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Diagnostic performance of heart-type fatty acid binding protein and high sensitive-cardiac troponin in patients in an emergency department sus pected of acute myocardial infarction

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ABSTRACT

Heart-type fatty acid binding protein (H-FABP) also referred to as mammary-derived growth inhibitor is a polypeptide structure that in humans transcribed by FABP3 gene. It is preferred to be investigated in combination with troponin to the diagnosis of myocardial infarction in patients suffering from chest pain. This study aims to evaluate the role of H-FABP in early diagnosis of MI in comparison with new generation cardiac troponin (hs-c'Tn) and to differentiate patients with ischemic chest pain from non-ischemic ones. This case-control study was performed at the Department of Biochemistry, Medical school, University of Baghdad, during the period from December 2017 to August 2018. It involved 36 patients presented with chest pain; 18 ischemic patients (AMI) and 18 non-ischemic patients (non-AMI) who served as pathological control. Serum investigations included measurements of FABP and hs-c'I'n using enzyme-linked immunosorbent assay (ELISA) method. The mean (±SD) value of serum FABP levels at 1-3 hours did not differ significantly between ischemic and non- ischemic subjects, while it was significantly increased at 6-9 hours in ischemic patients (p< 0.001). However, the mean value of serum levels of hs-c'I'n was significantly higher in AMI patients than in non- AMI ones at 1-3 hours (p<O.0. 04) and 6-9 hours (u<O.o. m). The results concluded that serum hs-c'Tn still the best biochemical marker in confirming the diagnosis of early acute MI and is superior of H-FABP in the rule in and rule out of MI.

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INTRODUCTION

Acute neurosis of cardiac muscle (or MI) is defined as the loss of heart muscle due to prolonged hypoxia (Janet et at, 2008). Cardiac ischemia occurred due to inadequate oxygen and nutrient supply to heart muscle that is beyond its demand. It is a consequence outcome of this imbalance. Also, the lining endothelial of heart arteries is damaged and is considered as a cause of chest pain of ischemia. Activator signals that are associated by activation of the sympathetic nervous system, by elevation in blood catecholamines and by upregulation of coronary blood flow as a compensatory to an increase in need of oxygen by cardiocyte (e.g. during exercise, mental stress or increase in heart, rate) induce vasodilatation in normal coronary vessels. However, in blockage coronary arteries accompanied by malfunctioned endothelial this stimulus can have produced unexpected vasoconstriction (Selwyn et al., 1997).

The predominant electrocardiographic observation during even of symptomatic or silent MI in patients with prolonged duration stable angina pectoris is a decrease in ST- segment. In the case of ischemia is caused by subendocardium, the ST-segment depression is suspected in ECG investigation (Mirvis et al., 2001). This pattern of subendocardial may be due to ischemia events of stable angina or unstable angina whether symptomatic or not. The characteristic EG of ST-segment depression with or without TV wave inversion usually results from insignificant thrombi blockage and less significant fibrin associated with more aggregated platelet. In case of thrombi attach to an unstable ruptured plaque within the intraluminal pericardial coronary arteries, complete occlusion may occur, with consequent interference with blood supply of nutrient and oxygen to the myocardium (Joint, 2000).

These events that lead to mal functional myocardium results in defective left ventricular (LF) function, which is associated with poor life quality and increased mortality (Boersma., 2003). The consent thing in that a vulnerable plaque constitutes the end common process pathway that leads to the atherothrombotic events (Casscells., 2006)" Heart-type fatty acid binding protein (H- FABP) also known as mammary-derived growth inhibitor is a belongs to a family of protein that in human being is synthesized by gene expression achieved by the FABP3 gene. The clinical application of H-FABP in the diagnosis of cardiac necrosis was firstly noticed in 1988 by Glatz (Glatz IF et al., 1988). It is concentrated in the cardiac muscle in a quantity that is much greater than that in skeletal muscle or other parts of the body; kidney, gastrointestinal tract, liver, CNS, lactating mammary glands and the placenta (Pelsers et al.,.2005).

Subjects and Methods

The present study was carried out at the Biochemistry Department, College of Medicine, University of Baghdad, and at Baghdad Teaching Hospital, during the period from December 2017 until August 2018. Eighteen patients with ischemic chest pain suspected of myocardial infarction (STEMI) based on clinical examination and ECG results as performed by Consultant Cardiologist. Also, the study included another 18 subjects with non - ischemic chest pain and served as pathological control. Blood samples were obtained from the peripheral vein of each patient and control at two occasions of their ED admission; at 1-3 hours of onset of their chest pain and then followed at 6-9 hours of that symptom. The blood sample left to clotting and then centrifuged. At 2500 rpm for 15 minutes to obtain serum which used for measurements of H-FABP and hs-c'I'n by ELISA method based on biotin double antibody sandwich technology. Statistical analysis involved the analysis of variance (ANOVA) and student´s t-test was used to obtain the significant difference between and among the studied groups. Also, linear regression was applied to test for correlation between varies studied biochemical and clinical parameters, and the significance of the r- value was assessed by related t-test. P-values of less than 0.05 were considered significant.

RESULTS

Table 1 depicts that mean (±SD) values of the age of ischemic group at 1-3 hours (52.8± 2.0 years) did not differ significantly from that of the pathological control group (non-ischemic chest pain; 49.4± 14.1 years). Similarly, the mean values of BMI (28.4± 4 .8. Kg/m2, 30.10± 7.1 Kg/m2, respectively) and gender percentage were not significantly different between the two groups.

Data presented in table 2 revealed the mean values of the measured biochemical markers of ischemic chest pain groups and pathological controls group. The value of mean of serum hs-c'I'n levels of ischemic patients at 1-3 hours (5.08 ± 0.89 ng/ml) and 6-9 hours (5.93± 1. 10 ng/ml) were significantly increased than those of pathological subjects group (3.98± 1.08 ng/ml, p<0.004, p< 0,001, respectively). However, the mean value of serum H-FABP levels did not differ significantly between ischemic patients and the pathological group at 1-3 hours (3.17 ± 0.73 ng/ml, 2.87± 1,10 ng/ml, respectively). But, that at 6-9 hours revealed significantly increased in ischemic chest pain group compared with pathological controls (3.17 ± 0.73 ng/ml, 4.28 ± 0.87 ng/ml, respectively; p< 0.001). Table (3) shows the receiver operator characteristics (ROC) of the validity of the studied biomarkers as differentiator of ischemic chest pain presented within 1-3 hours from that of controls; H-FABP (0.625) and hs- c'Tn (0.790)., Serum level of H-F ABP had poor ability to differentiate MI from controls within 1 - 3 hours of the onset of chest pain, while serum level of hs-c'Tn had. Fair ability to do that at a cut point of >4.2 ng/ml (SN=83%) SP=71%).

Table (4) depicts the ROC of the validity of the measured biomarkers as a predictor of IvII chest pain (after 6 - 9 hours) from pathological control: H-FABP (0.855) and. hs-c'I'n (O.905). Semm Ieve] ofhs-c'In hand. Excellent ability to diagnose and differentiate MI from pathological control with optimal cut point> 4.4ng/ml (SN=100%, SP=79%)~ also H~FABP had. Good ability to do that at 6 - 9' hours of chest pain with optimal cut point >3.1ng/ml (SN=100%, SP=6I%).

Table 1: Mean (±SD) Values of Demographic Data of Pathological control Group and Ischemic Chest Pain Group (1-3 hours)

Parameter	Pathological control group (non-ischemic chest pain) (n=18)	Ischemic chest pain group (1-3 hours) (n=18)
Age (years)^{NS}	49.4 ± 14.1	52.8 ± 2.0
BMI (Kg/m)^{NS}	28.4 ± 4.8	30.1 ± 7.1
Gender ^{NS}		
Female No %	8 (44.4%)	4 (22.2%)
Male No %	10 (55.6%)	14 (77.8%)

the t-test revealed Statistically non-significant (NS) differences between the two studied groups

Table 2: Mean (±SD) Values of Biochemical Markers of Pathological control Group and Ischemic Chest Pain Group (1-3 hours) and (6-9 hours)

Parameter	Pathological control group (non-ischemic chest pain) (n=18)	Ischemic chest pain group (1-3 hr.) (n=18)	Ischemic chest pain group (6-9 hr.) (n=18)
H-FABP (ng/ml)	3.17 ± 0.73	2.87 ± 1.10 ^{NS}	4.28 ± 0.87*
hs-cTn (ng/ml)	3.98 ± 1.08**	5.08 ± 0.89	5.93 ± 1.10

*ANOVA and t-test *significant increase in H-FABP ($p<0.001$) levels of ischemic patients at 6-9 hours compared to controls, **significant increase in serum hs-cTn levels in ischemic patients at 1-3 hours ($p< 0.004$) and at 6-9 hours ($p<0.001$) compared to controls, NS: non- significant difference in H-FABP in group I

Table 3: ROC analysis of the validity of the different markers as a predictor of MI (1 – 3 hours) from Pathological control

Parameter	ROC	p-value	Cut point	SN	SP	AC	PPV	NPV
H-FABP (ng/ml)	0.625	0.217	-	-	-	-	-	-
Hs-cTn (ng/ml)	0.790	<0.01	>4.2	83%	71%	77%	79%	77%

ROC: receiver operator characteristics, sensitivity (SN), specificity (SP), accuracy (AC), positive predictive value (PPV), negative predictive value (NPV)

Table 4: ROC analysis of the validity of the different markers as a predictor of MI (6-9 hr.) from pathological control

Parameter	ROC	p-value	Cut point	SN	SP	AC	PPV	NPV
H-FABP (ng/ml)	0.855	<0.01	>3.1	100%	61%	81%	72%	100%
hs-cTn (ng/ml)	0.905	<0.01	>4.4	100%	79%	90%	86%	100%

ROC: receiver operator characteristics, sensitivity (SN), specificity (SP), accuracy (AC), positive predictive value (PPV), negative predictive value (NPV)

DISCUSSION

The present study found that H-FABP plays a minor role in the rule in and! Or rule out of MI in a shorter interval period of chest pain (1-3 hours) with a ROC value of 0.6. 25" While the diagnostic performance of hs-cTn in the rule in of MI at an early period (1-3 hours) and differentiate it from non-ischemic chest pain was 77% and that of its rule out was 79% (ROC 0.79). So, serum measurement of H-FABP as a potential biochemical test appeared to be insufficient to rule in and out of acute MI in urgent and early ED admission; 1-3 hours (Schoenenberger et at.,2015).

However, the diagnostic utility of FABP was increased when the time interval of chest pain was increased; at 6-9 hours with the rule in of MI 72 % and a high one in rule out 100 % at a cut-off point of > 3.1 ng/ml and a ROC value of 0.855 (table 4). Sensitivity and specificity ofH~FABP in AlVII diagnosis has been reported to be 60% and 88% (Valle et at, 2008). Meanwhile, a Korean study reported specificity of (80.9. %,) and sensitivity (81.6%) (Kim et al., 2011). One study showed that cutoff point of 3.3 gr/l could predict AMI with 33.3% sensitivity and 96.7% specific it (Freund et al. 2012). Moreover, Study on a representative sample of the Netherlands adult population showed that H-FABP has sensitivity of 39% and specificity of 94% on the first hour of chest pain, while at 6-hour measurements has 43 % sensitivity and 94% specificity (Slot et al., 2013) Positive predictive value and negative predictive value in the above-mentioned study was 65% and 85% at baseline measurements, but after 6 hours from the onset they [leached to 72% and 83%, respectively. A recent study by (Willemsen et at) 2015) on 202 consecutive patients suggested that with a cutoff point of serum FABP' at 4 ng/ml, MU could be diagnosed

with 73.9% sensitivity and. 90.8% specificity. With a cutoff point of 3 ng/ml, HFABP was diagnostic for myocardia] infarction in (Freund et al., 2012) study, although positive predictive value of HF ABP and troponin together was not different from troponin alone (96% vs 95'%). Moreover) the highest sensitivity was for F-HFABP measured at 4 hours (88%) (Kalay., 2(10). The high negative predictive value of FABP in rule out of MI that found in the present study (table 4) was in agreement with that reported 'by (Anvari., 2018) who revealed high negative predictive value of H-FABP test can help to rule out AMI earlier in these patients and, therefore, it can reduce admission time at the emergency department as wen as the health care expenses. The mechanism that illustrates the leakage of FABP from the necrotic myocardium indicated that insulin-like growth factor 1 (IGF -1) signaling is inhibited micro RNA-I expression, which plays an important role in cardiac hypertrophy with a resultant increase in circulating H-FABP (Varrone., 2013), The energy production in heart failure differs significantly from that in a normal one (Neubauer., 2007; Doenst et al., 2013). In failure one, the predominant substrate utilization is glucose associated with reduced fatty acid oxidation (Binas., 1999.; Sack, 1996). Cardia cells uptake of fatty acid and the consequent oxidation by β= pathway are significantly reduced, and other FABPs do not balance for this process as was documented experimentally in FABP knockout mice (Binas., 1999), indicating that H-FABP plays an important role in fatty acid transport in the heart. However, adipocyte fatty acid-binding protein (FABP4) and H- FABP directly worsen heart muscle contraction via a reduction in intracellular Ca++ transient, which may involve in decrease the excitation-contraction coupling (Lamounier., 2009). Accordingly, it was suggested that H- FABP release from failure myocardium might participate in a vicious cycle through alteration of cardiac energy substrate and heart dysfunction, consequently leading to abnormal clinical outcomes (Otaki., 2017).

CONCLUSION

The results suggested that serum hs-oTn stil) the 'best biochemical marker in confirming the diagnosis of early acute MI and is superior of H-F ABP in the rule in and rule out of ML Serum measurement of H-FABP may be a complementary test supporting the function of serum cTn measurement.

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