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MINI REVIEW

Implication of Traditional Cardiac Markers and Myocyte-Specific Markers for the Prediction of Coronary Heart Diseases

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ABSTRACT

Coronary heart diseases are significant contributors to mortality worldwide. Early screening and prediction of the disease could be of immense help to control the mortality associated with the disease. However, for such predictions, the utilization of biomarkers that are accurate would be of immense help. Many traditional cardiac biomarkers, including troponins, creatine kinase-MB (CK-MB), and natriuretic peptides, have been extensively used for diagnosing myocardial injury and risk stratification. However, these markers primarily reflect myocardial damage rather than early disease progression. Emerging evidence suggests that monocyte-specific markers, such as soluble CD14 (sCD14), monocyte chemoattractant protein-1 (MCP-1), and CD16+ monocytes, play a critical role in vascular inflammation and atherogenesis, offering additional predictive value in CHD risk assessment. However, many of these are released in a time-bound fashion. Thus, there are early-stage, late-stage, and delayed markers that have been identified. There is no single definitive marker that has been utilized as a bonafide marker for the establishment of the disease. Though newer markers such as heart-specific fatty acid-binding protein (H-FABP) have been proposed to be of immense importance, there has been relatively less utilization of such markers in the detection of coronary heart disease. H-FABP has gained attention for its rapid release following myocardial ischemia, offering potential advantages in early CHD detection. This review critically evaluates the predictive value of traditional cardiac markers, H-FABP, and monocyte-specific markers in CHD. It aims to assess their individual and combined roles in risk assessment, early diagnosis, and prognosis.

Keywords: Cardiac markers; Cardiovascular disease; Troponins; CKMB; HFABP

INTRODUCTION

Cardiovascular diseases (CVD) are the topmost causative agents of mortality worldwide[1]. The cardiovascular diseases include two distinct categories, namely coronary heart diseases (CHD) and cerebrovascular diseases (stroke), respectively. Annually, 17 million deaths are due to CVD. In developed countries such as the USA, both CHD and stroke contribute to high mortality rates in individuals. Amongst CHD and stroke, CHD is more significantly associated with mortality than stroke. CHD is mainly due to the blocking of blood vessels that supply blood to the heart muscles. The main causes of CHD include atherosclerosis and angina. CHD has a high rate of mortality, with around 3.8 million men and 3.4 million women dying annually due to complications associated with CHD. South Asians are at high risk of CHD. Of the thousands of cases reported annually, most of these are from low- and middle-income countries. Due to a lack of proper hospital facilities and access to proper treatment, the death rate is high. CHD adds a significant burden to governments in terms of management in low-income and middle-income countries[2].

CHD is mainly due to inflammation or infection resulting from injury to the heart wall. Lipids have long been associated with the development of atherogenic lesions**.** LDL cholesterol (LDL-C) is the most predominant lipid that is found at elevated levels in patients with CHD. Plaque formation is the most significant feature associated with CHD. It is initiated by the formation of fatty streaks. Injury

to the arterial wall results in the deposition of lipids engulfed in macrophages. Once these fatty streaks are deposited, it results in the secretion of a large number of chemo attractants by adhered macrophages. Thus, an inflammatory response is established, resulting in further injury and the formation of atherosclerotic plaque. LDL in plaque undergoes oxidation, glycation, and other modifications, resulting in further enhancement and thickening of the plaque. This eventually results in blocking the lumen of the blood vessel. The rupture of the plaque results in the release of cardiac cell components and inflammatory markers into the bloodstream. The rupture is often associated with cardiac arrest and, if untreated, is fatal[3,4].

The identification of the symptoms associated with CHD in earlier stages would be of immense help in controlling the disease. The damage to the heart tissue results in release of AST, creatine kinase MB isozyme and lactate dehydrogenase isoenzyme 1. These enzymes are highly enriched in heart tissue when compared to other tissues and hence high levels of these in serum is associated with heart failure. Creatine kinase, myoglobin and glycogen phosphorylase isoenzyme BB have also been used as traditional markers for cardiac injury. Creatine kinase is abundantly expressed by skeletal muscle and the isoform MB is expressed by heart tissue. ST- 2 is a member of IL-1 receptor family and is expressed by cardiomyocytes in circulation. The high levels of ST-2 in blood are due to damage to endothelial cells of heart[5]. Traditionally biochemical markers related to the progression of disease have been utilized to confirm the atherosclerosis apart from scans that show clear block in heart. BNP is a protein associated with heart muscle stretch. High levels of BNP and pro BNP are indicative of heart failure. Cardiac troponin I is released upon necrosis of muscle cells indicative of heart failure. Copeptin is another such useful marker for cardiac failure confirmation[6,7]. The above- mentioned markers are not myocyte specific however are widely used due to their abundance in heart tissue.

Research gap analysis

In acute myocardial infarction, various biomarkers can be used for prediction, but not all traditional markers can be detected at the same time. Myoglobin, FABP, and glycogen phosphorylase isoenzyme BB are the earliest markers that can be detected. Troponin I and Troponin T are late markers. CK-MB is good for detection in the first 10–12 hours post-infarct. Troponins are quite specific markers whose alterations are visible till 7–14 days post-infarct. However, CK-MB returns to normal levels within 72 hours. Recent studies have highlighted the diagnostic limitations of using a single marker, emphasizing that a combination of early and late markers enhances diagnostic accuracy[8].

The correlation between FABP, ST-2, GDF-15, and suPAR in patients with cardiac injury with respect to normal patients is being studied[9]. The various biomarkers tested showed a significant increase in case of cardiac injury. The GDF-15 showed the best increase levels and had a profile like pro-BNP. In their multivariate model utilized for study on GDF-15, it was significantly associated with disease patterns. H-FABP has also been identified as a promising marker for both early detection and prognosis in CHD patients.

A comparative analysis of H-FABP, CK-MB, and Troponin I was conducted to identify the most sensitive marker. The study found that H-FABP is highly sensitive in detecting injury within 1–3 hours post-infarct, which is earlier than CK-MB and Troponin I. This aligns with findings from Ecollan et al.[10], and Ishii et al.,[11] who demonstrated that H-FABP levels rise significantly in pre-hospital Acute Myocardial Infarction (AMI) diagnosis.

Myocyte specific markers

Myocyte-specific markers comprise of cardiac troponins (cTnI and cTnT), creatine kinase-MB (CK-MB), myoglobin, myosin light chain kinase, brain natriuretic peptide (BNP) and heart-type fatty-acid-binding protein (FABP).

- **Cardiac Troponins:** cTnI (troponin I) and cTnT (troponin T) are structural proteins found in the heart muscle and are released into the bloodstream when there's myocardial damage, making them key biomarkers for detecting heart attacks (myocardial infarction). Troponin I is highly specific to the heart and is considered the gold standard biomarker for myocardial injury. Elevated levels of troponin in the blood indicate myocardial damage, aiding in the diagnosis and management of acute coronary syndrome (ACS).
- **Creatine Kinase-MB (CK-MB):** CK-MB is an enzyme primarily found in heart and skeletal muscle, but its presence in the blood in high concentrations can indicate myocardial damage. While not as specific as troponin, CK-MB is still used in conjunction with other biomarkers to help diagnose and monitor heart conditions.
- **Myoglobin:** Myoglobin is a protein found in heart and skeletal muscle that binds to oxygen. Myoglobin is released into the bloodstream after myocardial damage and is a sensitive but less specific early indicator of myocardial necrosis.
- **Myosin light chain kinase:** This enzyme is exclusively expressed by heart cells. It is a calcium/calmodulin-dependent serine/threonine kinase, belonging to the immunoglobulin superfamily. It phosphorylates the regulatory myosin light chains of myosin II to facilitate myosin binding to actin and therefore aid contractility.
- **Brain natriuretic peptide (BNP):** It is also known as B-type natriuretic peptide, a hormone produced by the heart in response to stretching caused by increased blood volume, and its measurement in a blood test

helps diagnose and assess the severity of heart failure.

- **Heart-type Fatty-Acid-Binding Protein (H-FABP):** H-FABP is a small cytosolic protein that is abundant in the heart and has low concentrations in the blood and in tissues outside the heart, as a clinically applicable marker of myocyte necrosis. It is the regulatory complex of the myofibrillar thin filament that plays a critical role in regulating excitation- contraction coupling in the heart. H-FABP may be an early cardiac marker, appearing in plasma 1-3 hours after cardiac damage.

The various myocyte specific components released by rupture of plaque or the inflammatory component in early stages could help in assessing the overall heart functioning[12].

H-FABP was tested as a diagnostic marker in patients with acute coronary syndrome. The patients exhibited non-cardiac chest pain. All such patients showed elevated levels of H-FABP when compared to controls. The study observed that H-FABP was a good marker in discriminating between ischemic heart and normal individuals. It was superior when compared to traditional markers used for the study. This suggests that H-FABP can serve as an early and reliable indicator for ischemic events, even in ambiguous cases.

An investigation in stable CHD patients found that high levels of H-FABP correlated with increased mortality, suggesting its prognostic value beyond acute infarcts. Despite its promise, a systematic review of 23 studies reported no universal consensus on its routine use as a cardiac biomarker, highlighting the need for further validation in large-scale clinical trials.

H-FABP is emerging as a molecule of prime importance in the detection of acute myocardial infarct. Vupputuri et al., studied its role in the detection of infarct patients[10]. Fifty-four patients were analysed for H-FABP levels where they complained of severe ischemic chest pain. Troponin and CK-MB were also tested. The study observed that H-FABP had sensitivity and specificity of 89% and 68%, respectively, and it was superior to troponin and CK-MB in detection of ischemia. The findings from Vupputuri et al., reinforce the need for further clinical studies to validate H-FABP's diagnostic value in different populations and settings[13].

CONCLUSION

Traditional cardiac markers remain the gold standard for CHD diagnosis, but they do not fully address the need for early disease detection. Emerging biomarkers such as H-FABP and other monocyte-specific markers show significant potential, but their clinical applicability remains underexplored. Future research should focus on integrating these biomarkers into predictive models, conducting large-scale validation studies, and establishing their role in early CHD detection and personalized cardiovascular risk assessment.

A multi-marker approach, combining H-FABP, traditional cardiac biomarkers, and inflammatory markers, could improve risk stratification, early diagnosis, and personalized management of cardiovascular diseases, ultimately leading to better prevention and treatment strategies.

Conflict of interest

The authors declare no conflicts of interest.

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