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Evaluation of C-Reactive Protein and CXCL16 in Acute Coronary Syndrome

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ACUTE coronary syndrome (ACS) is a life-threatening condition. Diagnosis and follow up depend on clinical examination, electrocardiogram (ECG), positron emission tomography (PET) and biochemical markers. Troponin is significantly used in the diagnosis and prognosis of ACS, however, its increase in absence of ACS prompts an evaluation for an alternative. CXCL16, an interferon γ regulated chemokine, in addition to the fact that it is expressed in atherosclerotic lesion. C-Reactive Protein (CRP) is up regulated in atheromatous plaque. The aim of the present study is to evaluate the importance of measurement of CRP and CXCL16 together with other biochemical markers of myocardial injury in the diagnosis and follow up of ACS.

The study included 90 participants, 60 patients of ACS (30 unstable angina and 30 myocardial infarction) and 30 healthy age and sex-matched participants who formed the control group. All patients and controls underwent the following laboratory investigations: Serum aspartate aminotransferase (AST), creatine kinase muscle band (CK MB), lactate dehydrogenase (LDH), troponin and CXCL16 by ELISA and CRP by Nephelometry. The mean values of CXCL16, CRP, AST, CK MB, LDH were highly elevated in ACS, while troponindid not significantly elevated in unstable angina patients compared to the controls. A significant positive correlation was found between CXCL16 and both CRP (r^2= 0.89) and troponin (r^2= 0.93) in myocardial infarction patients. It is concluded that CRP, and CXCL16 may be additional tools for the diagnosis and prognosis of ACS besides other biochemical markers.

Keywords: CRP, CXCL16, Acute coronary syndrome.

Introduction

Acute coronary syndrome (ACS) in an ischemic type of heart disease and include myocardial infarction (MI), with or without ST elevation, (STEMI and NSTEMI) and unstable angina (Kumar & Cannon, 2009). Diagnosis and classification of the patients depend on electrocardiogram (ECG), radionuclide heart imaging by positron emission tomography (PET) and serum biochemical markers of myocardial damage (Thygesen et al., 2012). PET scanners for non- invasive assessment of cardiovascular conditions were introduced into the diagnosis and management of ACS thirty years ago. Although PET is considered the best available technique for the evaluation of myocardial viability and perfusion, difficult production of positron – emitting radioligands of short physical half - life, generation of perfusion tracers which need on site cyclotron facility and the high PET imaging cost are many factors that limit the use of cardiac

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PET inthe clinical routine (Kazakaukaite et al., 2018).

Serum troponin I or T, and creatine kinase muscle band (CK MB) are biochemical markers of myocardial damage. Serum troponinis elevated 6-12hr after the onset of the pain. Nevertheless, markers of myocardial injury as CK-MB and cardiac troponin are not valuable in diagnosis of non-ST elevated myocardial infarction. It was observed that 22–50% of patients with unstable angina have positive troponin T or I. Elevated troponin indicates myocardial necrosis but is of low diagnostic sensitivity in ACS. Troponin elevations in the absence of ACS are also recorded in myocardial necrosis. This is signified by cardiac troponin elevation that may not necessarily be due to prolonged myocardial ischemia related to coronary atherothrombotic disease as in Acute Myocardial Infarction (AMI) (Panteghini, 2007). There is a great demand for other tests of valuable aid in clinical practice.

Inflammatory markers were found as good additional tests for detection of patients at risk for cardiovascular diseases. The cells (e.g. monocytes) involved in the formation of atherosclerotic plaque are stimulated to produce many different substances. These substances include inflammatory mediators such as interleukins 1 and 6 (IL1,IL6) and tumor necrosis factor alpha (TNFα), complement factors, chemokines such as IL8 and the monocyte chemoattractant protein-1 (MCP-1), adhesive molecules, metalloproteinases, collagenases, nitric oxide and CRP (Pasceri et al., 2000).

CRP, more specifically localized to the vascular intimae, has recently been reported to be active inside the atherosclerotic plaques together with macrophages, membrane attack complex C5b-9 (MAC) and oxidized low-density lipoprotein (LDL) (Meuwissen et al., 2006). Oxidized LDL particles precipitated in the wall of coronary arteries stimulate the immune response and cause rupture or erosion of atherosclerotic plaques (Morrow et al., 2000).

Pro-inflammatory stimuli increase the expression of CXCL16 by macrophage which stimulates vascular cell proliferation (Lehrke et al., 2007). CXCL16 is a chemokine that binds to its receptor CXCR 6 and has a role in vascular pathology in ACS. CXCL16 is expressed in two forms: A transmembrane form and a soluble form. The transmembrane form acts as a scavenger receptor for oxidized LDL, while the soluble form interacts with its receptor in response to monocyte chemotactic protein-1 induction in endothelial cell mediated by CRP. CRP co-localizes with the membrane attack complex in early atheromatous lesion, CRP, complement protein and their messenger ribonucleic acid, all of them are upregulated in atherosclerematous plaques (Pasceri et al., 2000).

The aim of the present study is to evaluate the importance of measurement of CRP and CXCL16 inflammatory markers together with other biochemical markers of myocardial injury in the diagnosis and follow up of ACS.

Materials and Methods

This study included two groups: Patient and control groups. The patient group included 60 patients with acute coronary syndromes (30 of them had unstable angina & 30 had myocardial infarction). They were from those admitted at the Coronary Care Unit, Ain Shams University, Cairo, Egypt. Their age ranged between 32 & 47 years with a mean value of 40±1.2 Years. The control group included 30 healthy age matched.

Inclusion criteria

Patients admitted at coronary care unit complaining of chest pain associated with ECG changes and positron emission tomography imaging evidence of new loss of viable myocardium in infarction cases.

Exclusion criteria

Included ages below 30 and above 50, non-coronary artery disease associated with a life expectancy less than one year in addition to known or suspected pregnancy.

Fasting blood samples were taken from patients and controls. Sera were separated as preferred schedule and kept at -20ºC. All individuals included in the study were subjected to the following: Full history taking, clinical examination and ECG and radionucleotide perfusion imaging of the heart by Positron Emission Tomography (PET scan) to detect areas of low blood flow and identify injured or dead tissue.

Laboratory investigations included

Serum AST, CK MB, LDH enzymatic activity was measured using semi-automated chemistry analyzer (BI-224) by spin react kit (Tietz, 1995).

Serum Troponin I concentration was measured by DRG Troponin I ELISA (C-Inc-EIA-2952) kit supplied by DRG, International, Inc., USA. C-reactive protein (CRP) was measured by Nephelometry using BN-prospect Dadebehring, GmbH, Hamburg, Germany. CXCL16 levels concentrations were measured using suitable ELISA kit specific for recombinant and natural human CXC motif ckemokine 16 No; e077IR provided by Wuhan EIAab science Co., Ltd, China according to the manufacturer's instruction on Infinite F50 TECAN ELISA instrument.

Informed consent was obtained from all participants in the study as subject privacy rights must be observed. This study follows the ethical standards of the institutional and national research committee given in the Declaration of Helsinki 1964, as revised in 2013. The authors declare no conflict of interest.

Statistical analysis

The significance of the difference between obtained values (mean, standard deviation and standard error) was carried out. Student's T test and Pearson's correlation coefficient were used to evaluate the effects of studied group compared to the control group.

Results

The mean values of CXCL16, CRP, AST, CKMB, LDH were significantly elevated (P< 0.001) in unstable angina and myocardial infarction patients as compared to healthy controls. Troponin levels were significantly elevated in myocardial infarction while not elevated in unstable angina compared to the control group (Table 1). AST and LDH significantly increased in ACS, but the level was higher in myocardial infarction compared with unstable angina.

The level of CXCL16 was significantly elevated (P<0.001) in ACS patients (unstable angina and myocardial infarction) as compared to healthy controls, however, the increase was more pronounced in myocardial infarction patients (Fig. 1).

Distribution of diabetes and hypertension in the myocardial infarction group of patients

Twenty five % of the patients were non-diabetics non-hypertensives, 41.6% were both diabetics and hypertensives, 8.3% diabetics but non hypertensives and 25% hypertensives and non-diabetics.

The level of CXCL16 was elevated in ACS patients with hypertension and DM (493.0±108.2) compared to non-DM non hypertensive patients (106.7±20.82) and controls (47.08±1.42), P value <0.001. The level of CXCL16 was highly elevated in patients with hypertension alone (302.3±150.7) yet the difference was not statistically significant compared to the controls (P>0.05). Diabetics but non hypertensives also had higher levels of CXCL16 than controls (88.0±1.73) yet no significant difference with controls was detected (P>0.05) as shown in Fig. 1.

TABLE 1. Laboratory investigations in the studied groups.

Parameters	Controls N= 30	Unstable angina N= 30	Myocardial infarction N= 30
CXCL16 (pg/ml)	47.08±4.9[a]	169.7±86.27[b]	315.0±254.4[c]
CRP (mg/L)	2.25±0.93[a]	4.63±1.6[b]	60.51±58.3[c]
AST (U/L)	8.17±3.2[a]	32.83±7.8[b]	113.6±23.98[c]
CKMB (U/L)	9.33±4.1[a]	14.75±6.44[b]	44.08±8.3[c]
LDH (U/L)	151.3±22.0[a]	268.0±95.4[b]	1001±128.1[c]
Troponin(µg/L)	0.01±0.01[a]	0.01±0.01[a]	20.85±7.3b*

Values with different superscript in the same row are significantly different at P<0.05.
*Highly significant (P<0.001)

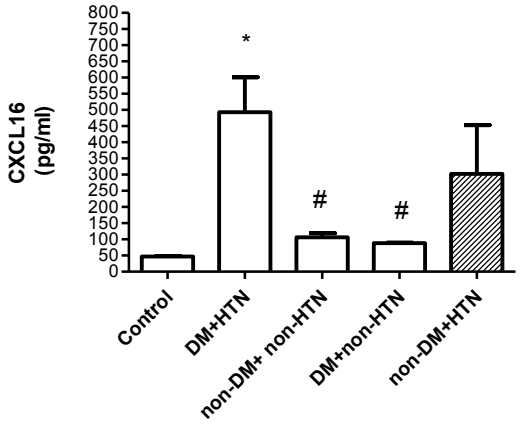

Fig. 1. Effect of diabetes and/or hypertension on CXCL16 in myocardial infarction group (*Significant difference with controls; ##significant difference with DM+HTN).

Correlation studies revealed a significant positive correlation between CXCL16 and both CRP (r^2= 0.89) (Fig. 2) and troponin (r^2= 0.93) (Fig. 3) in myocardial infarction patients.

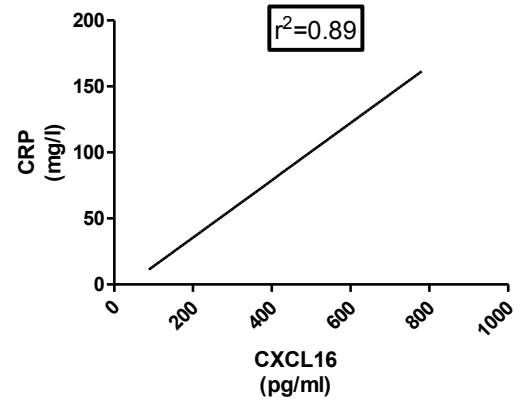

Fig. 2. Correlation analysis between CXCL16 and CRP in myocardial infarction.

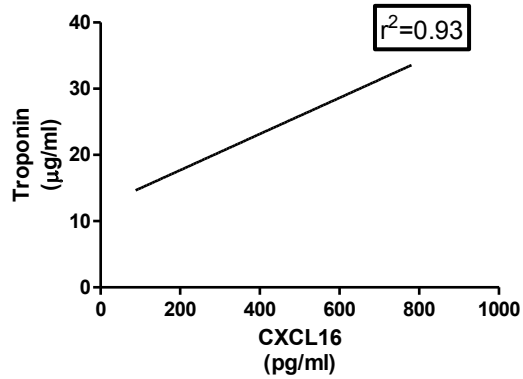

Fig. 3. Correlation analysis between CXCL16 and Troponin in myocardial infarction.

Discussion

Recent years have seen a spectacular rise in the importance of biomarkers in acute coronary syndrome (ACS). The most notable of these biomarkers is, without doubt, troponin. Its usefulness for the diagnosis, decision making, and prognostic stratification has been fully validated, and its use in daily clinical practice is now widespread. It should be pointed out that the kinetics of troponin release were studied in detail for different types of ACS right from the outset (Eggers & Lindahl, 2017). This approach has clearly laid a solid foundation which has contributed to the current popularity of this marker. However, it was soon evident that not all patients with ACS and elevated troponin had a very poor prognosis, and that patients with chest pain and normal troponin levels did not always have an excellent prognosis. Troponin elevation is also recorded in the absence of ACS. It has, therefore, became clear that other factors besides troponin levels and electrocardiographic findings need to be taken into account (Bodí & Sanchis, 2006).

Myocardial necrosis as signified by cardiac troponin elevation may not necessarily be due to prolonged myocardial ischemia related to coronary atherothrombotic disease as in AMI. Other non-ischemic pathophysiological conditions can cause myocardial necrosis and therefore elevation in cardiac troponin concentrations, e.g., hypoxia (lack of oxygen), chemicalinjury, physical (electrical, temperature, radiation) injury, immunologic injury, or infectious agents (Panteghini, 2007). These causes should be considered when interpreting troponin results. In general, in emergency department populations, where there is a low pre-testprobability (prevalence) of thrombotic coronary artery disease, elevation of troponin may be less predictive of ACS. Troponin elevation in the absence of ACS still hasprognostic value and can predict adverse short- and long-term survival in different clinical conditions associated with myocyte necrosis (Tate & Pantaghini, 2008).

Full clinical evaluation of the patients using new biomarkers is greatly needed. Besides troponin, the marker that has deserved most attention in the last decade is C-reactive protein (CRP) (Bodí & Sanchis, 2006). In addition, many cytokines have a role in development

of atherosclerosis. CXCL16, a chemokine of the CXC family is a pathogenic mediator in atherosclerosis involved in both inflammation and lipid metabolism as well as promotion of matrix degradation (Smith et al., 2008).

Inflammatory markers are valuable in the diagnosis and prognosis of myocardial cell injury as they have a role in the formation and fragmentation of atheromatous plaque as well as endothelial injury. The aim of the present study isto detect the value of measuring inflammatory markers as CRP and CXCL16 together with other biochemical markers of myocardial injury in ACS. The study included 60 patients (30 unstable angina and 30 myocardial infarction). Both inflammatory markers CXCL16 and CRP were significantly elevated is ACS, while troponin levels were elevated in myocardial infarction while not elevated in unstable angina. Accordingly, the inflammatory markers CXCL16 and CRP are of diagnostic sensitivity and specificity for ACS rather than cardiac troponin. Results of the present study documented significant positive correlation between CXCL16 and CRP in myocardial infarction patients. Similar association between CXCL16 levels with inflammatory and metabolic factors including CRP was found by Lehrke et al. (2007).

Hypertension and diabetes frequently occur in the same individuals in clinical practice (Volpe et al., 2015). Mechanical factors may explain the association between hypertension and ACS. High blood pressure denotes increased mechanical stress on blood vessels that contributes to endothelial dysfunction, atherosclerosis and plaque rupture. A significant evidence supports the presence of a prethrombotic state among hypertensive patients (Konstantinou et al., 2019). Patients with diabetes have significantly higher rates of cardiogenic shock. Researchers found that diabetes was an independent risk for both cardiogenic shock and mortality (Zhou et al., 2018). Results of the present study revealed that the level of CXCL16 was was more elevated in ACS patients with hypertension and diabetes than in ACS with no hypertension, and no diabetes. The results revealed that hypertension increases the risk of acute coronary artery lesions and corroborate the findings of Lehrke et al. (2007) that CXCL16 may play a pro inflammatory role in human atherosclerosis, particularly in acute coronary syndrome. Zhou et al. (2016) studied CXCL16 in diabetic patients with and without ACS and CXCL16 in both groups compared to controls.

In accordance with our results, Wang et al. (2016) who examined 20 inflammatory factors associated with coronary heart disease (ACS) and found 13 factors associated with moderate coronary artery lesion among them CXCL16. Xu et al. (2017) found that mounting evidence have uncovered the close association of CXCL16 with the development of diverse human inflammatory disease, including atherosclerosis, coronary artery disease and myocardial infarction.

Enhanced expression of both CXCL16 and CRP has been observed in atherosclerotic lesions obtained from humans. Elevated expression levels of CXCL16 was have been observed in myocardial infarction. Moreover, it has been reported that soluble CXCL16 in plasma could serve as a biomarker for acute coronary syndromes. Janson et al. (2009) assessed the association between CXCL16 levels obtained 24hr after admission and the time of death in 1351 patients with diagnosis of unstable angina non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction. The authors found an association between CXCL16 levels and long term mortality after adjustment for other risk factors.

In the current study, CXCL16 was elevated in ACS. However, Sheikine et al. (2006) found decreased CXCL16 levels in both stable and unstable angina. Lehrke et al. (2007) found a high level in acute coronary syndrome. Aslanian & Charo (2006) reported that CXCL16 has anti atherogenic effect. Nevertheless, the obtained results are in accordance with the fact that an increased level of CXCL16 is a strong indicator of congestive heart failure development and a reliable stable marker of inflammation. However, Mitsuoka et al. (2009) found that the presence or absence of risk factors, such as diabetes, smoking and hypertension did not significantly affect circulating CXCL16 and CRP in detection of ACS in Troponin negative patients.

Conclusion

Markers of myocardial cell damage (necrosis) such as troponin are invaluable diagnostic tools in ACS. Inflammatory markers such as CXCL16 and

CRP which are good early markers for diagnosis of ACS especially in troponin negative unstable angina patients where inflammatory markers are elevated independent of troponin.

Conflict of interest: The authors declare that there is no conflict of interest.

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تقييم البروتين المتفاعل سى و سى اكس سى ال 16 فى مرضى متلازمة الشريان التاجى الحادة

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سى اكس سى ال 16 عبارة عن مستقبلات كميائية للبروتين الدهنى منخفض الكثافة المؤكسد الذى يوجد بكثرة فى مرضى تصلب الشرايين التاجية. ينظم افراز السى اكس سى ال 16 الأنترفيرون جاما. يساعد سى اكس سى ال 16 الخلايا الليمفاوية تى على الهجرة إلى مكان تصلب الشرايين لتفرز الإستجابةالمناعية لهذا المرض. البروتين المتفاعل سي هو بروتين يوجد ضمن البروتينات المسئولة عن مهاجمة الغشاء الشريانى فى بداية الأصابة بمرض تصلب الشرايين.

تشمل الدراسة الحالية 90 فرد منهم 60 مرضى (30 يعانون من ذبحة صدرية غير مستقرة، 30 يعانون من احتشاء عضلة القلب الحاد) وأيضا 30 أصحاء كمجموعة ضابطة. جميع الأفراد خضعوا للإختبارات المعملية بجانب فحوصات القلب اللازمة. اشتملت التحاليل: ناقل الانين اسبارتين – انزيم الكرياتين كاينيز – رمز نازعة الهيدروجين اللاكتية – سى ار بى – التروبونين البروتين العضلى - سى اكس سى ال 16.

وقد اسفرت النتائج عن زيادة ملحوظة فى متوسط نسبة هذه الأختبارات ما عدا التربونين البروتين العضلى بالمقارنة بالأصحاء.

كانت الخلاصة أن دلالات الألتهاب اكثر إفادة فى تشخيص وتحديد خطورة مرضى متلازمة الشريان التاجى الحاد عن الدلالات الكميائية الأخرى.