Menoufia Medical Journal

PRINT ISSN: 1110-2098 - ONLINE ISSN: 2314-6788

journal hompage: www.menoufia-med-j.com

Volume 29 | Issue 2 Article 38

6-1-2016

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Recommended Citation

Amin El-Lakwah, Emtiaz F.; Soliman, Mahmoud A.; Ghanayem, Naglaa M.; Montaser, Said S.; and Abd El-Aziz, Walaa F. (2016) "Diagnostic impact of serum myoglobin and human heart-type fatty acid binding protein in patients with acute myocardial infarction," *Menoufia Medical Journal*: Vol. 29: Iss. 2, Article 38.
DOI: https://doi.org/10.4103/1110-2098.192446

Diagnostic impact of serum myoglobin and human heart-type fatty acid binding protein in patients with acute myocardial infarction

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Received 03 December 2014
Accepted 18 February 2015

Menoufia Medical Journal 2016, 29:423–430

Objective
The aim of the study was to assess the value of the serum concentrations of myoglobin and human heart-type fatty acid binding protein (H-FABP) in the early detection of acute myocardial infarction (AMI).

Background
Myoglobin and H-FABP are useful as biochemical markers of muscle injury. We conducted this investigation to detect whether both markers and their ratio were useful in the early detection of AMI.

Patients and methods
This study included 21 patients with AMI, 20 patients with skeletal muscle injury, and 10 normal healthy individuals. Their blood samples were obtained (within 6 h of onset of chest pain in AMI patients), and serum concentrations of creatinine, aspartate aminotransferase, H-FABP, myoglobin, cardiac troponin I, and creatine kinase-MB (CK-MB) were determined.

Results
It was found that H-FABP has higher sensitivity and predictive accuracy compared with myoglobin in the early detection of AMI: the sensitivity of H-FABP was 95% and that of myoglobin was 81%, and the sensitivity of their ratio was 90%. H-FABP is a more sensitive marker, but in our study its specificity was 90%, which was lower than that of myoglobin (99%) for the detection of AMI within 6 h after the onset of chest pain. Also, our study showed that myoglobin and H-FABP were directly proportional to troponin and CK-MB, in which there is significant positive correlation.

Conclusion
The diagnostic sensitivity of H-FABP is high, above that of myoglobin in patients presenting within 6 h of chest pain. H-FABP is a sensitive and specific marker for the early diagnosis of AMI. The lower specificity of H-FABP makes troponin and CK-MB superior for the diagnosis of AMI.

Keywords:
acute myocardial infarction, cardiac markers, heart-type fatty acid binding protein, myoglobin, STEMI

Menoufia Med J 29:423–430

1110-2098

Introduction

Acute myocardial infarction (AMI) is a common cause of sudden death [1]. Serial measurement of biochemical markers is now universally accepted as an important determinant in AMI diagnosis; however, the early diagnosis of AMI is still problematic. Therefore, a rapid method for early diagnosis of AMI is crucial [1].

Cardiac markers help assess acute coronary syndromes. Troponins and creatine kinase-MB (CK-MB) are highly cardiac specific. However, their concentrations in blood increase only from 4 to 6 h after onset of AMI [2].

Myoglobin is a small protein (18 kDa) that appears in the plasma after myocardial infarction (MI) and is considered a useful marker for the early detection of AMI. However, it lacks specificity because the myoglobin released from skeletal muscles cannot be distinguished from that released from the heart [3].

Heart-type fatty acid binding protein (H-FABP), a small cytoplasmic protein (15 kDa) involved in lipid homeostasis, is abundant in the heart muscle; in addition, H-FABP is a sensitive biomarker of myocardial necrosis that can be used to confirm or exclude a diagnosis of AMI [4].

H-FABP is found in abundance in cardiomyocytes but is also expressed (to a lesser extent) in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary glands, and placenta [5]. H-FABP could be of value as a marker

 DOI: 10.4103/1110-2098.192446

of myocardial ischemia, even in the absence of frank necrosis [6].

The plasma kinetics of H-FABP (15 kDa) closely resemble those of myoglobin (18 kDa), but H-FABP concentration in the heart muscle is greater than that in skeletal muscle and its normal baseline concentration is several-fold lower than that of myoglobin [7]. Both proteins are released into plasma after injury at about the same time and in a ratio similar to the concentration of the proteins in the tissue of origin. These advantages make H-FABP a potentially more suitable cardiac marker than myoglobin. Therefore, the measurement of the ratio of myoglobin over H-FABP could be useful for discriminating between cardiac and skeletal muscle damage [8].

The main disadvantage of myoglobin or H-FABP as early markers of myocardial injury is lack of complete specificity because of the presence of both in skeletal muscle. Severe skeletal muscle injury may result in the release of both proteins in sufficient quantity to interfere with the specificity of the assay [9].

H-FABP measured with troponin shows increased sensitivity of 20.6% over troponin at 3–6 h after onset of chest pain [8]. The prognostic value of elevated H-FABP is additive to that of troponin in low-risk and intermediate-risk patients with suspected acute coronary syndrome (ACS) [6].

It was recently reported that elevated levels of H-FABP measured in the first few days after an ACS event were associated with an increased risk of death, heart failure, and early recurrent ischemic events [10].

In the present study, we assessed the value of the serum concentrations of myoglobin and human H-FABP in the early detection of AMI as compared with skeletal muscle injury.

Patients and methods

This study was conducted from 2009 to 2012 at Cardiology and Medical Biochemistry Departments, Faculty of Medicine, Menoufia University, on 51 individuals: 21 patients with AMI, 20 patients with skeletal muscle injury, and 10 healthy individuals, who served as controls. They were classified into three groups.

Group I included 21 patients who were recently admitted to the ICU with STEMI. Their diagnosis was based on the Joint European Society of Cardiology/ American College of Cardiology Committee [11], which satisfies the diagnosis for an acute, evolving, or recent MI depending on either one of the following criteria:

(1) Typical rise and fall of biochemical markers of myocardial necrosis, with at least one of the following:
   (a) Ischemic symptoms;
   (b) Development of pathologic Q waves on ECG;
   (c) ECG changes indicative of ischemia (ST-segment elevation or depression); or
   (d) Coronary artery intervention (e.g. coronary angioplasty).
(2) Pathologic findings of an AMI.

Any one of the following criteria satisfied the diagnosis for established MI:

(1) Development of new pathologic Q waves on serial ECGs.
(2) Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause.
(3) Pathologic findings of a healed or healing MI.

Group II included 20 patients with skeletal muscle injury who underwent a recent abdominal or orthopedic operation with normal ECG.

Group III was the control group, which included 10 normal healthy individuals.

Methods

The diagnosis of AMI is based on ECG changes, pathological rise of biochemical markers, and clinical presentations.

All participants underwent the following:

(1) Full medical history taking.
(2) Full clinical Examination.
(3) 12-Lead ECG.
(4) Laboratory investigations, including:
   (a) Measurement of serum creatinine: determined by the fixed rate kinetic chemical method using Diamond Diagnostics International (Holliston, Boston, U.S.A) serum creatinine kits [12].
   (b) Measurement of serum aspartate aminotransferase (AST): determined by the kinetic method using ELITech (France) AST kits [13].
   (c) Measurement of serum troponin I: determined by enzyme-linked fluorescent assay technique using the VIDAS troponin I ultra kit provided by bioMérieux Inc. - Boston, MA, USA. Reference range: normal up to 0.11 μg/l [14].
   (d) Measurement of serum CK-MB: determined by enzyme-linked immunosorbent assay (ELISA)

using the kit provided by Oxis International Inc. (Foster City, CA, USA). Reference range: adult (normal) 2.0–5.2 ng/ml [15].

(e) Measurement of serum H-FABP: determined by ELISA using the kit provided by Biocheck Inc. (USA). Reference range: healthy individuals 1.6–19 ng/ml [16].

(f) Measurement of serum myoglobin: determined by ELISA using the kit provided by DRG International Inc. (New Jersey, USA). Reference range: normal (negative) 0–85 ng/ml [17].

Patients were selected from Menoufia University Hospital. Written informed consent was obtained from every participant and the study was approved by the Ethical Committee, Faculty of Medicine, Menoufia University.

Statistical analysis

All data were collected, revised, coded, and entered into the statistical package for the social sciences (SPSS, version 17; SPSS Inc., Chicago, Illinois, USA).

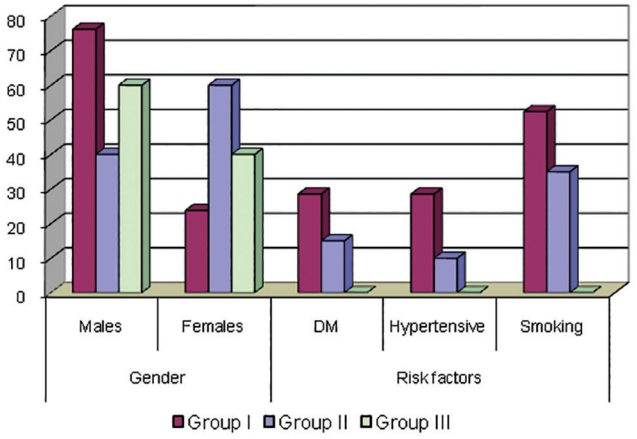
Results

Twenty-one patients were included in the AMI group, with a mean age of 57.29 ± 1 1.15 years; 20 patients were in the skeletal muscle injury group, with a mean age of 43.3 ± 13.81 years; and 10 healthy participants served as the control group, with a mean age of 47.4 ± 11.423 years.

Regarding age there was significant statistical difference between group I and group II (P = 0.002), whereas nonsignificant statistical difference existed between group III and each of group I and group II. Further, there was nonsignificant statistical difference between the studied groups as regards sex, diabetes mellitus, and diastolic blood pressure (P = 0.059, 0.064, and 0.129, respectively) and significant statistical difference as regards hypertension, history of smoking, and systolic blood pressure (P = 0.045, 0.004, and <0.001, respectively) (Table 1 and Fig. 1).

The results of the laboratory investigations in this study [H-FABP, myoglobin, cardiac troponin I (cTnI) and

Figure 1



Statistical comparison of demographic and clinical data in the studied groups. DM, diabetes mellitus.

Table 1 Statistical comparison of demographic and clinical data in the studied groups

Demographic and clinical data	*N* (%)			χ^2	*P*-value	Tukey's test (*P*-value)
	Group I (*n* = 21)	Group II (*n* = 20)	Group III (*n* = 10)			
Sex						
Males	16 (76.19)	8 (40)	6 (60)	5.671	0.059	–
Females	5 (23.81)	12 (60)	4 (40)			
DM	6 (28.57)	3 (15)	0 (0)	5.496	0.064	–
Hypertension	6 (28.57)	2 (10)	0 (0)	6.181	0.045	–
Smoking	11 (52.38)	7 (35)	0 (0)	11.261	0.004	–
				F		
Age (years)						
Mean ± SD	57.29 ± 11.15	43.3 ± 13.82	47.4 ± 11.42	6.846	0.002	0.002[1] 0.103[2] 0.668[3]
Range	35–75	28–70	30–62			
SBP (mmHg)						
Mean ± SD	133.81 ± 27.473	119 ± 5.525	117 ± 5.676	15.56	<0.001*	<0.001[1] <0.001[2] 0.748[3]
Range	80–170	110–130	110–130			
DBP (mmHg)						
Mean ± SD	84.762 ± 16.01	78.5 ± 4.89	78 ± 4.22	2.142	0.129	–
Range	50–100	70–90	70–80			

Group I: acute myocardial infarction patient; Group II: skeletal muscle injury patients; Group III: control; DBP, diastolic blood pressure; DM, diabetes mellitus; *F*, one-way ANOVA; SBP, systolic blood pressure; [1]Group I versus group II; [2]Group I versus group III; [3]Group II versus group III; $P < 0.05$ was considered statistically significant; *$P < 0.001$ was considered high statistically significant.

CK-MB] are presented as median and interquartile range in Table 2.

Troponin and CK-MB in the AMI group were significantly higher than the respective concentrations in the skeletal muscle injury group and the control group ($P < 0.001$), whereas nonsignificant difference existed between group II and group III (Table 2).

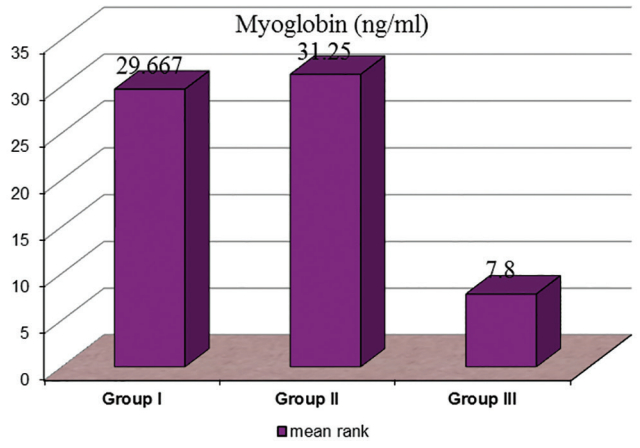
In the AMI group the serum concentration of H-FABP and myoglobin was significantly higher than the respective concentrations in the control group ($P < 0.001$). Also, in the AMI group the serum concentration of H-FABP was significantly higher than that in group II, whereas nonsignificant statistical difference existed between group I and group II as regards myoglobin (Table 2 and Figs. 2 and 3).

The ratio of myoglobin over H-FABP as shown in Table 2 was significantly higher in group II than in group I and group III ($P = 0.004$ and 0.008, respectively), whereas there was a nonsignificant difference in the ratio of myoglobin over H-FABP between the AMI group and the control group ($P = 0.519$).

The data from the ROC curve analysis are summarized in Tables 3 and 4 and Figs. 4 and 5.

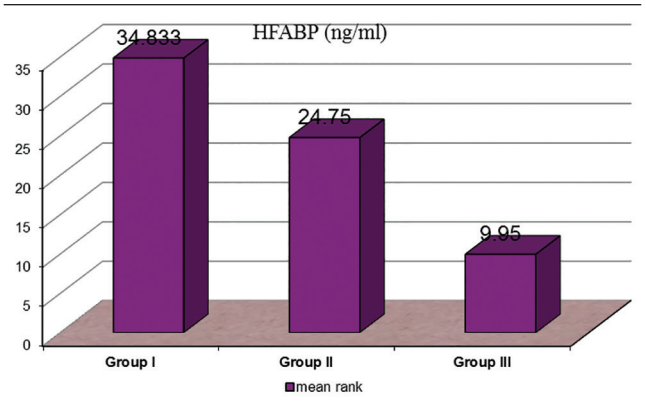
It shows that in the AMI group compared with the control group a cutoff value greater than 80.38 for myoglobin had the highest specificity and positive predictive value for differentiation between group I

Figure 2



Comparison between studied groups as regards myoglobin.

Figure 3



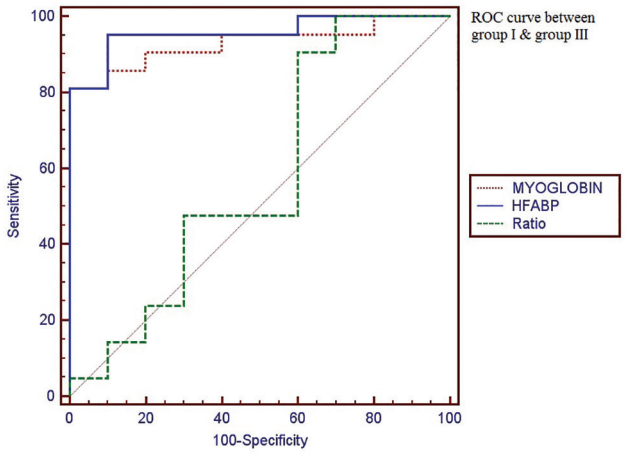
Comparison between studied groups as regards heart-type fatty acid binding protein (H-FABP).

Table 2 Cardiac markers and creatinine between the studied groups

Cardiac markers and creatinine	Median (IQR)			Kruskal–Wallis test		Mann–Whitney
	Group I	Group II	Group III	χ^2	*P*-value	
Creatinine (mg/dl)	1.2 (0.5)	0.7 (0.3)	–	3.919	<0.001	–
AST (IU/l)	33 (37)	21.5 (10.25)	21 (8.75)	9.184	0.01	0.007[1] 0.017[2] 0.930[3]
Troponin (μg/l)	0.49 (7.75)	0.01 (0)	0.015 (0.033)	32.467	<0.001	<0.001[1] <0.001[2] 0.051[3]
CK-MB (ng/ml)	6.5 (13.79)	2.4 (2.5)	1.4 (1.225)	28.223	<0.001	<0.001[1] <0.001[2] 0.061[3]
Myoglobin (ng/ml)	151.46 (342.02)	190.82 (296.34)	19.61 (21.103)	18.76	<0.001	0.735[1] <0.001[2] <0.001[3]
H-FABP (ng/ml)	55.33 (74.19)	26.36 (36.64)	14.89 (11.44)	19.216	<0.001	0.020[1] <0.001[2] 0.005[3]
Ratio	2.18 (2.97)	5.93 (7.44)	2.37 (4.18)	11.028	0.004	0.004[1] 0.519[2] 0.008[3]

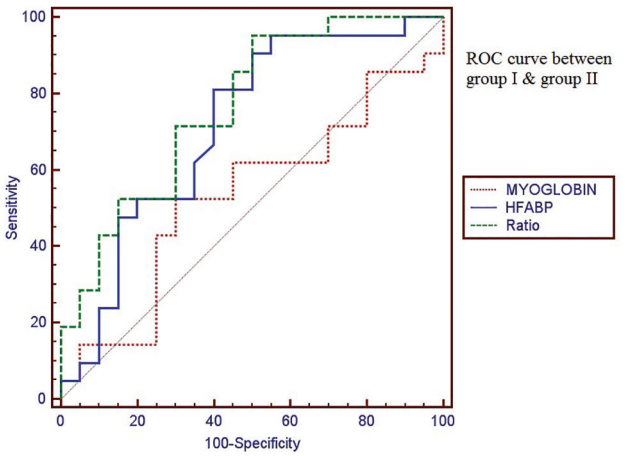
Group I: acute myocardial infarction patients; Group II: skeletal muscle injury patients; Group III: control; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB; H-FABP, heart-type fatty acid binding protein; IQR, interquartile range; [1]Group I versus group II; [2]Group I versus group III; [3]Group II versus group III; $P < 0.05$ was considered statistically significant.

Figure 4



ROC curve for differentiation between the acute myocardial infarction group and the control group. H-FABP, heart-type fatty acid binding protein.

Figure 5



ROC curve for differentiation between the acute myocardial infarction group and the skeletal muscle injury group. H-FABP, heart-type fatty acid binding protein.

Table 3 Cutoff value of myoglobin, heart-type fatty acid binding protein and ratio of myoglobin/heart-type fatty acid binding protein for differentiation between acute myocardial infarction group and control group

Markers	Myoglobin (ng/ml)	H-FABP (ng/ml)	Ratio of myoglobin/H-FABP
Cutoff point	>80.38	>20	>1.21
Sensitivity	81.0	95.2	90.5
Specificity	99	90.0	40.0
PPV	99	95.2	76.0
NPV	71.4	90.0	66.7
Accuracy	0.929	0.957	0.581

H-FABP, heart-type fatty acid binding protein; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Cutoff value of myoglobin, heart-type fatty acid binding protein, and ratio of myoglobin/heart-type fatty acid binding protein for differentiation between the acute myocardial infarction group and the skeletal muscle injury group

Markers	Myoglobin (ng/ml)	H-FABP (ng/ml)	Ratio of myoglobin/H-FABP
Cutoff point	≤151.46	>28.79	≤6.28
Sensitivity	52.4	81.0	95.2
Specificity	70.0	60.0	50.0
PPV	64.7	68.0	66.7
NPV	58.3	75.0	90.9
Accuracy	0.531	0.713	0.764

H-FABP, heart-type fatty acid binding protein; NPV, negative predictive value; PPV, positive predictive value.

and group III, followed by H-FABP and the ratio of myoglobin/H-FABP, where a cutoff value greater than 20 for H-FABP had the highest sensitivity and negative predictive value for differentiation between group I and group III, followed by the ratio of myoglobin/H-FABP and then myoglobin.

In the AMI group compared with the skeletal muscle injury group a cutoff value less than or equal to 6.28 for the ratio of myoglobin/H-FABP had the highest sensitivity and negative predictive value for differentiation between group I and group II, followed by H-FABP and myoglobin, where a cutoff value less than or equal to 151.46 for myoglobin had the highest specificity for differentiation between group I and group II, followed by H-FABP and then the ratio of myoglobin/H-FABP, and a cutoff value greater than 28.79 for H-FABP had the highest positive predictive value for differentiation between group I and group II, followed by the ratio of myoglobin/H-FABP and then myoglobin.

Discussion

The biochemical markers myoglobin, CK-MB isoenzyme, and cTnI or cardiac troponin T (cTnT) are currently used in the diagnosis of AMI [18]. These cardiac markers, however, are not satisfactory for detecting AMI in the early phase, especially within 3–6 h of the onset of AMI [19].

Therefore, rapid markers such as myoglobin and H-FABP could be used in the early diagnosis of AMI. Myoglobin is highly sensitive as an early marker but has a low cardiac specificity [20]. H-FABP concentration in the heart muscle is greater than that in skeletal muscle and its normal baseline concentration is several-fold lower than that of myoglobin. These advantages make H-FABP a potentially more suitable cardiac marker than myoglobin [7].

In the present study, there was nonsignificant statistical difference between the studied groups regarding sex, whereas there was a statistically

significant difference in patients with AMI compared with the control group regarding systolic blood pressure and smoking history. These differences agreed with those reported by McCann *et al.* [21]. However, unlike the results of Santos *et al.* [22], diastolic blood pressure differed significantly between patients with ACS and the control group. As previously reported, hypertensive patients have an increased risk for coronary artery disease compared with patients with normal blood pressure [23].

The current study showed that serum creatinine was significantly higher in patients with ACS as compared with patients with skeletal muscle injury. It was suggested that some degree of renal impairment existed in the ACS population [24]. Also, serum concentration of AST was significantly higher in AMI patients than in the control group and skeletal muscle injury patients. Elevated AST in the absence of increasing alanine aminotransferase indicates cardiac or skeletal muscle disease [25].

Our study showed that both troponin I and CK-MB were significantly higher in AMI patients (within 6 h of the onset of chest pain) compared with the control group. Again, these markers were found to be higher than in the skeletal muscle injury group. This agreed with a study by Pasaoglu *et al.* [26]. Troponin and CK-MB are more specific for myocardial injury but lack early sensitivity because their blood concentrations do not increase until 6–8 h after the onset of AMI [27].

Also, it was shown in the present study that the serum concentration of myoglobin (within 6 h of onset of chest pain) was significantly higher in AMI patients than in the control group. This was similar to a study by Pasaoglu *et al.* [26]. In contrast, comparison of serum concentration of myoglobin in patients with AMI and patients with skeletal muscle injury did not reveal a significant difference. This is in agreement with the results of Van Nieuwenhoven *et al.* [9]. Further, when AMI patients were compared with the control group, myoglobin sensitivity was 81% and specificity was 99%, with a cutoff value greater than 80%. This was similar to the results of De Winter *et al.* [28], in whose study myoglobin sensitivity was 84% and specificity was 96%.

As regards the serum concentration of H-FABP (within 6 h of onset of chest pain), it was significantly higher in AMI patients than in the control group. This was similar to the results of Pasaoglu *et al.* [26], and also significantly higher than that in the skeletal muscle injury group as studied by Van Nieuwenhoven *et al.* [9].

Again, there was a significant positive correlation between both myoglobin and H-FABP and both troponin and CK-MB.

Our results showed that H-FABP has higher sensitivity and predictive accuracy compared with myoglobin in the early detection of AMI (sensitivity of H-FABP was 95% and that of myoglobin was 81%; their ratio's sensitivity was 90%). Similar results were also reported by Ishii *et al.* [29].

H-FABP was found to perform better than or similar to myoglobin [30]. Both proteins are released into plasma after injury at about the same time and in a ratio similar to the concentration of proteins in the tissue of origin. Most studies have shown the diagnostic sensitivity of H-FABP (i.e. its ability to detect the presence of a MI) to be high, above that of myoglobin in patients presenting within 3–6 h of onset of chest pain. This superiority is attributable to an earlier and more rapid rise in H-FABP than in myoglobin [31].

However, our study found that the sensitivity of H-FABP was less when discriminating between myocardial and skeletal muscle injury where the ratio of myoglobin to H-FABP was higher. Sensitivity of H-FABP was 81%, that of myoglobin was 52%, and that of their ratio was 95.2%. This result is in agreement with those of Yoshimoto *et al.* [32] and Van Nieuwenhoven *et al.* [9].

The ratio of myoglobin to H-FABP was significantly higher in the skeletal muscle injury group than in AMI patients, whereas the difference was nonsignificant when AMI patients were compared with the control group. This was also reported by Van Nieuwenhoven *et al.* [9], who demonstrated that the ratio of myoglobin to H-FABP was found to be 10 times lower in the heart compared with skeletal muscle.

H-FABP is a more sensitive marker, but it has been criticized for its low specificity, owing to its presence in different tissues such as the skeletal muscles, liver, adipose tissue, gut, skin, kidney, and brain [33]. As shown in our study its specificity was 90%, which is less than that of myoglobin (99%) for the detection of AMI within 6 h of onset of chest pain. Again, this was similar to the report of Pasaoglu *et al.* [26]. In addition, it has been previously reported that the specificity of H-FABP, either alone or in combination with cTnT, for AMI diagnosis is low (69%, 95% confidence interval 58–79, and 71%, 95% confidence interval 60–80, respectively) [33]. Other studies demonstrated that the specificity of H-FABP can be improved using modern assays with no cross-reactivity and particularly in combination with high-sensitivity cTnT assay [7].

H-FABP is very useful cardiac marker for aiding emergency physicians make an earlier diagnosis of AMI in patients who present with recent onset of chest pain without typical changes in the ECG. That is because H-FABP can be detected much earlier (as short as 20 min after AMI) [34]. Its plasma kinetics closely resembles those of myoglobin but it is more cardiospecific than myoglobin. It was also found that its elevation appears within 3 h after AMI and levels return to normal within 12–24 h. Hence, it is considered a sensitive and specific marker of early detection of myocardial injury [35].

Although H-FABP can help detect myocardial damage at an early stage in patients with chest pain, it appears unsuitable as a stand-alone test for ruling out AMI [2].

Conclusion

Both myoglobin and H-FABP can be used as markers of cardiac and/or skeletal muscle cell necrosis.

The diagnostic sensitivity of H-FABP is high, above that of myoglobin in patients presenting within 6 h of onset of chest pain. H-FABP is a sensitive and specific marker for the early diagnosis of AMI.

Measurements of myoglobin and H-FABP as well as their ratio are useful for discriminating between AMI and skeletal muscle injury. However, the ratio of myoglobin to H-FABP cannot give a clear advantage over the measurement of H-FABP alone.

Lower specificity of H-FABP makes troponin and CK-MB superior for the diagnosis of AMI.

Conflicts of interest

There are no conflicts of interest.

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