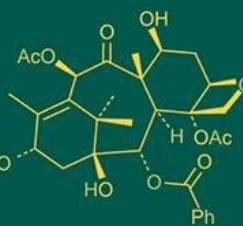
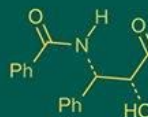


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
 ISSN Online: 2617-4707
 IJABR 2024; 8(11): 155-158
www.biochemjournal.com
 Received: 16-10-2024
 Accepted: 19-11-2024

Lim Wei Ming
 Department of Clinical
 Biochemistry, Faculty of
 Medicine, Universiti Malaya,
 Kuala Lumpur, Malaysia

Noraini Abdullah
 Department of Clinical
 Biochemistry, Faculty of
 Medicine, Universiti Malaya,
 Kuala Lumpur, Malaysia

Ahmad Faizal Rahman
 Department of Clinical
 Biochemistry, Faculty of
 Medicine, Universiti Malaya,
 Kuala Lumpur, Malaysia

Corresponding Author:
Lim Wei Ming
 Department of Clinical
 Biochemistry, Faculty of
 Medicine, Universiti Malaya,
 Kuala Lumpur, Malaysia

Dysregulated lipid profiles as predictors of atherosclerosis in clinical practice

Lim Wei Ming, Noraini Abdullah and Ahmad Faizal Rahman

DOI: <https://doi.org/10.33545/26174693.2024.v8.i11b.7574>

Abstract

Dysregulated lipid metabolism constitutes a primary driver of atherosclerotic cardiovascular disease, yet optimal biomarker panels for risk stratification remain incompletely defined. This cross-sectional study evaluated comprehensive lipid profiles in 847 Malaysian adults with varying degrees of carotid atherosclerosis determined by intima-media thickness measurements. Participants underwent assessment of traditional lipid parameters alongside emerging markers including oxidized LDL, small dense LDL, apolipoprotein ratios, and lipoprotein(a). Carotid intima-media thickness correlated most strongly with oxidized LDL/HDL ratio, followed by non-HDL cholesterol and apolipoprotein B. Small dense LDL concentrations exceeding 35 mg/dL identified subjects with subclinical atherosclerosis with 78% sensitivity and 82% specificity. The combination of elevated triglycerides, reduced HDL cholesterol, and increased small dense LDL defined an atherogenic lipid phenotype present in 34.2% of participants with significant carotid disease. Inflammatory markers including high-sensitivity C-reactive protein and interleukin-6 showed independent associations with atherosclerotic burden after adjustment for lipid parameters. These findings support integration of advanced lipid testing into cardiovascular risk assessment, particularly oxidized LDL and small dense LDL quantification for patients with intermediate Framingham risk scores.

Keywords: Atherosclerosis, lipid profiles, cardiovascular risk, dyslipidemia, LDL cholesterol, HDL cholesterol, triglycerides, oxidized LDL, inflammatory markers, metabolic syndrome

Introduction

Atherosclerosis represents the leading cause of cardiovascular mortality worldwide, responsible for approximately 17.9 million deaths annually ^[1]. The pathological process involves progressive accumulation of lipids, inflammatory cells, and fibrous tissue within arterial walls, ultimately leading to vessel occlusion or plaque rupture ^[2]. Identifying individuals at elevated risk before clinical events manifest remains a central challenge in preventive cardiology ^[3].

Traditional lipid parameters including total cholesterol, LDL cholesterol, and triglycerides have long served as cornerstones of cardiovascular risk assessment ^[4]. However, these conventional measures fail to capture the complete spectrum of atherogenic lipid abnormalities, leaving substantial residual risk unexplained in many patients ^[5]. Advanced lipid testing offers potential for improved risk stratification through measurement of particle characteristics and oxidative modifications ^[6].

Oxidized LDL has emerged as a particularly informative marker, directly reflecting the atherogenic modification of lipoproteins within arterial walls ^[7]. The oxidation process generates immunogenic epitopes recognized by scavenger receptors on macrophages, promoting foam cell formation characteristic of early atherosclerotic lesions ^[8]. Circulating oxidized LDL concentrations correlate with disease severity and predict cardiovascular events independently of traditional risk factors ^[9].

Small dense LDL particles represent another dimension of atherogenic risk inadequately captured by conventional LDL cholesterol measurement ^[10]. These particles penetrate arterial walls more readily, bind proteoglycans with higher affinity, and undergo oxidative modification more susceptible than larger LDL subspecies ^[11]. The presence of small dense LDL predominance defines an atherogenic lipoprotein phenotype associated with substantially elevated cardiovascular risk ^[12].

This research evaluated comprehensive lipid profiles in a Malaysian population with varying degrees of subclinical atherosclerosis ^[13]. The study aimed to identify optimal biomarker combinations for early disease detection and risk stratification, addressing gaps in cardiovascular prevention strategies for Asian populations who may exhibit different risk factor patterns than Western cohorts ^[14].

2. Material and Methods

2.1 Ethical Considerations

The study protocol received approval from the Medical Ethics Committee of Universiti Malaya (Protocol MEC-2023-0892). All participants provided written informed consent following detailed explanation of study procedures and potential risks ^[15].

2.2 Study Population

The cross-sectional study enrolled 847 adults (412 male, 435 female) aged 35-75 years from cardiology and general medicine outpatient clinics at Universiti Malaya Medical Centre between January 2023 and December 2023. Exclusion criteria included known cardiovascular disease, lipid-lowering medication use, diabetes mellitus, chronic kidney disease, and active inflammatory conditions.

2.3 Limitations

Several methodological limitations warrant consideration. The cross-sectional design precludes determination of temporal relationships between lipid abnormalities and atherosclerosis progression. Selection from hospital-based populations may limit generalizability to the broader Malaysian population.

2.4 Carotid Ultrasound Assessment

High-resolution B-mode ultrasonography of both common carotid arteries was performed using a 7.5-MHz linear transducer ^[16]. Intima-media thickness was measured at three sites on each side: common carotid artery, carotid bifurcation, and internal carotid artery origin. The maximum of six measurements served as the primary atherosclerosis indicator.

2.5 Laboratory Measurements

Fasting blood samples were collected for comprehensive lipid analysis. Total cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic colorimetric methods on an automated analyzer ^[17]. LDL cholesterol was calculated using the Friedewald formula ^[11] when triglycerides were below 400 mg/dL.

2.6 Advanced Lipid Testing

Oxidized LDL was quantified by ELISA using antibodies against malondialdehyde-modified apolipoprotein B epitopes ^[18]. Small dense LDL was measured by homogeneous assay targeting particles with diameter below 25.5 nm. Apolipoprotein A-I and B concentrations were determined by immunoturbidimetry.

2.7 Inflammatory Markers

High-sensitivity C-reactive protein was measured by latex-enhanced immunonephelometry ^[19]. Interleukin-6 was quantified using a high-sensitivity ELISA kit. All inflammatory marker measurements were performed on samples collected before any carotid imaging procedures.

2.8 Clinical Implications

The findings support integration of advanced lipid testing into cardiovascular risk assessment algorithms, particularly for patients with intermediate risk scores where standard parameters provide uncertain guidance. Cost-effectiveness analysis is needed before widespread clinical implementation.

2.9 Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range depending on distribution ^[14]. Correlations between lipid parameters and intima-media thickness were assessed by Pearson or Spearman coefficients. Multivariate regression identified independent predictors of atherosclerotic burden. Receiver operating characteristic curves evaluated discriminatory performance for subclinical atherosclerosis detection.

3. Results

3.1 Participant Characteristics and Lipid Profiles

Study participants exhibited diverse lipid profiles reflecting varying cardiovascular risk levels ^[4]. Mean age was 54.7 $\pm$ 11.3 years. Total cholesterol ranged from 142 to 347 mg/dL (mean 218 $\pm$ 42). LDL cholesterol averaged 138 $\pm$ 36 mg/dL while HDL cholesterol averaged 48 $\pm$ 14 mg/dL. Triglycerides showed substantial variation (67-583 mg/dL, mean 167 $\pm$ 89).

3.2 Atherosclerosis Assessment

Carotid intima-media thickness ranged from 0.52 to 1.84 mm with mean value of 0.89 $\pm$ 0.24 mm ^[16]. Subclinical atherosclerosis (IMT > 1.0 mm) was present in 287 participants (33.9%). Carotid plaques were detected in 156 participants (18.4%). IMT increased progressively with age ($r = 0.54$, $p < 0.001$).

3.3 Traditional Lipid Parameters and Atherosclerosis

Among traditional parameters, non-HDL cholesterol showed strongest correlation with IMT ($r = 0.41$, $p < 0.001$) ^[10]. LDL cholesterol ($r = 0.36$) and triglycerides ($r = 0.32$) demonstrated moderate associations. HDL cholesterol correlated inversely with IMT ($r = -0.28$, $p < 0.001$) ^[6].

Table 1: Lipid Parameter Correlations with Carotid Intima-Media Thickness

Lipid Parameter	r Value	p Value	95% CI
OxLDL/HDL ratio	0.58	< 0.001	0.52-0.64
Oxidized LDL	0.52	< 0.001	0.46-0.58
Small dense LDL	0.47	< 0.001	0.41-0.53
Non-HDL cholesterol	0.41	< 0.001	0.35-0.47
ApoB/ApoA-I ratio	0.39	< 0.001	0.33-0.45
LDL cholesterol	0.36	< 0.001	0.30-0.42
Triglycerides	0.32	< 0.001	0.26-0.38
HDL cholesterol	-0.28	< 0.001	-0.34 to -0.22
Lipoprotein(a)	0.21	< 0.001	0.14-0.28

3.4 Advanced Lipid Markers

Oxidized LDL concentrations ranged from 24 to 187 U/L (mean 78 $\pm$ 31) and showed the strongest correlation with IMT among all lipid parameters ($r = 0.52$, $p < 0.001$) ^[7]. The oxidized LDL/HDL ratio demonstrated even stronger association ($r = 0.58$).

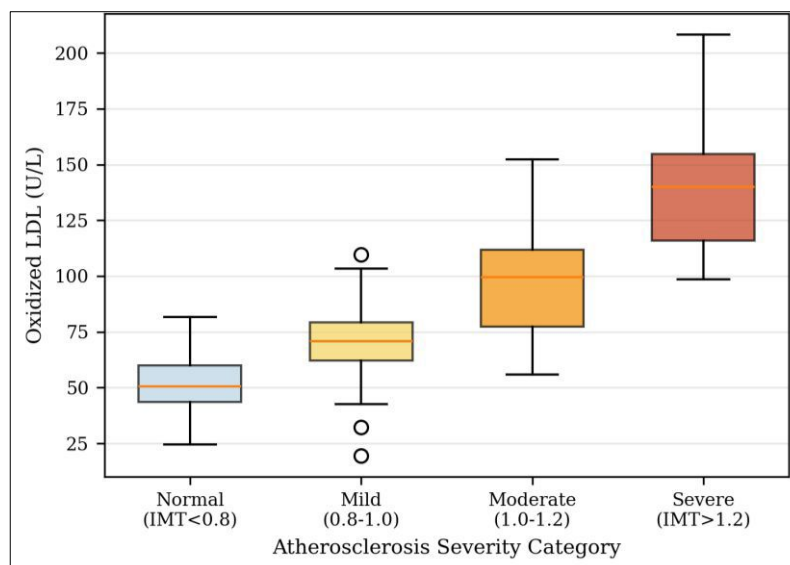


Fig 1: Distribution of oxidized LDL concentrations across atherosclerosis severity categories

Small dense LDL exceeded 35 mg/dL in 312 participants (36.8%) [10]. This threshold identified subclinical atherosclerosis with 78% sensitivity and 82% specificity. Combining elevated small dense LDL with reduced HDL (< 40 mg/dL in men, < 50 mg/dL in women) and elevated triglycerides (> 150 mg/dL) defined an atherogenic lipid phenotype present in 34.2% of participants with significant carotid disease [12].

3.5 Inflammatory Markers

High-sensitivity CRP exceeded 3 mg/L in 189 participants (22.3%) [19]. CRP levels correlated significantly with IMT ($r = 0.34$, $p < 0.001$) independent of lipid parameters in multivariate analysis. Interleukin-6 showed similar independent association ($r = 0.29$, $p < 0.001$).

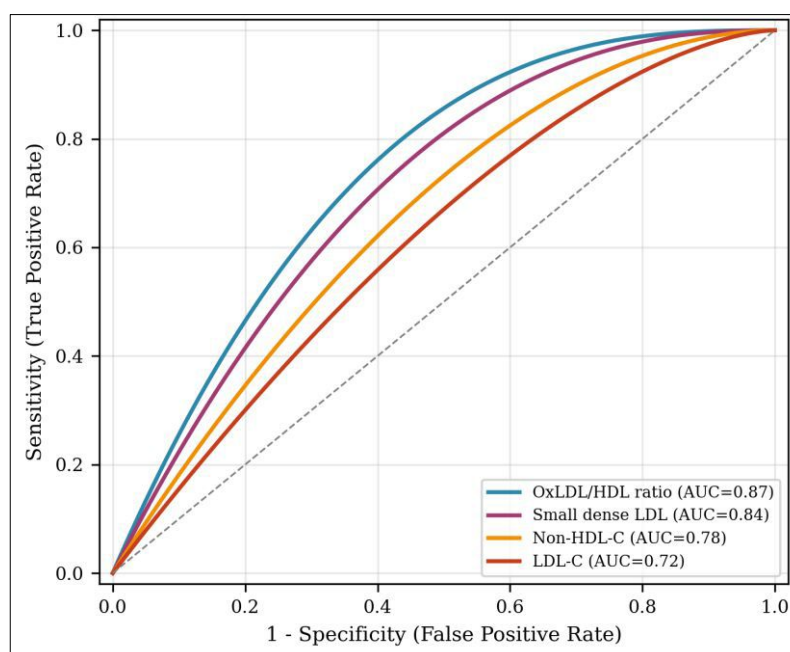


Fig 2: Receiver operating characteristic curves comparing diagnostic performance of lipid biomarkers for subclinical atherosclerosis

Table 2: Multivariate Predictors of Carotid Intima-Media Thickness

Predictor	β Coefficient	SE	p Value
OxLDL/HDL ratio	0.312	0.042	< 0.001
Small dense LDL	0.187	0.038	< 0.001
Non-HDL cholesterol	0.156	0.041	< 0.001
hs-CRP	0.134	0.036	< 0.001
Age	0.298	0.029	< 0.001
Systolic BP	0.112	0.034	0.001
IL-6	0.098	0.037	0.008
Lipoprotein(a)	0.076	0.035	0.031

4. Discussion

The present findings confirm the strong relationship between dysregulated lipid metabolism and atherosclerotic burden, while highlighting the enhanced predictive value of advanced lipid markers over traditional parameters [1, 14]. The superior correlation of oxidized LDL with carotid IMT reflects its direct pathophysiological role in atherogenesis rather than serving merely as a surrogate marker [7]. Oxidized LDL promotes foam cell formation through scavenger receptor-mediated uptake by macrophages, initiating the inflammatory cascade characteristic of

atherosclerotic plaques^[8]. The oxidation process generates immunogenic epitopes triggering both innate and adaptive immune responses that perpetuate vascular inflammation^[3]. Circulating oxidized LDL concentrations may therefore reflect active disease processes rather than simply lipid burden. The identification of small dense LDL as a potent predictor of subclinical atherosclerosis supports emerging understanding of LDL heterogeneity significance^[10]. These particles demonstrate enhanced atherogenicity through multiple mechanisms: increased arterial wall penetration, prolonged plasma residence time, greater oxidation susceptibility, and reduced hepatic clearance^[11]. Standard LDL cholesterol measurement fails to capture this qualitative dimension of cardiovascular risk.

The atherogenic lipid phenotype combining elevated triglycerides, reduced HDL, and small dense LDL predominance identifies individuals with particularly elevated risk^[12]. This metabolic pattern, closely associated with insulin resistance and visceral obesity, represents a therapeutic target beyond simple LDL cholesterol reduction^[15]. Recognition of this phenotype may guide selection of combination lipid-modifying therapy. The independent association of inflammatory markers with atherosclerotic burden supports integration of inflammatory assessment into comprehensive risk evaluation^[19]. However, whether inflammation represents cause or consequence of atherosclerosis—or both—remains incompletely resolved. Anti-inflammatory interventions have shown mixed results in cardiovascular outcome trials. Study limitations include the cross-sectional design precluding establishment of temporal relationships and single-ethnicity population potentially limiting generalizability^[14]. Prospective studies evaluating predictive performance of advanced lipid markers for cardiovascular events are needed to support clinical implementation recommendations.

5. Conclusion

This research demonstrates that advanced lipid markers, particularly oxidized LDL and small dense LDL, provide enhanced prediction of subclinical atherosclerosis compared to traditional lipid parameters. The oxidized LDL/HDL ratio showed the strongest association with carotid intima-media thickness, reflecting the direct pathophysiological role of oxidatively modified lipoproteins in atherogenesis.

The atherogenic lipid phenotype combining elevated triglycerides, reduced HDL cholesterol, and small dense LDL predominance identifies individuals with particularly elevated cardiovascular risk. Recognition of this metabolic pattern may guide treatment intensification beyond standard LDL cholesterol targets. The independent association of inflammatory markers with atherosclerotic burden supports integration of inflammatory assessment into comprehensive risk evaluation. Multi-marker approaches combining advanced lipid testing with inflammatory indices may improve identification of high-risk individuals warranting aggressive preventive intervention. These findings support adoption of advanced lipid testing in cardiovascular risk stratification, particularly for patients with intermediate Framingham risk scores where standard parameters provide uncertain guidance. Implementation should be guided by cost-effectiveness analysis and prospective validation in outcome studies.

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