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ORIGINAL ARTICLE

Association Between Carotid Intima-Media Thickness and Novel Lipid Parameters in Hypertensive Patients

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Abstract

Introduction Carotid Intima-Media Thickness (IMT) is a marker of subclinical atherosclerosis and cardiovascular risk. Dyslipidemia is a well-established risk factor for atherosclerosis and novel lipid parameters have recently emerged.

Aim The aim of our study was to assess the association between IMT and novel lipid parameters in hypertensive patients.

Methods We analyzed the IMT of 848 hypertensive patients followed at the Hypertension Unit of San Gerardo Hospital (Monza, Italy). Classic (total, HDL, LDL and non-HDL cholesterol and triglycerides) and novel indices (non-HDL/HDL, LDL/HDL, total cholesterol/HDL, log triglycerides/HDL and triglycerides-glycemia index) were measured and calculated.

Results Univariable analyses showed a significant correlation between IMT and most lipid parameters. Multivariable linear regression with IMT as continuous dependent variable revealed a significant association with total cholesterol (β = 0.108, $p = 0.001$), LDL cholesterol (β = 0.119, $p < 0.001$), non-HDL cholesterol (β = 0.126, $p < 0.001$), non-HDL/HDL (β = 0.134, $p < 0.001$), LDL/HDL (β = 0.140, $p < 0.001$) and total cholesterol/HDL (β = 0.134, $p < 0.001$). Logistic multivariable regression with IMT categorized as ≥or < 0.9 mm demonstrated a significant association with total cholesterol (OR = 1.100 per 10 mg/dL increase, $p = 0.003$), LDL cholesterol (OR = 1.130 per 10 mg/dL increase, $p = 0.001$), non-HDL cholesterol (OR = 1.110 per each unit increase, $p = 0.001$), non-HDL/HDL (OR = 1.368 per each unit increase, $p = 0.002$), LDL/HDL (OR = 1.583 per each unit increase, $p = 0.001$) and total cholesterol/HDL (OR = 1.368 per each unit increase, $p = 0.002$).

Conclusions Carotid IMT is significantly associated with various lipid parameters, with the strongest association observed for non-HDL/HDL, LDL/HDL and total cholesterol/HDL.

Keywords Intima media thickness · Novel lipid parameter · Arterial hypertension

1 Introduction

Carotid Intima-Media Thickness (IMT) is a marker of subclinical atherosclerosis and it is recognized as a manifestation of Hypertension-Mediated Organ Damage (HMOD).

While many studies established its role in predicting future CardioVascular (CV) events [1–9], others reported negative results [10–13]. In fact, recent guidelines questioned its utility in CV risk stratification, favoring the identification of atherosclerotic plaque instead [14, 15]. However, IMT remains valuable in research, particularly for assessing the impact of various factors (diseases or pharmacological therapies) on arterial structure. In this context it is important to further clarify the role of factors associated with IMT. Among them, dyslipidemia is a key CV risk factor and its association with IMT has been well documented [16–18]. Beyond classic lipid parameters (total, HDL - high-density lipoprotein, LDL - low-density lipoprotein and non-HDL cholesterol and triglycerides - TG), emerging novel lipid indices may provide better predicting value for CV risk stratification and early atherosclerosis identification [19–22]; however, the association between IMT and the latter hasn't been extensively investigated. These include non-HDL/HDL, LDL/HDL, total cholesterol/HDL, logTG/HDL and TG-glycemia index (TyG).

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Thus, our study aimed at evaluating the potential association between carotid IMT and both classic and novel lipid parameters in hypertensive patients.

2 Methods

2.1 Study Population

From September 2006 to October 2010, we consecutively enrolled 1180 essential hypertensive outpatients, aged from 18 to 80 years, followed by the Hypertension Unit of San Gerardo Hospital (Monza, Italy).

Patients were included if they had a definitive diagnosis of hypertension and a stable anti-hypertensive therapy for at least three months. Diagnosis of hypertension was defined as the presence of: (i) anti-hypertensive therapies; (ii) two office Blood Pressure (BP) values higher than 140/90 mmHg measured on two different occasions; (iii) one office BP value higher than 140/90 mmHg with either home BP or 24 h-Ambulatory BP monitoring showing average values higher than 135/85 mmHg.

Exclusion criteria were pregnancy, atrial fibrillation, previous CV events (acute coronary syndrome, previous coronary revascularization, angina pectoris, heart failure, stroke, transient ischemic attack and claudication), substance abuse and history of cancer.

The study protocol was approved by the institutional ethics review committee of the institution involved (San Gerardo Hospital Ethical Committee, number 638–2006) and all participants provided informed written consent after being informed of its nature and purpose.

As shown in Fig. 1, a total of 332 patients were excluded from the present analysis due to missing total cholesterol (n = 193), HDL cholesterol (n = 107) or IMT (n = 32) data. So, a total of 848 patients were included in the final analysis.

2.2 Data Collection

For each patient medical history was collected and a physical examination was performed. BP measurements were taken by a trained physician using an oscillometric automatic device (OMRON 705-IT, OMRON Healthcare Europe, Hoofddorp, The Netherlands) with the patient in the supine position for at least 5 min and with the arm placed at heart level. BP was measured twice and the mean was used for the analysis.

After BP evaluation, blood was drawn for biochemical evaluation and then carotid ultrasound was performed. Laboratory parameters include creatinine, glycemia, total

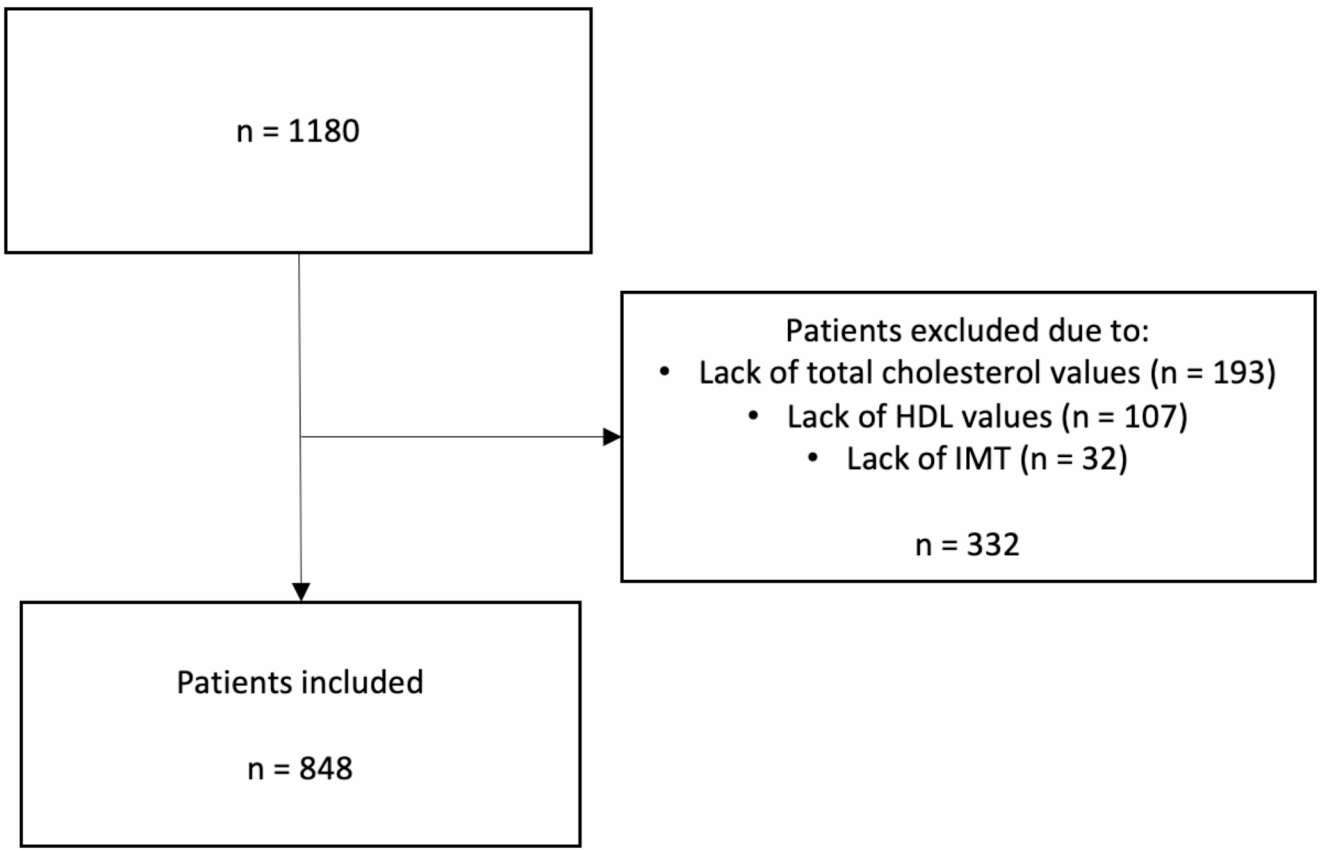

Fig. 1 Flow chart of included and excluded patients

cholesterol, HDL cholesterol and TG. LDL cholesterol was calculated using the Sampson formula [23, 24]. Additionally, derived lipid indices were computed: non-HDL cholesterol, non-HDL/HDL, LDL/HDL, total cholesterol/HDL, logTG/HDL and TyG (the natural logarithm of TG*glycemia). Glomerular Filtration Rate (GFR) was estimated by the Cockcroft-Gault equation. Height and weight were measured and used for Body Mass Index (BMI) calculation.

2.3 Carotid Ultrasonography

With the patient in the supine position with the neck in partial extension, we scanned the common carotid artery through an ultrasonography device (Philips Sonos 5500). The transducer was manually positioned perpendicularly to the longitudinal axis of the vessel under B-mode guidance and common carotid IMT was measured at the posterior wall site located 2 cm below the carotid bifurcation as the distance between the inner hypoechogenic and the middle anechogenic layers. Measurements were made by two operators blinded to the subject's clinical status, two measurements were obtained per patient and the mean value was used for the analysis. In our laboratory the intra-session within- and between-operator variability of IMT amounts to a coefficient of variation of the mean value of 2.5% and 2%, respectively. The corresponding value for the inter-session between-operator variability was 3.9%. Carotid HMOD was considered as an IMT ≥ 0.9 mm.

2.4 Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as counts and percentages. Between-groups differences were assessed by Student t-test for normally distributed continuous variables and the $\chi 2$ test (or by Fisher's exact test when appropriate) for categorical variables. Pearson's correlation coefficient was used to assess the relationship between IMT and lipid parameters. Linear (IMT as continuous dependent variable) and logistic (carotid HMOD as categorical dependent variable) multivariable analyses were performed. Each lipid parameter was analyzed individually within the models for age, sex, smoking status, BMI, systolic BP, GFR, diabetes mellitus and CV therapies (renin-angiotensin-aldosterone system inhibitors, beta-blockers, calcium channel-blockers, alpha-blockers, diuretics and statins) as covariates. SPSS 13.0 (SPSS, IBM, United States) was used for statistical analysis and two-sided p-value < 0.05 was considered statistically significant.

Table 1 Characteristics of the whole population and when patients were divided according to carotid hypertension-mediated organ damage (intima-media thickness ≥ 0.9 mm)

	Whole population	IMT < 0.9 mm	IMT ≥ 0.9 mm	*p*-value
Clinical and anamnestic data				
Number	848	698	140	
Age (years)	54.0 ± 13.6	51.7 ± 13.1	64.6 ± 10.1	< 0.001
Males (%)	56.4	54.4	62.9	0.076
Smokers (%)	15.0	15.3	12.9	0.859
DM (%)	7.8	7.2	10.0	0.294
BMI (Kg/m^2)	26.9 ± 4.1	26.8 ± 4.2	26.9 ± 3.7	0.794
SBP (mmHg)	141.0 ± 18.5	139.6 ± 17.7	147.4 ± 20.6	< 0.001
DBP (mmHg)	85.6 ± 12.1	86.1 ± 11.9	83.3 ± 13.0	0.012
HR (bpm)	66.2 ± 10.6	67.0 ± 10.7	62.7 ± 9.1	< 0.001
Biochemical data				
GFR (mL/min)	91.0 ± 20.3	93.3 ± 19.8	81.0 ± 18.9	< 0.001
Glucose (mg/dL)	90.8 ± 23.9	89.5 ± 22.8	96.7 ± 28.0	0.001
Lipid parameters				
Total cholesterol (mg/dL)	197.8 ± 35.2	196.3 ± 35.2	206.1 ± 34.4	0.003
LDL cholesterol (mg/dL)	122.5 ± 31.9	120.9 ± 31.7	130.5 ± 32.3	0.001
HDL cholesterol (mg/dL)	53.4 ± 13.8	53.7 ± 13.9	52.6 ± 13.3	0.387
Triglycerides (mg/dL)	121.7 ± 70.4	120.4 ± 68.9	127.4 ± 76.2	0.279
Non HDL (mg/dL)	144.4 ± 35.8	142.6 ± 35.5	153.5 ± 36.1	0.001
Non HDL/HDL	2.9 ± 1.1	2.9 ± 1.1	3.1 ± 1.2	0.009
LDL/HDL	2.4 ± 0.9	2.4 ± 0.9	2.6 ± 0.9	0.003
Total cholesterol/HDL	3.9 ± 1.1	3.9 ± 1.1	4.1 ± 1.2	0.009
LogTG/HDL	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.260
TyG	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.3	0.971
CV drugs				
ACE/ARB (%)	59.3	55.2	79.3	< 0.001
CCB (%)	29.1	27.5	37.9	0.019
B-blockers (%)	23.7	22.3	31.4	0.029
Alpha-blockers (%)	11.3	9.7	19.3	0.002
Diuretics (%)	30.4	26.9	47.9	< 0.001
Statins (%)	12.1	11.2	17.1	0.064

Table 1 (continued)

	Whole population	IMT <0.9 mm	IMT ≥0.9 mm	*p*-value
Arterial structural property				
IMT (mm)	0.68 ± 0.19			-

IMT: intima-media thickness; DM: diabetes mellitus; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; GFR: glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides; TyG: TG/glycemia index; ACE: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blockers

3 Results

3.1 Population's Characteristics

Table 1 shows the characteristics of the whole population enrolled (848 patients). Mean age was 54.0 ± 13.6 and 56.4% were males. Regarding CV risk factors, 15.0% were smokers, 7.8% had diabetes mellitus, mean BMI was 26.9 ± 4.1 Kg/m^2 and mean systolic and diastolic BP were 141.0 ± 18.5 mmHg and 85.6 ± 12.1 mmHg, respectively. The mean glycemia was 90.8 ± 23.9 mg/dL and the mean GFR was 91.0 ± 20.3 mL/min.

For lipid parameters, the mean total cholesterol was 197.8 ± 35.2 mg/dL, LDL cholesterol was 122.5 ± 31.9 mg/dL, HDL cholesterol was 53.4 ± 13.8 mg/dL and TG were 121.7 ± 70.4 mg/dL. Furthermore, Table 1 reports derived lipid parameters, in particular, non-HDL cholesterol was 144.4 ± 35.8 mg/dL, non-HDL/HDL ratio was 2.9 ± 1.1, LDL/HDL ratio was 2.4 ± 0.9, total cholesterol/HDL ratio was 3.9 ± 1.1, logTG/HDL ratio was 0.04 ± 0.01 and TyG was 4.1 ± 0.3.

Regarding antihypertensive treatments, 59.3% of the patients were on renin-angiotensin-aldosterone system inhibitors, 29.1% on calcium channel-blockers, 30.4% on diuretics, 23.7% on beta-blockers, 11.3% on alpha-blockers, while 12.1% were on statins. Finally, mean IMT was 0.68 ± 0.19 mm.

Table 1 also compares patients based on carotid HMOD (IMT <or ≥0.9 mm). Patients with an increased IMT (140 vs. 698 without carotid HMOD) were older (64.6 ± 10.1 vs. 51.7 ± 13.1 years, $p < 0.001$), had higher systolic BP (147.4 ± 20.6 vs. 139.6 ± 17.7 mmHg, $p < 0.001$) and higher glycemia (96.7 ± 28.0 vs. 89.5 ± 22.8 mg/dL, $p = 0.001$), while having lower GFR (81.0 ± 18.9 vs. 93.3 ± 19.8 mL/min, $p < 0.001$).

Among lipid parameters, patients with carotid HMOD exhibit higher values of total cholesterol (206.1 ± 34.4 vs. 196.3 ± 35.2 mg/dL, $p = 0.003$), LDL cholesterol (130.5 ± 32.3 vs. 120.9 ± 31.7 mg/dL, $p = 0.001$), non-HDL cholesterol (153.5 ± 36.1 vs. 142.6 ± 35.5 mg/dL, $p = 0.001$), non-HDL/HDL ratio (3.1 ± 1.2 vs. 2.9 ± 1.1, $p = 0.009$), LDL/HDL ratio (2.6 ± 0.9 vs. 2.4 ± 0.9, $p = 0.003$) and total cholesterol/HDL ratio (4.1 ± 1.2 vs. 3.9 ± 1.1, $p = 0.009$). No differences were seen for HDL cholesterol, TG, logTG/HDL ratio and TyG.

Patients with higher IMT were more frequently treated with renin-angiotensin-aldosterone system inhibitors, alpha-blockers and diuretics.

3.2 Univariate and Multivariable Analysis

Univariate analysis (Table 2) shows a significant correlation between IMT and several lipid parameters. Particularly, total cholesterol ($r = 0.12$, $p = 0.001$), LDL cholesterol ($r = 0.12$, $p = 0.001$), non-HDL cholesterol ($r = 0.12$, $p < 0.001$), non-HDL/HDL ($r = 0.09$, $p = 0.009$), LDL/HDL ($r = 0.10$, $p = 0.004$) and total cholesterol/HDL ($r = 0.09$, $p = 0.009$). HDL cholesterol, TG and TyG didn't show a significant correlation with IMT.

At multivariable linear regression with IMT as a continuous dependent variable (Table 3), we noticed significant associations with total cholesterol (β = 0.108, 95% CI 0.011–0.110, $p = 0.001$), LDL cholesterol (β = 0.119, 95% CI 0.011–0.128, $p < 0.001$), non-HDL cholesterol (β = 0.126, 95% CI 0.001–0.157, $p < 0.001$), non-HDL/HDL (β = 0.134, 95% CI 0.120–0.350, $p < 0.001$), LDL/HDL (β = 0.140, 95% CI 0.110–0.450, $p < 0.001$) and total cholesterol/HDL (β = 0.134, 95% CI 0.120–0.350, $p < 0.001$). On the contrary, no association was seen for HDL cholesterol, TG and TyG.

A logistic multivariable analysis with carotid HMOD (IMT ≥0.9 mm) as dependent variable found a significant association with total cholesterol (OR = 1.100 per 10 mg/dL increase, 95% CI 1.040–1.170, $p = 0.003$), LDL cholesterol (OR = 1.130 per 10 mg/dL increase, 95% CI 1.060–1.210, $p = 0.001$), non-HDL cholesterol (OR = 1.110 per unit increase, 95% CI 1.040–1.180, $p = 0.001$), non-HDL/HDL (OR = 1.368 per unit increase, 95% CI 1.120–1.672, $p = 0.002$), LDL/HDL (OR = 1.583 per unit increase, 95% CI 1.220–2.550, $p = 0.001$) and total cholesterol/HDL (OR = 1.368 per unit increase, 95% CI 1.120–1.672, $p = 0.002$). Similar to linear regression model, HDL cholesterol, TG and TyG index were not significantly associated with IMT.

4 Discussion

The primary finding of our study is that carotid IMT and carotid HMOD (IMT ≥0.9 mm) are significantly associated with both traditional and novel lipid parameters. The strongest associations were observed for non-HDL/HDL, LDL/

Table 2 Univariate correlation analysis between intima-media thickness and lipid parameters

	IMT	
Variable	r	p
Total cholesterol (mg/dL)	0.12	0.001
HDL (mg/dL)	−0.02	0.602
LDL (mg/dL)	0.12	0.001
TG (mg/dL)	0.04	0.233
Non HDL (mg/dL)	0.12	< 0.001
Non HDL/HDL	0.09	0.009
LDL/HDL	0.10	0.004
Total cholesterol/HDL	0.09	0.009
TyG	0.002	0.952

IMT = Intima-Media Thickness; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; TG = TriGlycerides; TyG = Triglycerides-Glucose Index

HDL and total cholesterol/HDL, while HDL cholesterol, TG and TyG index were not significantly related to IMT.

Previous studies assessed the relationship between lipid parameters and IMT, though none has comprehensively examined both traditional and novel lipid indices in a hypertensive population in a complete way, so our study has a point of novelty and strength in doing this. Our results align with findings from prior research indicating that LDL/HDL and total cholesterol/HDL ratios are associated with increased carotid IMT in the general population [25–27] and among diabetic patients [28]. In this latter study, also total cholesterol/HDL was associated with elevated carotid IMT or the presence of carotid plaque [28]. Furthermore, non-HDL/HDL ratio was correlated with carotid atherosclerosis in postmenopausal women in primary prevention settings [29]. However, a study in perimenopausal and menopausal women reported no significant association between total cholesterol/HDL, triglycerides/HDL, LDL/HDL and subclinical atherosclerosis [30].

Our findings suggest that novel lipid parameters may better reflect atherosclerotic burden compared to individual lipid markers. This could be due to their ability to integrate both atherogenic and protective lipid components. In fact, all of them don't only consider atherogenic components (LDL cholesterol, non-HDL or total cholesterol at the numerator) but also protective components (HDL at the denominator). Furthermore, the non-HDL/HDL ratio is also known to be significantly related to metabolic syndrome, a risk factor for atherosclerosis [29, 31].

However, without atherogenic components, HDL itself didn't relate to IMT in our study with similar results also for TG and TyG. Although TG present an atherogenic profile, the strength of the association is lower than other lipoproteins (non-HDL and LDL cholesterol) and this is probably the reason why they lack a significant association in our study [32]. Finally, more than an atherogenic index, TyG is a surrogate marker of insulin resistance [33] that is associated with an increased CV mortality [34]. Both metabolic syndrome [35] and insulin resistance [36–38] were associated with increased IMT values. Insulin resistance was commonly measured with homeostasis model assessment (or other derived indices) while TyG has been only recently evaluated and it yielded to mixed results. TyG was correlated with IMT [39] primarily in high CV risk patients, such as obese individuals [40, 41], ischemic stroke patients [42, 43] and individuals with established coronary atherosclerosis [44].

The only other study on primary prevention subjects showed a significant association between IMT and TyG [45]. However, their population differed from ours in terms of lipid lowering therapies use, hypertension prevalence and lipid profile characteristics and this could have led to different results. In fact, patients in this study had more frequently lipid lowering therapies (32.1% vs. 12.1% in our

Table 3 Multivariable regression models: linear regression for IMT as a continuous variable and logistic regression for imt ≥ 0.9 mm. Each model includes lipid parameters (analyzed individually) adjusted for age, sex, smoking status, BMI, systolic BP, GFR, diabetes mellitus and CV therapies (renin-angiotensin-aldosterone system inhibitors, beta blockers, calcium channel blockers, alpha blockers, diuretics and statins) as covariates

	IMT				IMT ≥ 0.9 mm			
	β	95% CI		p-value	OR	95% CI		p-value
		Lower limit	Upper limit			Lower limit	Upper limit	
Total cholesterol (mg/dL)	0.108	0.011	0.110	0.001	1.100	1.040	1.170	0.003
HDL (mg/dL)	−0.056	−0.200	0.001	0.107	0.991	0.973	1.100	0.348
LDL (mg/dL)	0.119	0.011	0.128	< 0.001	1.130	1.060	1.210	0.001
TG (mg/dL)	0.053	0.001	0.088	0.099	1.010	0.998	1.050	0.428
Non HDL (mg/dL)	0.126	0.001	0.157	< 0.001	1.110	1.040	1.180	0.001
Non HDL/HDL	0.134	0.120	0.350	< 0.001	1.368	1.120	1.672	0.002
LDL/HDL	0.140	0.110	0.450	< 0.001	1.583	1.220	2.550	0.001
Total cholesterol/HDL	0.134	0.120	0.350	< 0.001	1.368	1.120	1.672	0.002
TyG	0.044	−0.120	0.670	0.167	1.169	0.554	2.467	0.682

OR are for 10 mg/dL increase for total, HDL, LDL cholesterol and triglycerides and for each unit increase for the remaining values

IMT = Intima-Media Thickness; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; TG = TriGlycerides; TyG = Triglycerides-Glucose Index

study) and less frequently hypertension (44.7% vs. 100.0% in our study) as well as higher LDL (171.7 ± 49.5 vs. 122.5 ± 31.9 mg/dL in our study) and triglycerides (154.9 ± 130.9 vs. 121.7 ± 70.4 mg/dL in our study) leading to TyG values that were almost the double of those in our study (8.6 ± 0.6 vs. 4.1 ± 0.3).

Our study has some limitations. The most important one is its cross-sectional nature that prevents us from understanding whether the association found also has a cause-effect relationship. Second, the homogeneous hypertensive population limits the generalizability of our findings to broader populations. Additionally, despite the overall sample size, the subgroup of patients with carotid HMOD was relatively small, which may have affected our power to detect certain associations. Finally, IMT was assessed with manual measurements while an echo-tracking system would have given more accuracy in this evaluation [46]. However, our measurement approach aligns with methodologies used in most previous studies on this topic [25–30].

5 Conclusions

IMT, a marker of carotid HMOD, significantly relates to both classic and novel derived lipid parameters in hypertensive patients. The strongest associations were observed for non-HDL/HDL, LDL/HDL and total cholesterol/HDL ratios, suggesting that these novel indices may better reflect atherosclerotic burden. Further longitudinal studies are needed to confirm these findings and assess their prognostic implications.

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Data availability Data are available upon request to the corresponding author.

Declarations

Conflict of interest Authors have no conflict of interest to declare.

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