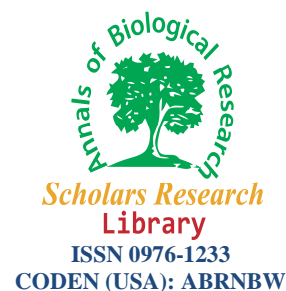




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Cardiac biomarkers: A boon for diagnosis of acute myocardial infarction patients

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ABSTRACT

Acute Myocardial infarction is responsible for substantial mortality and morbidity all over the world. Biomarkers assists in timely diagnosis, prediction and ease clinicians in tailoring appropriate therapy for high-risk patients of acute myocardial infarction. AMI patients can be stratified by symptoms, risk factors and electrocardiogram results but cardiac biomarkers also have significance in diagnosis and prognosis. Presently, troponin is the gold standard biomarker for myocardial insult and is used concurrently with creatine kinase-MB (CK-MB) and myoglobin for a quick and precise diagnosis of acute coronary syndrome (ACS). Novel biomarkers discussed here are Myoglobin, Creatine kinase, Lactate dehydrogenase, Ischaemia modified albumin (IMA), Troponin, Copeptin, Growth-differentiation factor-15(GDF-15), CD40L, Myeloperoxidase (MPO), ET1/CTproET1, ST2, Circulating microRNA's, B-type Natriuretic peptide, Mid-regional pro-atrial natriuretic peptide. This review focuses on a variety of promising biomarkers which provide diagnostic and prognostic information of acute myocardial infarction. This may facilitate doctors for appropriate therapy to high-risk patients.

Key words: Biomarkers, Circulating miRNA's, B-type Natriuretic Peptide, Troponin, Lactate Dehydrogenase.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes for death worldwide, responsible for 1 out of every 6 deaths [1,2]. Early phase treatment of myocardial ischemia to prevent necrosis with treatments like fibrinolysis, coronary artery bypass grafting and percutaneous coronary intervention have improved and remarkable outcome [3]. The traditional concept for predisposition of Coronary artery disease aims on a complex relationship between genetic and environmental, modifiable and non modifiable risk factors setting into action an inflammatory cascade of monocyte migration, lipid oxidation and atheromatous plaque formation in the heart tissue [4, 5]. Cardiac biomarkers provide prognostic information about the disease, which help clinicians in deciding how aggressively they need to treat the disease. The marker of interest is presumed to be released from the cardiac tissue which is under myocardial ischemic stress and so could be detected in collected blood sample of patient during diagnosis [6]. This article mainly focuses on biomarkers of acute myocardial infarction.

Biomarkers: Definition and characteristics

Biomarker is defined as a feature that is precisely measured and evaluated as an indicator of normal biological or pharmacological response to any therapeutic intervention. Following are the characteristics of an ideal biomarker of cardiac necrosis- cardiac specificity, early and stable release after necrosis, predictable clearance that should be

quantitatively measurable by cost effective methods. Cardiac specificity acts as distinctive characteristic for an ideal biomarker, being more sensitive in damage detection and in early appearance in blood [7].

Cardiac Biomarkers

Myoglobin is chiefly found in cardiac and skeletal muscles but is ubiquitous in almost all muscle cells [11]. Plasma level of myoglobin increases within 1-3 hrs after building of myocardial damage while plasma peak levels reaches in 6-9 hrs [8] because of its small size and high cytoplasmic contents [9]. In patients suffering with renal insufficiency and skeletal muscle trauma specificity of myoglobin is limited [10].

Lactate Dehydrogenase

LD has 5 isoenzymes types, amongst them LD1 is majorly found in cardiac muscle cells. With the progression of Myocardial Infarction, LD1 level rises and diagnosis of AMI is done when the ratio of LD1:LD2 occurs more than 1. During a study it was found that rise in LD1 level and LD1:LD2 ratio variation is detectable in 8-12 hrs post-MI with peak levels at 24-72hrs [12].

Creatine Kinase

There are 3 isoenzyme forms of Creatine Kinase (CK) found in our body- CK-BB (CK-1), CK-MB (CK-2) and CK-MM (CK-3) and participates in muscle contraction. CK-MB is particular in cardiac tissue, CK-BB is found in brain tissue and CK-MM in skeletal and cardiac tissue [13].

Release of CK-BB occurs during the death of myocardial tissue hence is not released in establishing ischemia [14] so CK-MB is believed to be a useful biomarker for detecting myocardial injury.

Troponin

Troponin is a protein released from myocytes when irreversible myocardial damage takes place and is the most prominent biomarker of myocardial necrosis, diagnoses MI with a history of ischemic pain. It functions by controlling the calcium mediated interaction of actin and myosin, causing contraction and relaxation of striated muscle [15]. Troponin I (cTnI) and Troponin T (cTnT) are released by cardiac muscle cells hence are staggeringly specific for the myocardium damage [16, 17]. Moreover cardiac troponin level is dependent on infarct size [18], thereby giving clinicians an idea of the prediction of infarct.

Copeptin (C-terminal-provasopressin)

Copeptin acts as an alternate to arginine vasopressin (AVP) having a regulatory effects on osmoregulation and cardiovascular homeostasis [19]. Post myocardial infarction copeptin is supposed to elevate peripheral vasoconstrictor action hence increases ventricular stress and afterload [20, 21] brings about the hypertrophy [22] and vasoconstriction of coronary arteries.

Heart fatty acid binding protein (hFABP)

H-FABP is a cytosolic soluble protein involved in fatty acid transport and metabolism in our body. It is found in large quantity in myocardium and in other tissues like brain, skeletal muscle and kidney [23]. Levels of H-FABP ascends early after AMI, peaks in blood within 6-8 hrs and falls to baseline values after 24-30 hrs so it is unreliable for patients showing >6 hrs from onset of symptoms due to fast renal clearance [24-26].

Ischaemia modified albumin (IMA)

US FDA (United States Food and Drug Administration) has already approved IMA as prominent biomarker of acute ischemia. During the ischemia, N-terminus of IMA is injured hence can't bind to metals that makes it possible to be measured by albumin cobalt-binding test [27].

Markers of myocyte rupture

CD40L is a cellular moiety released from activated platelets as well as lymphocytes that is responsible for inflammatory and coagulant pathways. CD40L is delivered in peripheral circulation during activation of platelets released from the intracoronary thrombus that has formed at the site of the unstable/ruptured plaque [28, 29].

Choline

It lies in the hydrophilic part of the bilayer phospholipid membrane of the cells, responsible in endothelial dysfunction. Choline is released in systemic circulation after breakdown of phospholipids and acts as a significant biomarker of plaque instability, ACS, ischemia and necrosis [30].

F2 isoprostanes

These are obtained as an active product of arachidonic acid metabolism, participates in formation of atherosclerosis. An elevated level of F2 isoprostanes is seen among the smokers, dyslipidemia patients and in the urine of unstable angina patients [31]. Prior studies found the increased levels of free F2 isoprostane in those inflicted with ACS as compared to those without, prognosticating the composite end-point of non-fatal myocardial infarction.

Growth-differentiation factor-15(GDF-15)

GDF 15 is prominent factor characterizing cardiac injury and adaptation. It is of prognostic and diagnostic importance for ACS as implicated by various *in-vitro* experiments on cardiac myocytes [32]. Post ischemia or after reperfusion injury serum GDF 15 level is elevated acting as an autonomous forecaster for mortality rate, which adds up prognostic value to recent cardiac biomarkers like BNP, cTnT during myocardial infarction [33, 34].

BNP/NTproBNP

One of the best known biomarker of cardiac stress is B-type Natriuretic Peptide (BNP) secreted by cardiomyocytes of ventricles in tension resulting in reduction in systemic vascular resistance, venous pressure and natriuresis. BNP has a short half life but is released with N-terminal portion of the pro-BNP peptide (NTproBNP) which is much more stable in serum and thus can be easily diagnosed [35].

Mid-Regional pro-Atrial Natriuretic Peptide (MRproANP)

This has a similar neurohormonal effect as of BNP after acute myocardial infarction. MRproANP is a novel discovered fragment, more stable peptide than N-ANP and ANP [36] due to assay epitopes being located inside of proANP molecule that makes it more stable against metabolizing enzymes. It is a good biomarker being capable of diagnosing and predicting death and heart failure like NTproBNP [37].

ST2

ST2 is an interleukin receptor like protein found released in serum during the myocardial stress [38]. ST2 interacts with interleukin IL33 which has a protective role and is seen released when myocardium is under the biomechanical stress and helps in reducing the atheroma burden [40]. In animal studies IL-33 opposes the action of angiotensin-II and phenylephrine induced cardiomyocyte degeneration [41]. ST2 anticipates cardiovascular death after AMI [39].

ET1/CTproET1

Endothelin-1(ET1) or the more stable C-Terminal portion of pro-Endothelin-1(CTproET1) is of prognostic importance in heart failure after myocardial infarction [42]. ET1 is a vasoconstrictor peptide lying in vascular endothelial cells but also found in renal, pulmonary, and smooth muscle cells [43]. Endothelin exacerbates the AMI, broaden the infarct and finally decreases the coronary blood flow [44].

Mid-Regional-pro-Adrenomedullin (MRproADM)

ADM (Adrenomedullin) was firstly seen in pheochromocytoma cells of adrenal gland, helps in increasing the levels of cAMP ensuing the vasodilation and hypotension thereby playing a cardioprotective role [45]. Function of ADM in heart is alike BNP i.e. elevation of nitric oxide generation causing vasodilatation, natriuresis and diuresis [46-48] and is reciprocally associated to the left ventricular ejection fraction (LVEF) [49, 50]. ADM is partially complexed with complement [51] and is swiftly cleared from circulation so unmanageable to be measured. Mid-regional fragment of the pro-Adrenomedullin (MRproADM) peptide is known to be more stable and secreted in equimolar concentrations as ADM and acts as a good prognostic of cardiac failure condition so indirect measurement of this peptide is done to diagnose and predict the heart failure [52].

HsCRP (High-sensitivity C-reactive Protein)

Earlier studies concluded the increased CRP(C-reactive protein) level was associated with the increased cardiovascular risk [53, 54]. HsCRP is biomarker of inflammation and plaque instability and mediates atherothrombosis [55-59].

Myeloperoxidase (MPO)

It is a haemoprotein generated by polymorphonuclear neutrophils (PMN) and macrophages. MPO catalyses the production of hypochlorite from chloride and hydrogen peroxide and is released during the inflammation as well as mediated in lipid oxidation in LDL. MPO is a marker of plaque instability and serve as a potential biomarker of AMI [60].

Circulating miRNAs

MicroRNA's are endogenous, small, singlestranded, noncoding RNAs that controls gene expression at the post transcriptional level by binding to target mRNAs [61]. When miRNAs completely bind to their target mRNAs, degradation of the target mRNAs is initiated. miRNAs participates in various biological processes, like secretion, excitation, conduction, proliferation, migration, differentiation, cell cycle, ageing, and apoptosis, by modifying protein expression of potential targets [62]. Circulating specific miRNAs e.g. miR-208, miR-499, and miR-133 acts as important biomarkers for diagnosis and prognosis of AMI [63].

CONCLUSION

By the past several decades the use of cardiac biomarkers has extraordinarily bettered the diagnosis of acute myocardial infarction. With the emergence of novel biomarkers sensitivity and specificity has greatly increased and time to diagnosis and treatment has decreased. Furthermore there is still a lot of scope for improvement and current review seems to suggest there are more markers still to come which will improve AMI, diagnosis, prognosis and prediction.

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