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Review Article

The Role of Apolipoprotein A and Apolipoprotein B as Biomarkers in Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, with atherosclerosis as a central pathological process driven by lipid imbalances. Apolipoproteins A (apoA) and B (apoB) are key regulators of lipid metabolism and atherogenesis, representing protective and pro-atherogenic roles, respectively. ApoA, primarily found in high-density lipoproteins (HDL), facilitates reverse cholesterol transport and exhibits anti-inflammatory and antioxidant properties, thereby reducing cardiovascular risk. In contrast, apoB, a major component of low-density lipoproteins (LDL) and other atherogenic lipoproteins, promotes cholesterol deposition and plaque formation within arterial walls. This article reviews the metabolic pathways of apoA and apoB, elucidates their opposing roles in the initiation and progression of atherosclerotic plaques, and highlights their clinical utility as biomarkers. The apoB/apoA-I ratio emerges as a superior predictor of cardiovascular risk compared to traditional lipid measures, enabling improved risk stratification and personalized management. Advancements in apoB quantification and the therapeutic potential of targeting apolipoproteins underscore their importance in future strategies to prevent and treat CVDs globally.

Keywords: apoB, apolipoprotein B, apoA, apolipoprotein A, atherosclerotic cardiovascular diseases, atherogenic lipoproteins, HDL, LDL.

I. INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, accounting for approximately 17.9 million deaths each year, according to data from the World Health Organization [1]. These conditions encompass a range of disorders affecting the heart and blood vessels, such as myocardial infarction and stroke. They are largely attributable to modifiable risk factors. Among these, dyslipidemias, defined as imbalances in blood lipids (notably cholesterol and triglycerides), play a key role in the development of atherosclerosis [2]. Atherosclerosis is a complex disease characterized by the formation of plaques composed of fats, inflammatory cells, and fibrous tissue within arterial walls. This accumulation leads to reduced blood flow, thereby increasing the risk of CVDs [3].

Apolipoproteins, particularly apolipoprotein A (apoA) and apolipoprotein B (apoB), play a crucial role in lipid metabolism and are directly involved in the process of atherogenesis [4]. ApoA, the main component of high-density lipoproteins (HDL), is associated with protective effects against atherosclerosis by facilitating the transport of excess cholesterol from the arteries to the liver [5]. Conversely, apoB, the principal component of low-density lipoproteins (LDL), is considered pro-atherogenic. It contributes to the deposition of cholesterol within arterial walls, thus promoting the formation of atheromatous plaques [6].

The metabolism of these apolipoproteins is based on complex interactions between various metabolic pathways. Alterations in circulating levels of apoA and apoB can indicate an increased risk of CVD. An excess of apoB is generally associated with a higher likelihood of plaque formation, whereas elevated apoA levels tend to correlate with a reduced risk [7]. Given their fundamental role in lipid metabolism, these apolipoproteins are also used as biomarkers for the

diagnosis and monitoring of CVDs. They not only help assess individual risk but also serve to evaluate treatment efficacy [8].

This article aims to detail the mechanisms involved in plaque formation, examine the role of apolipoproteins A and B in the atherogenic process, and discuss their utility as biomarkers in the prevention and management of cardiovascular diseases.

II. METABOLISM OF APOLIPOPROTEINS

Apolipoproteins are both structural and functional proteins that associate with lipids to form lipoproteins, enabling their transport through the bloodstream. They play a central role in the recognition of lipoproteins by their specific cellular receptors and are involved in numerous metabolic pathways related to lipid regulation, atherogenesis, and lipid homeostasis. Consequently, their metabolism represents a fundamental pillar in managing lipid profiles and preventing cardiovascular diseases [9].

Among the most extensively studied apolipoproteins, apolipoprotein A (apoA) and apolipoprotein B (apoB) hold a central position in assessing cardiovascular risk.

1. Apolipoprotein A (apoA)

Apolipoprotein A is primarily associated with high-density lipoproteins (HDL), commonly referred to as "good cholesterol" due to their protective effects against cardiovascular diseases. The two major isoforms of apoA are apoA-I, which is the most abundant and biologically active, and apoA-II [10].

ApoA-I is essential for HDL formation and for the activation of the enzyme lecithin-cholesterol acyltransferase (LCAT), which catalyzes the esterification of free cholesterol into cholesterol esters. This process facilitates the transport of excess cholesterol from peripheral cells to the liver as part of reverse cholesterol transport, thereby reducing atherogenic burden (10). Beyond its metabolic role, apoA-I endows HDL with anti-inflammatory and antioxidant properties. Notably, it helps limit the oxidation of LDL—a key step in the development of atherosclerosis—and reduces vascular inflammation, thus reinforcing HDL's protective role against cardiovascular diseases. A high level of apoA-I is therefore considered a favorable marker of cardiovascular health [11].

2. Apolipoprotein B (apoB)

ApoB primarily exists in two forms: apoB-100, which is produced by the liver and found in low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL); and apoB-48, which is synthesized in the intestine and is specific to chylomicrons [12]. ApoB-100 is essential for transporting cholesterol to peripheral tissues via LDL. It enables LDL to bind to their specific cellular receptors (LDLR), thereby promoting the internalization of cholesterol [13].

However, excessive accumulation of LDL especially in oxidized form leads to their retention in the arterial wall, triggering a local inflammatory response and initiating plaque formation [14]. As a result, lipoproteins containing apoB, particularly LDL, are recognized as highly atherogenic. Their ability to cross the vascular endothelium, initiate local inflammation, and promote smooth muscle cell proliferation makes them key contributors to atherosclerosis, thereby increasing the risk of cardiovascular events such as myocardial infarction and stroke [15].

Table 1: Apolipoproteins (16)

Lipoprotein	Main Composition	Main Function	Cardiovascular Effect	Associated Apolipoproteins
Chylomicrons	Very rich in triglycerides (TG)	Transport of exogenous (dietary) TG to tissues	Minimally atherogenic (rapidly cleared)	ApoB-48, ApoC-II, ApoE
VLDL (Very Low-Density Lipoprotein)	Rich in triglycerides (TG)	Transport of endogenous TG from the liver to tissues	Potentially atherogenic after conversion to LDL	ApoB-100, ApoC-II, ApoE
IDL (Intermediate-Density Lipoprotein)	Intermediate between VLDL and LDL	Precursor to LDL after TG removal	Moderately atherogenic	ApoB-100, ApoE
LDL (Low-Density Lipoprotein)	Rich in esterified cholesterol	Transport of cholesterol to cells	Highly atherogenic (promotes atherosclerosis)	ApoB-100
HDL (High-Density Lipoprotein)	Rich in proteins and phospholipids	Reverse cholesterol transport (back to the liver)	Anti-atherogenic (protects arteries)	ApoA-I, ApoA-II
Lp(a) (Lipoprotein(a))	LDL + Apo(a)	Independent risk factor for CVD	Highly atherogenic and pro-thrombotic	ApoB-100, Apo(a)

III. ATHEROGENESIS: KEY MECHANISMS AND THE ROLE OF APOLIPOPROTEINS

Atherogenesis is a complex, multifactorial process involving lipid accumulation, chronic inflammation, and endothelial dysfunction. It plays a pivotal role in the pathogenesis of cardiovascular diseases, particularly atherosclerosis, which can result in serious complications such as myocardial infarction or ischemic stroke. Among the principal actors in this process, apolipoprotein A-I (ApoA-I) and apolipoprotein B-100 (ApoB-100) hold central roles due to their opposing effects on disease progression: ApoB-100 promotes atherogenesis, whereas ApoA-I exerts a protective effect [18].

1. Initiation of the Atherosclerotic Plaque

Atherogenesis begins when low-density lipoproteins (LDL), which are rich in ApoB-100, cross the vascular endothelium and accumulate within the arterial intima. Under conditions of oxidative stress and pro-inflammatory enzymatic activity, these LDL particles become oxidized [19]. The presence of oxidized LDL stimulates the expression of endothelial adhesion molecules (VCAM-1, ICAM-1), thereby promoting the recruitment of circulating monocytes [20]. Once inside the arterial wall, monocytes differentiate into macrophages that internalize oxidized LDL via scavenger receptors. This leads to the formation of foam cells—an early hallmark of atherosclerosis [21]. This entire process, largely driven by ApoB-100, marks the initiation of atheromatous plaque development.

2. Protective role of HDL and Apolipoprotein A-I

In contrast to the pro-atherogenic pathway described above, high-density lipoproteins (HDL), which are enriched in ApoA-I, play a major anti-atherogenic role through multiple mechanisms:

- **Cholesterol Efflux:** ApoA-I activates the ABCA1 transporter, facilitating the efflux of free cholesterol from peripheral cells, including foam cells, onto HDL particles. This process - known as reverse cholesterol transport - allows cholesterol to be delivered to the liver for excretion, thereby reducing the lipid burden within the plaque [10, 2]).
- **Anti-inflammatory and Antioxidant Properties:** HDL particles inhibit LDL oxidation, suppress the expression of endothelial adhesion molecules, and limit immune cell recruitment. Furthermore, HDL modulates local inflammatory responses, thereby slowing plaque progression [11].

3. Progression and Complications of the Atherosclerotic Plaque

As inflammation persists and lipid accumulation advances, the atheromatous plaque enlarges and becomes increasingly unstable. Continued infiltration by macrophages, along with proliferation of smooth muscle cells, contributes to the development of a fibrous cap that encases a necrotic lipid core [20]. However, if this fibrous cap becomes thin or structurally weakened - often as a result of persistent inflammatory activity - it may rupture, exposing the highly thrombogenic core contents to the bloodstream. This rupture triggers the formation of an occlusive thrombus [19], which can obstruct blood flow and lead to acute ischemic events. Depending on the vascular territory involved, this may culminate in a myocardial infarction or an ischemic stroke [23].

IV. APOLIPOPROTEINS B AND A AS INDICATORS OF ATHEROSCLEROSIS

Apolipoproteins A-I (ApoA-I) and B (ApoB) serve as critical biomarkers in cardiovascular disease assessment by reflecting the balance between atherogenic and protective lipoprotein particles [23].

ApoB is the principal structural protein of atherogenic lipoproteins, including low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and intermediate-density lipoprotein (IDL). Each of these particles contains exactly one ApoB molecule, allowing ApoB quantification to directly represent the number of circulating atherogenic lipoproteins responsible for cholesterol deposition in arterial walls and subsequent plaque formation [20]. This unique stoichiometric relationship makes ApoB a superior marker compared to traditional lipid measurements such as LDL cholesterol (LDL-C), which estimate cholesterol mass rather than particle number and can be affected by variability and inaccuracies. Consequently, ApoB measurement provides a more precise and selective assessment of atherogenic burden and cardiovascular risk, including in individuals with normal LDL-C but elevated particle counts [24].

Building upon this, the clinical relevance of ApoB has been reinforced by multiple large prospective studies and randomized controlled trials [25], which demonstrate its superiority over LDL-C and non-HDL cholesterol in predicting cardiovascular events and guiding lipid-lowering therapy. Recognizing this, expert panels and international organizations have endorsed ApoB measurement as a standardized [26], reproducible, and widely accessible test [27]. Modern ApoB assays are automated, cost-effective, and primarily based on immunoassay techniques such as enzyme-linked immunosorbent assay (ELISA) and turbidimetric immunoassays, which offer high specificity and sensitivity [28]. Furthermore, efforts to enhance assay accuracy through advanced methods like mass spectrometry are ongoing, promising even greater precision in quantifying ApoB levels [29]. These developments support broader clinical adoption of ApoB testing to improve cardiovascular risk stratification and optimize patient management, especially in the era of potent lipid-lowering agents [25].

In contrast, apolipoprotein A-I (ApoA-I) is the major structural protein of high-density lipoprotein (HDL), which plays a protective role in cardiovascular

health [30]. ApoA-I facilitates reverse cholesterol transport, the process by which excess cholesterol is removed from peripheral tissues and delivered to the liver for excretion [17]. Lower plasma levels of ApoA-I are associated with impaired cholesterol clearance and increased risk of atherosclerosis, while higher levels correlate with enhanced HDL function and cardiovascular protection [31]. Thus, ApoA-I serves as an important biomarker reflecting the anti-atherogenic capacity of HDL particles. Measurement of ApoA-I complements ApoB assessment by providing insight into the balance between pro-atherogenic and anti-atherogenic lipoproteins, which is critical for a nuanced evaluation of cardiovascular risk [32]. Normal reference ranges for ApoB are approximately 70–110 mg/dL in men and 60–100 mg/dL in women, with levels above 120 mg/dL indicating elevated cardiovascular risk. For ApoA-I, normal values range from 120–180 mg/dL in men and 140–200 mg/dL in women, with lower levels linked to higher risk [33].

The ApoB/ApoA-I ratio provides clinicians with a comprehensive biomarker that captures the critical balance between pro-atherogenic and cardioprotective lipoprotein pathways. An elevated ratio signals a predominance of atherogenic particles over protective HDL components, demonstrating strong correlations with cardiovascular risk manifestations including myocardial infarction, stroke, and subclinical atherosclerosis [34]. Clinically validated thresholds identify optimal ratios below 0.7, while values exceeding 1.0 denote high-risk profiles. Importantly, this integrated metric outperforms conventional lipid ratios in predicting both coronary artery disease severity and future cardiovascular events [35].

VI. CONCLUSION

Apolipoproteins A and B play a crucial role in lipid metabolism and the development of cardiovascular diseases. ApoA, primarily associated with HDL, exerts atheroprotective effects by facilitating reverse cholesterol transport and mitigating inflammation. Conversely, ApoB drives atherogenesis by mediating the transport and retention of LDL and other atherogenic lipoproteins within the arterial wall. The ApoB/ApoA ratio has emerged as a powerful predictor of cardiovascular risk, offering superior discriminative value compared to traditional lipid parameters. Their integration into clinical practice allows for a more accurate assessment of this risk, paving the way for personalized patient management. Future research should focus on the development of targeted therapies, such as ApoA-I mimetics or ApoB inhibitors, to improve the prevention and treatment of cardiovascular diseases globally.

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