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Effectiveness of D-dimer and heart-type fatty acid-binding protein as tools for diagnosis of myocardial infraction

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Abstract
Background: The role of D-dimer and H-FABP as diagnostic markers in myocardial infarction (MI) is still a question. We aim to investigate the usefulness of D-dimer and H-FABP determination for the evaluation of myocardial infarction patients.
Methods: Forty patients with MI and 40 controls with a mean age of (57.37 ± 8.27), (57.47 ± 8.329) were conducted. D-dimer, H-FABP, and troponin I tests were determinate at admission using Up-Converting Phosphor Quantitative Immunoassay Analyzer.
Results: D-Dimer and H-FABP concentrations were greater significantly in MI patients than controls, as was cTnI level ($p<0.001$). The cut-off values of D-dimer, H-FABP, and troponin I for diagnosis of MI were 425ng/ml, 4.1 ng/ml, and 0.105 ng/ml respectively with. The sensitivity and specificity of D-dimer was 82.5.% and 65.0%, for H-FABP it was 77.5%, and 57.5% and for cTnI it was 82.5% and 62.5%, respectively for diagnosis of MI.
Conclusions: D-dimer as a biomarker for the early diagnosis of MI would be the ideal combination with cTnI to cover the complete diagnostic for MI.

Keywords: Myocardial infarction, acute coronary syndrome, D-dimer, Troponin I, Heart-type Fatty acid-binding proteins

Introduction

Acute coronary syndrome (ACS) is a common cause of presentation in emergency departments (EDs). Early detection and rapid rule-out of acute myocardial infarction (MI) have always been one of the great concerns to reduce mortality, morbidity, and hospitalization costs and avoid doing further diagnostic and unnecessary interventions in low-risk patients [1].
Routinely, the serial electrocardiograms (ECGs), biomarkers, and clinical decision rules have been used for the risk stratifications and diagnosis of ACS [2]. Cardiac enzymes start to rise within hours after onset of symptoms. On the other hand, more than 50–75% of the seven million patients with chest pain are admitted to the hospital because the initial clinical evaluation is not sufficient to rule in or rule out ACS. This problem results from the low sensitivity of the electrocardiogram (ECG) and initial clinical data to predict the presence of ongoing acute myocardial ischemia in those with ACS, which makes ECG has not shown to have a reliable sensitivity in early diagnosis of MI [3]. It is typically the culmination of a long and complex process where the formation of an occlusive thrombus within a coronary artery leads to cardiac ischemia and infarction. [4]. The coronary thrombus can occur in both symptomatic and asymptomatic patients with significant or less than 50% stenosis. Coronary thrombus is one of the frequent causes of sudden cardiac death [5, 6] Several markers involved in the formation and lysis of arterial thrombosis have been identified among which fibrinogen, plasmin-α2 anti-plasmin, prothrombin, and D-dimer can be noted. The D-dimer was used as a diagnostic marker in venous thromboembolism [7]. As a marker of rapid fibrin turnover and high thrombotic activation in both arterial and venous system, interest in D-dimer has grown over time, and its predictive role has been investigated in several acute and chronic cardiovascular care, [8]. In patients with MI, high circulating D-dimer levels have been correlated with recurrent MI and poor prognosis [9, 10]. However only few studies focused on the diagnostic value of D-dimer in the MI and ACS [11, 12].

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One of the biomarker proteins that arises after tissue damage is Heart-type Fatty Acid-Binding Protein (H-FABP) is a biochemical biomarker that has the potential to be used to detect heart attack, H-FABP released from the damaged heart cells into the blood very quickly, which is localized at high concentrations, especially during ischemia [13]. Thus, attempts continue to find a better marker to triage and a more rapid diagnosis of MI.

The aim of the present study is to assess possibility using of D-dimer or H-FABP as a diagnosis marker of MI patients.

Materials and Methods
Research design and setting
This case control study was conducted from February 2021 to June 2021 in the ED of Ibn -Albitar center for cardiac surgery located in Baghdad, Iraq. Inclusion criteria included patients with typical chest pain, which defines as a substernal pain, provoked by exertion, or relieved by rest or nitroglycerin- suspected ACS presented to ED with age greater than 18 years old, onset of symptoms less than 24 h. Exclusion criteria included, first, patients who had, angioplasty, or open-heart surgery within the prior 6 months; second, patients admitted with other causes known to elevate D-dimer level (e.g. upper gastrointestinal bleeding, acute intestinal ischemia, ischemic and hemorrhagic stroke, deep vein thrombosis, sepsis, and malignancy); and third, patients admitted more than 12 h after chest pain onset.

Data collection
The patients with typical chest pain for ACS and related clinical examination were enrolled in the study. Their data about age, sex, BMI, onset of pain, quality of pain, associated symptoms, and ACS risk factors such as dyslipidemia were collected. Forty patients were enrolled and 10 patients were excluded. Exclusion causes included, using heart medications like beta blockers, nitrate and aspirin (four patients), and using anticoagulants (six patients). All patients were subjected to ECG and blood sampling in order to measure serum level of D-dimer, H-FABP and troponin on ED presentation. In contrast 40 healthy persons were collected as control.

D-dimer, H-FABP and Troponin I
Serum sample was taken to determine D-dimer, H-FABP and Troponin I levels before receiving heparin. The levels of these biomarkers were measured by Up-Converting Phosphor Quantitative Immunoassay Analyzer (UPT).

Lipid profile
Serum sample was taken to determine cholesterol, triglyceride and, HDL as well as LDL was calculated by Friedewald equation (total cholesterol minus high-density lipoprotein -cholesterol minus triglycerides /5 (VLDL) in mg/dl).

BMI
Body mass index (BMI) is a measure of body fat based on height and weight and was calculated by weight in kilograms divided by height in meters squared.

Results
Baseline characteristics of studied groups clarified that 40 patients with a mean age of (57.37 ± 8.27 years), and 40 controls (57.47 ± 8.329 years) were matched in age and gender, as well as no significant difference in their BMI

($P>0.05$) (Table 1). Meanwhile the baseline characteristics of the study population predicted that the patients had higher total cholesterol and LDL-cholesterol - levels than the healthy controls ($p<0.01$), also There was clinical difference in VLDL-cholesterol and triglyceride levels between the patients and the healthy controls ($p<0.01$). But there was no difference in HDL-cholesterol levels between the patients and the healthy controls (p=0.75). D-Dimer and H-FABP concentrations were greater significantly in MI patients than controls, as was cTnI level (Table 2; $P < 0.001$).

Table 1: Baseline Characteristics of Patients with Myocardial Infarction Compared to control

Variable	Control group Mean ±SD	Patients group Mean ±SD	P value
Age(year)	57.47± 8.329	57.37 ± 8.27318	0.957
Sex(no. of female)	12(30%)	13(32%)	0.347
BMI(kg/m^2)	27.53 ± 0.082	27.37 ± 0.181	0.742
Ch (mg/dl)	127.0 ± 30.98	211.15 ± 30.76	0.000
Tri(mg/dl)	102.80 ± 26.83	206.07 ± 53.186	0.000
HDL(mg/dl)	43.07 ± 4.002	43.52 ± 7.94	0.750
LDL(mg/dl)	58.07 ± 3.37	122.97 ± 32.21	0.000
VLDL(mg/dl)	20.60 ± 5.39	41.62 ± 9.12	0.000

Table 2: Levels of diagnosis markers in MI patients compared to control

Variable	Control group Mean ±SD	Patients group Mean ±SD	P value
D-Dimer(ng/ml)	413.62 ± 71.41	1849.62 ± 538.89	0.000
HFABP(ng/ml)	4.03 ± 1.39	27.09 ± 4.16	0.000
cTnI(ng/ml)	0.1075 ± 0.037	2.196 ± 0.875	0.001

Based on the analysis of Pearson correlation, significant positive correlations were observed between D-dimer, H-FABP and age (P <0.01, r = 0.346), ($p<0.01$, r=0.361) respectively (Table 3), while a non-significant correlation of cTnI with age was indicated (p>0.05, r=0.191).

The results of lipid profile showed that there was a positive significant correlation ($p<0.05$) of H-FABP with cholesterol, triglycerides and low-density lipoprotein, while there was highly significant negative correlation ($p<0.01$) with high-density lipoprotein. Meanwhile positive significant correlation ($p<0.05$) of cTnI with cholesterol, triglycerides and very low-density lipoprotein were observed, while there was significant negative correlation ($p<0.05$) with high-density lipoprotein. By the other, there were no significant correlation between D-Dimer and lipid profile (Table 3). Highly significant positive correlation was observed between H-FABP and cTnI ($p<0.01$), while non-significant correlation of D-Dimer with both H-FABP and cTnI were observed.

Table 3: person correlation of D-Dimer, HFABP, and cTnI with studied variables

Variable	D-Dimer (ng/ml)	H-FABP (ng/ml)	cTnI(ng/ml)
Age(year)	0.346(*)	0.361(*)	0.191
BMI(kg/m^2)	0.225	0.287	0.199
Ch (mg/dl)	-0.032	0.354(*)	0.268
Tri(mg/dl)	0.277	0.340(*)	0.354(*)
HDL(mg/dl)	-0.129	-0.501(**)	-0.361(*)
LDL(mg/dl)	-0.022	0.386(*)	0.244
VLDL(mg/dl)	0.275	0.363(*)	0.389(*)
D-Dimer(ng/ml)	1	0.218	0.213
HFABP(ng/ml)	0.218	1	0.723(**)
cTnI(ng/ml)	0.213	0.723(**)	1

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

To find the cut-off point with the highest sensitivity and specificity of D-dimer, H-FABP and cardiac Troponin I serum levels in the diagnosis of MI, ROC curve was used. Based on the results of ROC curve, the best cut-off point for MI is 425 ng/ml in terms of D-dimer, 4.1 ng/ml and 0.105 ng/ml in terms of H-FABP and cTnI respectively (Table 4). The sensitivity and specificity of each marker as diagnosis tool of MI patients presenting with ACS is (82.5, 65) % (77.5, 57.5) % and, (82.5, 62.5) % for D-dimer, H-FABP, and cTnI respectively (Table 4).

Table 4: Operative Characteristics of D-Dimer, HFABP, and CTnI for the Diagnosis of Myocardial Infarction

	cTnI (ng/ml)	D-Dimer (ng/ml)	HFABP (ng/ml)
AUC	0.825	0.844	0.814
Cut off level (ng/mL)	0.105	425	4.1
Sensitivity,%	82.5	82.5	77.5
Specificity,%	62.5	65	57.5

Discussion
MI has a high mortality rate worldwide, but fast and reliable diagnosis can reduce mortality. Biomarkers are elevated because of cell death in the myocardium. Therefore, many biochemical parameters of heart-tissue origin have been used in the diagnosis of MI [14]. Nowadays, cTnI which is the gold-standard biomarkers for diagnosing MI [15]. Chest pain is a very common cause for presentation to the emergency room, and the rapid evaluation and diagnosis of the cause of acute chest pain is essential and often problematic for emergency physicians [16]. In some patients having a pre-existing cardiac abnormality, such as left ventricular hypertrophy or prior MI, the first ECG is uncertain and cannot be used to reach a diagnosis [17]. D-dimer is produced by destruction and the breakdown of fibrin clot at the site of injury by plasmin, which represents the manufacture of active thrombosis and its lysis [18, 19]. D-dimer level is expected to increase in acute ischemic events faster than in other cardiac markers because D-dimer is created faster than other markers in the course of the ACS pathophysiology [20]. On the other hand, studies have shown that D-dimer is in direct relationship with the occurrence or recurrence of cardiovascular diseases, so that patients whose D-dimer is in upper one-third of D-dimer levels, are 70% more at risk of CHD than those in lower one-third of D-dimer levels. D -dimer was used commonly as a marker in venous thromboembolism as well as aortic dissection, and some studies have been conducted on its role in the diagnosis of MI [21, 22]. This study was aimed to determine the diagnostic value of a D-dimer test for MI in patients with suspected ACS and the results showed that D-dimer can also be used as a diagnostic marker with appropriate sensitivity and specificity more than cTnI in the diagnosis of MI. Today, the measurement of troponin is considered as one of the most selective markers in the diagnosis of myocardial damage. Although, the fundamental flaw against them is an increase in their serum level 3-4 h after the onset of symptoms [23]. H-FABP is mainly found in the heart muscle. An elevated level of H-FABP early after the injury of myocytes, it can be tested in 30 minutes after onset of chest pain due to MI, reaches its peak in up to 8 hours and decreases to its original level after 24 hours [24]. This goes with the finding of the current study, which found that it is extremely significantly statistically associated with MI when compared to control individuals. Shi H *et al* study observed significant higher mean levels of H-FABP in MI cases, H-

FABP is a good biomarker of damaged cardiomyocytes, serum concentration of H-FABP increases in the first 1–2 h after symptom onset [25]. In the present study, the association of cardiac marker s (D-dimer, H-FABP and cTnI) (with MI was assessed and the correlation between (D-dimer, H-FABP) and cTnI was tested. We found significantly increased levels of all cardiac biomarkers in MI cases compared to controls ($p<0.01$), which is mostly consistent with the results of several previous studies that documented a role of these biomarkers in diagnosis of MI. Moreover, we found highly significant correlations between the H-FABP and cTnI ($P<0.01$), but there is no clinical significance between D-dimer with cardiac troponin I ($P> 0. 05$), and also there was no clinical significance between D-dimer and H-FABP.

Although LDL-C, TG, cholesterol concentrations are associated with combined and individual cardiovascular disease (CVD) outcomes including myocardial infarction (MI) [26]. A significant association between cTnI and H-FABP was observed with hyperlipidemia. However, sensitivity and specificity results indicated that D-Dimer is better than H-FABP in diagnosis of MI.

Conclusions
For early diagnosis, D-dimer has superior sensitivity and specificity for acute MI compared to initial H-FABP for patients presenting with chest pain onset. Measuring D-dimer, along with cTnI at the time of hospital admission improves early diagnosis and risk stratification of patients with acute chest pain.

Conflict of Interest
No conflict of interest relevant to this article was reported.

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