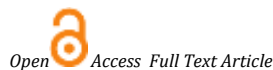


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Review Article

Three cardiac biomarkers and their efficacy: A review

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Abstract

Objectives: This study belongs to the overview of three versatile cardiac biomarkers for specific diagnosis and prognosis in cardiac patients.

Methods: A search performed in different search sites such as Web of Science, Pub Med, and Google scholar searches for relevant studies from 2015 to 2022. Search names included were "heart disease," "cardiac troponin," "acute coronary disease," "coronary artery disease," "new biomarker," "non-ST-elevation acute coronary syndrome," etc. Studies were included if they were prospective, retrospective, randomized controlled trials or reviews.

Findings: Troponin I & T along with CPK-MB can increase the diagnostic sensitivity and specificity when used collectively in the diagnosis of Myocardial infarction either acute or chronic conditions. These cardiac versatile biomarkers can diagnose re-infarct also with serial testing. Whereas sensitivity and specificity of Troponins I & T ranges from 84 to 96 and 80 to 95% respectively. When all three cardiac markers were combined, sensitivity and specificity will reach up to approximately 100%.

Novelty/ Improvement: This article provides the best available three versatile specific cardiac biomarkers in the diagnosis of myocardial infarction and reinfarction with about 100% accuracy.

Keywords: Cardiovascular Disease (CVD), Myocardial Infarction (MI), Acute Myocardial Infarction (AMI), Lactate Dehydrogenase (LDH), Creatine Kinase (CK), Heart type fatty acid binding protein (H-FABP).

1. Introduction

Cardiovascular disease (CVD) is the major cause of death internationally and is responsible for 46% of all deaths. Myocardial infarction (MI), called as a heart attack, is a myocardial injury due to myocardial ischemia. Its high morbidity and mortality have warranted many physicians to find for the best way to diagnose, stratify risk, and manage patients with suspected cardiovascular diseases. To diagnose a disease, it is the accuracy, specificity and sensitivity of the test or biomarker, that plays important role in diagnosis of the disease. A biomarker is that which can be used as either an indicator of a particular disease state or some physiological state of an individual. Enzymes, compounds, and proteins are released from the heart muscles after myocardial infarction or injury. These enzymes, compounds, proteins, or biomarkers have diagnostic and prognostic value. These enzymes, compounds and proteins are called cardiac biomarkers, helpful in diagnosis of Acute Myocardial Infarction (AMI). In general, there are three technical attributes of a biomarker, one, the marker must be present in peripheral body tissue and or fluid, it must be easy to quantify in assays that are both affordable and robust; and, its appearance must be associated as specifically as possible with damage of a particular tissue,

preferably in a quantifiable manner. There are many studies in this field, in terms of biomarkers associated with myocardial infarction and cardiovascular disease, but there are no 100% specific and sensitive markers which can give more than 98% accuracy to date. Cardiac tissue releases lactate dehydrogenase (LDH), creatine kinase (CK), Myoglobin, cardiac troponin, Heart type fatty acid binding protein (H-FABP), Myosin-binding protein C (cMyC). However, there are only few specific markers with high sensitivity and specificity. This topic is not discussed or reviewed till today. The present review highlights the best three highly sensitive and specific cardiac biomarkers in blood circulation that help diagnosis of cardiac disease with more than 98% accuracy when combined.

1.1 Ideal markers

For a diagnostic biomarker test, all patients with the disease would be detected (100% sensitivity) and no patients without the disease would be detected with the disease (100% specificity). In practice, no biomarker test has 100% sure clinical and analytical performance.

2.0 Methods

We performed Web of Science, Pub Med and Google scholar searches for relevant studies by searching the literature from 2015 to 2022. Search names were “heart disease,” “cardiac troponin,” “acute coronary disease,” “coronary artery disease,” “new biomarker,” “non-ST-elevation acute coronary syndrome,” etc. Studies were included if they were prospective, retrospective, randomized controlled trials or reviews. There are biomarkers for of AMI or minor myocardial injury but not all are ideal biomarkers.

2.1 Cardiac Troponin I

Troponins are three regulatory proteins found in the skeletal and cardiac muscles that are integral to muscle contraction. There are three important troponin proteins called troponin C discovered in 1980s, troponin I in 1987 and, troponin T in 1989. Troponins concentrations are raised significantly after

cardiovascular disease. Measurements of cardiac-specific troponins I and T are used as gold standard diagnostic and prognostic tests in myocardial infarction and acute coronary syndrome. Troponin I, present in cardiac tissue only, whereas Troponin T can present in both skeletal and cardiac tissue. These troponins are usually present in very small levels in the blood and are released in the blood in response to damage to cells. Cardiac troponin I involved in the diagnosis of AMI is more specific than Troponin T.¹ This test is for the diagnosis and management of cardiac diseases. The troponin test measures the amount of troponin in the blood sample. Troponin-I in serum detects the presence of troponin I in blood and presence in excessive amounts can be indicative of heart attack. Cardiac Troponin I or Troponin T - which are both very sensitive and specific and are the recommended laboratory tests for the diagnosis of myocardial infarction (MI).

Table 1: Specific biomarkers to diagnose acute myocardial infarction

S No	Biomarker	Start to raise biomarker levels after myocardial infarction	Reaching peak levels at	Returning to normal	Nature of the marker
1	Cardiac Troponin I	4 Hours	18-24 Hours	3-5 days	Specific, Non-Enzymatic
2	Creatinine Phospho Kinase-MB	4-6 Hours	18-24 Hours	2-3 days	Specific, Enzymatic
3	Cardiac Troponin T	6 Hours	24-48 Hours	10-14 days	Specific, Non-Enzymatic

When a patient has elevated levels of troponin and if there is a rise and fall of the results over a period, then it is likely that the person has endured some type of heart damage². Levels go up in the blood after 4 to 6 hours of heart injury and can remain elevated for even up to two weeks. Cardiac Troponin I start to raise its level 4 hours after myocardial infarction, reaching peak at 18-24 hours and 3-5 days to return to normal level. It is specific for Myocardial Infarction. It is a non-enzymatic marker. Serial testing at specific interval is required to rule out acute myocardial infarction. Troponins can be used to diagnose infarction and reinfarction. Cardiac troponin I is more useful for reinfarction diagnosis. Troponin I sensitivity and specificity ranges from 84 to 96% when used alone. Troponin overall sensitivity ranges from 97 to 100 % and specificity is from 94 to -97% depending on many factors, Positive predictive value ranging from 98 to-98% and Negative predictive value from 88 to 100%³. Reference range for Cardiac troponin I is between 0 and 0.04 ng/mL. Considered gold standard for diagnosing AMI.

2.2 Cardiac Troponin T

Troponin T test is useful to diagnose cardiovascular disease and to evaluate if symptoms are expected to worsen. Signs of heart attack include chest pain, radiating pain in back, and neck, rapid heartbeat, skipping a heartbeat, shortness of breath, cold sweats, light-headedness etc. Troponin T levels started to increase 6 hours after myocardial infarction, reaching peak levels at 24 to 48 hours and returning to normal after 10-14 days of the incident. Cardiac troponin T levels lower than < 0.03 ng/ml is normal. The 99th percentile cut-off point for cardiac troponin T is well-known at 0.01 ng/mL. An increased levels of troponin T and even slight elevations can pinpoint towards some cardiovascular damage. When a person has significantly elevated troponin T levels and a rise in the results from a series of tests performed over several hours, then in all probabilities it

means that the patient has had a recent heart attack. Sensitivity and specificity of Troponins T ranges from 80 to 95% . When the test shows normal troponin T values measured over specific time intervals, it rules out the possibility of any heart damage. Troponin T not only serves a diagnostic tool, but also can be useful for prognosis³. It is non enzymatic biomarker. There is point of care testing facility for troponins I&T, which are having less sensitivity and specificity.

2.3 Disadvantage of troponins

Troponin estimation involves immunological technique, that is expensive, less shelf life of reagents, number of samples to be analysed, and availability of the kit, used for estimation. Troponin can also increase in various diseases such as non-ST-elevation myocardial infarction (NSTEMI), unstable angina, pericarditis, Myocarditis, congestive heart failure, left ventricular hypertrophy, and renal failure. Decreased test specificity which is evident in its wider range of specificity and sensitivity. Troponin also been identified as a strong predictive test in some acute clinical situations, such as pulmonary embolism (PE). Chronic kidney disease is a clinical condition that is related with worse outcomes in coronary artery disease, and end stage renal disease patients are at high risk for adverse cardiovascular events. Troponin elevation in these patients has been shown to be a prognostic factor, though the mechanism of this relationship is unclear. Its levels are also increased in drug toxicity, Hypertension, Hypotension, renal failure, sepsis, and hypothyroidism ³⁻⁴. However, Troponin I have exception as it is specifically produced by heart muscle. This hurdle of un-specificity can be overcome by combination of other specific tests.

2.4 CPK MB

CK-MB was identified as a cardiac marker in 1972, normally present in minute quantities in blood as a part of

normal metabolism and is undetectable generally. CK-MB raises significantly after cardiovascular disease or acute myocardial infarction. Elevated CK-MB along with symptoms such as chest pain is indicative of a recent heart attack. CK-MB raised concentrations that are constantly fluctuating indicate a second or ongoing heart attack. If CK-MB is raised and the ratio of CK-MB to total CK exceeds 2.5-3, then it is of heart damage. CK has 3 isoform, CK MM, muscle specific, CK BB brain specific and cardiac specific CK MB. A creatine kinase-MB (CK-MB) test may be used as a follow-up test to an elevated creatine kinase (CK) to diagnose, whether the increase is due to heart damage or skeletal muscle damage. Creatine kinase-MB (CK-MB) is a form of an enzyme found primarily in heart muscle cells. This test quantifies the CK-MB level in the blood. CPK-MB levels started to raise 4 to 6 hours after myocardial infarction, reaching peak at 18 to 24 hours and returning to normal after 2-3 days of the incident. It is an enzymatic biomarker. CK-MB enzyme measurements remain as valuable parameters in the diagnosis of AMI.³⁻⁴

About 20% of total Creatin Kinase in the myocardium is in the MB form, giving sensitivity and specificity in the diagnosis of acute myocardial infarction. CK-MB has a ratio of 5% in skeletal muscle. Therefore, its raising level while trauma and inflammation reduce its specificity. Another limitation of CK-MB is that it cannot diagnose minor myocardial damage, as its high molecular weight.⁴ Total CK and CK-MB levels are correlated with infarct size and are important predictors of prognosis. CK-MB activity has also been found to be more sensitive and specific than CK-MB mass measurements. Normal reference values for serum CK-MB range from 3 to 5% (percentage of total CK) or 5 to 25 IU/L. CK MB is specific biomarker with sensitivity and specificity of 95%, however, seems to be more advantageous in detecting reinfarction, though it has limitations in terms of early diagnosis. Therefore, CK-MB with combination can increase the diagnostic specificity and sensitivity.

2.5 Disadvantages.

CPK-MB can also increase in, myocarditis, muscular dystrophy, Rhabdomyolysis, and polymyositis but these are not common disorders. Any form of strenuous exercise can also increase can also show high levels of this enzyme in the blood. High CK-MB level can also be seen if the kidney is damaged. Cancers such as prostate, breast, and other diseases such as pulmonary embolism, drugs toxicity, pericarditis, hypothyroidism, contusion, surgery, inflammation (muscular dystrophy, inflammatory muscle disease), muscle trauma, collagen tissue diseases (systemic lupus erythematosus), hyperthermia, Reye's syndrome, peripartum period, alcoholism, prolonged tachyarrhythmia, convulsions, acute cholecystitis, electric shock, cardioversion, and intramuscular injection all cause false-positive results in CK-MB measurements. Therefore, these conditions should be considered when using CK-MB as a biomarker in the diagnosis of AMI.³⁻⁴

There are other biomarkers for cardiovascular disease, which are not used by many due to lack of specificity and sensitivity. There are several types of tissue-specific fatty acid binding protein (FABPs), one is of heart-type. It is a soluble protein. It is not specific for cardiovascular disease as it is produced from other organs such as kidney and liver. However, Heart type fatty acid binding protein (H-FABP) at the early stage and troponin I at the late stage of cardiovascular disease, may give better diagnostic clarity. The myosin-binding protein C has three isoforms. cardiac myosin-binding protein C (cMyC) is expressed in the heart. cMyC is more concentration in

myocardium than troponin and it can raise earlier than troponin. But cMyC rises and falls more rapidly after AMI and lacking sensitivity and specificity. The earliest molecule released by the injured myocardium is myoglobin. Its blood levels start to increase within the first 30 minutes to 2 h after cardiac injury. Its specificity and positive predictive values are low. Therefore, these biomarkers are not suggestive of specific cardiac markers.

3.0 Results and Discussion

The biomarker in cardiovascular disease is wide-ranging, and while it incorporates several markers useful to the practice of cardio diagnosis. Cardio biomarkers played an important role in the management of cardiac diseases. The first cardiac biomarker identified in 1954 was an enzyme called Serum Glutamate Oxaloacetate Transaminase (SGOT) followed by another enzyme Lactate Dehydrogenase (LDH) in 1955. Only few markers were used by many physicians among multiple markers randomly such as cardiac enzymes, LDH, CK, CK-MB, SGOT and troponins (I, T & C) and other molecules Heart type fatty acid binding protein (H-FABP) and Myosine-binding protein C (cMyC). Due to lower sensitivities and specificities, these biomarkers may not give desired accurate diagnosis when used randomly. Serum Glutamate Oxaloacetate Transaminase (SGOT) and Lactate Dehydrogenase (LDH) are having low sensitivity and specificity. Now SGOT and LDH are outdated due to lack of cardiac specificity⁴. Myoglobin has no specificity, but it raises early and falls rapidly after Myocardial infarction. H-FABP was identified as a cardiac marker in 1972, also have low sensitivity 88% at 4 hours after MI. cMyC rise and fall rapidly after MI. MicroRNAs appear to be particularly promising in this regard, given that myocyte stress induced by anoxia, acidosis, and/or edema precedes myocardial necrosis in AMI patients and is rapidly reflected in circulating miRNAs levels. The rapid progress in molecular biomarker research must be matched, however, by similar progresses in laboratory techniques as well¹⁻⁴. Troponin on the other hand, show superior diagnostic efficacy.

Troponins are usually present in very small levels in the blood and is released in the blood in response to damage to cells. In addition to cardiovascular disease diagnosis, troponin also provides little evidence that lead to a higher risk of stroke.⁶ Troponin overall sensitivity 97-100 % and specificity is of 94-97%, Positive predictive value 98-100% and Negative predictive value 88-100%⁶. Galectin 3 was identified in 2004, a recent biomarker, need further research to bring it affordable techniques in larger use.

There are different types of methods to quantify these troponins. One method is routine blood tests which may take hours. Point of care testing for troponin studies revealed that the test performance was less sensitive than standard troponin test.⁷ Cardiac proteins involved in the diagnosis of Acute Myocardial Infarction are troponins. However, point of care testing needs further multiple evaluations to confirm the capability and diagnostic efficacy. Troponin I & T along with CPK-MB can maximise the efficiency of the accurate diagnosis of cardiac myocardial infarction and reinfarction. CK MB is specific biomarker with sensitivity and specificity of 95%, positive predictive value 98% and affordable, and low-cost techniques are required for larger use in clinical setup. There is a recent study about Galectin -3, regulates many biological activities, involving diagnostic role in psoriasis, and cardiometabolic comorbidities, especially in patients with history of obesity, however, it requires further validation studies before including cardiac panel. When all these three cardiac markers, Troponin I&T and CK-MB were combined, sensitivity and specificity will reach up to approximately 100%.and positive predictive value 100%.

4.0 Conclusion

Three biomarkers namely Troponin I & T along with CPK-MB can increase the diagnostic sensitivity and specificity when used collectively in the diagnosis of Myocardial infarction either acute or chronic conditions. These cardiac versatile biomarkers can also diagnose re-infarct with serial testing. There is point of care testing for troponins I&T, which are less sensitivity and specificity. However, these biomarkers are priced at high levels specifically troponins. Prices can be decreased by finding alternative methods of analysis. Whereas sensitivity and specificity of Troponins I & T ranges from 84 to 96 and 80 to 95% respectively. When all three cardiac markers were combined, sensitivity and specificity will reach up to approximately 100%. The best is yet to come in the form of biomarkers, that would allow rapid, accurate and reliable AMI diagnosis that too under point of care testing. MicroRNAs in this area of diagnosis is an important achievement, and Galectin 3 is a recent biomarker, both need further research to bring it affordable techniques in larger use.

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