Role of heart fatty acid binding protein in early detection of non-ST-elevation myocardial infarct and its comparison with other cardiac markers

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Abstract

Objectives: To determine the role of heart fatty acid-binding protein in early detection of non-ST-elevation myocardial infarction and its comparison with two other cardiac markers.

Methods: The cross-sectional study was conducted at Abbasi Shaheed Hospital, Karachi, from June 2012 to June 2014, and comprised patients presenting at the emergency department within two hours of chest pain and who were subsequently referred to the cardiology department with a provisional diagnosis of either unstable angina or non-ST-elevation myocardial infarction. Relevant history was taken on a specific proforma and electrocardiogram as well as
routine investigations were done in the emergency department. Blood samples from the subjects were tested for the diagnosis of myocardial infarction through detection of heart fatty acid-binding protein, Troponin-I and Creatine kinase-myocardial band. Sensitivity and specificity of the three markers were calculated keeping coronary angiography as the gold standard. Data was analysed using SPSS 17.

Results: Out of 250 patients, 153 (61.2%) were males. The overall mean age was 54.45±13.92 years. Sensitivity and specificity of heart fatty acid-binding protein were 80.6% and 78.5% (p<0.05), for Troponin-I, 37.7% and 75% (p>0.05), and for Creatine Kinase-myocardial band, 29.5% and 67.8% (p>0.05).

Conclusion: Heart fatty acid-binding protein was found to be a good diagnostic tool for the detection of non-ST-elevation myocardial infarction.

Key Words: Non ST-elevation myocardial infarct, Cardiac markers, Heart fatty acid-binding protein, Troponin-I, Creatine kinase isoenzyme MB, Angiography.

Introduction

Cardiovascular disease (CVD) is estimated to be the number one cause of death worldwide. Among other causes, coronary artery disease (CAD) is supposed to be the most fatal and prevalent manifestation of CVD. CVD is expected to be affecting more than 23 million people annually by 2030\(^1,2\). Although chest pain can be a manifestation of non-cardiac disease, cardiac chest pain alone constitutes 50% of all cases presenting with chest pain\(^3\). Chest pain of cardiac origin usually needs aggressive management and monitoring in order to prevent sudden cardiac death, which is the most dreadful manifestation of CAD\(^4\).

Acute coronary syndrome (ACS) encompasses a spectrum of CAD, including unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)\(^5\). Studies have shown that patients with NSTEMI constitute the majority (54%) of acute myocardial infarction (AMI) in-patients. A diagnosis of ACS usually needs significant ST-T changes
in electrocardiogram (ECG) and/or increased levels of myocardial disease markers in plasma. The absence of such changes, however, is not enough to exclude ACS, and it makes ACS diagnosis difficult to make in its early phase. Early diagnosis, however, is essential and early risk stratification is important to ensure the accurate, timely and cost-effective management of non-ST elevation acute coronary syndrome (NSTE-ACS) patients. In order to assess patients with confirmed ACS diagnosis, several scoring methods can be used, including the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scores.

The current study was planned to determine the early diagnostic role of heart fatty acid-binding protein (H-FABP) in NSTEMI compared to the role of like cardiac troponin (cTn-I) and creatine kinase-myocardial band (CK-MB).

**Patients and Methods**

The cross-sectional study was conducted at Abbasi Shaheed Hospital, Karachi, from June 2012 to June 2014. After approval from the institutional ethics committee, the sample size was calculated using epitool online sample size calculator for sensitivity and specificity employing the reported diagnostic accuracy of cardiac biomarkers at 95% confidence level and 80% power. The sample was inflated to avoid underpowered analysis. Those included were subjects of either gender aged >25 years presenting at the emergency department (ED) within two hours of the onset of chest pain lasting for >20 minutes suspected of having NSTE-ACS. Those excluded were case having recently been diagnosed STEMI or percutaneous coronary intervention (PCI) / coronary artery bypass grafting (CABG) within the preceding 30 days, renal failure with serum creatinine level >1.5 mg/dl or any known renal disease, and non-ACS patients.

All patients were enrolled after obtaining informed consent. Any patient with a working diagnosis of ACS was registered initially and several CAD
determinants, like onset and duration of chest pain, quality of pain, risk factors
and history of CAD, were noted. Blood sample was taken and tested for H-
FABP, Troponin-I (Trop-I) and CK-MB irrespective of the ECG findings and
clinical history. Data was collected based on positive biomarker results,
meaning any of the 3 biomarkers within two hours interval after onset of chest
pain diagnosed as NSTEMI, and negative biomarker result within 2 hours’ time
interval after onset of chest pain was labelled as unstable angina (UA). After
giving initial management, all patients were referred for coronary angiography.
Qualitative determination of H-FABP was done using rapid chromatographic
immunoassay Cardio-Detect kit with a cut-off value of 7.0ng/ml which is a
visual-based qualitative test. To assess serum qualitative level of Trop-I,
immune-chromatographic qualitative Cardiac-I Kit with a cutoff value of 0.5
ng/mL was used. Heparinised plasma samples were drawn for CK-MB and
quantitative analysis was done using spectrophotometer method on a semi-
automated analyser (Photometer). Normal mean CK-MB level was taken as
13.9±1.08 IU/L and the study protocol required all cardiac biomarkers to be
tested within 2 hours of onset of chest pain.
Coronary angiogram was performed using standard techniques as per hospital
protocol and data was recorded by follow-up of patients either through direct
contact with patients or through indirectly-collected angiogram results from the
referred hospital. Significant CAD was defined as a lesion with ≥50% stenosis
of the left main (LM) artery or ≥70%stenosis in any major coronary artery or its
branches.
Data were organized on Microsoft Excel 2007 and was analysed using SPSS 17.
Continuous variables were presented as mean ± standard deviation and
categorical variables as frequencies and percentages., and. Sensitivity and
specificity of the cardiac biomarkers were calculated and all parameters were
analysed using cross-tabulation, while significant differences were assessed
using chi-squared test. P<0.05 was considered statistically significant.
Results
Of the 250 subjects, 153 (61.2%) were males. The overall mean age was 54.45±13.92 years. The most common age range was 35-44 years (Figure 1). On admission, 194 (77.6%) patients had typical chest pain and 101 (52%) had chest heaviness with or without pain radiating to the left shoulder. Presented symptoms were sweating in 22 (11.3%) patients, palpitation 41 (21.1%), nausea 9 (4.6%), vomiting 4 (2%) and dyspnoea 17 (8.7%). Also, 25 (10%) patients, specifically diabetics, presented with atypical chest pain like epigastric pain or and right shoulder pain, and 31 (12.4%) presented with dyspnoea. Hypercholesterolemia was the most common risk factor 106 (42.4%) followed by hypertension (HTN) 103 (41.2%), smoking 86 (34.4%) and diabetes 73 (29.2%). Further, 53 (21.2%) patients were obese and 30 (20%) had a positive family CAD history.
Overall, 85 (34%) patients were diagnosed as NSTEMI, while 165 (66%) were UA. True-positive (TP) and true-negative (TN) values for all the three cardiac biomarkers were assessed (Figure 2). Using coronary angiogram as the gold standard, the sensitivity and specificity of sensitivity and specificity of H-FABP were 80.6% and 78.5% (p<0.0001), for Trop-I, 37.7% and 75% (p=0.211), and for CK-MB, 29.5% and 67.8% (p=0.0791).
Discussion
The study was conducted to determine the early diagnostic role of H-FABP in NSTEMI in order to focus on early diagnosis for maximum salvage of the injured myocardium. Studies9,10 demonstrated that H-FABP level rises within one to three hours of the initial myocardial injury and returns to the baseline level within 12-24 hours and, thus, can be considered an initial diagnostic cardiac marker. Of note, the level of Trop-I sometimes remains undetectable even in the setting of existing CAD and myocardial injury, thus, raising questions on reliability of Trop-I assay as a single diagnostic disease marker.
This may warrant the need of some other biomarker of myocardial injury like FABP.

The current study excluded all patients having STEMI because its diagnosis does not depend on cardiac biomarkers. A study\textsuperscript{11} using qualitative H-FABP as a diagnostic marker of cardiac disease within the first six hours in patients with STEMI reported the sensitivity of H-FABP as 95% in comparison with Trop-I (76%) and CK-MB (38%). In the current study, H-FABP assessment within two hours revealed 19 false-positive (FP) and 6 false-negative (FN) patients. FP result of H-FABP mostly developed in patients who had renal impairment during admission in the coronary care unit (CCU). Naroo et al.\textsuperscript{12} also showed that renal failure could result in FP H-FABP levels. Literature has also reported that H-FABP could be regarded as a sensitive marker for minor myocardial injury with ischemia but no detectable levels of standard cardiac biomarkers in the blood\textsuperscript{13}. This could also be a reason for FP findings in ischemic patients with UA that could not have been detected by our reference standard Trop-I, and we labelled these results as FP due to our standard settings. The results for FN were also reviewed to find the reason, but no precise reason was found except that relatively high number of early presenters within an hour after the onset of symptoms may be the factor for FN results which was comparable with the outcome of Willemsen et al. who also included early presenters in their study\textsuperscript{14}. Trop-I assessment within two hours revealed 61 FP and 7 FN patients. The reason for FP elevation of troponin was the existence of fibrin in the specimens or development of endogenous antibodies secondary to rheumatoid factor (RF) in some of our known rheumatoid arthritis (RA) patients or heterophilic antibodies derived from immunotherapies in a few of our patients who previously were treated for chronic liver diseases. This is in line with Tanindi et al.\textsuperscript{15}. Likewise, reason for FN part of our findings could be the development of auto-antibodies against the central segment of Trop-I in some of the patients having auto-immune diseases, like systemic lupus erythematosus.
(SLE) or ulcerative colitis, that delay the diagnosis and, thus, we missed the
definite diagnosis. Nevertheless, an FN troponin value may result due to
mismatch of the timing of sample drawn and extent of the infarction. This is
also reported by a study that peak troponin values will be low in patients with
minor myocardial infarcts. CK-MB assessment within two hours revealed 69
FP and 9 FN patients. The reason for FN result of CKMB in acute myocardial
injury compared others biomarkers could be due to the fact that slightly elevated
Trop-I levels may be found due to the presence of unbound component of
troponin in the cardiac myocytes, which is about 6% of cTnT and 3% of cTnI,
but CK-MB levels remained in the reference range. Similar findings were
reported by Tanindi et al. We observed FP result of CK-MB in a fraction of
patients presenting with hypertensive crisis along with neurological ischemia or
stroke. Although this scenario can point towards a diagnosis of ACS, but normal
troponin along with elevated CK-MB suggests that the surge in CK-MB is non-
cardiac in origin which is common in patients with ischemic stroke. Ay et al, also reported similar findings.

The demographic data of the current study showed mean age of 54.20±13.86
years while one study done in Pakistan reported 60±5.0 years in their
population. The reason for younger age in our population may due to the fact
that most patients had at least three or more co-morbidities. We also found the
male gender to be more prone to CAD, which has also been reported earlier.

It is also postulated in literature that young and female gender imply lower
CAD risk due to oestrogen’s protective effects. This might be a reason that most
women with clinical CAD are generally older than men. alone study also
reported that young women who, by chance, lose their natural protection against
CAD, are at especially high risk compared with women who develop heart
disease after menopause. Besides, it was also concluded from the study that
there were three most important cardiovascular risk factors which were more
prone to myocardial infarction or UA were hypercholesterolemia, HTN and
smoking, followed by diabetes, obesity and family history. The current supported the findings of Chiha et al\textsuperscript{23} that approximately 44\% reduction in ACS resulted after modification of these three most important cardiovascular risk factors.

The comparison of diagnostic utility of all the 3 cardiac biomarkers revealed that H-FABP was superior in sensitivity than other biomarkers when measured on admission, and was characterised by sensitivity of 80.6\% and specificity of 78.5\% respectively in all patients who came within two hours of onset of symptoms. Shama et al. reported that FABP is a superior biomarker for early-hour detection due to higher sensitivity in comparison with other biomarkers\textsuperscript{24}. Another study done\textsuperscript{25} on 67 patients with acute chest pain in the first three hours suspected of AMI, UA and non-cardiac chest pain reported the sensitivity and specificity of H-FABP to be 81.8\% and 88.2\% respectively while the sensitivity of Trop-T and CK-MB were 81.8\% each, and specificity was 76.5\% and 41.2\% respectively. The superior specificity of H-FABP might be due to higher permeability of the endothelial barrier for small proteins that enable H-FABP to exhibit an early and significant release after myocardial injury and make it more easily being detected.

In terms of limitations the study comprised hospital-based referral population which is fairly representative of an ED setting and may not necessarily reproduce results for the general population. Also, owing to the limited numbers of H-FABP kits, we could not compare H-FABP with other biomarkers in the late time period > 2 hours.

**Conclusion**

H-FABP was found to be a better diagnostic tool in NSTE-ACS, especially in the early time period window, after chest pain. As an early marker, it can reliably diagnose ACS. Compared to cardiac troponin, H-FABP is emerging as a diagnostic marker to rule out non-AMI patients in the early acute phase.
Disclaimer The text is based on an MD thesis.

Conflict of Interest: None.

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References


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Provisionally Accepted for Publication
Figure 1: Age distribution of the study population.

Figure 2: Diagnostic accuracy of heart fatty acid-binding protein (H-FABP), Troponin-I and Creatine kinase isoenzymes M and B (CK-MB) in <2 hours after onset of chest pain using coronary angiography as gold standard.