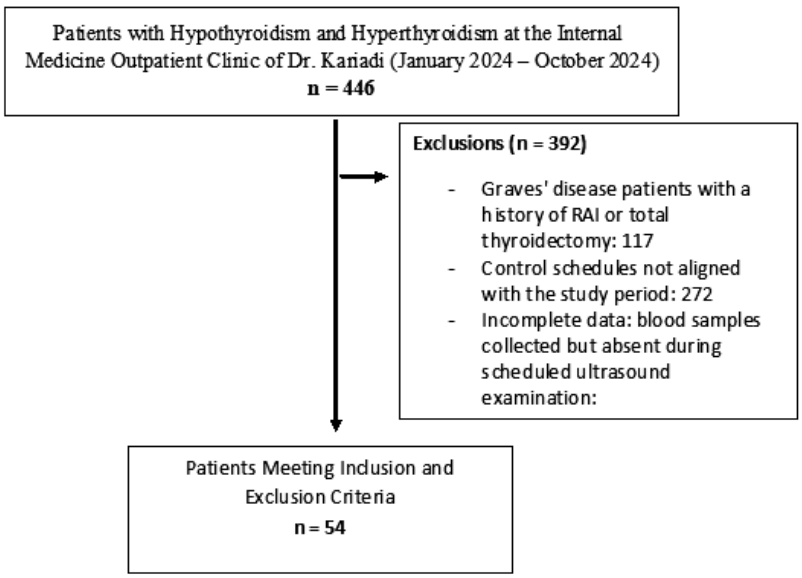

Figure 1. The flowchart of participant enrollment in this study.

groups: <30 years (n=14, 25.9%), 30–50 years (n=25, 46.3%), and >50 years (n=15, 27.8%). Most participants had completed high school as their highest education level (n=26, 48.1%) (Table 1).

Clinical characteristics of patients with hypothyroidism. Among the 27 participants with hypothyroidism, the most frequent symptoms were malaise (n=25, 92.6%) and weight gain (n=15, 55.6%). Other common symptoms included constipation (n=10, 37%) and dry skin (n=14, 51.9%). Most patients had been diagnosed with hypothyroidism for more than 6 months (n=20, 74.1%). All patients were being treated with levothyroxine. The most prevalent comorbidities were hypertension (n=8, 29.6%) and dyslipidemia (n=6, 22.2%) (Table 2).

Clinical characteristics of patients with hyperthyroidism. The 27 participants with hyperthyroidism most commonly presented with weight loss (n=17, 63%), palpitations (n=23, 85.2%), and heat intolerance with excessive sweating (n=18, 66.7%). A majority had diffuse goiter (n=15, 55.6%) and had been diagnosed with hyperthyroidism for more than 6 months (n=18, 66.7%). Thiamazole was the most common antithyroid medication used (n=25, 92.6%). Few patients had a history of smoking (n=2, 7.4%) or other autoimmune diseases (n=0) (Table 2).

Assessment of triglycerides, fasting blood glucose (FBG), TyG index, complement C5, and Lp(a). The mean triglyceride level was 117.88±72.39 mg/dL, and the mean FBG level was 95.44±12.13 mg/dL. The mean TyG index was 4.57±0.29. No significant differences were found in triglyceride levels, FBG levels, or TyG index between hypothyroid and hyperthyroid patients (Tables 3).

Complement C5 levels had a median of 8.67 mg/dL (range: 5.53–93.32 mg/dL) in the total sample. Hypothyroid patients showed a median C5 level of 8.67 mg/dL (range: 5.53–44.88 mg/dL), while hyperthyroid patients had a slightly higher median of 8.71 mg/dL (range: 5.57–93.82 mg/dL). The difference between the two groups was not statistically significant (p=0.052) (Tables 3).

Lp(a) levels showed a median of 15.37 mg/dL (range: 13.72–17.13 mg/dL) for the overall sample. Hypothyroid patients had a median Lp(a) level of 15.37 mg/dL, similar to hyperthyroid patients with a median of 15.50 mg/dL. The difference was not statistically significant (p=0.583) (Table 3).

Participants were categorized by a TyG Index cutoff of 4.5, with values ≥4.5 indicating potential insulin resistance. Among hypothyroid patients, 17 (63%) had potential insulin resistance, compared to 13 (48.1%) in the hyperthyroid group. A chi-square test showed no significant difference between the groups (p=0.411).

cIMT measurements. cIMT was assessed in 54 patients. Mean cIMT of the right and left carotid arteries were 0.57±0.11 mm and 0.56±0.13 mm, respectively. Maximum cIMT values were 0.71±0.14 mm for the right and 0.72±0.23 mm for the left carotid artery (Table 4). The cIMT values in hypothyroid and hyperthyroid patients are presented in Table 4. No significant differences were observed between the two groups for any of the cIMT parameters (p>0.05, Mann-Whitney test).

Table 1
Characteristics of study participants

Variable	Hypothyroidism (n=27)	Hyperthyroidism (n=27)	Total (n=54)
Gender			
Male	4 (14.8%)	7 (25.9%)	11 (20.4%)
Female	23 (85.2%)	20 (74.1%)	43 (79.6%)
Age (years)			
<30	7 (25.9%)	7 (25.9%)	14 (25.9%)
30–50	10 (37.0%)	15 (55.6%)	25 (46.3%)
>50	10 (37.0%)	5 (18.5%)	15 (27.8%)
Education Level			
Elementary School	2 (7.4%)	2 (7.4%)	4 (7.4%)
Middle School	4 (14.8%)	1 (3.7%)	5 (9.3%)
High School	13 (48.1%)	13 (48.1%)	26 (48.1%)
College/University	8 (29.6%)	11 (40.7%)	19 (35.2%)

Table 2
Clinical characteristics of patients with hypothyroidism (n=27) and hyperthyroidism (n=27)

Patients with hypothyroidism		**Patients with hyperthyroidism**	
Clinical Characteristics	**Value**	**Clinical Characteristics**	**Value**
Early sign and symptom N (%)		Early sign and symptom N (%)	
Malaise	25 (92.6%)	Weight loss	17 (63%)
Weight gain	15 (55.6%)	Diarrhea	12 (44.4%)
Constipation	10 (37%)	Insomnia	13 (48.1%)
Excessive sleepiness	8 (29.6%)	Excessive sweating, heat intolerance	18 (66.7%)
Hoarseness	1 (3.7%)	Palpitations	23 (85.2%)
Dry skin	14 (51.9%)	Dyspnea on exertion	18 (66.7%)
Reduced sweating	2 (7.4%)	Increased appetite	20 (74.1%)
Periorbital edema	5 (18.51%)	Tremor	20 (74.1%)
		Exophthalmos	12 (44.4%)
Diffuse goiter [N (%)]	13 (48.1%) 1 (3.7%)	**Diffuse Goiter [N (%)]**	15 (55.6%)
		Nodualr Goiter [N (%)]	2 (7.4%)
Billewicz index	–10.55±14.91 (–11; [–38]–25)*	Wayne Index	23.00±6.83 (23; 2–33)*
		New Castle Index	35.96±9.72 (37; 16–52)*
Duration of diagnosis (months)	47.70±57.23 (36; 1–216)*	Duration of diagnosis (months)	18.03±19.17 (12; 1–72)*
<6 months [N (%)]	7 (25.9%)	<6 months [N (%)]	9 (33.3%)
>6 months [N (%)]	20 (74.1%)	>6 months [N (%)]	18 (66.7%)
		Thyroid Treatment	
		PTU	1 (3.7%)
Levothyroxine use [N(%)]	27 (100%)	Thiamazole	25 (92.6%)
Statin Use [N (%)]		Statin Use [N (%)]	
No statin	22 (81.5%)	Tidak Konsumsi	22 (81.5%)
Simvastatin 10 mg	1 (3.7%)	Simvastatin 10 mg	2 (7.4%)
Simvastatin 20 mg	2 (7.4%)	Atorvastatin 10 mg	2 (7.4%)
Atorvastatin20 mg	2 (7.4%)	Rosuvastatin 20 mg	1 (3.7%)
Comorbidities [N(%)]		Comorbidities [N(%)]	
Diabetes Mellitus	3 (11.1%)	Diabetes Mellitus	3 (11.1%)
Hypertension	8 (29.6%)	Hypertension	5 (18.5%)
Dyslipidemia	6 (22.2%)	Dyslipidemia	7 (25.9%)
Other autoimmune diseases [N(%)]		Other autoimmune diseases [N(%)]	0
Rheumatoid Artritis	1 (3.7%)		
Systemic lupus erythematosus (SLE)	3 (11.1%)		
Unspecified autoimmune history	1 (3.7%)		
Smoking history [N(%)]	1 (3.7%)	Smoking history [N(%)]	2 (7.4%)
Body Weight (kg)	57.67±15.45 (55; 31–94)*	Body Weight (kg)	59.40±15.90 (54; 35–95)*
BMI (kg/m^2)	24.03±5.24 (24.8; 13.8–34.5)*	BMI (kg/m^2)	23.6±5.12 (23.9; 13.8–34.5)*
Initial Laboratory Parameters		Initial Laboratory Parameters	
TSH (serum) (mIU/L) (n=27) (Normal: 0.51–4.94)	32.3±40.79 (14; 4.98–150)*	TSH (serum) (mIU/L) (n=27)	0.02±0.17 (0.01; 0.01–0.5)*
FT4 (serum) (pmol/L) (n=27) (Normal: 10.6–19.4)	8.54±4.32 (9.2; 0.01–16)*	FT4 (serum) (pmol/L) (n=27)	57.26±79.94 (30.76; 14–429.49)*
Anti TPO (IU/L) (n=11)	1113.11±3020.60 (146.8; 3–10.200)*	TRAb (n=2)	6.79±4.90 (6.79; 3,29–10.3)*

*Data represent Mean±SD (Median; Min–Max). Abbreviations: BMI – body mass index; FT4 – free thyroxine; TPO – thyroid peroxidase; TRAb – TSH receptor antibodies; TSH – thyroid-stimulating hormone.

Table 3
Triglyceride levels, FBG, TyG Index, complement C5, lipoprotein(a) values in all patients and patients with hypothyroidism and hyperthyroidism

Variable	Mean±SD	Median	Min–Max	p-value
Triglycerides (mg/dL)	117.88±72.39	87.50	36–308	
FBG (mg/dL)	95.44±12.13	95.00	68–131	
TyG Index	4.57±0.29	4.52	3.99–5.19	
Complement C5 (mg/dL)	14.24±17.07	8.67	5.53–93.32	
Lipoprotein(a)	15.50±0.88	15.37	13.72–17.13	
Patients with hypothyroidism (n=27)				
Triglycerides (mg/dL)	133.0±83.41	94.50	51–308	
FBG (mg/dL)	97.03±12.02	95.00	73–131	
TyG Index	4.63±0.31	4.63	4.20–5.19	
Complement C5 (mg/dL)	9.70±7.18	8.67	5.53–44.88	
Lipoprotein(a)	15.44±0.88	15.36	13.94–17.09	
Patients with hyperthyroidism (n=27)				
Triglycerides (mg/dL)	102.78±57.03	85	36–293	0.311$^{\gamma}$
FBG (mg/dL)	93.85±12.26	97	68–114	0.610$^{\gamma}$
TyG Index	4.51±0.27	4.52	3.99–5.10	0.283$^{\gamma}$
Complement C5 (mg/dL)	18.78±22.26	8.71	5.57–93.82	0.421$^{\gamma}$
Lipoprotein(a)	15.57±0.90	15.39	13.72–17.13	0.568$^{\gamma}$

All patients (n=54); $^{\gamma}$Mann-Whitney test; p<0.05 considered statistically significant; Abbreviations: FBG – fasting blood glucose; TyG – triglyceride-glucose index.

Table 4
Carotid intima-media thickness (cIMT) measurements in all patients and patients with hypothyroidism and hyperthyroidism

Variable	Mean±SD	Median	Min–Max	p-value
Mean IMT Right (mm)	0.57±0.11	0.55	0.36–0.91	
Mean IMT Left (mm)	0.56±0.13	0.54	0.36–1.07	
Max IMT Right (mm)	0.71±0.14	0.68	0.36–1.08	
Max IMT Left (mm)	0.72±0.23	0.64	0.36–1.4	
Patients with hypothyroidism (n=27)				
Mean IMT Right (mm)	0.60±0.12	0.56	0.43–0.91	
Mean IMT Left (mm)	0.58±0.14	0.57	0.36–1.07	
Max IMT Right (mm)	0.73±0.12	0.68	0.52–1.08	
Max IMT Left (mm)	0.75±0.23	0.68	0.48–1.40	
Patients with hyperthyroidism (n=27)				
Mean IMT Right (mm)	0.55±0.09	0.55	0.36–0.81	0.222$^{\gamma}$
Mean IMT Left (mm)	0.55±0.12	0.54	0.36–0.85	0.436$^{\gamma}$
Max IMT Right (mm)	0.69±0.16	0.68	0.36–1.03	0.349$^{\gamma}$
Max IMT Left (mm)	0.69±0.24	0.60	0.36–1.40	0.141$^{\gamma}$

All patients (n=54); $^{\gamma}$ Mann-Whitney test; p<0.05 considered statistically significant.

To further investigate the distribution of cIMT values, we categorized them into percentiles. Both hypothyroid and hyperthyroid patients predominantly exhibited higher cIMT values, with a majority falling into the >P75 percentile for all cIMT parameters (Table 5). This indicates a higher prevalence of subclinical atherosclerosis in both groups.

Correlation of TyG index with cIMT. To investigate the relationship between insulin resistance and cIMT, we examined correlations between the TyG index and various cIMT parameters in both hypothyroid and hyperthyroid participants. In hypothyroid patients, a weak positive correlation was observed between the TyG index and left max cIMT (r=0.387, p=0.046). However, no significant correlations were found for other cIMT parameters (Table 6). In hyperthyroid patients, a moderate positive correlation was observed between the TyG index and mean right cIMT (r=0.436, p=0.023). No significant correlations were found for other cIMT parameters in hyperthyroid patients (Table 6).

Correlation of complement C5 with cIMT. To explore the potential role of inflammation in atherosclerotic changes in thyroid dysfunction, we investigated the association between complement C5 levels and cIMT. In hypothyroid patients, a trend towards a positive correlation was observed between complement C5 levels and cIMT although this did not reach statistical significance for most cIMT measurements.

Table 5
Carotid intima-media thickness (cIMT) percentile categories in patients with hypothyroidism and hyperthyroidism

Variable	Percentile	Hypothyroidism (n=27) N (%)	Hyperthyroidism (n=27) N (%)
Mean IMT Right	<P25	0 (0%)	1 (3.7%)
	P25–P50	2 (7.4%)	3 (11.1%)
	P50–P75	4 (14.8%)	3 (11.1%)
	>P75	21 (77.8%)	20 (74.1%)
Mean IMT Left	<P25	2 (7.4%)	1 (3.7%)
	P25–P50	9 (33.3%)	4 (14.8%)
	P50–P75	2 (7.4%)	9 (33.3%)
	>P75	14 (51.9%)	13 (48.1%)
Max IMT Right	<P25	0 (0%)	1 (3.7%)
	P25–P50	0 (0%)	0 (0%)
	P50–P75	1 (3.7%)	2 (7.4%)
	>P75	26 (96.3%)	24 (88.9%)
Max IMT Left	<P25	1 (3.7%)	0 (0%)
	P25–P50	8 (29.6%)	2 (7.4%)
	P50–P75	3 (11.1%)	3 (11.1%)
	>P75	13 (55.6%)	22 (81.5%)

Table 6
Correlation test of triglyceride-glucose (TyG) index with various carotid intima-media thickness (cIMT) parameters in patients with hypothyroidism and hyperthyroidism

	Mean cIMT		Max cIMT	
	Right	Left	Right	Left
Patients with hypothyroidism				
p-value	0.957$^{\delta}$	0.186$^{\delta}$	0.179$^{\delta}$	0.046$^{\delta}$
Correlation Coefficient	0.011	0.262	0.266	0.387
Patients with hyperthyroidism				
p-value	0.023$^{\delta}$	0.256$^{\delta}$	0.097$^{\delta}$	0.303$^{\delta}$
Correlation Coefficient	0.436	0.226	0.326	0.206

$^{\delta}$Spearman test; significant p<0.05.

However, a significant positive correlation was found between C5 levels and maximum left cIMT (p=0.040, r=0.397), suggesting a potential role for complement activation in early atherosclerotic changes in this patient group (Table 7). In hyperthyroid patients, a significant positive correlation was observed between complement C5 levels and mean right cIMT (p=0.027, r=0.426), indicating a potential link between elevated C5 levels and early atherosclerotic changes, particularly in the right carotid artery. While other cIMT measurements exhibited positive correlations with complement C5, these did not reach statistical significance (Table 7).

Correlation of Lp(a) with cIMT. To evaluate the potential contribution of Lp(a) to atherosclerosis in the context of thyroid dysfunction, we analyzed its relationship with cIMT in both hypothyroid and hyperthyroid participants. In the hypothyroid group, no significant correlations were found between Lp(a) levels and any cIMT parameter (mean right, max right, mean left, max left) (Table 8). Similarly, in the hyperthyroid group, no significant correlations were observed between Lp(a) levels and any cIMT measurement (Table 8).

Impact of risk factors on cIMT. We assessed the influence of several potential risk factors on cIMT, including gender, age, duration of thyroid medication, and statin use (Table 9). Our analysis revealed that older age was associated with increased cIMT, particularly for mean right and left cIMT. Gender, duration of thyroid medication and statin use did not significantly impact cIMT (Table 9).

Discussion

This study is the first to comprehensively explore the association between insulin resistance, complement activation, and Lp(a) with subclinical atherosclerosis in thyroid dysfunction. A significant positive correlation between the TyG index and cIMT in hypothyroid and hyperthyroid patients highlights insulin resistance's role in promoting vascular inflammation and endothelial dysfunction. Additionally, the correlation between complement C5 levels and cIMT underscores the complement system's contribution to atherosclerotic plaque formation.

Table 7
Correlation between complement C5 levels and various carotid intima-media thickness (cIMT) parameters in patients with hypothyroidism and hyperthyroidism

	Mean cIMT		Max cIMT	
	Right	**Left**	**Right**	**Left**
Patients with hypothyroidism				
p-value	0.091$^{\delta}$	0.128$^{\delta}$	0.262$^{\delta}$	0.040$^{\delta}$
Correlation Coefficient	0.332	0.300	0.224	0.397
Patients with hyperthyroidism				
p-value	0.027$^{\delta}$	0.183$^{\delta}$	0.105$^{\delta}$	0.089$^{\delta}$
Correlation Coefficient	0.426	0.264	0.319	0.334

$^{\delta}$Spearman test; significant p<0.05.

Table 8
Correlation between lipoprotein(a) levels and various carotid intima-media thickness (cIMT) parameters in patients with hypothyroidism and hyperthyroidism

	Mean cIMT		Max cIMT	
	Right	**Left**	**Right**	**Left**
Patients with hypothyroidism				
p-value	0.597$^{\delta}$	0.166$^{\delta}$	0.719$^{\delta}$	0.620$^{\delta}$
Correlation Coefficient	0.107	0.274	–0.73	0.100
Patients with hyperthyroidism				
p-value	0.909$^{\delta}$	0.289$^{\delta}$	0.478$^{\delta}$	0.294$^{\delta}$
Correlation Coefficient	0.023	–0.212	0.142	–0.210

$^{\delta}$Spearman test, significant p<0.05.

Table 9
Statistical test of confounding factors with carotid intima-media thickness (cIMT)

Variable		Freq	cIMT Mean±SD; (min–max)							
			Mean cIMT Right	p-value	Mean cIMT Left	p-value	Max cIMT Right	p-value	Max cIMT Left	p-value
Gender	Male	11	0.61±0.14 (0.43–0.91)	0.526[γ]	0.60±0.19 (0.41–1.07)	0.691[γ]	0.71±0.15 (0.51–1.08)	0.698[γ]	0.78±0.29 (0.56–1.36)	0.597[γ]
	Female	43	0.57±0.10 (0.36–0.88)		0.56±0.11 (0.36–0.82)		0.71±0.14 (0.36–1.03)		0.70±0.22 (0.36–1.40)	
Age	<30 years	14	0.53±0.12 (0.36–0.81)	0.027[#]	0.46±0.08 (0.36–0.63)	0.002[#]	0.69±0.17 (0.36–1.03)	0.392[#]	0.65±0.26 (0.36–1.40)	0.027[#]
	30–50 years	25	0.58±0.10 (0.43–0.91)		0.60±0.14 (0.43–1.07)		0.71±0.15 (0.52–1.08)		0.72±0.23 (0.51–1.36)	
	>50 years	15	0.60±0.10 (0.50–0.88)		0.60±0.10 (0.47–0.82)		0.73±0.09 (0.60–0.93)		0.78±0.22 (0.56–1.40)	
Duration of Thyroid Medication	<6 months	16	0.57±0.10 (0.43–0.82	0.762[γ]	0.57±0.11 (0.36–0.82)	0.798[γ]	0.73±0.14 (0.52–1.02)	0.628[γ]	0.59±0.24 (0.48–1.4)	0.607[γ]
	>6 months	38	0.57±0.12 (0.36–0.91)		0.56±0.14 (0.36–1.07)		0.70±0.14 (0.36–1.08)		0.72±0.23 (0.36–1.4)	
Satatin Use	No	44	0.56±0.11 (0.36–0.91)	0.090[γ]	0.56±0.13 (0.36–1.07)	0.624[γ]	0.70±0.14 (0.36–1.08)	0.299[γ]	0.71±0.23 (0.36–1.4)	0.502[γ]
	Yes	10	0.63±0.12 (0.52–0.82)		0.58±0.13 (0.41–0.82)		0.75±0.11 (0.60–0.93)		0.75±0.25 (0.56–1.4)	

[γ]Mann-Whitney test, significant p<0.05. [#]Kruskal Wallis test, significant p<0.05.

Cheng et al. (2023) have demonstrated threshold and saturation effects in the relationship between FT4, TSH, and the TyG index, suggesting distinct mechanisms of insulin resistance in hypo- and hyperthyroidism. Thyroid hormones may influence insulin secretion directly and indirectly by inhibiting glucose-induced insulin secretion and reducing β-cell responsiveness. Hypothyroidism impairs glucose uptake, elevates insulin levels, and suppresses hepatic glucose production. Hyperthyroidism enhances glucose utilization, increasing insulin demand in peripheral tissues and impairing hepatic insulin sensitivity.

In our study, 77.8% of hypothyroid and 74.1% of hyperthyroid patients exhibited cIMT values above the 75th percentile. Consistent with Isaila et al. (2024) review has shown an increased cIMT in subclinical hypothyroidism (mean difference 0.08, 95% CI 0.05–0.10, p<0.01), our findings reaffirm the link between thyroid dysfunction and carotid wall thickening. Zhang et al. (2024) have identified FT4 as an independent risk factor for increased cIMT mediated by apoA-I, suggesting a U-shaped relationship between FT4 and atherosclerosis risk. The complement system also appears integral to thyroid disease. Zhao et al. (2022) have provided insights into the role of the complement system in thyroid disease. They investigated the expression of complement components in thyroid tissue and serum of patients with Hashimoto's thyroiditis (HT), GD, and papillary thyroid cancer (PTC). Results showed that Membrane Attack Complex (MAC) deposition was detected in thyroid tissues of HT, GD, and PTC patients, but not in control groups. The staining intensity of MBL, Bb, C4d, C3d, and MAC was significantly higher in HT and PTC groups compared to controls (all p<0.05).

Interestingly, no significant association between Lp(a) and cIMT was observed, likely due to levothyroxine therapy in all hypothyroid patients. Becerra et al. (1999) have shown that levothyroxine reduces Lp(a) levels, mitigating early atherosclerosis risk in hypothyroidism. Similarly, Sulu et al. (2024) have found no association between Lp(a) and Graves' ophthalmopathy or cIMT in hyperthyroidism, suggesting that other factors may play more critical roles in cardiovascular risk.

Several limitations of this study should be acknowledged. First, the cross-sectional design limits the ability to establish causal relationships between the studied variables, including the TyG index, Lp(a), complement activation, and cIMT. Second, all hypothyroid patients in this study were on levothyroxine therapy, while all hyperthyroid patients had previously received PTU or thiamazole. Third, differences in the duration of treatment

among patients at the time of sample collection may have influenced the outcomes. Future longitudinal studies with larger cohorts are needed to address these limitations and further clarify the relationships between thyroid dysfunction, lipid metabolism, and subclinical atherosclerosis.

In conclusion, our study highlights the multifaceted interplay between thyroid dysfunction, metabolic dysregulation, and vascular pathology. These findings emphasize the importance of comprehensive cardiovascular risk assessment in thyroid patients and support the potential of targeted therapies and insulin resistance management, in mitigating atherosclerosis progression.

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