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Serum Levels of CRP, H-FABP, PCT, Lp-PLA2 and Cytokines in Relation to Weight, Blood Pressure and Glycemic State in Patients with Stable Angina

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Abstract

Background: Ischemic heart disease (IHD) is one of the leading causes of death and disability worldwide. It is an imbalance between oxygen demand and supply. The disease is caused by decline of blood supply to the heart muscle as a result of coronary occlusion.

Objectives: This study was designed to determine the possible new biomarkers in diagnosis of stable angina to facilitate faster therapeutic programs and also to study the cytokines roles in pathophysiology of stable angina.

Methods: The current case-control research was performed on 86 stable angina patients, and 86 healthy subjects in Nasiriyah Heart Center. Serum Trop I, MYO, CK-MB, H-FABP, PCT, Lp-PLA2 and CRP hs, were assayed by immunoassay. Lipid profile and blood sugar and detected by photometric assays. Serum IL-9, TNF-α and IL-1β were determined by ELISA and IL-6 by immunoassay.

Results: The study revealed that serum troponin I level was insignificantly changed in stable angina. However, compared with control, significant increase in the level of myoglobin, CK-MB, hsCRP, Lp-PLA2, PCT and H-FABP, were recorded in the stable angina patients. The patients also showed significant increase in the serum levels of total cholesterol, triglycerides, VLDL and LDL, while HDL was significantly decreased. Significantly elevation of serum levels of TNF-α, IL-9, IL-6 and IL1β were also noted in the patients in comparison with healthy control. According to these investigations, there were many variations in the levels of these biomarkers when the patients of stable angina divided according to their weight, blood pressure and glycemic state.

Conclusion: According to the results we conclude that, in addition to cTnI, CK-MB and MYO several other markers such as Lp-PLA2, hs-CRP, PCT and H-FABP are sensitive, and can utilized as indicators in diagnosis of stable angina.

Keywords: **Stable angina, IHD, Cytokines, Biomarkers, Lipid profile**

Introduction: Ischemic heart disease (IHD) is the leading cause of death and disability, with an estimated prevalence of one in six in Western countries [1].

IHD can be viewed as an imbalance between the demand and supply of oxygen, the most common cause is the reductions in the blood supply to the cardiac muscle as a result of coronary artery disease (CAD) [2-3].

ACS (unstable angina and myocardial infarction) was consider as diagnostic challenge to the clinicians [4]. Missing the diagnosis of ACS increased the morbidity and mortality that can be prevented with appropriate treatment [5]. Elevated levels of troponin I, creatine kinase and myoglobin, are the main biomarkers for diagnosis of ischemic heart disease [6]. Using of this combination of biomarkers facilitate rapid exclusion of acute myocardial infarction. Myoglobin elevation is advantageous because it occurs 1 to 2 hours after the symptoms onset, and the clinical trials revealed its sensitivity in diagnosing myocardial infarction in the first hours of presentation [7]. However, there are limitations regarding using of myoglobin alone. Myoglobin is less specificity for cardiac necrosis in patients complain trauma of skeletal muscle and renal failure [8]. In addition, serum myoglobin increases and decreases rapidly in acute myocardial infarction, a single determination may be normal in patients with early onset and those presenting within 24 hrs of the symptoms onset [9]. cTnI and CK-MB, on the other hand, appeared 3-6 hrs after the onset of symptoms and their elevation was continued respectively for 7-10 days and 24-36 hours [10].

Heart fatty acid binding protein (H-FABP) might be a beneficial marker in early diagnosing ischemic heart diseases according to many trials. It is small cytoplasmic protein abundant in tissues characterized fatty acid metabolic activity, such as heart. It is essential for homoeostasis of myocardium, since 50-80% of the heart energy was generated by lipid oxidation and H-FABP facilitate transport of insoluble fatty acids. After myocardial damage, H-FABP diffuses through the interstitial space, faster than troponins and appears in the blood 90 minutes after the symptoms onset, reaches the peak level within 6 hrs. It also gave prognostic prediction better than troponins in acute myocardial infarction [11-12].

Inflammatory biomarkers, such as hs-CRP, chemokines and cytokines, play many roles in the initiation and progression of coronary artery disease. The levels of hs-CRP are markedly higher in acute coronary syndrome with unstable angina and adversely affected the prognosis of coronary artery disease [13]. Furthermore, lipoprotein-associated phospholipase A2 (Lp-PLA2) has been proposed as an inflammatory marker of cardiovascular disease. Procalcitonin has also been implicated as a biomarker of early atherosclerosis [14].

The inflammatory events played important roles in the initiation and progression of ischemic heart disease. The experimental and clinical studies confirmed that the cardiovascular diseases were associated with inflammatory events [15-17]. Different heart diseases, including atherosclerosis, coronary heart disease and congestive heart failure, were associated with elevated levels of proinflammatory cytokines such as IL-6, IL-1β, interferon-γ and TNF-α [18].

These cytokines played a potential role in the atherosclerotic plaque formation[19]. Our study aims to evaluate the serum concentrations of additional biomarkers and cytokines (interleukin-1β, -6, -9) and tumor necrosis factor-(α) in stable angina patients and also to clarify their correlation with the disease risk factors.

Patients and Methods: This study is case-control trial carried out on Eighty six stable angina patients, in Heart Center of Nasiriyah from Oct. 2021 to Oct. 2022. 86 age-matched healthy subjects were taken as serve as a control group. Patients with myocardial infarction, unstable angina, and any other heart disease, and those taking statins drugs were excluded from the trial. Blood samples were collected and serum CK-MB, Trop I, MYO, CRP hs, H-FABP, Lp-PLA2 and PCT were assayed by immunoassay (Nipigon Health corp.). Blood sugar (Randox) and serum triglycerides, total cholesterol (Biolabo), HDL-c, LDL-c and VLDL-c (Cobas) were investigated by using photometric assays. Serum IL-6 was measured by immunoassay (ECL) and serum IL-9, IL-1β and TNF-α were determined by ELISA (Wuhan Fine Biotech Co.), with the using of operational manuals.

Thi-Qar Health ethical committee has authorized the research, and an informed consents was received from all members.

The differences between patients and healthy subjects were analyzed with using of t- test (SPSS, version 26). P-value 0.05 or lower, was considered as significant.

Results: The results revealed that there was no significant changes in the level of troponin I in stable angina group in comparison with control group (0.0210±0.0034 vs 0.0200±0.0038 ng/ml, P=0.054). However, in patients with stable angina, serum level of 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), PCT (0.056±0.05 vs 0.026±0.02 ng/ml, P<0.01), Lp-PLA2 (127.6±19.2 vs 105.0±22.7 ng/ml, P<0.01), hsCRP (28.90±5.50 vs 7.35±3.51 nmol/l, P<0.01), and H-FABP (6.59±2.71 vs 4.90±1.43, ng/ml, P<0.001) were significantly elevated. The serum level of TNF-α (5.2±4.6 vs 2.6±1.7 ng/ml, 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

Table 1: Biomarkers, cytokines and lipid profile in patients with stable angina in comparison with the healthy control group.

Parameters	Patients Group	Control Group	P. value
Trop I (ng/ml)	0.0210±0.0034	0.0200±0.0038	(NS)
MYO (ng/ml)	62.02±8.40	49.40±6.00	<0.01
CK-MB (ng/ml)	3.02±1.46	2.15±1.91	<0.001
Lp-PLA2 (ng/ml)	127.6±19.2	105.0±22.7	<0.01
hsCRP (nmol/l)	28.90±5.50	7.35±3.51	<0.01
H-FABP (ng/ml)	6.59±2.71	4.90±1.43	<0.001
PCT (ng/ml)	0.056±0.05	0.026±0.02	<0.01
IL-6 (Pg/ml)	7.9±6.8	4.3±2.2	<0.001
IL1β (nmol/l)	11.5±3.6	4.6±3.2	<0.001
IL-9 (Pg/ml)	3.7±2.5	2.5±1.6	<0.01
TNF-α (ng/ml)	5.2±4.6	2.6±1.7	<0.001
LDL (mg/dl)	90.7±8.5	79.5±28.5	< 0.05
VLDL (mg/dl)	38.3±14.5	27.1±11.3	<0.01
HDL (mg/dl)	36.0±10.2	43.0±9.2	<0.01
Total cholesterol (mg/dl)	171.1±24.5	161.2±25.1	< 0.05
Triglycerides (mg/dl)	184.7±37.7	131.8±27.3	<0.001

pg/ml, P<0.01), IL1β (11.5±3.6 vs 4.6±3.2 nmol/l, P<0.001), were also significantly increased in stable angina group in comparison with healthy control. The serum level of triglycerides (184.7±37.7 vs 131.8±27.3, mg/dl, P<0.001), total cholesterol (171.1±24.5 vs 161.2±25.1 mg/dl, P< 0.05), LDL-c (90.7±8.5 vs 79.5±28.5 mg/dl, P< 0.05) and VLDL-c (38.3±14.5 vs 27.1±11.3 mg/dl, P<0.01), were significantly higher and serum HDL-c was significantly lower (36.0±10.2 vs 43.0±9.2 mg/dl, P <0.01) in stable angina group compared with control (table 1).

When the patients of stable angina were subgrouped according to weight, blood pressure and glycemic state, hs CRP was significantly elevated in diabetic normotensive, normal weight (15.50±6.92 nmol/L, P<0.01), diabetic normotensive overweight (18.40±10.00 nmol/L, P<0.01), diabetic, hypertensive overweight (41.50±13.00 nmol/L, P<0.001), nondiabetic normotensive overweight (51.80±13.70 nmol/L, P<0.001) and nondiabetic hypertensive overweight (17.30±2.96 nmol/L, P<0.01) compared with control (7.35±4.17 nmol/L). H-FABP showed significant elevation only in diabetic normotensive normal weight (6.06±2.18 ng/ml, P<0.05), diabetic normotensive overweight (7.40±5.79 ng/ml, P<0.05) and diabetic hypertensive overweight (7.73±4.57 ng/ml, P<0.05) compared with control (4.89±1.43 ng/ml), while it showed no significant variations in nondiabetic normotensive overweight and non diabetic hypertensive overweight subgroups. Serum CK-MB was significantly increased in diabetic normotensive normal weight 3.60 ±1.60 ng/ml, P<0.05) and diabetic normotensive overweight patients (3.26±1.65 ng/ml, P<0.05) in comparison with control (2.15±1.91 ng/ml), while, no significant differences were noted in diabetic hypertensive overweight, nondiabetic normotensive overweight and nondiabetic hypertensive overweight subgroups. Trop I showed no significant changes in all subgroups stable angina patients in comparison with control. MYO

showed significant elevation only in diabetic normotensive normal weight (67.4±21.7 ng/ml, P<0.05), diabetic normotensive overweight (57.9±19.1 ng/ml, P<0.05) and diabetic hypertensive overweight (60.3±16.5 ng/ml, P<0.05) in comparison with control (49.4±16.0 ng/ml), while it showed no significant variations in nondiabetic normotensive overweight and non diabetic hypertensive overweight subgroups. Lp-PLA2 and PCT levels were significantly elevated in all subgroups of stable angina patients compared with control (table 2).

Table 2: The levels of serum biomarkers in stable angina patients in relation with weight, pressure and glycemic state.

Groups \ Parameters		No	hs CRP (nmol/L)	H-FABP (ng/ml)	CK-MB (ng/ml)	Trop I (ng/ml)	MYO (ng/ml)	Lp-PLA2 (ng/ml)	PCT (ng/ml)
Control		86	7.35±4.17a	4.89±1.43a	2.15±1.91a	0.02004±0.00384a	49.40±16.00a	105.0±22.70a	0.0261±0.0215a
Subgroups of patients	Diabetic, normotensive, normal weight	11	15.50±6.92b	6.06±2.18b	3.60±1.60b	0.02160±0.00157a	67.4±21.7b	120.27±26.59b	0.0560±0.0839b
	Diabetic , normotensive, overweight	28	18.40±10.00b	7.40±5.79b	3.26±1.65b	0.02086±0.00143a	57.9±19.1b	127.2±33.00c	0.0317±0.0240b
	Diabetic, hypertensive, overweight	27	41.50±13.00c	7.73±4.57b	2.83±1.30a	0.02061±0.00140a	60.3±16.5b	133.12±31.30c	0.04360±0.0445b
	Nondiabetic, normotensive, overweight	8	51.80±13.70c	5.98±2.56a	2.55±0.62a	0.02100±0.00141a	53.40±19.80a	120.22±34.70b	0.0900±0.04800c
	Nondiabetic, hypertensive, overweight	12	17.30±2.96b	5.78±1.34a	2.83±0.18a	0.02100±0.00141a	71.11±13.10c	137.30±65.70c	0.0325±0.0318b

Similar letter horizontally means not significant

Serum IL-6 showed no changes in diabetic normotensive overweight (5.93±2.57 Pg/ml), diabetic hypertensive overweight (6.60±3.38 Pg/ml), but it was significantly elevated in diabetic normotensive overweight (8.83±5.79 Pg/ml, P<0.01), nondiabetic normotensive overweight (7.43±1.81 Pg/ml, P<0.05) and nondiabetic hypertensive overweight (7.99±0.41 Pg/ml, P<0.05) compared with control (4.33±2.23 Pg/ml). Serum IL-9 showed only significant changes in nondiabetic normotensive overweight (0.884±1.03 Pg/ml, P<0.01) and nondiabetic hypertensive overweight (1.20±1.08 Pg/ml, P<0.05) compared with control (2.52±1.61Pg/ml). Similarly, IL-1β was elevated only in nondiabetic, hypertensive overweight (2.17±2.32 nmol/l, P<0.05) compared with control (4.62±3.23 nmol/l). TNF-α was significantly increased in diabetic normotensive normal weight patients (5.82±2.23 ng/ml, P<0.01) and diabetic normotensive overweight (4.64±2.81 ng/ml, P<0.05) in comparison with control (2.64±1.70 ng/ml), and showed no changes in other groups of patients with stable angina (table 3).

Table 3: The levels of serum cytokines in stable angina patients in relation with weight, blood pressure and glycemic state.

Parameters / Groups		No	IL-6 (Pg/ml)	IL-9 (Pg/ml)	IL-1β (nmol/l)	TNF-α (ng/ml)
Control		86	4.33±2.23a	2.52±1.61a	4.62±3.23a	2.64±1.70a
Subgroups of patients	Diabetic normotensive, normal weight	11	8.83±5.79b	2.80±1.56a	5.53±2.84a	5.82±2.23b
	Diabetic , normotensive, overweight	28	5.93±2.57a	2.40±1.89a	5.96±4.68a	4.64±2.81b
	Diabetic, hypertensive, overweight	27	6.60±3.38a	2.46±2.38a	3.95±4.92a	3.20±1.91a
	Nondiabetic, normotensive, overweight	8	7.43±1.81b	0.88±1.03c	0.311±0.63c	2.60±2.37a
	Nondiabetic, hypertensive, overweight	12	7.99±0.41b	1.20±1.08b	2.17±2.32b	3.76±1.51a

Similar letter horizontally means not significant

Serum triglycerides was significantly (P< 0.01) elevated in all subgroups of patients with stable angina. Serum cholesterol was elevated only in diabetic hypertensive overweight and nondiabetic hypertensive overweight subgroups. LDL was elevated significantly in diabetic normotensive normal weight and nondiabetic normotensive overweight subgroups only, while VLDL was significantly increased in all subgroups of patients with stable angina. HDL was significantly declined in diabetic normotensive normal weight and nondiabetic normotensive overweight subgroups in comparison with control group. All diabetic subgroups of stable angina patients revealed significant increase in the level of serum glucose in comparison with nonbiabetic subgroups and control group (table 4).

Table 4: Lipid profile in stable angina patients in relation with weight, blood pressure and glycemic state.

Groups \ Parameters		No	TG (mg/dl)	CHOL (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	Glucose (mg/dl)
Control		86	131.8±47.34a	161.2±25.06a	43.01±9.207a	79.51±28.55a	27.08±11.33a	99.00±9.10a
Subgroups of patients	Diabetic, normotensive, normal weight	11	177±45.4b	169±31.1a	31.56±9.735b	84.40±21.60a	35.70±11.27b	160.0±46.6b
	Diabetic, normotensive, overweight	28	192±39b	170.0±33.44a	38.46±10.26a	84.86±30.36a	40.54±16.57b	162±40.6b
	Diabetic , hypertensive, overweight	27	184.2±57.81b	174.6±33.63b	36.00±10.20a	96.53±37.86b	36.21±10.03b	186±44.0c
	Nondiabetic, normotensive, overweight	8	193.1±46.36b	167.5±17.73a	34.50±7.819b	102±41.2b	43.50±15.89c	88.13±8.839a
	Nondiabetic, hypertensive, overweight	12	177.5±102.5b	175.0±7.071b	39.50±13.44a	86.00±33.94a	35.5±20.5b	90.00±7.071a

Similar letter horizontally means not significant

Discussion:

Coronary artery disease (CAD) remains an important cause of morbidity and mortality worldwide. Stable angina patients may showed an unexpected course, thus new diagnostic markers are still required [20].

CRP was markedly increased in all subgroups of stable angina patients (diabetic normotensive normal weight, diabetic normotensive overweight, diabetic, hypertensive overweight, nondiabetic normotensive overweight and nondiabetic hypertensive overweight) compared with control. These results were in agreement with the results recorded by Jeong et al. [21]. However, inflammation played a role in initiation and progression of atherogenesis. CRP was increased in patients with stable angina, but its concentration didn't reach the concentation recorded in MI patients [21]. H-FABP showed significant elevation only in diabetic normotensive normal weight, diabetic normotensive overweight and diabetic hypertensive overweight compared with control, while it showed no significant variations in nondiabetic normotensive overweight and non diabetic hypertensive overweight subgroups. These findings were in agreement with previous study carried out by Beysel et al. [22].

A multicenter, prospective study was performed on patients with ischemic heart disease to determine, the efficacy of using serum H-FABP level in diagnosis and prognosis, H-FABP

appeared as a potential prognostic biomarker. Its high level was associated with increase of the hospital readmission and mortality [23-27].

Serum CK-MB was significantly increased in diabetic normotensive normal weight and diabetic normotensive overweight patients compared with control, while, no significant changes were recorded in diabetic hypertensive overweight, nondiabetic normotensive overweight and nondiabetic hypertensive overweight subgroups, the same results were recorded by Mackay [28] and Sun et al. [29]. Trop I and CK-MB were the biomarker of choice in diagnosing myocardial infarction, according to the European Society of Cardiology and American College of Cardiology [30]. Determination of CK–MB within 24 hrs of the symptoms onset, showed a 98% predictive value [31]. Trop I showed no significant changes in all subgroups of stable angina patients in comparison with control in this trial, which was in consistent with previous trials [32-33]. However, its level was increased and utilized as diagnostic biomarker even with normal CK-MB level, in myocardial infarction [34].

MYO showed significant elevation only in diabetic normotensive normal weight, diabetic normotensive overweight and diabetic hypertensive overweight compared with control, while it showed no significant variations in nondiabetic normotensive overweight and non diabetic hypertensive overweight subgroups of patients with stable angina. Myoglobin is elevated moderately in stable angina. However, it beneficial for exclusion of acute MI, but is less beneficial if it estimated later on [35-36].
Lp-PLA2 was significantly elevated in all subgroups of stable angina patients compared with control. Many trials showed that the level of Lp-PLA2 was increased significantly in patients with stable angina. Several researches confirmed that Lp-PLA2 enhanced atherosclerosis promotion by different pathways [37-39]. High Lp-PLA2 level in stable angina patients correlated with poor coronary function. It linked between endothelial dysfunction and inflammatory changes. These trials suggested the using of Lp-PLA2 as a biomarker for determination of the risk level in coronary artery disease [40-41].

Serum triglycerides was significantly elevated in all subgroups of patients with stable angina. Serum cholesterol was elevated only in Diabetic hypertensive overweight and nondiabetic hypertensive overweight subgroups. LDL was elevated significantly in diabetic normotensive normal weight and nondiabetic normotensive overweight subgroups only, while VLDL was significantly increased in all subgroups of patients stable angina. HDL was declined significantly in diabetic normotensive normal weight and nondiabetic normotensive overweight subgroups in comparison with control group. In light of other studies hyperlipidemia and elevation of atherogenic index represented the high risk factor associated with atheroseclerosis. The total cholesterol, triglycerides, LDL and VLDL cholesterols were found to be strongly associated with severity of ischemic heart disease [42-43].

PCT was elevated significantly in all subgroups of stable angina (except nondiabetic normotensive overweight subgroup) in comparison with control. These results were in agreement with that noted by Ling *et al*. [44]. PCT levels were correlated with the extent of

atherosclerosis and even associated with an adverse outcome [45-46]. The high PCT level within 48 hrs of admission usually associated with elevation of early and 6 month mortality[47].

Our research revealed that, TNF-α, IL-6, IL-1β and IL-9, were elevated in some subgroups of patients. It was also recorded previously that the IL-6 serum level was significantly increased in stable angina patients compared to controls [48-50]. IL-6 might influence the ischemic heart disease development by many mechanisms. It increased platelet counts, blood viscosity, and fibrinogen deposition was accelerated [51]. Elevation of TNF-α was also recorded previously [52-53]. In atherosclerosis, huge amounts of TNF-α was secreted by Th cells, TNF-α enhanced the atherosclerosis progress and the enlargement of the plaque [54], while using of inhibitors of TNF-α can suppress atherosclerosis development [55].

The significant increase of IL-1β in our study was in consistent with many studies [56-57]. IL-1β is released during ischemia and enhanced infiltration of neutrophil into the myocardium. Neutrophils were subsequently activated, under the synergistic effect of other cytokines, interacted with endothelial cells, produced reactive oxygen species and aggravated myocardial damage [58]. The ischemic injury is followed by healing processes manifested by a strong inflammatory response [59].

An increase of serum IL-9 was noted in patients with coronary artery diseases [60-61], with elevation of the IL-9 and IL-9R expression in the atherosclerotic plaques compared with healthy controls [62]. IL-9 was part of atherosclerosis pathophysiology. Using of IL-9 exacerbated atherosclerosis, which can prevented by IL-9 neutralization. IL-9 enhanced the expression of VCAM-1 in the endothelial cells of the aorta via STAT3-dependent pathway, while, by IL-9 induced increasing of the size of the plaque can be prevented by neutralization of VCAM-1 [63]. Measuring of the serum cytokines indicated that the inflammatory conditions represented part of the pathophysiological events of ischemic heart disease and correlated with the course of clinical significant of the coronary artery disease [49-50, 64].

Conclusion:

According to the results we can conclude that, in addition to cTnI, MYO and CK-MB several other markers such as Lp-PLA2, hs-CRP, PCT and H-FABP are sensitive, and can used as indicators in diagnosis of stable angina.

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