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Diagnostic Value of CRP, H-FABP, PCT, Lp-PLA2 and Cytokines in Stable Angina

Amer Muayad Hussein[1], Ernez Hajri Samia[2] and Al-Snafi Ali Esmail[3]*

[1]Ibn El Jazzar Faculty of Medicine, University of Sousse, Tunisia.
[2]Department of Cardiology, Farhat Hached Hospital-Sousse, Ibn El Jazzar Faculty of Medicine, University of Sousse, Tunisia.
[3]Department of Pharmacology, College of Medicine, University of Thi-Qar, Thi-Qar 64001, Iraq.
*Corresponding Author E-mail: aboahmad61@yahoo.com

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Coronary artery disease (CAD) is a significant cause of worldwide mortality and morbidity. This study aims to evaluate the levels of serum H-FABP (fatty acid-binding protein), hs-CRP (high sensitivity- CPR), Lp-PLA2 (lipoprotein PLA2), PCT (procalcitonin) and cytokines, in addition to routinely used diagnostic tests, Troponin I (Trop I), Myoglobin (MYO) and Creatine kinase MB (CK-MB) in patients with stable angina to determine their sensitivity in diagnosing stable angina and facilitating faster decision-making in the emergency unit. The current study was performed on 86 patients complaining stable angina, at Nasiriyah Heart Center from October 2021 to October 2022. Eighty-six, healthy subjects (age-matched) were taken as a control group. Blood samples were collected in the emergency department. Serum levels of hs CRP, H-FABP, CK-MB, Trop I, MYO, Lp-PLA2 and PCT were determined using electro-chemiluminescence immunoassay. Blood sugar and serum total cholesterol, triglycerides, LDL, VLDL and HDL were determined using Cobas C311 photometric assays. Serum IL-6 was determined by using electro-chemiluminescence immunoassay, while, IL-9, IL-1ß and TNF-a were assayed by ELISA. The study showed that the level of troponin I didn't significantly change in patients with stable angina. However, compared with healthy controls, patients showed a significant increase in serum levels of CK-MB, myoglobin, hs-CRP, H-FABP, Lp-PLA2 and PCT. Significantly elevated levels of serum IL-6, IL1ß, IL-9 and TNF-a were also recorded in patients with stable angina compared to healthy controls. The results also revealed that patients with stable angina had significantly elevated serum levels of serum triglycerides, total cholesterol, LDL and VLDL with a significant decline of serum HDL compared to healthy controls. We can concluded that, in addition to cTnI, CK-MB and MYO, other biomarkers such as hs-CRP, H-FABP, Lp-PLA2 and PCT are sensitive; and can serve as diagnostic indicators of stable angina pectoris for fast treatment. Furthermore, the detection of inflammatory biomarkers was found to be an additional diagnostic parameter in stable angina.

Keywords: Biomarkers; Cytokines; Ischemic heart disease (IHD); Lipid profile; Stable angina.

Coronary artery disease (CAD) is a significant cause of worldwide mortality and morbidity, with an incidence of one in every 6 deaths in Western countries [1]. In the past, coronary heart disease showed high incidence in older ages [2]. However, nowadays, de to accelerated lifestyle changes, economic stresses, and other factors, the incidence of coronary heart disease has increased in middle-aged adults [3].

In stable angina, increased oxygen demand occurs only with physical exertion. Increased myocardial oxygen demand from exercise is due to increases of heart rate and blood pressure, as well as increased the contractility of the myocardium, among other factors [4].

Many biochemical markers are sensitive and specific for myocardial ischemia and can be easily and rapidly measured in serum [5]. Elevated levels of CK-MB activities, Trop I, and MYO are routinely used in early diagnosis of acute coronary syndrome [6].

Heart-fatty acid binding protein (H-FABP) could be an important biomarker for the early diagnosis of coronary syndrome according to many recent investigations. FABPs are relatively low molecular weight cytoplasmic proteins that are prominent in tissues with high metabolism of fatty acid, such as the heart [7].

Different cardiac diseases, including coronary syndrome and atherosclerosis, are associated with elevation of serum proinflammatory cytokines and CRP [8-13]. Furthermore, lipoprotein-associated phospholipase A2 (Lp-PLA2) has been considered as one of the inflammatory biomarker of many cardiovascular diseases [7]. Procalcitonin (PCT) is also implicated as an inflammatory marker of early atherosclerosis [14].

The current study aims to investigate the diagnostic values of additional biomarkers in stable angina. The establishment of new diagnostic tests will enhance the diagnostic abilities to facilitate fast decision making in emergency units.

METHODS

Patients and exclusion criteria

The current study was performed on 86 patients complaining stable angina, at Nasiriyah Heart Center from October 2021 to October 2022. Eighty-six, healthy subjects (age-matched) were taken as a control group. Patients with unstable angina, myocardial infarction, and any other heart disease, and those on statins therapy were not included in the study, to avoid interference with the studied parameters.

Blood samples were drawn in the emergency department. Serum CRP hs, H-FABP, CK-MB, Trop I, MYO, Lp-PLA2 and PCT were determined by electro-chemiluminescence immunoassay (Nipigon Health Corp., Canada). Blood sugar (Randox, United Kingdom) and serum total cholesterol, triglycerides (Biolabo / France), LDL, VLDL and HDL (Cobas /Germany) were determined using Cobas C311 photometric assays. Serum IL-6 was determined by electro-chemiluminescence immunoassay (ECL, Canada) and serum IL-9, IL-1â and TNF-á were assayed by ELISA (Wuhan Fine Biotech Co., Ltd., China), according to operational manuals.

Ethical approval

The ethical committee at Thi-Qar Health Directorate has approved the research, and informed consent was taken from all participants.

Statistical analysis

The significant variations between groups were assayed using the Student t-test (SPSS, version 26). Proportions were analyzed by Chi-square. If the p-value is 0.05 or less, the differences were considered significant.

RESULTS

Characteristics of patients

Eighty six patients with stable angina and eighty-six healthy subjects were studied in this research. The patient's mean age was 44.0±10.9 years and the healthy subjects mean age was 41.9±10.1 years (P = 0.192). Among the patients, 47(54.65%) were males and 39 (45.35%) were females and among the healthy subjects, 73(84.88%) were males and 13(15.12%) were females (P<0.001). Among the patients and control groups, 39 (45.35%) and 40 (46.51%) respectively were smokers (P = 0.823). There was no significant variation in the frequency of overweight [41 (47.67%) vs 37 (43.02%), P = 0.080] and obesity [28 (32.56%) vs 19 (22.10%), P = 0.080] between patients and the control group respectively. However, the group of patients with stable angina showed more frequent occurrence of hypertension [27 (31.40%) vs 1 (1.16%), P < 0.001] and diabetes [39 (45.35%) vs 1 (1.16%), P < 0.001] compared to the healthy control (Table 1).

Biomarkers in stable angina

Table 2 showed that the level of troponin I was not significantly changed (0.0210±0.0034 vs 0.0200±0.0038 ng/ml, P = 0.054) in stable angina. However, in comparison with the healthy control,

the stable angina patients showed a significant elevation of serum CK-MB level (3.02±1.46 vs 2.15±1.91 ng/ml, P < 0.001), myoglobin (62.02±8.40 vs 49.40±6.00 ng/ml, P < 0.01), hsCRP (28.90±5.50 vs 7.35±3.51 nmol/l, P < 0.01), Lp-PLA2 (127.6±19.2 vs 105.0±22.7 ng/ml, P < 0.01), H-FABP) 6.59±2.71 vs 4.90±1.43, ng/ml, P < 0.001) and PCT (0.056±0.05 vs 0.026±0.02 ng/ml, P < 0.01).

Lipid profile in stable angina

As shown in Table 3, the stable angina patients exhibited significantly higher serum level of total cholesterol (171.1±24.5 vs 161.2±25.1 mg/dl, P < 0.05), triglycerides (184.7±37.7 vs 131.8±27.3, mg/dl, P < 0.001), LDL cholesterol (90.7±8.5 vs 79.5±28.5 mg/dl, P < 0.05), and VLDL cholesterol (38.3±14.5 vs 27.1±11.3 mg/dl, P < 0.01), with a significant decline in serum HDL cholesterol (36.0±10.2 vs 43.0±9.2 mg/dl, P < 0.01).

Cytokines in stable angina

In comparison with healthy control group, the patients with stable angina showed significantly elevated serum levels of IL1â (11.5±3.6 vs 4.6±3.2 nmol/l, P < 0.001), IL-6 (7.9±6.8 vs 4.3±2.2 Pg/ml, P < 0.001), IL-9 (3.7±2.5 vs 2.5±1.6 pg/ml, P < 0.01) and TNF-á (5.2±4.6 vs 2.6±1.7 ng/ml, P < 0.001) (Table 4).

DISCUSSION

Coronary artery disease is a significant cause of worldwide mortality and morbidity. Patients with stable CAD can have an unexpected clinical course, therefore, additional diagnostic and predictive biomarkers are still required [15].

Table 1. The characteristics of patients with stable angina in comparison with healthy control group

Parameters		Control Group	Patients Group	P. value
Patient number		86	86	
Age (yrs)		41.9±10.1	44.0±10.9	NS
Gender	Male	73 (84.88%)	47 (54.65%)	<0.001
	Female	13 (15.12%)	39 (45.35%)	
Smoking		40 (46.51%)	39 (45.35%)	NS
Hypertension		1 (1.16%)	27 (31.40%)	<0.001
Obesity	Normal weight(18.5 – 24.9) Kg/m^2	30 (34.88%)	17(19.77%)	NS
	Overweight(25.0 – 29.9) Kg/m^2	37 (43.02%)	41 (47.67%)	
	Obese, ≥30 Kg/m^2	19 (22.10%)	28 (32.56%)	
Diabetic		1 (1.16%)	39 (45.35%)	<0.001

NS: non-significant

Table 2. Serum biochemical markers levels in stable angina in comparison with the healthy control group

Serum biochemical markers	Control Group	Patients Group	P. value
hsCRP (nmol/l(	7.35±3.51	28.90±5.50	<0.01
H-FABP)ng/ml (	4.90±1.43	6.59±2.71	<0.001
CK-MB) ng/ml(	2.15±1.91	3.02±1.46	<0.001
Trop I (ng/ml (	0.0200±0.0038	0.0210±0.0034	(NS)
MYO) ng/ml (	49.40±6.00	62.02±8.40	<0.01
Lp-PLA2)ng/ml (	105.0±22.7	127.6±19.2	<0.01
PCT (ng/ml (	0.026±0.02	0.056±0.05	<0.01

CK-MB: Creatine kinase, H-FABP: heart type fatty acid binding protein, hsCRP: High sensitive C reactive protein, Lp-PLA2: Lipoprotein-associated phospholipase A2, MYO: Myoglobin, NS: non-significant, PCT: Procalcitonin, Trop I: Troponin I,

Table 3. Lipid profile and blood sugar in stable angina in comparison with the healthy control group

Parameters	Control Group	Patients Group	P. value
Triglycerides (mg/dl)	131.8±27.3	184.7±37.7	<0.001
Total cholesterol (mg/dl)	161.2±25.1	171.1±24.5	< 0.05
HDL (mg/dl)	43.0±9.2	36.0±10.2	<0.01
LDL (mg/dl)	79.5±28.5	90.7±8.5	< 0.05
VLDL (mg/dl)	27.1±11.3	38.3±14.5	<0.01

Table 4. Serum cytokines levels in stable angina in comparison with the healthy control group

Parameters	Control Group	Patients Group	P. value
IL-6 (Pg/ml)	4.3±2.2	7.9±6.8	<0.001
IL-9 (Pg/ml)	2.5±1.6	3.7±2.5	<0.01
IL1β (nmol/l)	4.6±3.2	11.5±3.6	<0.001
TNF-α) ng/ml(	2.6±1.7	5.2±4.6	<0.001

Our results showed a slight nonsignificant elevation in serum Troponin I level in patients with stable angina. Previous studies have also, recorded a slight increase in serum troponin I level in patients with stable angina. The elevation was positively correlated with the extension and severity of atherosclerosis. The necrosis of cardiomyocytes was unlikely to be the main cause of the increased levels [16-17]. Patients of stable angina with elevated troponin levels showed poor long-term prognoses, with higher earlier heart failure and sudden death [18].

In our study, patients with ischemic heart diseases also showed significant elevation of the serum levels of CK-MB and MYO. Increased serum level of CK-MB in stable angina was also recorded by many authors. Furthermore, readmission and mortality, were more frequently occurred in patients with high CK-MB [19-21].

Myoglobin was also moderately increased in stable angina [22]. However, myoglobin is useful for early exclusion of myocardial infarction, but is less useful when blood sample was taken later. Therefore, the elevation of serum myoglobin must be used with other assessments to aid in the diagnosis [23-24].

Our results also revealed that the serum level of hs-CRP was elevated significantly in patients with stable angina. The previous studies mentioned that inflammation played an essential roles in atherogenesis initiation and progression. Although hs-CRP was elevated in stable angina, but its level was significantly less than the level recorded in patients with acute myocardial infarction [25-26]. Increased hs-CRP level was proportional to the necrotic core in the culprit lesion, the length of the lesion was positively correlated with the hs-CRP level. In stable angina, elevation of hs-CRP reflected the inflammatory severity of the atherosclerotic plaque [27].

H-FABP was also significantly elevated in stable angina in the current research. In studying the value of H-FABP in diagnosis and prognosis in a multicenter, prospective study carried out on patients with stable coronary artery disease, it appeared that H-FABP was a potential prognostic biomarker for future outcomes. Many studies reported that high H-FABP increased the hospital readmission and mortality [28-32].

According to our results, the patients with stable angina also showed significantly increased serum Lp-PLA2 levels. Many previous studies revealed that its level was significantly increased in stable angina. Several evidences suggested the Lp-PLA2 promoted atherosclerosis by several pathways [33-35]. Higher level of Lp-PLA2 in stable angina was associated with poor intracoronary function (coronary arteriosclerosis,

vasoconstriction, and poor outflow). Lp-PLA2 is an important factor linked between inflammatory changes and endothelial dysfunction, which enhances the development of CAD. These studies recommended the use of Lp-PLA2 as a useful tool for assessing the level of risk in CAD [36-39].

We also recorded that procalcitonin (PCT) was significantly elevated in stable angina. PCT is the precursor of the hormone calcitonin, it was a biomarker utilized in the diagnosis of sepsis. It indicated the severity of bacterial infection when it progressed into sepsis, its high level was correlated with high mortality [40-41]. The impact of PCT in cardiovascular diseases was also studied, it appeared that in patients with CAD, the extent of atherosclerosis and its adverse outcome were positively correlated with PCT levels [42-44]. The high level of PCT within 48 hours post-admission reflected an inflammatory condition that associated with increased early and six-month mortality [14].

Recent researches showed that the atherosclerosis is an inflammatory disease. Inflammatory cytokines were participated in its initiation and progression, and their serum levels strongly predict coronary artery disease [45-47].

Our study revealed that IL-6 was significantly elevated in stable angina, many previous studies recorded that serum IL-6 levels were elevated significantly in patients with stable angina in comparison with control [48-51]. The IL-6 genetic deficiency enhanced atherosclerotic plaques induced by pathogen and/or diet [52]. While, the lipids and other vascular risk were beneficially modified with the clinical using of tocilizumab, the IL-6 receptors blocker [53]. IL-6, which is largely produced by mononuclear cells, and may affected the initiation and development of coronary artery disease via a number of mechanisms. It increased blood viscosity, platelet counts and accelerated fibrinogen deposition [54].

The current study also showed that the serum TNF-á level was increased significantly in stable angina compared with control. The same results were previously recorded by many authors [55-56]. In atherosclerosis, Th cells secrete large amounts of TNF-á and promoted the progression of atherosclerosis and plaque enlargement [57]. Many TNF-á inhibitors suppressed the development of atherosclerosis [58].

The significant elevation of IL-1â in our study was in agreement with many previous studies [51, 59-60]. IL-1â is released during ischemia and triggered neutrophil infiltration into the myocardium. After reperfusion, under the synergistic action of IL-1â with other cytokines and complements, neutrophils are subsequently activated and interact with endothelial cells, generating reactive oxygen species (ROS) and aggravating myocardial injury [61]. The ischemic damage was followed by remodeling and healing process that was characterized by a potent inflammatory response. In injured tissue, the inflammatory response was amplified by cryopyrininflammasome. Caspase-1, cleaves pro-IL-1â once the inflammasome has been triggered by injury. Furthermore, leukocyte chemotaxis was induced by IL-1â in injured myocardium and promoted chemokine and cytokine production, and enhanced the inflammatory response [62].

The serum IL-9 level was also significantly increased in stable angina in the current study. Elevation of plasma IL-9 has been recorded in ischemic heart diseases and acute ischemic stroke [63-64]-64]. It was also increased significantly in coronary atherosclerosis, with elevation of the IL-9R expression and IL-9 level in the atherosclerotic plaques [65]. It was one of cytokines which involved in the pathophysiology of atherosclerosis. Treatment with IL-9 exacerbates atherosclerosis, while, neutralization of IL-9 prevents atherosclerosis development. IL-9 enhances VCAM-1 expression in aortic endothelial cells through a STAT3-dependent pathway, while, neutralization of VCAM-1 protected from the increasing of plaque size induced by IL-9 [66].

In general, elevation of the serum cytokines may reflect the severity of inflammation in atheroseclerosis, it represented part of the pathogenesis of unstable angina and is positively correlated with the course of clinical and hemodynamically significant coronary artery disease [49-50, 67].

CONCLUSIONS

Early diagnosis remains the main principles in the treatment of stable angina. This study aims to investigate the benefit of additional biochemical markers in diagnosis of stable angina pectoris. The study revealed that hs-CRP, H-FABP,

PCT, Lp-PLA2 and cytokines are sensitive, and can serve as diagnosis indicators of stable angina pectoris. The elevation of some cytokines in patients of stable angina may open the door for subsequent studies to investigate the participation of cytokines in pathogenicity of the disease, and to study their suppression as a new therapeutic approach.

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Conflict of Interest

There is no conflict of interest.

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