Role of heart fatty acid-binding protein (h-FABP-type III) as a diagnostic biomarker in acute coronary syndrome

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Objective
To determine the role of heart-type fatty acid-binding protein (h-FABP type III) as a diagnostic biomarker in acute coronary syndrome in the early detection of myocardial ischemia or myocardial necrosis (30 min to 6 h from onset of chest pain).

Background
Cardiac biomarkers play an important role in the diagnosis of acute coronary syndrome. Cardiac troponins have been the preferred biomarker, but because of their delayed appearance in the serum, there is still a need for reliable. h-FABP, a small (15 kDa) cytoplasmic tissue-specific protein, is mainly expressed by cardiac biomarkers.

Methods and results
The patients were classified into two main groups. Group I included patients who presented with ST-segment elevation myocardial infarction (STEMI, $n = 25$) and group II included patients who presented with non-STEMI/unstable angina (NSTEMI/UA, $n = 25$) within 20 min and 6 h of acute chest pain. Blood h-FABP levels were measured using a QuickSens test (semiqualitiative) and were compared with first cTn-I and creatine kinase-MB at the time of admission and second troponin 12 h from onset of chest pain. Then, according to the serum level of h-FABP, the patients were classified into two subgroups: h-FABP-positive patients and h-FABP-negative patients. The diagnostic sensitivity, specificity, and receiver operating characteristic curve were evaluated. Serum h-FABP was significantly elevated within 20 min to 6 h. In terms of the relation between h-FABP and second troponin, h-FABP showed a sensitivity of 92.59%, a specificity of 52.17%, a positive predictive value of 69.44%, a negative predictive value of 85.71%, and an accuracy of 74%. Our results showed that h-FABP was significantly higher than other biomarkers less than 6 h after the onset of chest pain.

Conclusion
h-FABP can be used as an early diagnostic cardiac biomarker in the early detection of patients with an acute coronary syndrome within 30 min to 6 h of onset of chest pain.

Keywords:
acute coronary syndrome, heart-type fatty acid-binding protein, myocardial ischemia, myocardial necrosis

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Introduction

Diagnosis and exclusion of acute coronary syndrome (ACS) [which includes myocardial infarction (MI) and unstable angina (UA)] often pose a diagnostic challenge to the clinicians [1].

Missing an ACS may lead to excess morbidity and mortality that could have been prevented with optimal treatment. The diagnosis of MI is made on the basis of clinical symptoms, ECG changes, and the characteristic pattern of changes in some serum enzymes such as creatine kinase (CK), creatine kinase isoenzyme MB (CK-MB), lactate dehydrogenase isoenzyme I, and cardiac-specific proteins such as troponins [2].

Cardiac biomarkers play an important role in the diagnosis of ACS. An ideal marker that can predict the onset of the disease could aid in reducing the deaths because of ACS. Cardiac troponins have been the preferred biomarker, but because of their delayed appearance in the serum, there is a still a need for a reliable biomarker [3].

Heart-type fatty acid-binding protein (h-FABP), a small (15 kDa) cytoplasmic tissue-specific protein, is mainly expressed by myocytes. They are a class of proteins that bind long-chain fatty acid and play an important role in the intracellular utilization of fatty acids. h-FABP can be transported from severely damaged cardiomyocytes to the blood more rapidly than other markers such as cT-nI and CK-MB. Recent research suggests that human h-FABP might potentially be useful as an early cardiac marker. It appears in plasma 1–3 h. after cardiac damage, and may be the earliest available plasma marker of acute myocardial injury and returns to normal values in 12–24 h. It may have better

diagnostic accuracy than other cardiac markers in the early stages after symptom onset, although the clinical impact of this better diagnostic performance remains unclear [4].

Patients and methods

Study participants

This study was carried out on 50 patients: 25 patients presented with ST-elevation MI (STEMI) and non-ST-elevation MI/UA (NSTEMI/UA). The patients were recruited from the Intensive Care Unit, Cardiology Department, Menoufiya University Hospital, between May 2012 and August 2014. The protocol of this study was approved by the local ethics committee, Faculty of Medicine, Menoufiya University, and written informed consent was obtained from every patient participating in this study. Patients presenting with acute chest pain more than 20 min and less than 6 h suspected of having acute myocardial infarction (AMI) and UA were enrolled consecutively in the study. These patients were also classified according to the result of serum h-FABP into two groups (h-FABP-positive patients and h-FABP-negative patients). Complete assessment of history including patients' symptoms and medical history such as diabetes mellitus, hypertension, and previous ischemic event was performed, A general clinical examination was also performed, and ECG and laboratory investigations were documented at admission using a predefined protocol.

Inclusion criteria

Patient who presented to the emergency department or the Intensive Care Unit 30 min to 6 h from the onset of symptoms, patients who provided signed informed consent, and adult patients 18 years or older were included in this study. There were no exclusion criteria. The standard diagnosis was made after a critical review of all the clinical pictures and relevant information by a senior cardiologist. Patients presenting with STEMI in ECG were characterized by the following: typically, ST-segment elevation in AMI, measured at the J point, should be found in two contiguous leads and be at least 0.25 mV in men younger than 40 years of age, at least 0.2 mV in men older than 40 years of age, or at least 0.15 mV in women in leads V2–V3 and/or at least 0.1 mV in other leads (in the absence of left ventricular hypertrophy or left bundle branch block) [5]. In patients with inferior MI, right precordial leads (V3R and V4R) were recorded to identify concomitant right ventricular infarction [5]. Similarly, ST-segment depression in leads V1–V3 suggests posterior myocardial ischemia, especially when the terminal T-wave is positive (ST-elevation equivalent), and may be confirmed by concomitant ST-elevation of at least 0.1 mV recorded in leads V7–V9 [5]. Patients did not have persistent ST-segment elevation. These patients had persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudonormalization of T waves, or no ECG changes at presentation. At presentation, the working diagnosis of non-ST-elevation ACS, on the basis of the measurement of troponins, was further qualified as NSTEMI or UA [6].

Exclusion criteria

Patients with one of the following criteria were excluded: patients younger than 18 years of age, patients presenting with completed MI and chest pain more than 6 h, patients who had renal insufficiency or any renal disease impairing creatinine clearance, patients who had chronic liver disease, patients with known skeletal muscle disease, and patients receiving DC shock.

Laboratory analysis

Only one venous blood sample (10 ml) was withdrawn by sterile venous puncture and clean dry syringes from the cubital vein of every patient investigated at the time of admission to the hospital within 6 h after the onset of symptoms. Blood samples were obtained for the determination of total cholesterol, triglyceride, creatinine, cTn-I, CK-MB, and h-FABP. Methods of performing the test include the following steps: the sealed bag should be opened, the test should be removed and then placed on a horizontal surface. The test must be performed at room temperature before use. The test should be labeled with the patient's identification. A venous blood sample (10 ml) was withdrawn by sterile venous puncture from the cubital vein and transferred to clean dry syringes. The test result was assessed after 15 min [7].

Interpretation of the results [7]

The results can only be evaluated 15 min after the sample has been applied. The red/purple line (C) indicates whether the test has worked properly. [The test has to be repeated if the control line (C) does not appear, even if only the test line (T) appears.]

Negative: (<10.0 ng/ml) when a red/purple line appears in the upper section panel (control line 'C'), indicating that the test has worked properly. There is, however, no test line (T). This indicates that the concentration of h-FABP in the sample is less than 10 ng/ml. Patients with an elevated h-FABP base value can show a very weak test line.

Positive: (≥10.0 ng/ml) when a red/purple line appears in the upper section panel (control line 'C'), indicating that the test has worked properly and another red/

purple line appears in the lower section panel [test line (T)]. This indicates that the concentration of h-FABP in the sample was greater than 10 ng/ml. The stronger and wider the line, the higher the h-FABP value.

Invalid: a red/purple line in the control range must always appear after the test has been performed. However, if there is no red/purple line, the test is invalid and must be repeated.

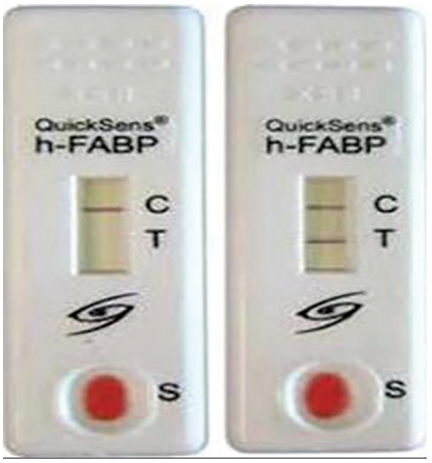
Statistical analysis

Results were statistically analyzed and described as mean ± SD and percentage. Student's *t*-test and the Mann–Whitney test (nonparametric test) were used for the assessment of the two main groups and the two subgroups. c^2 (×2) test, sensitivity, specificity, positive and negative predictive values, diagnostic accuracy, and receiver operating characteristic curve were used to assess the diagnostic validity of h-FABP and cTn-I. *P* values less than 0.05 were considered statistically [8].

Results

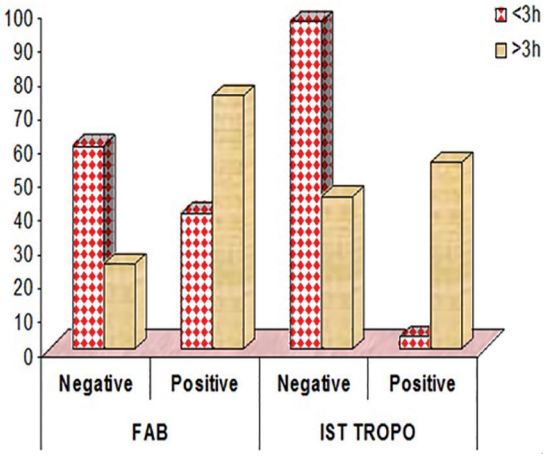
Fifty patients were enrolled in the study and divided into two main groups: Group1 included patients with acute STEMI (*n* = 25, 15 men and 10 women). Their ages ranged between 42 and 65 years, mean age 52.360 ± 6.525 years. Group 2 included patients with NSTEMI/UA (*n* = 25, 15 men and 10 women). Their ages ranged between 40 and 65 years, mean age 55.880 ± 7.149 years. There were no statistically significant differences in the age of the patients between the two main groups (*P* = 0.075), and there were no significant differences in the sex distribution (*P* = 1.000). In terms of the risk factors of the patients, there was no statistically significant difference between the two groups in the prevalence of hypertension (*P* = 0.152), smoking (*P* = 0.569), dyslipidemia (*P* = 1.00), history of ischemic heart disease (*P* = 0.566), or positive family history (*P* = 0.248), whereas there was a statistically significant difference between the two groups in the prevalence of diabetes mellitus (*P* = 0.047). There was nonstatistically significant difference between the two main groups in the serum level of triglycerides (*P* = 0.695), the serum level of LDL (*P* = 0.111), the serum level of HDL (*P* = 0.658), the serum level of cholesterol (*P* = 0.419), and the serum level of creatinine (*P* = 0.700). According to onset of chest pain, 18 patients had negative h-FABP and 12 patients had positive h-FABP less than 3 h from onset of chest pain, whereas 29 patients had negative first troponin and one patient had positive troponin at the same time (<3 h from onset of chest pain, five patients had negative h-FABP and 15 patients had positive h-FABP in >3 h and <6 h), whereas nine patients had negative first troponin and 11 patients had positive first troponin at the same time (Figs. 1–5 and Tables 1–4).

Figure 1



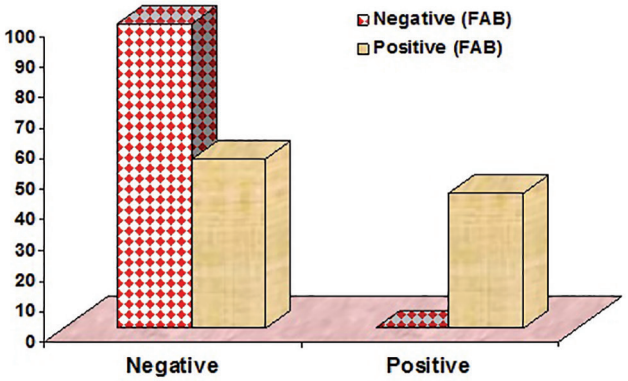
Two examples of QuickSens h-FABP on the right side show h-FABP positivity and those on the left side show h-FABP negativity [2]. h-FABP, heart-type fatty acid-binding protein.

Figure 2



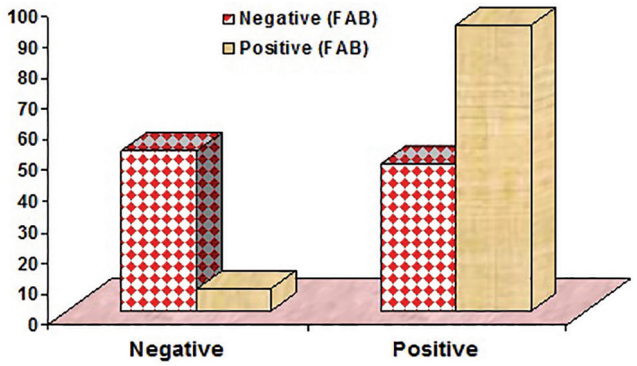
Comparison between the serum level of h-FABP, first troponin, and the serum level of CK-MB in terms of onset of chest pain. CK-MB, creatine kinase-MB; h-FABP, heart-type fatty acid-binding protein.

Figure 3



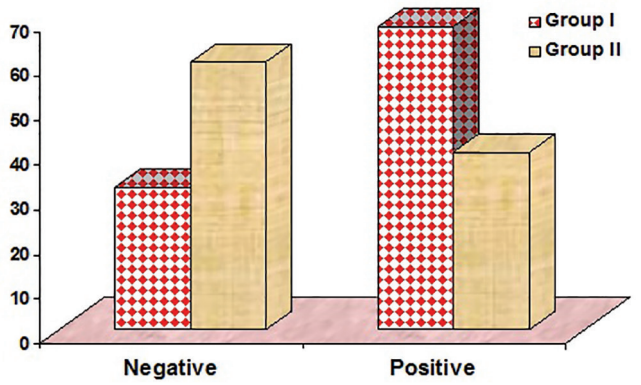
Comparison of subgroups of FAB in the serum level of first troponin. FAB, fatty acid-binding protein.

Figure 4



Comparison of subgroups of h-FAB in the serum level of second troponin. h-FABP, heart-type fatty acid-binding protein.

Figure 5



Comparison of the two main groups in the serum level of h-FAB. h-FABP, heart-type fatty acid-binding protein.

Table 1 Relation of onset of pain and heart-type fatty acid-binding protein

Variable	Onset of chest pain [*N* (%)]			*P*-value
	<3 h	>3 h	Total	
h-FAB				
Negative	18 (60.00)	5 (25.00)	23 (46.00)	0.013*
Positive	12 (40.00)	15 (75.00)	27 (54.00)	
First troponin				
Negative	29 (96.67)	9 (45.00)	38 (76.00)	<0.001*
Positive	1 (3.33)	11 (55.00)	12 (24.00)	
CK-MB				
Range	20–150	26–124	20–150	0.544
Mean ± SD	58.60 ± 29.37	63.65 ± 27.47	60.62 ± 28.457	

CK-MB, creatine kinase-MB; h-FABP, heart-type fatty acid-binding protein; *Means significant.

Table 2 Relation of heart-type fatty acid-binding protein and first troponin

First troponin	h-FAB [*N* (%)]			*P*-value	
	Negative	Positive	Total		
Negative	23 (100.00)	15 (55.56)	38 (76.00)	<0.001*	
Positive	0 (0.00)	12 (44.44)	12 (24.00)		
Total	23 (100.00)	27 (100.00)	50 (100.00)		
ROC curve	Sensitivity	Specificity	PPV	NPV	Accuracy
	44.44	100	100	60.52	70

h-FABP, heart-type fatty acid-binding protein; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; *Means significant.

Table 3 Relation of heart-type fatty acid-binding protein and second troponin

Second troponin	h-FAB [*N* (%)]			*P*-value	
	Negative	Positive	Total		
Negative	12 (52.17)	2 (7.41)	14 (28.00)	<0.001*	
Positive	11 (47.83)	25 (92.59)	36 (72.00)		
Total	23 (100.00)	27 (100.00)	50 (100.00)		
ROC curve	Sensitivity	Specificity	PPV	NPV	Accuracy
	92.59	52.17	69.44	85.71	74

h-FABP, heart-type fatty acid-binding protein; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; *Means significant.

Discussion

The diagnosis and exclusion of ACS, which includes MI and UA), often pose a diagnostic challenge to clinicians; missing an ACS may lead to excess morbidity and mortality that could have been prevented with optimal treatment. Cardiac biomarkers play an important role in the diagnosis of ACS [3].

A growing number of studies have shown that h-FABP is a sensitive marker for the diagnosis of MI [12,13]. The characteristic release of h-FABP after AMI is such that an increase is detectable as early as 1.5 h after the onset of symptoms, reaches a peak level after 4–6 h, and the level returns to baseline within 20 h because of rapid renal clearance [9].

Studies evaluating the diagnostic accuracy of h-FABP have reported variable sensitivities and specificities [7,10,12,13].

In this study, it was found that the h-FABP biomarker test was positive in patients with acute typical ischemic chest pain in the context of ACS who came to the emergency department within 30 min to 6 h of chest pain onset. Our results support the evidence that h-FABP is an early marker of ischemia, that it is detected before any detectable change in cTn-I, as well as in CK-MB, and can be detected even in the absence of myocardial necrosis. This is especially useful to rule out ischemia in the early stage, thereby making h-FABP a potentially useful biomarker for early detection of cardiac ischemia.

In this study, it was found that 12 patients (40%) had positive h-FABP and 18 patients (60%) had negative h-FABP within less than 3 h of chest pain onset, whereas 29 patients (96.6%) had negative first troponin and one patient had positive first troponin (3.33%) within less than 3 h of chest pain onset.

Table 4 Fatty acid-binding protein in different groups

FAB	Groups [*N* (%)]			*P*-value
	Group I	Group II	Total	
Negative	8 (32.00)	15 (60.00)	23 (46.00)	0.047*
Positive	17 (68.00)	10 (40.00)	27 (54.00)	
Total	25 (100.00)	25 (100.00)	50 (100.00)	

FAB, fatty acid-binding protein; *Means significant.

Our results are in agreement with those of Valle *et al.* [10] who compared the effectiveness of h-FABP with conventional biomarkers in a multicenter study in emergency room patients with suspected ACS lasting less than 6 h. A total of 419 patients were analyzed. AMI was diagnosed in 148 patients (35%). h-FABP sensitivity was 60% (89 out of 148 patients), significantly higher than troponin T [19% (28 out of 148 patients); $P < 0.05$]. The specificity of troponin T, however [99% (270 out of 271 patients)], was better than that of h-FABP [88% (237 out of 271 patients)], although this was not statistically significant.

Figiel *et al.* [11] carried out a study including 52 patients who were suspected to have ACS with chest pain lasting less than 6 h. The sensitivity of h-FABP (84%) was superior to that of cardiac troponin T (cTnT), which had a sensitivity of 50%.

Our results are in agreement with those of Seino *et al.* [12], who compared the diagnostic efficacy of a newly developed whole-blood rapid test for h-FABP with that of a rapid cTnT test in 129 consecutive patients with suspected cardiac ischemia, 31 of whom had a diagnosis of AMI. The respective temporal sensitivities of h-FABP and cTnT tests were 100 versus 50% at 3 h and 100 versus 100% at more than 12 h after the onset of symptoms. The respective specificities were 63 versus 96.3% at 3 h and 75 versus 87.5% at more than 12 h. The negative predictive values were 100 versus 86.7% at 3 h and 100 versus 100% at more than 12 h. The rapid h-FABP assay was suggested to effectively exclude non-AMI patients within 3 h of onset.

In this study, it was found that h-FABP was more sensitive than CK-MB in the early detection of acute myocardial ischemia and or infarction and this is in agreement with Okamoto *et al.* [13], who evaluated the usefulness of h-FABP testing in a group of almost 200 patients with chest pain lasting less than 12 h. The overall sensitivity of h-FABP was 92.9% compared with 18.6% for CK-MB.

Pelsers *et al.* [14] also showed the superior sensitivity of h-FABP compared with other biomarkers in patients with ACS.

The data in our study are in complete agreement with the study of Cavus *et al.* [15], in which, during the first hour of myocardial injury, h-FABP was superior to troponin T by showing a positive result (h-FABP level of >6 ng/ml in patients), whereas troponin T showed a negative result. This trend changed at the fourth hour of myocardial injury, where the sensitivity and specificity of h-FABP became equal to those of CK-MB and troponin T.

Alhashemi [16] showed that h-FABP is a very useful cardiac marker to enable the emergency physician to make a decision and diagnose AMI in patients who present with recent onset of chest pain without typical changes in the ECG as h-FABP can be detected as early as 20 min following AMI.

Schreiber and Miller [17] reported that h-FABP is released within 2–3 h after symptom onset, peak early (6 h), and return to the normal baseline concentration within 24 h; this was confirmed in our study.

Nakata *et al.* [18] found that elevated h-FABP at presentation was associated with an increased need for emergent hospitalization, coronary angiography, and interventional therapy in 133 patients with suspected ACS. Similarly, a retrospective study of 90 patients with ACS found that h-FABP measured at presentation was associated independently with an increased risk of death or recurrent ischemic events during follow-up.

Nagahara *et al.* [19] proved that h-FABP is highly specific for cardiomyocyte injury (necrosis).

Study limitations

First, the major limitation of our study involves the relatively small number of patients under study with ACS.

Second, there was no consistent 'gold standard' test for myocardial ischemia; therefore, in our study, the diagnostic performance of h-FABP qualitative testing was performed against the final diagnosis, which was made by the interpretation of the results of appropriate tests.

Third, only a single blood sample was obtained for the study. Sequential measurements were not investigated.

Fourth, qualitative point-of-care tests were used to measure h-FABP.

Conclusion

h-FABP can detect early myocardial injury (infarction) and can exclude other acute noncardiac chest pain causes within 6 h. h-FABP can be useful in the early diagnosis of acute chest pain in comparison with other traditional biomarkers such as CK-MB and cTn-I.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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