Study of some Cardiac Biomarkers and Oxidative Stress markers in Patients with Acute coronary syndromes

Mohammed O. Hamzah*; M.Sc., Ala'a G. Hussein**; F.I.C.M.S, Kismat M .Turki***; PhD

** Clinical Biochemistry/ College of Medicne / Al-Nahrain University*
*** College of Medicne / Al-Nahrain University*
****. Clinical Biochemistry/ College of Medicne / University of Baghdad*

Abstract

Background: Acute Coronary Syndromes (ACS) represents a pathological, diagnostic, and risk continuum from unstable angina through myocardial infarction (MI) with or without ST-segment elevation. These three conditions share a very similar pathology, although treatment differs. Elevated markers of inflammation, in particular hs-CRP, are associated with an increased risk of future cardiovascular events in healthy subjects, Increased oxidative stress and the generation of the free oxygen radicals can result in modification of LDL to oxidized LDL that could lead to atherosclerotic lesions, Elevated levels of CK-MB have been regarded as biochemical markers of myocyte necrosis.
Objective: The aim of this study was to investigate the predictive value of CK-MB and oxidative stress (MDA) in acute coronary syndromes.
Patients and Methods: One hundred one (101) cardiac patients were admitted to the coronary care unit, Ibn alnafees Hospital and Al kindy Hospital over the period July 2009 and March 2010 with the clinical diagnosis of acute coronary syndrome their ages range was (24-84) years, the number of male was (65) (64.36%) and female was (37) (36.63%).39 healthy control (age, sex, matched) were enrolled in this study. All cardiac patients have routine ECG, cardiac biomarkers measurements especially(CK-MB), serelogical markers (hs-C-RP),lipid profile test and oxidative stress markers(MDA).10 ml of blood needed for assessment of the above makers.
Results: Oxidative Stress and Cardiac Biomarkers in Patients with Acute Coronary Syndromes (ACS) 101 were found significantly high in patients with ACS as compared to healthy subjects but significantly decreased in HDL-cholesterol in ACS patients as compared to healthy controls. ACS is associated with greater than normal lipid peroxidation.
Conclusion: Our study shows a significantly increase in lipid peroxidation and cardiac biomarkers in the circulation of patients with ACS. A significant decrease level of HDL-C were observes only in ACS patients. These finding suggest these biomarkers may be useful diagnosis of patients with ACS.
Keywords: acute coronary syndromes**,** Oxidative stress, cardiac biomarkers

الخلاصة

الخلفية العلمية: المتلازمة التاجية الحادة تمثل حالة مرضية وتشخيصية وخطرة استمرارا من الذبحة الصدرية غير المستقرة مرورا باحتشاء العضلة القلبية مع او بدون قطعة ال اس تي الظاهرة على مخطط القلب الكهربائي ,هذه الظروف الثلاثة تكون متشابهة على الرغم من اختلاف العلاج.ارتفاع معلمات الالتهابات بصورة خاصة البروتين التفاعلي نوع سي تكون مصحوبة مع زيادة خطورة للأوعية القلبية في الناس الاصحاء.كما وزيادة الاجهاد التأكسدي وتحرير جذر الاوكسجين الحريمكن ان ينتج في تحوير البروتين الدهني الواطى الكثافة الى

البروتين الدهني الواطى الكثافة المؤكسد والذي يؤدي بدوره الى اصابات (جروح) الشرايين المتصلبة.كما ويجب ذكر ان ارتفاع النظير كرياتنين كاينيز نوع ام بي يمكن اعتباره كمعلم حياتي لتنخر خلايا القلب.

الهدف: الهدف من هذه الدراسة هو للتحري عن القيمة التنبؤية للنظير كرياتنين كاينيز نوع ام بي وعامل الاجهاد التأكسدي(المالوندای الديهايد)في مرضى المتلازمة التاجية الحادة .

المرضى والطرق:101 مرضى بالقلب اللذين كانوا راقدين في وحدة العناية المركزة في كل من مستشفى ابن النفيس ومستشفى الكندي للفترة من 2009 - 2010 حيث كانوا مشخصين سريريا بانهم يعانون من مرض المتلازمة التاجية الحادة واللذين معدل اعمارهم تتراوح بين (24-84) سنة. كما وتضمنت الدراسة 39 من الناس الاصحاء كمجموعة سيطرة متماثلين مع المرضى من ناحية العمر والجنس كانوا قد سجلوا في هذه الدراسة.كل مرضى القلب اجريت لهم فحوصات روتينية لمخطط القلب الكهربائي وكذلك تم قياس المعلمات الحياتية وخاصة النظير كرياتنين كاينيز نوع ام بي كما وقد تم قياس صورة للدهون في الدم وكذلك معلمات الاجهاد التأكسدي (المالوندای الديهايد).وقدم تم سحب 10 مل لاجل قياس المعلمات أعلاه.

النتائج: وجد ان هناك ارتفاع مميز في عوامل الاجهاد التأكسدي والمعلمات الحياتية القلبية في مرضى المتلازمة التاجية الحادة واللذين عددهم 101 مقارنة بالناس الاصحاء,ولكن وجد انخفاض مميزفي مستوى البروتين الدهني العالي الكثافة في مرضى المتلازمة التاجية الحادة مقارنة بالناس الاصحاء, وكذلك وجد ايضا ارتفاع فوق الطبيعي للدهون المؤكسدة في مرضى المتلازمة التاجية الحادة.

الاستنتاج: دراستنا بينت بأن هناك زيادة مميزة في الدهون المؤكسدة ومعلمات القلب الحياتية في الدورة الدموية لمرضى المتلازمة التاجية الحادة.وكذلك انخفاض مميزللبروتين الدهني العالي الكثافة في مرضى المتلازمة التاجية الحادة فقط.من خلال هذه الملاحضات نقترح بأن هذه المعلمات ربما تكون مفيدة في تشخيص مرضى المتلازمة التاجية الحادة.

الكلمات المفتاحية: المتلازمة التاجية الحادة,الاجهاد التأكسدي,المعلمات الحياتية.

Introduction

Coronary atherosclerosis is the cause of CHD [(1)]. Typical symptoms are chest pain and dyspnoea on exertion and are the result of reduced blood flow to myocardium. The reduction in blood flow is, in turn, caused by atherosclerotic plaques narrowing the coronary vascular lumen and thus decreasing the nutritional blood flow. In the event of sudden rupture or erosion of the plaque, a thrombogenic mass bulges into the arterial lumen, activates thrombocytes and the coagulation system.

The result of this cascade of events is an occlusive thrombus which immediately reduces or discontinues the blood flow to the myocardium and leads to acute coronary syndromes (ACS) including unstable angina, acute myocardial infarction or sudden cardiac death [(2)] .Plaque rupture is the main cause of fatal acute myocardial infarction and/or sudden cardiac death. These three conditions share a very similar pathology, although treatment differ [(3)].

Acute myocardial infarction (AMI) is one of the major causes of mortality and morbidity in the world [(4)]. The most common cause of an AMI is atherosclerotic coronary artery disease (CAD) with erosion or rupture of a plaque causing transient, partial or complete arterial occlusion.

Heart cannot continue to function without adequate blood flow, and if it is severely compromised, death is inevitable. Several risk factors for coronary heart disease have been well documented, including hypertension, hyperlipidemia, diabetes, a ppositive family history, smoking, obesity and inactivity. However, these factors explain only part of attribute cardiovascular disease. [(5, 6)]

Myocardial antioxidants inhibit or delay the oxidative damage to sub cellular proteins, carbohydrates, lipids and DNA. There is evidence that antioxidants can protect against free radical defense, which is responsible for reperfusion-induced damage and

lipid peroxidation, and may thereby inhibit thrombosis, myocardial damage and arrhythmias during AMI. Antioxidant status is a critical tool for assessing redox status [7]. The antioxidant status or related antioxidants may play an important role in protecting the organism from free-radicals-mediated damage [8]. The role that such compounds play in AMI development is important, since their presence may decrease the damage resulting from blood ROS during reperfusion.

There has been a growing interest in studying the role of lipid peroxidation and antioxidant status in shock patients. There is evidence that antioxidants can protect against free radical production, which is responsible for reperfusion-induced damage and lipid peroxidation, and may thereby inhibit thrombosis, myocardial damage and arrhythmias during AMI. The present study was undertaken to assess the serum levels of high sensitive C-reactive protein (hs C-RP), lipid profile, oxidative stress(MDA),and cardiac biomarker creatine kinase MB(CKMB) in patients with ACS.

Subjects and Methods

Subjects

The study consisted of 140 subjects divided into three groups, 39 with UA their age range (21-70), 62 with AMI their age range (39-70). The other 39 subjects age and sex matched healthy subjects as controls (had no history or clinical evidence of cardiac diseases or any chronic disease). The patients had been admitted to the Coronary Care Units (CCU) of Ibn alnafees Hospital and Al kindy Hospital, between July 2009 and March 2010.The clinical examination and diagnosis were performed by specialized physicians.

Estimation Cardiac Biomarkers

Creatine kinase (CK-MB) was measured by CK-MB Kit (Fluid Stable), on photometric systems using optimized UV test according to DGKC (German Society of Clinical Chemistry) and IFCC (International Federation of Clinical Chemistry and Laboratory Medicine). hs-C-RP was determined in serum using comercially available ELISA and performed as recommended in leaflet with kit. (Wiesbaden. Germany)

Estimation of Lipid Peroxidation

Lipid peroxidation product (malondialdehyde MDA) was estimated by measurement of thiobarbituric acid reactive substances in plasma by the method of Buege and Aust (1978) [9]. The pink chromogen produced by the reaction of thiobarbituric acid with malondialdehyde, a secondary product of lipid peroxidation was estimated. The absorbance of clear supernatant was measured against reference blank at 535 nm.

Statistical Analysis

All data were expressed as mean ± SEM. The statistical significance was evaluated by Student's t- test using Statistical Package for the Social Sciences (SPSS Cary, NC, USA) version 12.0.

Result

As expected, the patients had significantly higher level of total cholesterol, triglyceride, LDL-cholesterol and VLDL-cholesterol levels but lower HDL-cholesterol levels than the healthy controls. There are significant increase in the levels of CK-MB, CRP and MDA in serum of ACS patients when compare to control subjects as shown in table 1.

Table 1. The Anthropometric and biochemical variables among the three studied groups.

Parameters	Control	Unstable angina	Acute myocardial infarction	P(ANOVA)-(T-Test)
NO.	39	39	62	……
Mean±SEM	33.95± 6.57	47.07 ±12.49	56.70±1.58	AMI x UA: p< 0.01 ACS x C: P<0.0001
Hs-CRP(mg/l)	2.35	5.66	9.08	AMI x UA: p< 0.460 ACS x C: P<0.001
CKMB(IU/L)	…….	10.61	2.38	AMI x UA: p<0.311 ACS x C: P<0.001
MDA(µmol/l)	0.58	1.33	1.63	AMI x UA: p<0.001 ACS x C: P<0.00001
TG (mg/dl)	97.51	192.12	234.32	AMI x UA: p< 0.001 ACS x C: P<0.001
TC (mg/dl)	169.30	268.22	274.79	AMI x UA: p<0.05 ACS x C: P<0.001
HDL-c (mg/dl)	40.86	34.76	33.44	AMI x UA: p<0.001 ACS x C: P<0.001
LDL-c (mg/dl)	109.70	193.20	195.98	AMI x UA: p<0.719 ACS x C: P<0.001

Discussion

Oxidative stress has been regarded as one of the most important contributors to the progression of atherosclerosis [(10)]. Increased lipid peroxidation is thought to be a consequence of oxidative stress, which occurs when the dynamic balance between prooxidant and antioxidant mechanism is impaired. In ischemia, the ATP is drastically reduced and is converted to hypoxanthine and then to uric acid by xanthine oxidase upon reperfusion. It has been suggested that increased lipid peroxides levels in blood of patients with AMI [(11)]. The increase in the concentration of MDA in the circulation of total ACS patients indicating increased lipid peroxidation. Results obtained in the present study agree with previous study done by Peking *et al*.,in 2004[(12)] who showed that plasma levels of malondia-aldehyde were significantly increased in unstable angina and acute myocardial infarction patients when compared with control subjects. Changes in the concentration of plasma lipids including cholesterol are complications frequently observed in patients with MI and certainly contribute to the development of vascular disease. Cholesterol has been singled out as the primary factor in the development of atherosclerosis. HDL is regarded as one of the most important protective factors against arteriosclerosis. HDL's protective function has been attributed to its active participation in the reverse transport of cholesterol.

Numerous cohort studies and clinical trials have confirmed the association between a low HDL and an increased risk of coronary heart disease [(13)]. The concentration of LDL correlates positively whereas HDL correlates inversely to the development of coronary heart disease. Smokers have significantly higher serum cholesterol, triglyceride, and LDL levels, but HDL is lower in smokers than in non-smokers [(14)]. Evidence suggests that oxidatively modified LDL contribute to the pathogenesis of atherosclerosis. Increased oxidative stress and the generation of the free oxygen radicals

can result in modification of LDL to oxidized LDL that could lead to atherosclerotic lesions [15].

Elevated levels of CK-MB have been regarded as biochemical markers of myocyte necrosis [16]. CK and more particularly its isoenzyme CK-MB still have a formal place in defining myocardial infarction. These enzymes normally exist in cellular compartment and leak out into the plasma during myocardial injury due to disintegration of contractile elements and sarcoplasmic reticulum [5, 17]. The cardiac-specific troponins are highly sensitive and specific markers of myocardial damage and therefore cardiac troponins are the preferred markers for the diagnosis of myocardial infarction [5, 18]. In this study, increased CK-MB levels were found in patients AMI as compared to healthy controls. The mean CK-MB value was just above the reference range that adapted from the kit. This is considered reliable because peak activity of CK-MB is usually seen at 18 to 24 hours and return to baseline level by 36 to 40 hours [19].

In sixty two patients with AMI, another sample was collected from them; the mean CK-MB values of this group was significantly high and in some cases reach 9times more than the upper normal value. The CK-MB values of this group confirm the diagnosis of MI as the mode of release of CK-MB in this group suggest myocardial injury because non cardiac release of CK generally follows a flatter curve, with elevations that both rise and disappear more slowly than seen with an acute MI [20].

Inflammation plays a role in the development of atherosclerosis and coronary heart disease [21]. Elevated markers of inflammation, in particular CRP, are associated with an increased risk of future cardiovascular events in healthy subjects, in patients with stable or unstable coronary artery disease and acute myocardial infarction [22, 23]. Although the prognostic value of CRP in patients with acute coronary syndromes has not been tested in large studies, several data indicate that CRP is an important marker of risk also in this clinical setting [24, 25]. CRP has been reported to be elevated during AMI [26]. In this study, the CRP level in serum of UA and AMI patients was higher as compared to healthy controls. Patients with acute coronary syndrome have elevation in CRP in association with their presenting symptoms , in patients with AMI, CRP levels correlated with the presences of plaque rapture and an early study examine CRP in acute coronary syndrome found that CRP identified a subset of patients with severe unstable angina at increased risk for death and MI [27] and that agree with results obtained in this study, elevated level of CRP in circulation of patients with acute MI is higher than unstable angina,[28].

Elevated CRP levels were also observed in cardiovascular, hypertension group, respectively.

The significant rise in MDA levels ($p<0.001$), a lipid peroxidation product, in patients is indicative of elevated oxidative stress in ACS patients. This indicates severe damage to antioxidant system, which is unable to combat oxidative stress and inflammation [29].

In conclusion, the present study shows a significant increase in total lipid peroxidation (MDA) and cardiac biomarkers (CK-MB) in the circulation of patients with Acute Coronary Syndromes. Therefore these biomarkers may be useful diagnosis of patients with ACS.

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