Biochemical Assessment of Risk Factors in Coronary Artery Disease (CAD) Patients: A Comprehensive Review

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ABSTRACT

Coronary artery disease (CAD) remains one of the leading causes of mortality and morbidity worldwide. The disease primarily develops due to atherosclerosis, a chronic inflammatory condition characterized by endothelial dysfunction, lipid accumulation, oxidative stress, thrombosis, and vascular inflammation. Biochemical markers play a crucial role in the early diagnosis, risk stratification, prognosis, and therapeutic monitoring of CAD. This review comprehensively evaluates traditional and emerging biochemical risk factors associated with CAD, including lipid profile abnormalities, inflammatory markers, cardiac biomarkers, glycemic indicators, renal biomarkers, coagulation factors, electrolytes, and novel genetic markers. Traditional lipid parameters such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol remain central to cardiovascular risk assessment. Inflammatory markers including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) provide insight into vascular inflammation and plaque instability. Cardiac biomarkers such as troponins, CK-MB, BNP, and NT-proBNP are essential for myocardial injury detection and prognosis. Emerging biomarkers including lipoprotein(a), homocysteine, genomic markers, and omics-based approaches are increasingly contributing to personalized cardiovascular medicine. The review also discusses current risk prediction models, limitations of biomarker interpretation, controversies in clinical application, and future perspectives involving artificial intelligence and precision medicine. Current evidence supports a multi-marker approach integrating biochemical, clinical, imaging, and genetic data for comprehensive CAD management.

Keywords: Coronary artery disease, atherosclerosis, biochemical markers, lipid profile, hs-CRP, troponin, HbA1c, inflammation, cardiovascular risk assessment.

INTRODUCTION

Coronary artery disease (CAD), also referred to as ischemic heart disease, is one of the most prevalent cardiovascular disorders globally and a major cause of premature death and disability. CAD develops when coronary arteries become narrowed or obstructed due to atherosclerotic plaque formation, resulting in reduced myocardial blood supply and oxygen delivery [1]. The disease may manifest clinically as stable angina, unstable angina, myocardial infarction, heart failure, arrhythmias, or sudden cardiac death. The burden of CAD has increased substantially over recent decades, particularly in low- and middle-income countries. According to the World Health Organization (WHO), cardiovascular diseases account for approximately one-third of global deaths, with ischemic heart disease contributing significantly to this burden [2]. India and other South Asian countries exhibit particularly high CAD prevalence, often affecting individuals at younger ages compared to Western populations.

Atherosclerosis is a multifactorial process involving dyslipidemia, chronic inflammation, oxidative stress, endothelial dysfunction, thrombosis, insulin resistance, and genetic susceptibility [3]. Biochemical markers\reflecting these pathological mechanisms have become indispensable tools for early diagnosis, risk assessment, prognosis, and monitoring of CAD.

This review aims to critically evaluate traditional and emerging biochemical markers associated with CAD, discuss their clinical significance, limitations, and future applications, and emphasize the importance of integrated multi-marker strategies in cardiovascular risk assessment.

Pathophysiology Of Coronary Artery Disease

Atherosclerosis and Endothelial Dysfunction

Atherosclerosis is the principal pathological process underlying CAD. It begins with endothelial injury caused by hypertension, smoking, diabetes mellitus, hyperlipidemia, oxidative stress, and inflammatory mediators [4]. Endothelial dysfunction results in increased vascular permeability, reduced nitric oxide availability, leukocyte adhesion, and inflammatory cell recruitment.

Low-density lipoprotein cholesterol (LDL-C) penetrates the damaged endothelium and undergoes oxidative modification to form oxidized LDL (ox-LDL). Ox-LDL stimulates macrophage activation and foam cell formation, producing fatty streaks that gradually progress into mature atherosclerotic plaques [5].

Inflammation and Oxidative Stress

Inflammation plays a central role in plaque initiation, progression, and rupture. Cytokines such as IL-6, IL-1β, and TNF-α contribute to vascular inflammation and destabilization of atherosclerotic plaques [6]. Oxidative stress generated by reactive oxygen species promotes endothelial injury, LDL oxidation, smooth muscle proliferation, and thrombosis.

Plaque Rupture and Thrombosis

Advanced plaques may rupture due to thinning of the fibrous cap and persistent inflammatory activity. Plaque rupture exposes thrombogenic material, resulting in platelet activation, fibrin formation, and thrombus development, ultimately leading to acute coronary syndrome and myocardial infarction [7].

Traditional Biochemical Risk Factors

Lipid Profile

Total Cholesterol

Elevated total cholesterol levels are associated with increased cardiovascular risk. Although total cholesterol alone lacks specificity, it remains useful in cardiovascular screening programs [8].

Low-Density Lipoprotein Cholesterol (LDL-C)

LDL-C is considered the primary atherogenic lipoprotein and the principal therapeutic target in CAD management. Elevated LDL-C promotes endothelial dysfunction, foam cell formation, and plaque development [9]. Small dense LDL particles possess particularly high atherogenic potential due to increased susceptibility to oxidation.

High-Density Lipoprotein Cholesterol (HDL-C)

HDL-C exerts atheroprotective effects through reverse cholesterol transport, antioxidant activity, and anti-inflammatory mechanisms. Reduced HDL-C levels are independently associated with increased CAD risk [8].

Triglycerides

Hypertriglyceridemia is commonly associated with metabolic syndrome, obesity, diabetes mellitus, and insulin resistance. Elevated triglycerides contribute to small dense LDL formation and endothelial dysfunction [10].

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Table 1: Lipid Profile and Cardiovascular Risk

Parameter	Desirable Level	High Risk
Total Cholesterol	<200 mg/dL	≥240 mg/dL
LDL-C	<100 mg/dL	≥130 mg/dL
HDL-C	>40 mg/dL	<40 mg/dL
Triglycerides	<150 mg/dL	≥200 mg/dL

Inflammatory Biomarkers

High-Sensitivity C-Reactive Protein (hs-CRP)

hs-CRP is a sensitive marker of systemic inflammation synthesized by the liver in response to IL-6 stimulation. Elevated hs-CRP levels are strongly associated with endothelial dysfunction, plaque instability, and adverse cardiovascular outcomes [11].

Clinical interpretation of hs-CRP levels:

- <1 mg/L = Low risk
- 1–3 mg/L = Moderate risk
- 3 mg/L = High cardiovascular risk

4.2 Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine produced by macrophages and endothelial cells. Elevated IL-6 levels contribute to plaque progression and adverse cardiovascular events [12].

Tumor Necrosis Factor-Alpha (TNF-α)

TNF-α promotes endothelial dysfunction, oxidative stress, leukocyte adhesion, and plaque destabilization. Increased TNF-α levels are associated with metabolic syndrome, insulin resistance, and severe CAD [13].

Cardiac Biomarkers

Cardiac Troponins

Cardiac troponin T (cTnT) and troponin I (cTnI) are highly specific biomarkers for myocardial injury and are considered the gold standard for diagnosing myocardial infarction [14]. High-sensitivity troponin assays allow earlier detection of myocardial damage and improved risk stratification.

Creatine Kinase-MB (CK-MB)

CK-MB was historically used in myocardial infarction diagnosis. Although less specific than troponins, CK-MB remains useful for detecting reinfarction due to its shorter duration of elevation [15].

BNP and NT-proBNP

Brain natriuretic peptide (BNP) and NT-proBNP are markers of ventricular dysfunction and heart failure. Elevated levels are associated with poor prognosis in CAD and post-myocardial infarction patients [16].

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Table 2: Major Cardiac Biomarkers in CAD

Biomarker	Primary Role	Limitation
Troponin	Myocardial injury detection	Elevated in CKD and sepsis
CK-MB	Reinfarction detection	Lower specificity
BNP/NT-proBNP	Heart failure prognosis	Influenced by renal dysfunction

Glycemic and Metabolic Biomarkers

Fasting Blood Glucose and HbA1c

Diabetes mellitus is a major cardiovascular risk factor. Chronic hyperglycemia promotes endothelial dysfunction, oxidative stress, and vascular inflammation [17]. HbA1c reflects long-term glycemic control and independently predicts cardiovascular events.

Insulin Resistance and HOMA-IR

Insulin resistance contributes to atherogenic dyslipidemia, inflammation, endothelial dysfunction, and thrombosis. HOMA-IR is widely used to estimate insulin resistance and cardiovascular risk [18].

Metabolic Syndrome

Metabolic syndrome involves central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL-C. The coexistence of these abnormalities significantly increases CAD risk [19].

Emerging And Novel Biomarkers

Homocysteine

Hyperhomocysteinemia is associated with endothelial dysfunction, oxidative stress, thrombosis, and vascular smooth muscle proliferation [20]. Elevated homocysteine levels may result from vitamin B12 or folate deficiency.

Lipoprotein(a) [Lp(a)]

Lp(a) is a genetically determined lipoprotein with strong pro-atherogenic and pro-thrombotic properties. Elevated Lp(a) is independently associated with premature CAD and adverse cardiovascular events [21].

Genetic and Omics-Based Biomarkers

Advances in genomics, proteomics, metabolomics, and transcriptomics have identified novel biomarkers involved in CAD pathogenesis. Polygenic risk scores and microRNA profiling show promise for personalized cardiovascular medicine [22].

Renal Biomarkers in Cad

Serum Creatinine and eGFR

Chronic kidney disease significantly increases cardiovascular risk. Reduced estimated glomerular filtration rate (eGFR) and elevated serum creatinine are associated with endothelial dysfunction, inflammation, and accelerated atherosclerosis [23].

Microalbuminuria

Microalbuminuria reflects systemic endothelial dysfunction and predicts cardiovascular morbidity and mortality in diabetic and non-diabetic populations [24].

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Coagulation And Thrombotic Markers

Fibrinogen

Fibrinogen is an acute-phase reactant and coagulation factor associated with thrombosis, blood viscosity, and vascular inflammation [25]. Elevated fibrinogen levels independently predict CAD events.

D-Dimer

D-dimer reflects active fibrinolysis and thrombus formation. Elevated levels are associated with acute coronary syndrome and increased cardiovascular risk [26].

Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 inhibits fibrinolysis and contributes to persistent thrombosis following plaque rupture. Elevated PAI-1 levels are frequently observed in obesity and insulin resistance [27].

Electrolytes And Other Biochemical Parameters

Sodium and Potassium

Electrolyte imbalance may contribute to arrhythmias and adverse cardiac outcomes. Hypokalemia increases the risk of ventricular arrhythmias, whereas hyperkalemia may cause severe conduction abnormalities [28].

Calcium and Magnesium

Coronary artery calcification is an established predictor of cardiovascular risk. Magnesium deficiency contributes to endothelial dysfunction, vasospasm, and arrhythmias [29].

Uric Acid

Hyperuricemia is associated with hypertension, metabolic syndrome, oxidative stress, and endothelial dysfunction. Elevated serum uric acid independently predicts CAD risk [30].

Risk Assessment Models

Framingham Risk Score

The Framingham Risk Score estimates 10-year cardiovascular risk using age, sex, smoking status, blood pressure, cholesterol levels, and diabetes status [31].

ASCVD Risk Calculator

The ACC/AHA ASCVD risk calculator estimates lifetime and 10-year cardiovascular risk and guides statin therapy decisions [32].

Critical Evaluation of Biomarkers

Although biomarkers significantly improve CAD diagnosis and prognosis, no single biomarker possesses ideal sensitivity and specificity. Traditional lipid markers may fail to identify patients with inflammatory or genetic risk factors. Inflammatory biomarkers such as hs-CRP lack specificity because they increase in several non-cardiac inflammatory conditions.

Current evidence increasingly supports a multi-marker strategy integrating lipid profile, inflammatory markers, glycemic indicators, renal biomarkers, coagulation factors, and imaging findings rather than reliance on isolated laboratory parameters.

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Clinical Significance of Biochemical Assessment

Early Diagnosis

Biochemical markers facilitate early detection of subclinical CAD before clinical symptoms develop. Early identification allows timely preventive intervention and improved patient outcomes.

Risk Stratification

Multi-marker approaches provide superior cardiovascular risk assessment and help identify high-risk individuals requiring aggressive management.

Therapeutic Monitoring

Biochemical markers are useful for monitoring therapeutic response. LDL-C assesses statin effectiveness, HbA1c evaluates glycemic control, and BNP monitors heart failure treatment response.

LIMITATIONS AND CHALLENGES

Despite significant advances in biomarker research, several limitations remain. Many biomarkers demonstrate biological variability influenced by age, sex, ethnicity, comorbidities, and systemic inflammation. Several inflammatory biomarkers lack disease specificity and may produce false-positive results.

Advanced biomarker testing such as IL-6, Lp(a), genomic profiling, and proteomics remains expensive and inaccessible in many healthcare settings. Furthermore, most cardiovascular risk models were developed using Western populations and may not accurately reflect cardiovascular risk in South Asian populations.

Therefore, biomarkers should not be interpreted in isolation. Integration of laboratory findings with clinical assessment and imaging remains essential for accurate CAD diagnosis and management.

Future Perspectives

Future developments in CAD biomarker research include artificial intelligence, machine learning, genomics, proteomics, metabolomics, wearable biosensors, and precision medicine approaches.

Artificial intelligence algorithms integrating biochemical, clinical, and imaging data may improve prediction of acute cardiovascular events and enable individualized treatment strategies [33]. Polygenic risk scoring and omics-based technologies may further enhance personalized cardiovascular risk assessment.

CONCLUSION

Coronary artery disease is a complex multifactorial disorder involving dyslipidemia, inflammation, endothelial dysfunction, oxidative stress, thrombosis, and metabolic abnormalities. Biochemical markers provide valuable insight into these pathological mechanisms and play critical roles in diagnosis, prognosis, therapeutic monitoring, and cardiovascular risk assessment.

Traditional biomarkers such as LDL-C, HDL-C, troponins, and HbA1c remain clinically important, while emerging biomarkers including Lp(a), homocysteine, inflammatory cytokines, and genomic markers continue to improve understanding of CAD pathogenesis.

No single biomarker adequately captures the complexity of CAD risk. Therefore, integrated multi-marker approaches combining biochemical, clinical, imaging, and genetic data offer superior diagnostic accuracy and individualized patient management.

Future advancements in artificial intelligence, genomics, proteomics, and precision medicine are expected to further transform cardiovascular risk prediction and personalized treatment strategies.

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