

Diagnosis of Myocardial Infarction by Biomarkers-A Review

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Abstract: Cardiovascular diseases are major causes for morbidity and mortality worldwide, among this myocardial infarction is one of them. Myocardial infarction can be diagnosed by physical examination of the patient, electrocardiogram, angiography and biomarkers. Since 40 years, cardiac biomarkers were extensively using for diagnosis of cardiac abnormalities. AST was the first biomarker used in year 1954. Myoglobin, Creatinine kinase, Troponin, lactate dehydrogenase were established biomarkers and Myeloperoxidase, Copeptin, Growth differentiation factor (GDR-15), Heart type fatty acid-binding protein (H-FABP), B-type natri-uretic peptide (BNP) and N-terminal fragment of pro-BNP, High sensitive C-reactive protein (hs-CRO), Placental growth factor (PIGF), Whole blood choline (WBCHO) and plasma choline, Pentraxin 3 (PTX-3), Pregnancy associated plasma protein A (PAPPA), Soluble cluster of differentiation 40 ligand, Ischemia modified albumin (IMA) were emerging biomarkers. In this review we mainly focused in the diagnostic and prognostic information of various biomarkers used for diagnosis of myocardial infarction.

Keywords: Cardiovascular diseases, myocardial infarction, diagnosis, biomarkers.

INTRODUCTION:

Globally each year >17 million deaths are reported due to Cardiovascular diseases (30% of all deaths) [1]. In India 10.5 million deaths occur annually, out of this 20.3% of men and 16.9% of women died due to cardiovascular disease. 15% -20% of deaths due to Cardiovascular diseases in 1980's, 1990's were increased to 20.3% in 2013[2]. Coronary heart disease is the major contributor of cardiovascular diseases [1]. Myocardial Infarction (MI) is the one of the manifestation of coronary heart disease.

Myocardial Infarction (MI) is one of the most common causes of morbidity and mortality world wide. MI causes 31.7% of deaths in India [3]. Incidence of MI in India is 64.37/1000 people[4]. In 1970, World Health Organization (WHO) defined myocardial infarction by the presence of 2 of the 3 following characteristics:

1. Chest pain
2. development of Q waves in electrocardiogram (ECG)
3. Elevation of total creatine kinase (CK), CK-myocardial band (MB), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) enzymes level in blood [5, 6].

A new definition for myocardial infarction was proposed in 1990's by the Joint European Society of Cardiology and the American College of Cardiology Committee, accenting the importance of sensitive and serological biomarkers for the diagnosis of acute myocardial infarction (AMI), and introduced cardiac troponins (cTn) as the gold standard [7].

Biomarker

Biomarker is a substance used as an indicator of biologic process, pathogenic process or pharmacological response to a therapeutic intervention.

Cardiac biomarkers

During heart damage cardiac biomarkers are substances that released into blood and are useful for diagnosis of non diagnostic ECG but not used for patients with ST segment elevation.

AST was first cardiac biomarker used in the year 1954. Later in 1959 total CK level assessed for acute myocardial infarction. In 1960 for diagnosis of acute myocardial infarction LDH was used. In 1979 WHO recommended CK, LDH and AST for diagnosis of acute myocardial infarction.

Ideal characteristics of cardiac biomarkers:

1. High specificity
- Absent in non-myocardial tissues
- Not detectable in blood of non-diseased subjects

2. High sensitivity

- High concentration in myocardium after myocardial injury
- Rapid release for early diagnosis
- Long half-life in blood for late diagnosis

3. Analytical characteristics

- Measurable by cost-effective assay
- Simple to perform
- Rapid turnaround time
- Sufficient precision and trueness

4. Clinical characteristics

- Ability to influence therapy
- Ability to improve patient outcome [8-10].

Past and present myocardial infarction biomarkers:

- Creatine Kinase
- Troponin
- Lactate dehydrogenase
- Myoglobin

Creatine kinase

Creatinine kinase enzyme found in the skeletal muscle and has role for muscle contraction. Total CK starts to rise within 3 to 8 hours after MI, peaks at 10 – 24 hours and returns to normal by 3 – 4 days [11]. It has 2 sub-units: M and B which forms 3 iso-enzymes.

They are:

- CK-MB
- CK-MM
- CK-BB

CK-MB

Total CK is not cardiac specific but CK-MB is sensitive and specific for myocardial infarction. CK-MB detectable 4-8 hours after 1st chest pain and peaks at 18-24 hours post MI. Apart from MI, CK-MB also increases in another conditions like: Renal failure, non cardiac surgery, chest trauma, asthma, pulmonary embolism, chronic and acute muscle diseases, head trauma, hyperventilation, hypothyroidism.

CK-MB isoforms

CK-MB has two isoforms: CK-MB₁, CK-MB₂. CK-MB₂ releases after MI from myocardium which is in tissue form. Peripherally CK-MB₂ converts to CK-MB₁. In normal condition CK-MB₁ is more than CK-MB₂. The ratio between CK-MB₂/CK-MB₁ is <1. But in cardiac damage CK-MB₂ is elevated and ratio is >1.7. In serum CK-MB₂ is detected within 2-4 hours after onset of symptom and peaks at 6-9 hours. As CK-MB present in both cardiac and skeletal muscle, Relative index (RI) is used to measure the cardiac damage.

$$RI = \frac{CK-MB}{Total\ CK} \times 100$$

If Relative index is $\geq 5\%$ then it is MI [12].

Troponin

Troponin is a complex of 3 proteins which regulates interaction between thick and thin filaments during muscle contraction. Troponin is present in cardiac and skeletal muscle fibers. Troponin complex consists of Troponin T, Troponin I and Troponin C. Troponin C is similar in both cardiac and skeletal muscle but Troponin I and Troponin T amino-acid sequence is different in cardiac and skeletal muscle. Presence of those troponins in blood indicates cardiac necrosis. They are sensitive and specific markers even for minor myocardial necrosis [13-16].

Cardiac Troponin T and Troponin I rise 4-8 hours after Myocardial infarction, peaks at 12-24 and elevated in upto 12-24 hours. Elevation of cardiac troponins without ischemic heart disease can be observed in [17]:

- Acute rheumatic fever;
- Amyloidosis;
- Cardiac trauma;
- Cardiotoxicity from cancer therapy;
- Chronic renal failure;
- Congestive heart failure;
- Hypertension;
- Myocarditis;
- Postoperative noncardiac surgery;
- Pulmonary embolism;
- Sepsis

Advantages of Troponin over other biomarkers

1. Most extensive diagnostic window in 4-5 days after MI.
2. Cardiac damage peak concentration of Troponin release can be used quantitatively.
3. Highest stability in blood (6-10 days).
4. Best diagnostic marker in unstable angina [18].

Lactate Dehydrogenase

Lactate dehydrogenase is an enzyme of anaerobic metabolism which converts pyruvate to lactate. It has 5 enzymes: LDH₁, LDH₂, LDH₃, LDH₄, LDH₅. Normally LDH₁ concentration is less than LDH₂. Ratio of LDH₁ to LDH₂ is <0.7. But in MI LDH₁ concentration increases and LDH₁ to LDH₂ ratio becomes >1. After 10 hours of MI the LDH₁:LDH₂ raises above baseline, peaks at 24-48 hours and elevates in blood for 14 days [19].

Myoglobin

Myoglobin is a heme protein of cardiac myocyte that releases rapidly into blood than other biomarkers. Myoglobin may rise 1-3 hours after MI, peaks at 6-9 hours and come to baseline within first 24 hours [11].

Future markers

- Myeloperoxidase
- Copeptin
- Growth differentiation factor (GDR-15)

- Heart type fatty acid-binding protein (H-FABP)
- B-type natriuretic peptide(BNP) and N-terminal fragement of pro-BNP
- High sensitive C-reactive protein (hs-CRO)
- Placental growth factor (PIGF)
- Whole blood choline(WBCHO) and plasma choline.
- Pentraxin 3(PTX-3)
- Pregnancy associated plasma protein A(PAPPA)
- Soluble cluster of differentiation 40 ligand
- Ischemia modified albumin(IMA)

Myeloperoxidase

Polymorphonuclear leucocytes and macrophages produce myeloperoxidase which are metalloproteases. It involved in the production of reactive oxygen species. This reactive oxygen species are involved in the development of atheroma and plaque stability. Increased Myeloperoxidase is marker of plaque instability [20-22].

Co-peptin

Co-peptin, the C-terminal part of the arginine vasopressin precursor peptide. It raises earlier than Troponin T (within 4 hours of onset of symptoms). At a cut off level of 14.0 pmol/L,co-peptin is combinedly measured along with Troponin T had sensitivity of 98.8% and specificity of 77.1% when compared with cTnT alone or with combination of other biomarkers without co-peptin. So co-peptin can be used as additional biomarker to cardiac Troponin T for early diagnosis of acute myocardial infarction [23, 24].

Growth differentiation factor (GDF-15):

GDF-15 is a member of the transforming growth factor beta cytokine superfamily [25,26]. Studies conducted by Nora Schaub et al showed that GDF-15 has additional prognostic value when used combination along with highly sensitive cardiac Troponin T [27].

Heart type fatty acid-binding protein (H-FABP):

Heart type fatty acid-binding protein is low molecular weight protein found in cytosol of cardiac tissue. It transports the fatty acid sites of beta-oxidation in mitochondria and peroxisomes and to endoplasmic reticulum from plasma membrane for lipid synthesis. Heart type fatty acid-binding protein concentration increases after 30 minutes of MI injury and peaks at 6-8 hours and comes to normal level at 24 hour [28].

B-type natriuretic peptide (BNP) and N-terminal fragement of pro-BNP:

BNP is secreted by right and left ventricular myocytes and released in response to stretch, volume overload, and elevated filling pressures. Serum levels of BNP are elevated in patients with asymptomatic LV

dysfunction as well as symptomatic HF. The presence of acute heart failure in patients with ACS is a well known predictor of adverse cardiac events. A serum BNP of < 100 pg/ml has a good negative predictive value and typically excludes HF as primary diagnosis in dyspnoeic patients. BNP levels correlate with the severity of HF and predict survival [20, 30].

Placental growth factor (PLGF):

Placental Growth Factor belongs to the family of platelet derived proteins. It is a potent chemo-attractant for monocytes and regulates vascular endothelial growth. It has 2 iso-forms: PGF-1 and PGF-2. Placental Growth Factor has a major role in the prognosis of myocardial infarction and other coronary heart diseases [31, 32].

Whole blood choline(WBCHO) and plasma choline:

Phospholipase D enzymes catalyses membrane phospholipids lead to generation of choline and phosphatidic acid. Whole blood choline(WBCHO) and plasma choline increases with stimulation of phospholipase D (PLD) and the activation of cell surface receptors in coronary plaque destabilization and tissue ischemia [33]WBCHO was not a marker for myocardial necrosis but indicated high-riskUA in patients without acute MI (sensitivity, 86.4%; specificity,86.2%) [34].

Pentraxin 3(PTX-3)

Pentraxin 3(PTX-3) belongs to pentraxin family which is a specific marker for vascular inflammation caused by vascular endothelial cells, vascular smooth muscles, endothelial cells, neutrophils, macrophages and neutrophils due to inflammatory stimuli [35]. It is a prognostic biomarker in unstable angina pectoris, myocardial infarction and heart failure [36, 37].

Pregnancy associated plasma protein A (PAPPA)

Pregnancy associated plasma protein A(PAPPA) is a metalloprotease produced by syncytiotrophoblasts of placenta, fibroblasts, vascular smooth muscle cells. It has active role in atherosclerotic plaque rupture [38]

Soluble cluster of differentiation 40 ligand

Soluble cluster of differentiation 40 ligand released into blood circulation during thrombogenesis by activation of inflammatory and coagulant pathways. It indicates plaque rupture and MI [39].

Ischemia-modified albumin (IMA)

Ischemia-modified albumin (IMA) released during ischemic conditions, so it enables prior detection of ischemia and come to baseline within 6-12 hours [40].

CONCLUSION

Over past few years the use of biomarkers extensively increased for diagnosis because of their sensitivity, specificity and they playing an important role in detection of disease, risk stratification, diagnostic based treatment of myocardial infarction. Currently the best biomarker for detection of myocardial infarction is cardiac Troponin. However, there are further emerging biomarkers which are in research stage that has chances of more diagnostic, prognostic characteristics.

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