Prognostic Value of Heart-Type Fatty Acid Binding Protein in Patients with Acute Coronary Syndrome

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Abstract

Background: Heart-type fatty acid-binding protein is released into the circulation following myocardial ischemia and necrosis and therefore may be a prognostic value when caring for patients admitted to hospital with a clinical diagnosis of ACS.

Objective: To establish the prognostic value of rapid Heart-type Fatty Acid-Binding Protein (H-FABP) test in patients with Acute Coronary Syndrome (ACS).

Patients and Methods: Ninety patients admitted to Critical Care Department with acute coronary syndrome (within 24 h duration), irrespective of (ECG) changes, were subjected to detailed and full history taking and thorough clinical examination, 12 lead ECG, an echocardiography, full laboratory investigation, including cardiac enzymes, troponin, and H-FABP, coronary angiography to assess the severity of coronary artery disease using modified Ginssini score, and follow-up for the incidence of cardiac events either during hospitalization, or during six-months follow-up.

Results: Mean patient age was 56 years (SD 12), 88% was male, H-FABP test was performed within 24h after symptom onset, and was elevated in 80% of the patients. The value of H-FABP correlated with the severity of coronary artery lesion as determined by modified ginsini score ($r=0.749$, $p<0.001$), and with long hospital stay ($p<0.001$). Increasing H-FABP concentration remained statistically significant as Independent predictors of long-term risk (namely; heart failure with 75% and 92% sensitivity and specificity respectively at H-FABP 43.95ng/ml, and recurrent ischemia with 71% and 96% sensitivity and specificity respectively at H-FABP 44.50 ng/ml) during six-months follow-up.

Conclusion: Increasing H-FABP value has a prognostic role in prediction of incidence of heart failure and ischemic heart disease during six-month follow-up, irrespective of troponin level.

Key Words: Heart type fatty acid binding protein (H-FABP) – Acute coronary syndrome.

Introduction

DESPITE enormous research interest in cardiac biomarkers in recent years, very few have estab-lished themselves unequivocally in routine clinical practice. Cardiac troponin remains the cornerstone in the risk stratification of patients with suspected ACS. One of the important criteria for a biomarker is to be able to inform clinical decision-making and thus influence patient management [1]. Heart-type fatty acid binding protein has emerged as an independent prognostic marker for patients with ACS in multiple studies [2-5]. All these studies consistently showed that elevated H-FABP is associated with an increased risk of long-term adverse outcomes (death, recurrent MI) irrespective of troponin results among patients with non-ST-elevation ACS (defined by the presence of ischemic chest pain and at least one of either elevated troponin or ECG changes indicative of myocardial ischemia). The prognostic value of H-FABP was independent not only of clinical risk factors and troponin but also other biomarkers such as hs CRP and BNP [2], particular sub-group analyses of patients without elevated troponin in studies by O'Donoghue et al., [3] and Kilcullen et al., [2] showed that H-FABP was an independent predictor of long-term adverse events among troponin-negative patients which is consistent with the hypothesis that H-FABP is a marker of myocardial ischemia.

Aim of the study:

1- To determine whether elevated H-FABP is associated with an increased risk of the occurrence of major adverse cardiac events (namely recurrent ischemia and sudden death), and heart failure among patients with ACS irrespective of troponin values during six-months follow-up.

2- Whether the level of H-FABP correlates with the severity of coronary artery disease (using modified Ginssini score), and hospital stay.
3- Whether increased level of H-FABP correlates with in-hospital adverse cardiac events (namely arrhythmia, recurrent ischemia and sudden cardiac death).

Patients and Methods

Between October 2007 – July 2009, it is a prospective, randomized clinical trial which included ninety patients admitted to the critical care department with acute coronary syndrome after exclusion of the following:
1- Age <18 years.
2- Patients with complaints lasting more than 24 hours, as H-FABP levels usually return to normal 24 hours after onset of myocardial ischemia [6].
3- Renal failure requiring dialysis; it has been shown that the mean plasma concentration of H-FABP in the patients with chronic renal failure requiring dialysis is 21 to 25 times higher than in normal adults [7].
4- Pregnancy, heart failure.
5- Patients with a history of recent muscle injury (<3 days), including intramuscular injection, and those with acute or chronic skeletal muscle damage or disorders including rhabdomyolysis, dermatomyositis, muscular dystrophy, and polymyositis [8].
6- Critically ill patients, including those with cardiogenic shock, septic, intubated and ventilated patients.
7- Patients who had had a recent myocardial infarction or received fibrinolytic therapy or angioplasty within the last 14 days prior to presentation to the ED.

All patients were subjected to detailed and full history taking and thorough clinical examination, 12 lead ECG, an echocardiography, full laboratory investigation, including cardiac enzymes, troponin, and H-FABP, coronary angiography to assess the severity of coronary artery disease using modified Gissini score, and follow-up for the incidence of cardiac events (namely arrhythmias, recurrent ischemia or sudden cardiac death) during hospitalization, and (recurrent ischemia, heart failure or sudden death) during six-months follow-up.

Laboratory investigations: Blood samples withdrawn from the patients on admission for the routine tests which includes: Compete blood count (EDTA blood), Coagulation profile (citrated blood), and Liver and kidney functions (whole blood). Cardiac biomarkers including: CPK, CPK (MB), and troponin measured for all patients on admission (serum samples) to be repeated every 4-6 hours for up to 3 sets in ve troponin patients. Also heart-fatty acid binding protein as a specific cardiac biomarker.

Principle of the H-FABP assay: The test contains two different specific monoclonal antibodies for H-FABP, one of which is gold-labelled and the other one biotinylated. The sample liquid releases the gold-labelled and the biotinylated anti-H-FABP antibodies out of their matrices. If the sample to be examined contains H-FABP, the antibodies form a sandwich complex with the analyte (anti-H-FABP-antibody (gold-labelled) and anti-H-FABP-antibody (biotinylated)), this complex flows over the test strip.

Depending on the concentration of H-FABP in the sample, a red/purple line becomes visible at the T-marking, hence the intensity of the test line increases proportionally to the concentration of H-FABP. If the sample does not contain H-FABP, no complex can be formed and therefore no test line will appear. The excess gold-labelled antibodies bind unspecific on the control line (C) and indicate that the test has worked properly.

Performing the test: By applying 120ul serum in the sample reservoir, the test result become ready after 15 minutes.

Interpretation of the test result: The red/purple control line (C) indicates the test has worked properly, if the control line does not appear, the test should be repeated, the test also should be repeated if the test line (T) appear, but the control line does not.

Negative test: <5.4ng/ml: A red/purple line appears in the upper section of the panel (control line C) indicating that the test worked properly, however, no test line appear ,this indicates that the concentration of H-FABP in the sample was <5.4 ng/ml.

Positive test: >5.4ng/ml: A red/purple line appears in the upper section of the panel (control line C) indicating that the test worked properly, and another red/purple line in the lower section (test line T) indicates a positive result. To determine the exact concentration Quick Sense reader is used.

Statistical analysis: Data were prospectively collected and coded prior to analysis using the professional Package for Social Sciences (SPSS version 16.0). Continuous variables.

Were expressed as mean and Standard Deviation (SD). Categorical variables were expressed as frequency and proportion. Student- t Test (t) was used for comparison between two groups as regards
normally distributed (parametric) quantitative data. Chi-Square Test ($\chi^2$) was used for comparison between two groups as regard qualitative data. A Receiver Operating Characteristic (ROC) analysis was performed to define a cutoff value of different markers.

Results were considered statistically significant if $p<0.05$.

![Image](image.png)

Fig. (1): How to read H-FABP test.

Results

I- Baseline patients characteristics:

Patient’s characteristics are presented in table below, as shown in this table STEMI was the final diagnosis in 55% of the patients, and 80% had elevated H-FABP.

II- H-FABP and coronary angiography:

As shown in the figure below; the value of H-FABP correlated with the severity of coronary artery lesion as determined by modified ginsini score ($r=0.749, p<0.001$).

III- H-FABP and hospital stay:

Also the value of H-FABP correlated with patients hospitalization (H-FABP was 18.50±14.55 ng/ml in patients with hospital stay ≤ 5 days, compared to 44.70±16.44ng/ml in those hospitalized for more than 5 days), ($p<0.001$).

IV- H-FABP and in-hospital cardiac adverse events:

The present study showed that H-FABP not a sensitive marker for in-hospital adverse cardiac events (namely; Arrhythmia, re-infarction, and sudden death), where H-FABP was 26.45±10.57 ng/ml in patients developed arrhythmias, compared to $20.43\pm16.74$ng/ml in patients not complicated by arrhythmias, also H-FABP was $36.50\pm16.26$ ng/ml in patients complicated by re-infarction, compared to $20.47\pm16.35$ in those without re-infarction, and regarding sudden cardiac death H-FABP was $32.03\pm23.14$ng/ml in patients with sudden cardiac death, compared to $20.44\pm16.20$ng/ml in those not experienced sudden cardiac death). ($p$-value 0.389, 0.174, and 0.232 respectively).

V- Prognostic value of H-FABP:

The present study showed that increasing H-FABP concentration remained statistically significant as independent predictors of long-term risk (namely; heart failure and recurrent ischemia) in patients with acute coronary syndrome ($p<0.001$). ROC analysis was done to demonstrate H-FABP levels as an individual risk determinant in patients developed symptoms of heart failure during six-months follow-up, from the ROC analysis the optimum cut-off value of H-FABP was $43.95$ng/ml, AUC was observed to be 0.944 with 95% CI (0.884-1.004). At this cut-off value, sensitivity and specificity for development of heart failure were found to be 75% and 92% respectively. Also when getting ROC analysis as an individual risk determinant in patients developed Ischemic attacks during six-months follow-up; the optimum cut-off of H-FABP was found to be $44.50$ng/ml, AUC was 0.927 with 95% CI (0.842-1.011), with 71% sensitivity and 96% specificity, however no statistically significant relation found between the H-FABP value and the incidence of sudden cardiac death at six-months follow-up ($p=0.170$) at the present study.

VI- Regression analysis:

Also univariate regression analysis was done to determine potential predictors of cardiac events (heart failure, IHD, sudden death) as defined in this study.

However, multiple regression showed that only H-FAB was a significant predictor for cardiac events, ($p$-value 0.003, OR 1.00-1.09) during six-months follow-up.
Table (1): Baseline patient's characteristics.

**Age (yrs) (mean ± std)** 55.53±11.72 years

**Gender:**
- Male % 87.8%
- Female % 12.2%

**Risk factors:**
- Current smoker % 40%
- Hypertension % 60%
- Diabetes % 45.6%
- Dyslipidemia % 22.2%
- Previous IHD % 26.7%

**Final diagnosis:**
- STEMI % 55%
- Non-STEMI % 45%

**Laboratory data:**
- +ve 1st cardiac enzymes % 26.7%
- +ve 2nd cardiac enzymes % 72.2%
- +ve H-FABP (>5.4ug/ml) % 78.9%

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**Table (2)**

<table>
<thead>
<tr>
<th></th>
<th>&lt;HF</th>
<th>&lt;HFAB</th>
<th>p</th>
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<td>HF</td>
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<td>15</td>
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**Table (3):** Regression analysis for cardiac events during six-months follow-up.

<table>
<thead>
<tr>
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<th>95.0% C.I. for EXP (B)</th>
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<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>H-FAB</td>
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<td>1.11</td>
</tr>
<tr>
<td>Troponin (2nd set)</td>
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<td>9.19</td>
<td>1.16</td>
</tr>
<tr>
<td>Ginsini score</td>
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<td>1.04</td>
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Fig. (2): Correlation between value of H-FABP, and ginsini score.

Fig. (3): Relation between hospital stay and H-FABP value.

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Fig. (4): Relation between value of H-FABP and cardiac events during hospital stay.
Heart-type Fatty Acid-Binding Protein (H-FABP) is a low-molecular-weight protein involved in the intracellular uptake and buffering of free fatty acids in the myocardium [9]. It was first noted to be a marker of Myocardial Infarction (MI) in 1988 [10]. Because it is rapidly released from the cytosol into the circulation after myocardial ischemia and necrosis [11], H-FABP has been shown to be a sensitive early marker of MI [12,13]. Recently heart-type fatty acid binding protein has emerged as an independent prognostic marker for patients with ACS in multiple studies [2-5].

The present study evaluated the prognostic utility of H-FABP at six-months follow-up; where it found that; increasing concentration of H-FABP was a predictor for developing heart failure symptoms at six-months follow-up (p<0.001), where sensitivity and specificity was found to be 75% and 92% respectively at H-FABP level of 43.95ng/ml [AUC 0.944 with 95% CI (0.884-1.004)]. Also the current study showed that increasing concentration of H-FABP was a predictor of recurrent ischemia that warrant intervention during six-months follow-up (p<0.001), with 71% sensitivity and 96% specificity at H-FABP level of 44.50ng/ml AUC 0.927 with 95% CI (0.842-1.011). However the present study showed no relation between increasing concentration of H-FABP and the incidence of sudden cardiac death during six-months follow-up (p=0.170). The prognostic utility of H-FABP might be explained by a possible role for H-FABP in denoting the presence of myocardial ischemia either in the presence or the absence of myocardial necrosis denoted by detecting raised levels of troponin [2]. Confirmatory to these results; univariate regression analysis was done to determine potential predictors of cardiac events (heart failure, IHD, sudden death). Which showed that only H-FAB was a significant predictor for cardiac events, (p-value 0.003, OR 1.00-1.09) during six-months follow-up.

Similar to the present study those published by O’Donoghue et al., [3] and showed that elevated H-FABP was an independent predictor of death, recurrent MI, congestive heart failure or the composite of these end points (HR, 1.9; 95% CI, 1.3 to 2.7), during 10-months follow-up of 2287 patients with ACS, even among subgroup of troponin-negative patients which is consistent with the hypothesis that H-FABP is a marker of myocardial ischemia, another study published by Kilcullen et al., [2] showed that elevated H-FABP predicts long-term mortality during 12-months follow-up of 1448 patients with ACS independent of GRACE clinical risk factors, troponin and hs CRP. The adjusted all-cause mortality HR among unstable angina patients (Trop-ve) was 11.35 (95% CI 2.00 to 64.34; p=0.006), also McCann et al., reported on the prognostic value of H-FABP measured on admission in 550 patients presenting to a coronary care unit with ischemic-type chest pain recruited over a period of three years [14]. Patients were followed-up for one year from the time of admission for the primary outcome measure of death or recurrent MI which occurred in 54 of the 550 patients (9.8%). Significant univariate predictors of death or MI included elevated levels of H-FABP (defined as >5g g/L measured using the Randox Biochip assay) as well as peak cTnT, NT-pro-BNP, fibrinogen, and D-dimer. When incorporated in a logistic regression model along with clinical risk factors and other biomarker results, elevated H-FABP remained an independent predictor of adverse
outcomes, as was elevated peak cTnT and NT pro-BNP. Viswanathan et al., [15] also demonstrated that the prognostic value of elevated H-FABP is additive to troponin in low-and intermediate-risk patients with suspected ACS. The H-FABP concentration was an independent predictor of death or myocardial infarction during 12-months follows of 1080 patients after multivariate adjustment. Patients with H-FABP concentrations 6.48ng/l had significantly increased risk of adverse events (adjusted hazard ratio: 2.62, 95% confidence interval: 1.30 to 5.28, p=0.007).

This study showed that; increasing H-FABP correlated with the severity of coronary angiography (assessed by modified Gimsini score), (r=0.749, p<0.001). Which could be explained by the fact that; H-FABP is released not only during myocardial necrosis but also during acute myocardial ischemia [16], so level of H-FABP is an indicative of angiographic severity, also H-FABP value was an indicator of long hospital stay (more than 5 days) (p<0.001) in current study, which attributed to occurrence of complication, or multiple angiographic lesions that require further intervention.

The current study showed that: H-FABP value not a predictor of cardiac events (Arrhythmia, re-infarction, and sudden death) during hospital stay (p-value 0.389, 0.174, 0.232 respectively). And when univariate regression analysis was performed to determine potential predictors of cardiac events during hospital stay, it found that only the age was a significant predictor for the cardiac events (p-value 0.01, OR 1.02-1.16) during hospitalization.

Conclusion:
- Increasing H-FABP value has a prognostic role in prediction of incidence of heart failure and ischemic heart disease that require intervention during six-month follow-up, irrespective of troponin level.
- Increasing H-FABP value correlates well with the severity of angiographic lesions, and with long hospital stay.

References
الملخص العربي

لعب الدالات البيوبكيميائية للقلب دورًا متزايدًا الأهمية في تشخيص متلازمة الشريان التاجي الحادة (ACS)، ومن هذه الدالات الحديثة البروتين المرتبط بالحمض الدهني القلبي حيث تم تطويرها في عام 1988 وحيث أنه يتميز بالظهور المبكر بالدم بعد ساعة من حدوث تقصيب ضغط القلب مما أدى إلى أهمية استخدام الصبيح في التشخيص المبكر للعوامل الحادة للشريان التاجي.

وبناءً على أحدث الدراسات التي نشرت بين عام 2005 و2010 ركزت على استخدام القيمة التنوبية للبروتين المرتبط بالحمض الدهني القلبي في مرضى متلازمة الشريان التاجي الحادة (ACS).


كما يهدف هذا البحث إلى تقييم القيمة التنوبية للبروتين المرتبط بالحمض الدهني القلبي، حديث تقييمات أخرى من القصور الحاد للشريان التاجي، وذلك من خلال المتابعة الدورية للمرضى.

تتضمن الدراسة:
- مجموعة من المرضى وعدهم تسمى ريب قد تم حجزهم بدو الأعراض الأولية للعوامل الحادة للشريان التاجي طبقًاً
- الدراسات الشرفية.
- التقييم الكliníكي والاختبارات العملية الروبتية، وبعض الاختبارات الخاصة بالدراسة (متضمنة قياس إنزيمات الرب وليبرونين) والبروتين المرتبط بالحمض الدهني القلبي.
- تم عمل موجات صووتيّة على القلب، مع عمل قسطرة قلبية لجميع المرضى، مع تقييم شدة هرم الشريان التاجي باستخدام مقاييس Ginssini.
- وقد تم مناقشة المرضى على مدار ستة أشهر لمحاولة حدد تقييمات أخرى من القصور الحاد للشريان التاجي، اعتباراً من القصور الحاد للشريان التاجي.

باستخدام إجابة بطريقة محذولة من حيث:
- قيمة البروتين المرتبط بالحمض الدهني القلبي ترتبط مع شدة قصور الشرايين التاجية، ومع الإقامة بالمستشفى.
- وجود زيادة نسبة الربوتيين المرتبط بالحمض الدهني القلبي وحيدود اعتبار بعض قصور للحمض الدهني القلبي والدائم للعوامل المتابعة لمرضي قصور الشريان التاجي.
- وجود زيادة نسبة البروتين المرتبط بالحمض الدهني القلبي وحيدود نتائج قصور للحمض الدهني القلبي وحيدود اعتبار بعض قصور النتائج لمرضي قصور الشريان التاجي.

وتوصي الدراسة بالآتي:
- الاستفادة من القيمة التنوبية للبروتين المرتبط بالحمض الدهني القلبي في حدود إعالة عضلة القلب ونباتات أخرى لقصور الشريان التاجي.