The role of h-FABP and Myoglobin in Determining Disease Severity and Prognosis in STEMI

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ABSTRACT

Introduction: Acute coronary syndrome (ACS) remains as a single biggest cause of death worldwide. Heart-type fatty acid -binding protein (h-FABP) and myoglobin are small proteins present in the myocyte cytosol. In cases of myocardial damage, they can freely pass into the bloodstream. Thus, they might be useful in the diagnosis of ACS. The aim of this prospective study was to search the relationship between h-FABP and myoglobin levels and disease severity and mortality.

Methods: One hundred-forty-nine male patients with ST-elevation myocardial infarction constituted our study population. Two groups occurred according to low (<23) and high (≥23) SYNTAX score as group 1 and group 2. Blood specimens were taken for h-FABP and myoglobin analysis at hospital admission and at 12 h. Patients underwent coronary angiography for diagnosis and treatment, and the SYNTAX score was calculated. Participants were followed up for 72 months, and cardiovascular mortality rates were recorded.

Results: H-FABP at admission and h-FABP level at 12th h were lower in group 1 than in group 2 (p<0.001). We did not find significant differences between the myoglobin levels measured at the time of hospital entrance and at the 12th h in both groups. During 72-month follow-up, 123 patients survived and the survivors had a lower SYNTAX score, and a lower h-FABP level at admission. In the univariate analysis, h-FABP levels at admission and at 12 h were found to be independent predictors of coronary artery disease (CAD) severity. However, h-FABP levels did not predict mortality.

Conclusion: In patients with ACS, measuring h-FABP levels at admission and in the late period (12th hour) are helpful, not only in the diagnosis but also severity and seriousness of CAD.

Keywords: Myoglobin, heart-type fatty acid binding protein, myoglobin, myocardial infarction, SYNTAX score, heart-type fatty acid binding protein

Introduction

Cardiovascular disease is an important health problem worldwide, which is a chief source of death in industrialized countries and its incidence is increasing in developing countries (1). Acute coronary syndrome (ACS) is diagnosed by electrocardiogram (ECG) and biomarkers, particularly cardiac troponin (cTn). The main way to prevent major complications and deaths from ACS is early diagnosis (2).

Many biomarkers have been used and developed for early diagnosis, but nowadays it is also important to have an idea about the prognosis in the short and long term. High sensitivity markers and ECG have achieved 100% sensitivity in diagnosis and exclusion, but there is still an ongoing search for new biomarkers for prognosis.

Heart-type fatty acid -binding protein (h-FABP) has been suggested as an important predictor of early diagnosis of myocardial damage and is a potential prognostic indicator for long-term fatality (3). H-FABP presents in the cytosol and carries long -chain fatty acids (4). Myoglobin is also present in cytosol with a molecular weight of 17.8 kd and is one of the preliminary cardiac markers delivered into the plasma when myocardial necrosis occurs. Since it is also present in the skeletal muscle, the increase in myoglobin measured in circulation is not limited to cardiac muscle damage (5). Myoglobin measurement is especially helpful at an early stage of ACS, but since it is specific for myocardium, it is not easy to decide whether elevations in myoglobin concentration is the result of myocardial or skeletal muscle damage (6). The myoglobin test may be
useful only if it is to be used alone. It is proposed that myoglobin could be integrated with other tests to diagnose ACS (7).

The risk classification in patients with ACS is critical to determining the appropriate treatment and follow-up method (8). The most commonly used risk stratification systems are the Global Registry of Acute Coronary Events (GRACE) and Thrombolysis In myocardial infarction (MI) scoring systems. These systems incorporate additional points for positive cardiac markers (9). Studies have shown that the inclusion of new non-necrosis biomarkers in classical risk stratification systems may increase the sensitivity/specificity of risk estimation (10-12).

Here, we sought to question the relationship between h-FABP and myoglobin levels and ACS disease severity and long-term mortality in STEMI patients.

**Methods**

The study was started after the approval of the ethics committee. One hundred forty-nine male patients who applied to our emergency department with chest pain and other symptoms suggestive of ACS and with STEMI findings on 12-lead ECG were included in the study. Those under 18 years of age, with active infection, malignancy, chronic diseases including musculoskeletal system, contraindications for coronary angiography, chronic renal failure, previous pulmonary thromboembolism, MI, cerebrovascular event, trauma, surgery, and cardiopulmonary resuscitation within 72 h, unconscious patients were excluded from the study.

After obtaining informed consent from the patients, in addition to routine examinations, 2 mL venous blood was taken to the EDTA tube for h-FABP and myoglobin. To measure and evaluate h-FABP (TOYO-Turkey) and myoglobin (TOYO-Turkey), the gold absorption immunofluorescence assay method and Turklab ICA-Rapid Test Reader (Trio, Info Rapidan Test-Turkey) instrument were used. The patients’ current diseases, cardiovascular risk factors [diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL)] were questioned and recorded. Blood was drawn again for h-FABP and myoglobin 12 h after the start of the symptoms. The diagnosis of STEMI based on cardiac symptoms, 12-lead ECG findings, and elevated cardiac enzymes underwent coronary angiography for diagnosis and treatment by a specialist cardiologist.

Coronary angiography was performed using a Judkins catheter from the femoral artery. SYNTAX score of each patient was calculated according to anatomical lesion characteristics including bifurcations, chronic total occlusions, thrombus, calcification and small diffuse disease. All of the calculations were carried out using the website program: https://syntaxscore.org. Patients were split into two groups according to the severity of ACS. The first group consisted of patients with a SYNTAX score of less than 23, and the second group consisted of patients with a score 23 or higher.

The follow-up period of the patients was 72 months. Patients who lost to follow-up were investigated from the state’s death notification system available only to doctors and those who died were identified. Non-cardiac deaths were excluded from the 5-year mortality assessment.

**Statistical Analysis**

The normality assessment of the data was made by evaluating the skewness and kurtosis of the data, and the Kolmogorov-Smirnov test. Normally, and non-normally distributed data were expressed as means ± standard deviations medians (interquartile ranges), respectively. Categorical data were expressed as percentages. Comparisons of the groups were made using of Independent sample-t test or Mann-Whitney U test for normally and non-normally distributed data, respectively. Univariate logistic regression analysis was conducted to find the predictors of coronary artery disease (CAD) severity and mortality. Variables that had significance in univariate analysis were put into multivariate analysis. The discriminatory ability of FAB and FAB12 in determining the CAD severity was analyzed using the receiving operating characteristic (ROC) curve analysis. Statistical significance was considered significant if p<0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software.

**Results**

The median age of the 149 male patients with STEMI was 54.65 years. DM was diagnosed in 25.5% (n=38), HT in 49.7% (n=74), and HL in 47% (n=70) of the patients. Mean age, presence of DM and HT, mortality rate, h-FABP at admission, and h-FABP level at 12th h were lower in group 1 than in group 2. The left ventricular ejection fraction (LVEF) was significantly higher in group 1 (p<0.001). We did not find significant differences between the myoglobin levels measured at the time of admission to the hospital and at the 12th h in both groups (Table 1).

During the 72-month follow-up, 123 patients survived and the survivors had a lower mean age, a lower prevalence of DM, a lower LVEF, a lower SYNTAX score, and a lower h-FABP level at admission. Myoglobin values were not different between the survivor and non-survivor groups (Table 2). In the univariate analysis: in addition to age, presence of DM, presence of HT and left ventricular EF level, and h-FABP levels at admission and at 12 h were found to be independent predictors of CAD severity (Table 3). However, h-FABP level was not found to be a predictor of mortality (Table 4).

In determining the severity of CAD, in the evaluation of h-FABP level at the time of application and at the 12th h by ROC analysis, it had a discriminatory power of >16.95 at the time of admission and >21 ng/mL at the 12th h (Figure 1).

**Discussion**

cTns are regarded as the best laboratory test for the diagnosis of acute MI (AMI) (13). In AMI, troponins rise to a measurable level in the circulation 3 h after the onset of chest discomfort. This limits the earlier diagnosis of MI (14).

When myocyte injury occurs, h-FABP quickly passes through the interstitial spaces into the blood. Since it is much smaller than troponin, it passes into the blood faster than troponin (15). It is measurable in the blood as early as 1-3 hours after the onset of chest pain, reaches its maximum values in 6-8 h, and returns to normal concentrations within 24-30 h (16). As expected, in our study, the h-FABP level of the patients was elevated during the first admission.

Reddy et al. (17) emphasized the significance of using a pair of biomarkers (h-FABP and h-sTnT) together in the initial diagnosis of ACS. It was recommended that troponin T- and h-FABP be used together to
improve the diagnosis of ACS in the emergency room after the onset of chest pain. Furthermore, when these two biomarkers are used together, they have 100% negative predictive value (17). In this study, h-FABP was also added to routine cardiac biomarkers (cTnT, CK-MB) in patients presenting with chest pain and ST elevation on ECG, and this multiple biomarker analysis was helpful for early diagnosis. Increased h-FABP is a helpful early diagnosis of MI via facilitating early release of patients with chest pain but not MI from the hospital. The addition of h-FABP

| Table 1. Demographic, clinical, and laboratory parameters of patients with low and intermediate-high anatomical SYNTAX score I |
|---------------------------------|-----------------|-----------------|-----------------|---|
| All population, (n=149) | SxS <23, (n=105) | SxS ≥23, (n=44) | p |
| Age, year (median ± SD) | 54.6±12.4 | 53.3±12 | 58.9±12.8 | 0.036 |
| Hypertension, n (%) | 74 (49.7) | 46 (43.8) | 28 (63.6) | 0.027 |
| Diabetes mellitus, n (%) | 38 (25.5) | 19 (18.1) | 19 (43.2) | 0.001 |
| LVEF (%) (median ± SD) | 46.7±8.7 | 48±7.9 | 43.8±9.9 | 0.007 |
| SYNTAX score, median (IQR) | 13 (8.5-26) | 10 (7.5-13.5) | 29 (27-33.5) | 0.023 |
| Mortality, n (%) | 26 (17.4) | 10 (9.5) | 16 (36.4) | <0.001 |
| h-FABP (ng/mL) median (IQR) | 8.5 (5-43) | 5 (5-25) | 36 (10-71) | <0.001 |
| h-FABP 12 th (ng/mL) median (IQR) | 11 (5-69) | 5 (5-50.5) | 51 (16.8-122.6) | <0.001 |
| Myoglobin (ng/mL) median (IQR) | 136 (51-285) | 126 (50-240) | 196 (71-323) | 0.062 |
| Myoglobin 12 th (ng/mL) median (IQR) | 121 (75-253) | 120 (73-206) | 145 (82-298) | 0.143 |

Syx: Syntax score I, SD: Standard deviation, LVEF: Left ventricular ejection fraction, IQR: Interquartile range, h-FABP: Heart-type fatty acid -binding protein, PCI: Percutaneous coronary intervention

Table 2. Demographic, clinical, and laboratory parameters of survivors and non-survivors patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivor, (n=123)</th>
<th>Non-survivor, (n=26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year (median ± SD)</td>
<td>52.1±11.1</td>
<td>66.3±11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>58 (47.2)</td>
<td>16 (61.5)</td>
<td>0.183</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>27 (22)</td>
<td>11 (42.3)</td>
<td>0.030</td>
</tr>
<tr>
<td>LVEF (%) (median ± SD)</td>
<td>47.9±7.9</td>
<td>43.8±9.7</td>
<td>0.010</td>
</tr>
<tr>
<td>SYNTAX score, median (IQR)</td>
<td>11 (8-17)</td>
<td>30.8 (19-35.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>h-FABP (ng/mL) median (IQR)</td>
<td>5 (5-39)</td>
<td>17.9 (5-61.7)</td>
<td>0.057</td>
</tr>
<tr>
<td>h-FABP 12 th (ng/mL) median (IQR)</td>
<td>10 (5-64)</td>
<td>47 (5-77)</td>
<td>0.381</td>
</tr>
<tr>
<td>Myoglobin (ng/mL) median (IQR)</td>
<td>139 (58-289)</td>
<td>85 (50-256)</td>
<td>0.650</td>
</tr>
<tr>
<td>Myoglobin 12 th (ng/mL) median (IQR)</td>
<td>121 (75-256)</td>
<td>121 (66-238)</td>
<td>0.975</td>
</tr>
</tbody>
</table>

SD: Standard deviations LVEF: Left ventricular ejection fraction, IQR: Interquartile range, h-FABP: Heart-type fatty acid -binding protein, PCI: Percutaneous coronary intervention

Table 3. Factors that were independently associated with the CAD severity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>p</th>
<th>Model 1 multivarite analysis</th>
<th>p</th>
<th>Model 2 multivarite analysis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.036 (1.010-1.063)</td>
<td>0.006</td>
<td>1.037 (1.012-1.062)</td>
<td>0.003</td>
<td>1.031 (1.006-1.056)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.914 (1.036-3.537)</td>
<td>0.038</td>
<td>1.309 (0.679-2.526)</td>
<td>0.422</td>
<td>1.364 (0.715-2.520)</td>
<td>0.346</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.563 (1.411-4.655)</td>
<td>0.002</td>
<td>1.694 (0.877-3.274)</td>
<td>0.117</td>
<td>1.960 (1.045-3.675)</td>
<td>0.036</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.953 (0.923-0.984)</td>
<td>0.003</td>
<td>0.960 (0.928-0.994)</td>
<td>0.023</td>
<td>0.963 (0.929-0.999)</td>
<td>0.044</td>
</tr>
<tr>
<td>h-FABP</td>
<td>1.009 (1.004-1.013)</td>
<td>&lt;0.001</td>
<td>1.008 (1.003-1.013)</td>
<td>0.008</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>h-FABP 12th</td>
<td>1.008 (1.003-1.012)</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
<td>1.005 (1.001-1.010)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, h-FABP: Heart-type fatty acid -binding protein

Table 4. Factors that were independently associated with the mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>p</th>
<th>Multivarite analysis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.083 (1.047-1.120)</td>
<td>&lt;0.001</td>
<td>1.066 (1.028-1.106)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.318 (1.064-5.049)</td>
<td>0.034</td>
<td>1.595 (0.680-3.740)</td>
<td>0.283</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.943 (0.904-0.984)</td>
<td>0.006</td>
<td>0.968 (0.926-1.013)</td>
<td>0.164</td>
</tr>
<tr>
<td>SxS l</td>
<td>1.132 (1.087-1.179)</td>
<td>&lt;0.001</td>
<td>1.109 (1.062-1.159)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>h-FABP</td>
<td>1.006 (1.000-1.013)</td>
<td>0.048</td>
<td>0.999 (0.992-1.006)</td>
<td>0.750</td>
</tr>
</tbody>
</table>

LVEF: Left ventricular ejection fraction, SxS l: SYNTAX score I, h-FABP: Heart-type fatty acid -binding protein
to hs-cTn in patients admitted to the emergency room with chest pain without ischemic ECG findings makes easier to define it as a low risk (up to 40%) (18). Since our study included patients with STEMI, h-FABP levels in patients who had chest pain but who did not have any ECG findings were not evaluated.

Studies have shown that in patients who were accepted to hospital with chest discomfort and diagnosed with ACS, the evaluation of plasma h-FABP on admission might provide additional information on risk stratification. The importance of biomarkers in both the diagnosis and prognosis of ACS has been demonstrated by these studies. Prognostic guidance of biomarkers is superior to electrocardiographic guidance only (19,20).

Increased serum FABP4 levels were related to worse 30-day outcomes in patients with ACS, regardless of age, gender, renal function, and body mass index (21). The results of that study were partly alike to our study. In our study, higher SYNTAX scores were observed in patients with higher h-FABP levels and 5-year mortality of those patients was also higher. Especially h-FABP levels measured at the 12th h were remarkably higher in the group 2. In the same study, circulated FABP4 levels were found to be notably higher in females and subjects with body mass index (BMI) >25 kg/m² compared with men and normal weight (21). In our study, to minimize this effect, we only included male patients with BMI <25 kg/m².

In the early 2000s, Goto et al. (22) showed that h-FABP had positive interaction with brain natriuretic peptide (BNP) concentration in acute decompensated heart failure patients. Subsequently, Setsuta et al. (23) showed that h-FABP has a role in myocyte necrosis or apoptosis and causes worsening in heart failure status. Additionally, Hoffmann et al. (24) showed that additional h-FABP measurements in decompensated heart failure enhanced the diagnostic specificity and predictive value of NT-proBNP tests (25). In the patients with cardiac surgery, Jo et al. (26) showed that h-FABP was a more practical marker for detecting myocyte damage than CK-MB and cTnT. Another study showed that; permanently elevated h-FABP levels could have prognostic value because they can indicate progressive myocardial damage despite effective therapy and clinical progress (27). In our study, the h-FABP level at admission was found to be higher in non-survivor patients, and h-FABP levels at both admission and at the 12th h were found to be independent predictors of CAD severity. However, we cannot say that h-FABP is a predictor of mortality.

In addition to the role of myoglobin in the diagnosis of MI, it has been investigated whether it is useful for risk stratification in patients with ACS.

In patients with MI with poor prognosis and high mortality risk, skeletal muscle damage may be the cause of myoglobin elevation rather than heart muscle damage. Both hypotension and decreased renal perfusion lead to the release of myoglobin from the skeletal muscle, which may contribute to mortality after ACS (28).

There are some studies have suggesting that myoglobin adds a small amount of prognostic information to CK-MB and troponins, these studies are small sample-sized studies. There is a need for further studies on this subject (28-32).

In our study, although myoglobin levels tended to be higher in patients with a high SYNTAX score at admission to the hospital and at the 12th h, this elevation was not statistically significant (p=0.062, p=0.143).

We investigated the relationship between 5-year cardiac mortality and myoglobin. In patients who died of cardiac causes within 5 years, myoglobin levels at admission and at 12 h were not different between survivor and non-survivor patients. Our results do not support the results by Spangenthal et al. (28).

As mentioned above, many studies have been conducted on the specificity and sensitivity of h-FABP in the diagnosis of ACS. In our study, in addition to these studies, the relationship between the levels of h-FABP and myoglobin in the first 3 h and 12 h in the diagnosis of STEMI was evaluated. SYNTAX scores were used for this evaluation. In addition to these scores, a 72-month follow-up of patients was performed, and real-life death data were included in the evaluation.

In our study, h-FABP and myoglobin values measured at admission and at the 12th h were higher in patients with higher SYNTAX scores, but only h-FABP values were found to be predictive of CAD severity. H-FABP and myoglobin are not biomarkers routinely analyzed in patients presenting to the emergency department with chest pain. After newly developed HS-troponins, it cannot be expected to replace them in diagnosis. However, looking at the h-FABP values measured at the time of admission to the hospital or at the 12th h in selected patients, with the help of the determined cut-off values (in our study, we determined the cut-off for h-FABP as 16.95 at the time of admission and 21 ng/mL at the 12th hour) can help predict disease severity and determine the treatment strategy.

**Conclusion**

In patients with ACS, measuring h-FABP levels at admission and in the late period (12th hour) are helpful, not only in the diagnosis but also severity and prognosis of CAD. However, it is necessary to develop a...
precise test that allows quick and economical measurements of h-FABP. Additionally, an internationally consistent standardization should be made, and a consensus on the h-FABP threshold should be reached. To achieve this, further prospective randomized clinical trials are needed.

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinical Research Ethics Committee (date: 05.08.2019/decision no: 2019-15).

Informed Consent: After obtaining informed consent from the patients, in addition to routine examinations.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

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