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A study of high sensitivity c-reactive protein ,fibrinogen, troponin I and lipid profile in patients with acute myocardial infarction

دراسة بروتين ج المتفاعل عالي الحساسية,الفايبرينوجين,تروبونين آي وصور الدهون في مرضى إحتشاء عضلة القلب الحاد

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Abstract:

This study was conducted on 70 patients with acute myocardial infarction (52 males ,18 females) and 30 (22 males,8 females) apparently healthy subjects were taken as control group from October 2010 till August 2011.Blood collected in coronary care unit at Merjan Teaching Hospital in Hilla city within 12 hours of myocardial infarction attack and all the subjects were fasting at time of sample taking. The patients were diagnosed as having AMI depending on positive troponin I tests ECG finding plus clinical features of AMI, The sera obtained from the patients were used to determine the effect of AMI on high sensitivity c-reactive protein (hsCRP),fibrinogen, troponin I, total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides (TGs),very low density lipoprotein-cholesterol (VLDL-C), and low density lipoprotein-cholesterol (LDL-C) concentrations. The results show a highly significant increase in high sensitivity c-reactive protein (hsCRP), fibrinogen, troponin I, total cholesterol, triglycerides, very low density lipoprotein-cholesterol and low density lipoprotein-cholesterol concentration ($p<0.001$), while highly significant decrease in high density lipoprotein-choleterol($p<0.001$) in sera of patients group compared to control group, also the results of this study showed positive significant correlation ($r = 0.30$, $p<0.01$) between increment of hsCRP and fibrinogen in patients group on other hand positive but not significant correlation ($r =0.044$, $p>0.05$) of the above two parameters in control group.

Conclusion: Acute myocardial infarction associated with elevation of acute phase proteins. .HsCRP and fibrinogen combination can be used in prediction of early events of atherosclerosis and post infarction complication and how to prevent them. Lipid profile and quantitive determination of cardiac troponin I are always advisable in post AMI.

الخلاصة:

أجريت هذه الدراسة على سبعين مريض مصاب بإحتشاء العضلة القلبية الحاد (اثني وخمسين ذكر وثمانية عشر أنثى) وعلى ثلاثين شخص سوي(اثني وعشرين ذكر وثمان إناث)كمجموعة سيطرة في فترة امتدت من تشرين الأول سنة ٢٠١٠ حتى آب سنة ٢٠١١. تم الحصول على عينات الدم من المرضى في وحدة إنعاش القلب في مستشفى مرجان التعليمي في مدينة الحلة خلال اثني عشر ساعة من حصول إحتشاء العضلة القلبية الحاد,علما إن الأشخاص في كلتي المجموعتين (المرضى ومجموعة السيطرة) كانوا في حالة صيام وقت اخذ عينات الدم. تم تشخيص حالة المرضى اعتمادا على إختبارالتروبونين آي الموجب و تخطيط القلب الكهربائي بالاضافة للميزات الطبية لإحتشاء العضلة القلبية الحاد.

مصول الدم التي تم الحصول عليها استخدمت لدراسة تأثيرإحتشاء عضلة القلب الحاد على تراكيز بروتين ج المتفاعل عالي الحساسية والفايبرينوجينوالتروبونينآيوعلى صورالدهون لدى المرضى.

أظهرت نتائج هذه الدراسة زيادة معنوية عالية **($p<0.001$)** في معدلات تراكيز بروتينج المتفاعل عالي الحساسية,الفايبرينوجين,التروبونين آي ,الكوليستيرول الكلي,الكليسيريدات الثلاثية,البروتينات الدهنيه واطئه الكثافة جدا

والبروتينات الدهنية واطئة الكثافة ونقصان معنوي ملحوظ **(p<0.001)**في البروتينات الدهنية عالية الكثافة في مصول مرضى إحتشاء عضلة القلب الحاد حين مقارنتها بمجموعة السيطرة.كما أظهرت نتائج هذه الدراسة وجود ارتباط ايجابي و ملحوظ في معدلات بروتين ج عالي الحساسية والفايبرينوجين **(r = 0.30 ,p<0.01)** لدى مرضى إحتشاء العضلة القلبية ووجود ارتباط ايجابي غير ملحوظ **(r =0.044 , p>0.05)** في مصول مجموعة السيطرة .إن نتائج هذه الدراسة تثبت ارتباط وتزامن ارتفاع نسب بروتينات الطور الحاد مثل بروتين ج المتفاعل عالي الحساسية والفايبرينوجين مع حصول إحتشاء العضلة القلبية الحاد وإمكانية استخدامهما كوسيلة للتنبؤ بالمضاعفات المستقبلية وكيفية تفاديها كما إن قياس نسب تروبونين آي وصور الدهون من الاختبارات التي يوصى بها حين حصول الاحتشاء الحاد للعضلة القلبية.

Introduction:

Acute myocardial infarction (AMI) is a clinical state induced by the thrombus formation following the disruption of unstable atherosclerotic plaque[1]. Atherosclerosis, the main cause of myocardial infarction is an inflammatory disease in which immune mechanism interact with metabolic risk factors to initiate, propagate and activate lesions in the arterial tree of the heart [2]. Classical symptoms of acute myocardial infarction include sudden chest pain (typically radiating to the left arm or left side of the neck), shortness of breath, nausea, vomiting, palpitations, sweating, and anxiety[3]. Clinical features are not enough for perfect diagnosis of AMI,ECG changes, echocardiography and serum cardiac markers are more accurate for diagnosis of cardiac damage [4].The major risk factor for AMI are hyperlipidemia [5], diabetes mellitus[6] hypertension[7], smoking [8], male gender[9]and family History of coronary heart disease[10]. C-reactive protein(CRP) is an acute phase reactant that responds as a sensitive, though nonspecific, marker of systemic inflammation. It`s synthesized by the liver in response to stimuli from circulating inflammatory cytokines[11]. An expanding body of research now indicates that CRP likely plays a direct, active inflammatory role in blood vessels leading to development of atherosclerosis[12].New researches show that in the patients with manifested chronic atherosclerotic disease ,there is a continuous need for refinement of prognosis by using some of the emerging biomarkers, one of these biomarkers, CRP measured by high-sensitivity assays(hsCRP) [13]. Since the inflammation plays a major role in all stages of atherosclerosis, from lesion initiation to plaque rupture and ultimately, the clinical thrombotic complication , CRP will increase in all these stages and can be measured in high sensitivity assays to evaluate degree of atherosclerosis and its expected future complications [14]. In a recent scientific statement, the centers for disease control and prevention and American Heart Association recommended the following interpretation of hs-CRP results: <1 mg/L low risk,1-3mg/L average risk,> 3mg/L high risk [15]. Fibrinogen is an acute phase protein synthesized by liver, in addition to that it play important role in coagulation cascade[16]. Fibrinogen is well known risk factor for AMI and stroke[17][18], so high-levels of fibrinogen is one of the dangerous factors contributing to coronary heart diseases [19][20] [21].

.Cardiac specific troponin is a regulatory protein that regulates the contractile apparatus of striated muscle of the heart, this apparatus is made from parallel arrays of thick and thin filaments organized into sarcomeres, contraction is attributable to the sliding of thick filaments past thin filaments that leads to tension producing cross bridges between actin and myosin and force generation. This process is controlled by sarcoplasmic Ca^{2+} and regulated by troponin and tropomyosin located in the thin filament[22]. Although there are several biomarkers of cardiac damage, troponin I has emerged as the indicator of choice for the detection of cardiomyocyte injury [23][24][25] .For accurate diagnosis of patients with suspected acute coronary syndrome, blood levels of troponin must be elevated in a clinical setting of acute myocardial infarction [26]. Cardiac specific troponin I is used as an aid in diagnosis of myocardial infarction since it becomes elevated in the blood approximately 4-8 hours following myocardial injury or necrosis reaches its peak 12 hours and remain elevated for 3-10 days[27]. The major lipids present in the plasma are fatty acids, TGs, cholesterol and phospholipids, are all transported in plasma as lipoprotein particles chylomicrons (CM), very low density lipoprotein-cholesterol (VLDL-C), intermediate density lipoprotein-cholesterol (IDL-C), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) [28].

Patients and Methods:

The study was conducted over a period of eleven months from October 2010 till August 2011. Samples collected in coronary care unit in Merjan Teaching Hospital in Hilla city, all the patients were fasting at time of sample taking. The tests were performed in the laboratory of biochemistry department in college of Medicine/Babylon University. This study included seventy patients with AMI whom had positive troponin I tests, ECG with ST-segments elevation in addition to clinical features of AMI and thirty were taken as control group. The patients group included (52 men and 18 women), aged (37-80) year with mean ± SD of 58.46±10.8 year. The control group included (23 men and 7women) apparently healthy individuals aged 28-72 year with mean ± SD 54.23±12.6 year, they were not smoker, free of DM, hypertension and family history of IHD. Venous blood samples were drawn from AMI patients within 12 hours of myocardial infarction attack. Serum hsCRP concentration was determined by DRG International kit (USA). Serum Fibrinogen was determined by Spinreact kit (Spain), Serum Troponin I was determined by VIDAS Troponin I Ultra(TNIU)(France) .Serum total cholesterol, triglycerides and HDL-cholesterol concentration were determined by Biolabo SA kit (France). VLDL-cholesterol concentration was calculated by dividing triglycerides value by 2.19 [29]. LDL-cholesterol concentration was calculated by using Friedewald equation [30].

$$\text{LDL-C (mmol/L)} = \text{Total-choleterol-HDL-C} - \frac{TG}{2.22} \qquad TG/2.19$$

Results:

In this study, we found that all patients with AMI had at least one of the risk factors as shown in table(1):

Table (1): The rates of major risk factors among patients group.

Risk Factor	No. of Patients	Percent(%)
Smoking	54	77.1
Hypertension	42	60
Diabetes Mellitus	40	57.1
Family history of IHD	35	50

The results showed a high significant increase in (total cholesterol, triglycerides, VLDL and LDL concentration),while a high significant decrease in HDL concentration in sera of AMI group compared with those of the control group as was shown in table(2)

Table (2): Serum total cholesterol, HDL, TG, VLDL and LDL concentration in AMI patients and control group.

Parameter(mmol/L)	Control(n=30)	Patients(n=70)	P-value
Total Cholesterol	3.9 ± 0.43	5.0 ± 0.99	P< 0.001
HDL Cholesterol	1.3 ± 0.1	1.0 ± 0.6	P< 0.001
Triglycerids	0.8 ± 0.3	1.6 ± 0.6	P< 0.001
VLDL-Cholesterol	0.4 ±1.0	0.7 ± 0.3	P< 0.001
LDL-Cholesterol	2.3 ± 1.0	3.3 ± 0.3	P< 0.001

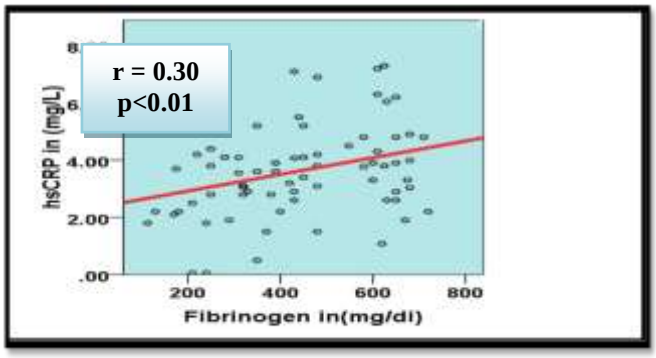
HsCRP, Fibrinogen and Troponin I concentrations were measured in sera of seventy patients and thirty healthy (control group). The results showed a significant increase in above parameters

concentrations in sera of patients group compared with those of the control group as was shown in table (3) .

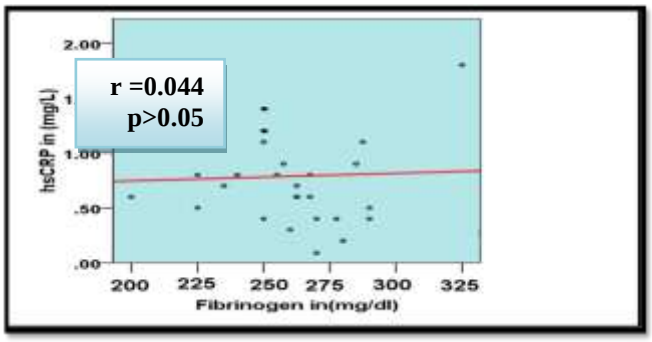
Table (3): Serum hsCRP, Fibrinogen, Troponin I concentration in AMI patients and control group.

Parameter	Control(n=30)	Patients(n=70)	P-value
hsCRP (mg/L)	0.79 ± 0.4	3.6 ± 1.6	P< 0.001
Fibrinogen (mg/dl)	257.2±48.6	440.7±171.6	P< 0.001
TroponinI(µg/L)	0.003±0.002	22.8 ±3.34	P< 0.001

The results of linear regression analysis showed significant positive correlation (r = 0.30, p<0.01) in serum hsCRP concentration with fibrinogen concentration in AMI patients group, non significant positive correlation (r =0.044, p>0.05) between them in control group as was shown in figures (1) and (2).



Figure(1):The correlation of hsCRP and fibrinogen concentrations of patients group.



Figure(2):The correlation of hsCRP and fibrinogen concentrations of control group.

Smoking, hypertension, diabetes mellitus and family history of ischemic heart disease were the major risk factor for AMI and this in agreement with many studies[31].One of the major findings of the present study was the significant increase in serum hsCRP concentration observed in AMI group compared to those control group. The results of the present study were in agreement with. Liuzzo *et al*. study[32],this study measured hsCRP in 31patients with severe unstable angina, and 29 patients with AMI,20 out of 31 patients of unstable angina had level of hsCRP ≥3.0 mg/l,22 out of 29 patients with AMI had level of hsCRP ≥3.0 mg/l, in both groups patients with hsCRP≥ 3.0 mg/l were more prone to further ischemic episodes and death in comparison with those of hsCRP level less than 3.0 mg/l whom had good prognostic value. Several studies show that there`s association between AMI attacks and increment of hsCRP level and even use it as a marker of cardiac damage and as prognostic value, since the inflammation plays a major role in all stages of atherosclerosis ,from lesion initiation to plaque rupture and, ultimately, the clinical thrombotic complication [14],also the results of present study show a high significant increasing in fibrinogen concentration in sera of AMI patients group compared to those control group . Fibrinogen has a well-documented association with cardiovascular disease; plasma concentration of total fibrinogen show strong relationship with myocardial infarction [33].The results of this study are in agreement with Laurance P. study[34],this study show a strong relationship between myocardial infarction and increase level of fibrinogen ,the difference between the mean of plasma fibrinogen level of patients with AMI and control group can be explained by its behavior as an acute phase reactant which is increased after inflammation, tissue necrosis and any condition of Oxidative stress [35].The positive correlation between fibrinogen and hsCRP concentrations in sera of patients group referred to their nature as acute phase reactant proteins which can be increased in any condition induced by

inflammation or tissue damage or necrosis as myocardial infarction [36] ,and this in agreement with Louise J Maple *et al* study [37] which was set up to investigate correlation of hsCRP concentration with fibrinogen in sera of patients with AMI. The results of this study show marked and significant positive correlation between the two parameters above. The result of present study show significant increase in Troponin I level in sera of patients with AMI when compared with those control group ,presence of cardiac specific Troponin I in circulation is a very important predictor for presence of cardiac cells damage or necrosis[38]. ,These results in agreement with Monica *et al* study [39] which showed significant increase in cardiac specific Troponin I in sera of patients with AMI. The results of this study show significant increase in total cholesterol, triglycerides, LDL-Cholesterol, VLDL-Cholesterol and significant decrease in HDL-Cholesterol concentrations in sera of patients with AMI when compared with those of control group. Lipid profile is a useful tool in determining the risks of cardiovascular diseases. LDL-C is bad cholesterol being associated in deposition of cholesterol on the walls of arteries and HDL-C is good cholesterol being associated in carrying cholesterol out of the blood system and is more compact than LDL-C[40].

Conclusion:

1- Acute myocardial infarction associated with elevation of acute phase proteins as indicated by elevatedhighsensitivityc-reactiveproteinandfibrinogen.

2-In acute myocardial infarction elevation of hsCRP is positively correlated with elevation of fibrinogen concentrations ,this combination can be used for prediction of future complications and how to prevent them.

3-Both hsCRP and Fibrinogen can be used as new parameters in studying early events of atherosclerosis in families with history of CHD and taking early preventive measures.

4-Quantative determination of cardiac Troponin I concentration in sera of acute myocardial infarction patients is important for stratification of treatment and future preventive methods. 5-High total cholesterol, triglycerides, VLDL-cholesterol ,LDL-cholesterol and low HDL-cholesterol concentrations are important risk factors in the development of coronary artery disease so complete lipid profile is always advisable.

References

1- Mallinson.T:Myocardial Infarction, Focus on First Aids(2010); (15):15

2-Hannson GK .Atherosclerosis and coronary arthery disease.
N Eng J Med(2005) ; 352:1685–1695

3-Robert B. The World Health Report Changing History. World Health Organization. (2004) pp. 120–4.

4-Erhardt L, Herlitz J, Bossaert L. "Task force on the management of chest pain" Eur. Heart J. (2002); 23 (15): 1153–76

5-Ropert A.and Jane E.(2005).Hyperlipidemia(High Blood Fat).Clinical Endocrinology and Metabolism;90(30)

6-Hurst RT,LeeR W. Increase incidence of coronary atherosclerosis in type 2 diabetes mellitus:mechanism and managements.Ann.Inter. med. (2003)139;(10),804-834.

7-Mason PJ.,Mason JE.,Sesso HD. Blood pressure and risk of secondary cardiovascular events in women:the women`s antioxident cardiovascular study(WACS). (2004);190(13):1623-1629.

8-Rossi S. Australian Medicines Handbook 2006. Adelaide: 2006. ISBN 0-9757919-2-3

9-Wilson PW, Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. "Prediction of coronary heart disease using risk factor categories" .Circulation.(1998) ;97 (18): 1837–47.

10-Jishi F,Hudson PR,Williams CP.Troponin I ,laboratory issue,and clinical out comes in adirect general hospital:crossover study with traditional markers of AMI in atotal of 1990 patients,Clinical Pathology 2004:57:1027-32.

11-Thygesen K, Alpert JS, White HD. "Universal definition of myocardial infarction". Eur. Heart J. (2007)28 (20): 2525–38

12-Szmitko PE, Wang CH,Weisel RD, Almeida JR *et al*.New Marker of inflammation and endothelial cell activation. 2003; 108:1917-23.
13-Jilal I,Devaraj S,Venugobal SK.C-reactive protein:risk marker or mediator in atherothrombosis.hypertension.2004;44:6-11.
14-Libby P.Inflammation in atherosclerosis.Nature2002;420:868-74.
15-Pearson TA,Mensah GA,Alexandar RW,Anderson JL *et al*.Markers of inflamation and cardiovascular disease:application to clinical and public health practice:a statement for healthcare professional from the Centers for Disease Control and Prevention and the American Heart Association.Circulation 2003;107;499-511.
16-Ernst E.Fibrinogen as a cardiovascular risk factor interrelationship with infections and inflammation.European.Heart Journal1993;118:956-963.
17-Vangoor MP,Gornez-Garcia EB.Leebeek FW *et al*,The fibrinogen gene polymorphism and fibrinogen levels in ischemic strok:acase –control .study J Neural Neurosurgery psychatry.2005jan;76(1):12n 1-3
18-Danesh J,Lewwington S,Thompson SG,LoweGD,Collins R,kostis JB,*et al*.Plasma fibrinogen level and the risk of major CVD and nonvascular mortality:an individual participant meta-analysis.JAMA 2005:294;1799-809.
19-Liu Z.L. Ukomadu C. Fibrinogen-like protein 1, a hepatocyte derived protein is an acute phasereactant. Biochem. Biophys. Res. Commun. 2008, 365, 729–734.
20-Rijken, D.C.; Dirkx, S.P.G.; Luider, T.M.; Leebeek, F.W.G. Hepatocyte-derived fibrinogen related protein-1 is associated with the fibrin matrix of a plasma clot. Biochem. Biophys. Res.Commun. 2006; 350, 191–194.
21-Paraskevas K.I.; Baker, D.M.; Vrentzos, G.E.; Mikhailidis, D.P. The role of fibrinogen and fibrinolysis in peripheral arterial disease. Thromb. Res. 2008, 122, 1–12.
22- Adhikari BB and Wang K. Interplay of troponin- and myosinbasedpathways of calcium activation in skeletal and cardiacmuscle: the use of W7 as an inhibitor of thin filament activation. Biophys J (2004) 86: 359–370.
23. Jaffe AS. Babuin L . Troponin: the biomarker of choice for the detection of cardiac injury. Can Med Assoc J(2005) ; 173:1191–1202.
24. Apple FS. Myocardial infarction redefined: role of cardiac troponin testing. Clin Chem.(2001) ; 47:377–379
25. The Joint European Society of Cardiology/American College Cardiology Committee (2000) Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for theRedefinition of Myocardial Infarction. J Am Coll Cardiol36:959–969.
26-Douglas PS, O'Toole ML, Hiller WD, Hackney K, Reichek N.Cardiac fatigue after prolonged exercise. (1987) Circulation76:1206–1213.
27-Jishi F.,Hudson PR.,William CP.,Troponin I,laboratory issue,and clinical outcomes in direct general hospital:crossover study with tradtional marker of AMI in total of1990 patients,clinical pathology,2004;57:1027-32.
28- Smith A., Beckett G., Walker J. Disorders of plasma lipids and lipoproteins. Lectures Notes on Clinical Biochemistry. 6th ed. Blackwell Science. (2000); 101–104.
29- Godkar P. Textbook of Medical Technology, Clinical Biochemistry; Principles and Practice, Bhalani publishing house, Bombay. India. (1994). 223–225.
30-Carl A. and Edward R. (2006). Tietz text book of clinical Biochemistery and Molecular Diagnostics; 4th ed.Saunders company.pp 948.
31-World Health Organization. Non communicable Diseases and Mental Health, Geneva..Cardiovascular Disease Programme. Integrated Management of Cardiovascular Risk. Report of a WHO Meeting, Geneva, 2002: 35.
32- Liuzzo G,Biasucci LM,Gallimore JR.The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina.N Engl JMed 1 1994;331:417-24.

33- Wilson, T.L.; Campbell, G.A.; Mutharasan, R. Viscosity and density values from excitation level response of piezoelectric-excited cantilever sensors. Sens. A ctuat. A 2007, 138, 44–51.
34-Laurence P. Control of Fibrinogen Biosynthesis,Cardiovascular Eng(2010)10:78- 83
35- Carter AM, Catto AJ, Grant PJ: Association of the alpha-fibrinogen Thr 312 Ala polymorphism with post stroke mortality in subjects with atrial fibrillation. 1999; 99: 2423-2424.
36- Yan RT, Fernandes V, Yan AT, Cushman M, Redheuil A, Tracy R, Vogel-Claussen J, Bahrami H, Nasir K, Bluemke DA, et al.: Fibrinogen and left ventricular myocardial systolic function: The Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2010, 160(3):479-486.
37-Louise J Maple B, Joan C, Nirjhar N, Allison H and Kerin O. (Fibrinogen and associated risk factors in a high-risk population: urban indigenous australians, the druid Study) Journal: Cardiovascular Diabetology ISSN: 14752840 Year: 2010 Volume: 9 Issue: 1 Pages: 69-69. 38- Blumenschein TM, Tripet BP, Hodges RS and Sykes BD Mapping the interacting regions between troponin T and C.Binding of TnT and TnI peptides to TnC and NMR mapping of the TnT-binding site on TnC. J Biol Chem (2001);276: 36606–36612 .
39- Monica X. WANG L and BRIAN D. Structural based insights into the role of troponin in cardiac muscle pathophysiology. Springer. Printed in the Netherlands, Journal of Muscle Research and Cell Motility(2005) 25: 559–579.
40-Faiqa F., Muhammad N.,Saman B. Dietary effects on hemo lipid profile;in university students of middle income group.Professional Med J. (2006);13(4):621-626.. .