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Advanced Lipid Parameter: Implications for Atherosclerosis and Metabolic Syndrome

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, emphasizing the urgent need for improved biomarkers that allow earlier and more precise risk detection. Traditional lipid profiles, such as total cholesterol, LDL-C, HDL-C, and triglycerides, have been widely used for risk assessment, yet they often fall short in accurately identifying individuals at high risk, especially those with metabolic abnormalities. Advanced lipid parameters have emerged as promising tools in the era of precision medicine. Apolipoproteins are critical in lipid metabolism and cardiovascular disease (CVD) risk assessment. Apolipoprotein A (ApoA), the principal protein component of high-density lipoprotein (HDL), is involved in anti-inflammatory, anti-atherogenic processes and reverse cholesterol transport. Decreased ApoA1 levels correlate with metabolic syndrome and increased cardiovascular risk. In contrast, Apolipoprotein B (ApoB), the main structural protein of low-density lipoprotein (LDL) and other atherogenic lipoproteins, is a strong predictor of atherogenic lipoprotein burden and cardiovascular events. ApoB levels reflect the total number of circulating atherogenic particles more accurately than LDL cholesterol concentration. Lipoprotein(a) or Lp(a) is a genetically determined LDL-like particle with prothrombotic and proatherogenic properties, independently contributing to CVD risk. Small dense LDL (sdLDL) particles are highly atherogenic due to their susceptibility to oxidation and enhanced arterial wall penetration. Advanced lipid parameters, including ApoA, ApoB, Lp(a), and sdLDL, provide superior predictive value over conventional lipid profiles for cardiovascular risk stratification and are essential in the early detection and management of metabolic syndrome and coronary artery disease. Incorporating these parameters into clinical practice may improve personalized therapeutic strategies.

Keywords: advanced lipid parameter, metabolic syndrome, apolipoprotein A, apolipoprotein B, lipoprotein (a), sdLDL

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally, largely driven by modifiable risk factors such as dyslipidemia. Traditional lipid parameters, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), have been widely used for cardiovascular risk assessment. However, these conventional markers often fail to reflect the complexity of lipid metabolism fully and may not adequately predict cardiovascular events in all populations. Recent research has emphasized the significance of advanced lipid biomarkers, such as apolipoproteins, lipoprotein(a), and small dense LDL

particles, which provide more detailed insights into atherogenic risk and the underlying pathophysiology of metabolic syndrome and CVD.[1–3] Understanding these parameters offers potential for improved risk stratification, early detection, and personalized therapeutic interventions. This review aims to evaluate the current evidence on advanced lipid parameters and their role in enhancing cardiovascular risk prediction beyond traditional lipid profiles.

METHODS

This was a narrative review to summarize the current understanding of advanced lipid parameters, including their clinical relevance in metabolic syndrome and cardiovascular risk assessment and management. We included original research articles, reviews, and clinical guidelines published in the last ten years. Additionally, textbooks and guidelines were included regardless of publication year if considered significant to the topic. The findings of this review were presented descriptively to provide a comprehensive overview of the roles and implications of advanced lipid markers in cardiovascular disease prediction and therapy.

RESULT AND DISCUSSION

ApoA

Apolipoprotein A (ApoA) is the main protein component in HDL. It has a structure similar to plasminogen and contains a unique protein domain called kringle. The number of kringles varies, which in turn affects the size of ApoA. ApoA plays a role in regulating inflammation, healing processes, and modulating cellular cholesterol efflux. However, smaller apo(a) results in smaller Lp(a), which leads to increased capacity for oxidized phospholipid binding, greater subendothelial accumulation, inhibition of plasmin activity (thrombogenic), and synergism with sdLDL and oxidized LDL.[4]

Metabolic syndrome is a condition consisting of several states, including obesity, hypertension, dyslipidemia, and impaired glucose metabolism, all of which increase the risk of type II diabetes mellitus and atherosclerosis.[5] This syndrome arises due to three main processes: hormonal activation, chronic inflammation, and insulin resistance. There is evidence of apolipoproteins being involved in these mechanisms, such as ApoA1, which has anti-inflammatory and anti-atherogenic properties, making it beneficial for cardiovascular health. Decreased ApoA1 levels are associated with the occurrence of metabolic syndrome, indicating that this parameter can serve as a potential indicator for identifying metabolic syndrome in at-risk patients.[2] In addition to increased TG levels and decreased HDL-C levels, metabolic syndrome is also associated with increased apolipoprotein B (ApoB) and decreased apolipoprotein A1 (ApoA1).[5]

ApoA is considered anti-atherogenic because of its roles in reverse cholesterol transport, activation of the LCAT enzyme, and prevention of LDL oxidation. Meanwhile, ApoB is the main structural protein in LDL and is atherogenic. The ApoB/ApoA1 ratio is a better marker of CAD risk compared to the LDL-C/HDL-C ratio.[1] This ratio reflects the balance between atherogenic and anti-atherogenic lipoproteins. The ApoB/ApoA1 ratio is associated with carotid intima-media thickness and flow-mediated dilation of the brachial artery in adults.[5]

ApoB

Serum ApoB levels can indicate the total concentration of LDL-C, IDL-C, VLDL-C, and Lp(a), since each of these particles contains only one ApoB100 molecule. Therefore, ApoB levels can be used to assess the atherogenic status of lipids. ApoB is the main structural protein component of all atherogenic lipoproteins. There are two forms of ApoB: ApoB100, which is synthesized in the liver and is a component of VLDL, IDL, and LDL; and ApoB48, synthesized in the intestines and present in chylomicrons. Clinically, ApoB100 is more

relevant in determining circulating atherogenic lipoproteins.[6]

In conditions with elevated triglycerides—such as obesity, diabetes mellitus, or consumption of high simple carbohydrate diets—there can be an increase in triglyceride-rich VLDL production. High-fat diets can also increase the concentrations of triglyceride-rich VLDL and chylomicrons. The uptake and clearance of lipoproteins containing ApoB occur in the liver. ApoB100 contains eight proteoglycan-binding sites, including those that interact with LDL receptors. The primary proteoglycan-binding sites are site A at residues 3148–3158 and site B at residues 3359–3369, which also bind to LDL receptors. Lipoproteins with ApoB bind to proteoglycans through ionic interactions between negatively charged sulfate and carboxyl groups of glycosaminoglycans and the positively charged lysine and arginine residues on ApoB100. This binding of ApoB100 to proteoglycans in the arterial wall is considered a key mechanism in LDL retention in the subendothelium. ApoB48 is primarily found in chylomicrons and is cleared through the heparan sulfate proteoglycan (HSPG) pathway, as it lacks the LDL receptor binding domain.[6]

Several studies have identified apolipoprotein B (ApoB) as a key predictor of inflammatory markers and insulin resistance, due to its association with interleukin-6 (IL-6), haptoglobin, and alpha-1 antitrypsin. In states of insulin resistance, the inhibitory effect of insulin on lipase activity is diminished, leading to increased lipolysis. This process elevates free fatty acid levels and promotes the modification of atherogenic lipoproteins, including ApoB.[2]

According to the Insulin Resistance Atherosclerosis Study (IRAS), individuals with elevated ApoB and normal LDL-C levels have a higher risk of hyperinsulinemia, obesity, dyslipidemia, and thrombosis compared to those with elevated LDL-C but normal ApoB levels. Insulin is known to suppress ApoB secretion pathways and enhance ApoB clearance, further emphasizing its regulatory role.[5]

Evidence also suggests that patients with recurrent coronary syndrome can present with normal cholesterol levels in conventional lipid profiles. Despite achieving recommended LDL-C targets, these patients may still face a high risk of cardiovascular events. In this context, ApoB has emerged as a more reliable biomarker for cardiovascular risk assessment. It demonstrates greater sensitivity and specificity than LDL-C in predicting events such as myocardial infarction.

Patients with elevated ApoB levels are more likely to exhibit >75% coronary artery stenosis, larger lesion sizes, greater plaque volumes, and more extensive necrotic cores compared to those with lower ApoB levels. Notably, statin therapy tends to reduce LDL-C levels more significantly than ApoB levels, indicating the need for more advanced lipid monitoring strategies. ApoB reflects the presence of all atherogenic lipoproteins—including LDL-C, VLDL-C, IDL-C, and lipoprotein(a)—rather than just LDL cholesterol. It also directly measures the number of atherogenic particles, providing a more accurate representation than cholesterol concentration alone, which can vary based on lipid metabolism. One limitation of ApoB testing, however, is its cost and relative impracticality in routine clinical settings.[6] Apolipoprotein measurements reflect the number of circulating lipoproteins, not merely cholesterol content. Consequently, the ApoB/ApoA1 ratio has been proposed as an individualized marker for insulin resistance and metabolic syndrome. Nonetheless, current evidence suggests that the ApoB/ApoA1 ratio does not outperform ApoB levels alone in predicting coronary heart disease.[2]

Lipoprotein(a)

Lipoprotein(a) or Lp(a) was first described by Kåre Berg in 1963 as an LDL-like lipoprotein. Lp(a) consists of a lipid core containing cholesterol esters and

triglycerides, with an outer layer of phospholipids, free cholesterol, ApoB-100, and ApoA, which is attached to ApoB-100 via a single disulfide bond. Lp(a) is synthesized in the liver, beginning with the production of apo(a) in hepatocytes followed by its binding to ApoB-100. Plasma Lp(a) levels correlate with its production rate.[4] Lp(a) has similar density and composition to LDL, but at lower concentrations. Elevated Lp(a) levels can be familial (autosomal dominant) and have been linked to an increased risk of coronary heart disease, cerebrovascular disease, and stroke.[7] Elevated plasma Lp(a) is a genetically determined and independent risk factor for cardiovascular disease (CVD). Lp(a) can penetrate the endothelium and accumulate in the subendothelial space, making it both thrombogenic and atherogenic. Numerous studies have shown that high levels of Lp(a) are associated with a greater incidence of CVD, accelerated disease progression, and increased CVD mortality.[4]

Lp(a) can interfere with normal thrombolysis due to its similarity to plasminogen. In vitro, Lp(a) competes with plasminogen and plasminogen activators for fibrin binding.[7] Research has shown that approximately 20% of the general population has elevated Lp(a) levels, putting them at higher risk for atherothrombosis. Mechanisms include impaired fibrinolysis, increased cholesterol deposition in arterial walls, and inflammation of the vascular wall. Current therapies to lower Lp(a) levels focus on controlling LDL-C and other cardiovascular risk factors.[3]

The association between serum Lp(a) and metabolic syndrome remains controversial and unclear. Some studies show lower Lp(a) levels in patients with metabolic syndrome compared to those without, while others report significantly higher levels in the metabolic syndrome group. A study in China involving middle-aged and elderly individuals showed a strong inverse relationship between Lp(a) levels and metabolic syndrome incidence.[8] Hormonal changes and insulin resistance, which are also associated with metabolic syndrome, may modulate hepatic Lp(a) production, which is genetically determined. A German study showed an inverse relationship between Lp(a) and metabolic syndrome influenced by hormones—Lp(a) levels were lower in men and postmenopausal women with metabolic syndrome, but higher in premenopausal women. These findings align with many other studies across populations. Insulin and estrogen are believed to modulate hepatic Lp(a) synthesis. Other research shows that estrogen can reduce Lp(a) levels in healthy postmenopausal women.[3]

For at-risk populations, Lp(a) testing should be performed at least once in a lifetime. Lp(a) size varies, resulting in inter-individual variability in results. Kits measuring Lp(a) mass are more susceptible to variation than those measuring molarity, though commercial kits commonly report Lp(a) in mg/dL.[4] Lp(a) shows pre-mobility in agarose gel electrophoresis and can be quantified with this technique. Lp(a) is genetically heterogeneous, with its concentration and associated CAD risk related to isoform size, hence qualitative assessment of isoform distribution is also feasible.[9]

The normal Lp(a) level is <30 mg/dL.[10] Lp(a) levels can be detected within months of birth and remain relatively stable throughout life. Levels above 42 mg/dL are associated with increased atherosclerosis risk. Some studies suggest that women are more likely to have elevated Lp(a) levels.[4]

Lp(a) is a genetically independent risk factor for macrovascular diseases due to atherosclerosis, including CAD, stroke, and peripheral artery disease. Elevated Lp(a) levels (>30 mg/dL) are linked to an increased risk of premature CAD. Lp(a) was found to be significantly higher in young patients (<45 years) with myocardial infarction compared to controls. A study in India indicated that this advanced lipid parameter is a better predictor for premature CAD than conventional lipid parameters.

Advanced lipid parameters can be used for early screening and diagnosis of CAD, enabling corrective actions such as dietary modifications, medication, and monitoring therapeutic targets.[1]

Small Dense LDL (sdLDL)

LDL can be divided into two categories based on size, weight, and lipid composition: large buoyant LDL (lbLDL) and small dense LDL (sdLDL). SdLDL is associated with a higher risk of coronary artery disease (CAD) due to increased oxidation, reduced binding to LDL receptors, and enhanced binding of sdLDL to the arterial wall. Numerous studies have demonstrated that sdLDL is a strong and independent predictor of CAD occurrence and correlates with the severity of CAD. SdLDL tends to promote LDL oxidation, which upregulates pro-inflammatory genes leading to monocyte recruitment into the subendothelial space. Oxidized LDL is then absorbed by monocytes, resulting in foam cell formation—the basis of atherosclerosis. SdLDL is linked not only to the incidence and prevalence of CAD but also to increased morbidity and mortality, depending on the number of foam cells formed from oxidized LDL.[1] SdLDL contains less cholesterol ester and more triglycerides, has a lower cholesterol/ApoB ratio, and is highly atherogenic.[9]

Metabolic syndrome also acts as a risk factor for CAD alongside diabetes, hypertension, smoking, sedentary lifestyle, and abnormal lipid levels, including elevated total cholesterol, triglycerides (TG), and LDL-C, as well as decreased HDL-C. Multiple studies have shown that high LDL and TG levels combined with low HDL levels are associated with increased CAD risk. Conversely, reductions in TG and increases in HDL levels are linked to improvements in CAD status. However, conventional lipid parameters cannot fully explain CAD occurrence in patients with normal LDL and HDL levels. A study by Bansal et al. showed that 66.66% of CAD cases occurred in patients with total cholesterol <200 mg/dL and 33.33% in those with LDL <100 mg/dL. These findings highlight the need for advanced lipid parameters to explain CAD in patients with normal conventional lipid profiles.[1]

LDL-C, which reflects the cholesterol content of LDL particles, has traditionally been used to measure LDL levels. However, epidemiological studies and clinical trials suggest that LDL particle number (LDL-P) is a better alternative marker for cardiovascular disease (CVD) risk. Many patients who achieve LDL-C targets still develop atherosclerosis, indicating that LDL-C alone is insufficient as a determinant of atherosclerotic risk. Smaller LDL particles, such as sdLDL, which are widely distributed in the blood of patients with atherosclerosis, are more predictive. The cholesterol and other component contents of LDL-P vary depending on lifestyle, medication use, and the influence of proteins and enzymes that modify LDL size and composition, especially cholesterol and triglyceride content. Therefore, LDL-C levels do not reliably represent LDL-P concentrations in the blood. For example, in hypertriglyceridemic patients, increased sdLDL levels with relatively low cholesterol and high triglycerides can cause falsely low LDL-C readings. Each LDL particle contains one molecule of ApoB100, so ApoB100 levels correlate with LDL-P levels. LDL-P is a better predictor of CVD risk than other parameters, including LDL-C. The risk is exacerbated when LDL particles are smaller, as they more easily penetrate the subendothelium, are taken up by macrophages, and form foam cells.[11]

SdLDL has been proven to be more atherogenic than other LDL subclasses. Elevated sdLDL levels are associated with atherosclerosis in patients with hyperlipidemia, metabolic syndrome, and diabetes mellitus. SdLDL levels can predict increased intima-media thickness (IMT) and insulin resistance in diabetic patients. SdLDL circulates longer in the bloodstream than larger LDL particles, increasing the likelihood of subendothelial penetration.

The small size of sdLDL facilitates penetration through the subendothelium, binding to glycosaminoglycans, and uptake by macrophages, which leads to the formation of atherosclerotic plaques. SdLDL is more readily phagocytosed by macrophages due to its increased susceptibility to oxidation and stronger binding to proteoglycans in the endothelial layer.[11] The atherogenicity of sdLDL stems from its ease of penetration into the arterial wall, poor binding to LDL receptors, and prolonged circulation time in the blood. SdLDL levels can be estimated by calculating the LDL/ApoB ratio.[6]

Detection of LDL Subclasses

LDL can be divided into four subclasses based on density, size, electric charge, and protein composition: large LDL (LDL I), medium LDL (LDL II), and small LDL (LDL III and LDL IV). LDL particles can be separated by ultracentrifugation, gel electrophoresis, or HPLC. Ultracentrifugation separates LDL particles based on density, but the results vary depending on the ultracentrifugation method used. This technique may produce overlapping subclass outputs due to the destructive centrifugal forces. Gradient gel electrophoresis (GGE) separates LDL particles based on size, shape, and electric charge. GGE analysis is time-consuming and requires calibration. Several diagnostic companies have introduced advanced lipid parameter tests, including LDL particle number (LDL-P), small and medium LDL, LDL patterns, ApoA, ApoB, and Lp(a). The LDL-P parameter can provide important information about cardiovascular disease (CVD) risk in individuals with a personal or family history of early-onset heart disease, especially when total cholesterol and LDL-C levels are not significantly elevated.[11]

Lipoprotein Fractionation Analysis

Several methods exist for lipoprotein subfraction analysis based on their physical and chemical differences. Common laboratory techniques include gel electrophoresis, density-gradient ultracentrifugation, nuclear magnetic resonance (NMR) spectroscopy, and ion mobility analysis. These tests are not yet widely adopted as international guidelines and are typically performed in patients with intermediate risk or when there is a discrepancy between clinical presentation and conventional biomarker measurements.[12]

1. **Gel Electrophoresis**

   This method qualitatively separates lipoproteins based on a combination of charge and size by staining lipoproteins with specific lipid dyes such as Sudan Black, Oil Red O, and Fat Red 7B. These dyes react with ester bonds in triglycerides and cholesterol esters. However, lipoprotein cholesterol levels can be quantitatively measured enzymatically using cholesterol oxidase.[12] The analysis is conducted on agarose gel buffer (pH 8.5), where separated lipoproteins are stained with specific lipid dyes (Sudan Black). The electrophoretic pattern is visually assessed by comparing patient samples to normal control samples or quantified relatively using densitometry. Under normal conditions, chylomicrons remain at the application point. HDL (α-lipoprotein) migrates the fastest, LDL (β-lipoprotein) the slowest, and VLDL (pre-β lipoprotein) migrates in between. Lp(a) migrates similarly to VLDL, resulting in proximity on the electrophoretic pattern. Lipoproteins rich in free cholesterol and phospholipids are poorly stained and often underestimated in electrophoresis.[7,13]

   Lp(a) has a density similar to LDL but migrates like VLDL during electrophoresis. If Lp(a) is detected, it is followed by quantitative measurement using immunoturbidimetric assays. When Lp(a) levels are significantly elevated, LDL-C values require correction using the following formulas:

Lp(a)-C = 0.3 × [Lp(a) mass]
LDL-C (mg/dL) = TC – HDL-C – (triglycerides/5) – Lp(a)-C

2. **Density-Gradient Ultracentrifugation**
   This method separates lipoproteins based on density and lipid/protein ratios. Chylomicrons, containing the highest lipid content, have the lowest density, while HDL, with about 50% lipid content, exhibits higher density. Density-gradient ultracentrifugation not only determines lipoprotein nomenclature but also measures total cholesterol, triglycerides, HDL, LDL, IDL, Lp(a), ApoA-I, and ApoB. It can classify VAP (vertical auto profile) lipids such as large buoyant LDL (pattern A) and small dense LDL (pattern B), which are strongly associated with cardiovascular disease (CVD) risk.[12] Although ultracentrifugation is effective in differentiating lipoprotein classes, it is technically complex, time-consuming, expensive, and generally used for research rather than routine clinical service.[7]
3. **Nuclear Magnetic Resonance (NMR) Spectroscopy**
   NMR lipoProfile quantifies lipoprotein particle subclasses based on specific NMR spectral characteristics. This technique is widely used to determine LDL and HDL particle concentrations. The migration of LDL particles into the arterial wall is influenced by particle number. In conditions with increased small dense LDL (sdLDL), conventional LDL-C measurements tend to be underestimated, potentially affecting atherosclerosis risk assessment. NMR testing is useful in such cases for evaluating coronary heart disease (CHD) risk. [6] NMR spectroscopy quantifies the signal spectra of terminal methyl groups present in lipoprotein particles. Signal resonance is influenced by lipoprotein size, enabling calculation of particle numbers in each lipoprotein subclass. This technique does not require physical separation of lipoproteins, plasma separation from blood cells, or extensive pre-analytical sample preparation. An FDA-recognized example is the NMR LipoProfile.[12] The NMR LipoProfile measures 400 MHz proton spectra from plasma or serum, deconvoluting signals to yield amplitudes representing the concentration of lipoprotein subclasses. Plasma NMR signals originate from methyl protons in lipid groups carried by LDL, HDL, and VLDL subclasses, each with distinct frequencies and line shapes.[14]
4. **Ion Mobility Analysis**
   Ion mobility evaluates lipoprotein subclasses by differential phase gas electrophoretic mobility. The principle is based on particles with specific sizes and charges exhibiting distinct behaviors when subjected to laminar airflow combined with an electric field. However, this technique requires extensive pre-analytical preparation to isolate lipoproteins.[12]

CONCLUSION

Advanced lipid parameters such as apolipoprotein A (ApoA), apolipoprotein B (ApoB), lipoprotein(a) [Lp(a)], and small dense LDL (sdLDL) provide valuable insights beyond traditional lipid profiles in assessing cardiovascular risk. ApoA exerts anti-atherogenic and anti-inflammatory effects, whereas ApoB serves as a more precise marker of atherogenic particle burden. Elevated Lp(a) is an independent, genetically determined risk factor for cardiovascular disease, contributing to both thrombogenesis and atherogenesis. SdLDL particles, characterized by their small size and increased susceptibility to oxidation, further exacerbate atherosclerotic risk. Together, these advanced markers improve risk stratification, particularly in individuals with metabolic syndrome or those exhibiting normal conventional lipid levels but high cardiovascular risk. Incorporating advanced lipid testing into clinical practice

can enhance early detection and guide personalized therapeutic interventions to reduce cardiovascular morbidity and mortality.

Declaration by Authors

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