The association between Oxidized low - density lipoprotein and high sensitivity C reactive protein in acute coronary syndromes patients

Abbas Mosad Ajeed MS.c, Clinical Biochemistry Al- Yarmouk College University/ Parmacy

The association between Oxidized low - density lipoprotein and high sensitivity C reactive protein in acute coronary syndromes patients

Abbas Mosad Ajeed MS.c, Clinical Biochemistry Al- Yarmouk College University/ Parmacy

The association between Oxidized low - density lipoprotein and high sensitivity C reactive protein in acute coronary syndromes patients

Abbas Mosad Ajeed MS.c, Clinical Biochemistry Al- Yarmouk College University/ Parmacy

The association between Oxidized low - density lipoprotein and high sensitivity C reactive protein in acute coronary syndromes patients

Abbas Mosad Ajeed MS.c, Clinical Biochemistry Al- Yarmouk College University/ Parmacy
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 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. Increased blood levels of oxidized low density lipoprotein (ox-LDL) could play a role in these circumstances.

Objective: The aim of this study was To measure circulating levels of oxidized-low-density lipoproteins (ox-LDL) in patients with AMI (Q-MI & Non-Q-MI), unstable angina and controls, and to investigate their correlation with hs-CRP in acute coronary syndromes.

Patients and Methods: Ninety (90) cardiac patients were admitted to the coronary care unit, Ibn alnaees Hospital and Al kindy Hospital over the period July 2013 and March 2014 with the clinical diagnosis of acute coronary syndrome their ages range was (25-84) years, healthy control (age,sex,matched) were enrolled in this study. All cardiac patients have routine ECG,cardiac biomarkers measurements especially Troponine I, (CK-MB),serological markers (hs-C-RP) and Ox-LDL.10 ml of blood needed for assessment of the above makers.

Results: Ox-LDL and hs-CRP in Patients with Acute Coronary Syndromes (ACS) 90 were found significantly high in patients with ACS as compared to healthy subjects, and also a significant positive correlation was observed between Ox-LDL & hs-CRP in Q-MI but positive related in UA & Non-Q-MI.

Conclusion: OxLDL and hs-CRP levels are higher in ACS patients, and a significant positive correlation was observed between Ox-LDL & hs-CRP in Q-MI,Ox-LDL and hs-CRP might be markers of destabilization of ACS.

Keywords: acute coronary syndromes, Oxidized-LDL, hs-C-reactive protein.

1. Introduction

Acute coronary syndromes (ACS) occur because of the destabilization of atherosclerotic plaques, which may undergo rupture or erosion, with subsequent thrombosis and vessel occlusion [1]. Many findings indicate that plaque destabilization correlates with the location and activation of inflammatory cells both within the plaque [2,3] and in the systemic circulation [4]. Although the identification of vulnerable patients remains a challenge [5,6], a correlation between markers of systemic inflammation, such as C-reactive protein and pregnancy-associated plasma protein-A, with the presence of complex, vulnerable coronary plaques has recently been found in patients with stable and unstable angina. [7,8,9]. Among factors involved in the initiation, progression and destabilization of plaques, oxidized-low-density lipoproteins (ox-LDL) are thought to play a key role [10]. Increased circulating levels of ox-LDL have been shown to be associated with angiographically proven coronary artery
disease (CAD) [11, 12], thus suggesting that circulating ox-LDL is a significant marker of CAD. However, studies that measured ox-LDL (or auto-antibodies against ox-LDL) in the plasma of patients with different clinical manifestations of CAD, reported conflicting results [13, 14]. Recently, it has been shown that macrophage-rich, vulnerable, rupture prone carotid plaques have higher content of ox-LDL than macrophage-poor, stable plaques [15] and are associated with elevated levels of ox-LDL in plasma [11]. However, the correlation between circulating ox-LDL levels and presence of vulnerable coronary plaques has never been investigated. We therefore measured the plasma concentration of circulating ox-LDL in patients with ACS to evaluate the correlation between ox-LDL levels and hs-CRP, Ox-LDL and hs-CRP were also determined in a group of control subjects without CAD.

2. Subjects and Methods

The population consisted of 120 subjects divided into three groups, 30 with UA their age range (25-75), 60 with AMI their age range (37-75). The other 30 subjects age and sex matched healthy subjects were studied as controls (This group includes 39 subjects who had no history or clinical evidence of cardiac diseases or any chronic disease). All patients had been admitted to the Coronary Care Units (CCU) of Ibn al Nafees Hospital, between July 2012 and March 2013. The clinical examination and diagnosis were performed by physician specialized in Ibn Al-Nafees Cardiac Specialty Teaching hospital and AL-KindyTeaching hospital. hs-CRP was determined in serum using commercially available ELISA and performed as recommended in leaflet with kit. (Wiesbaden.Germany). Plasma circulating ox-LDL, collected from whole blood into Vacutainer tubes containing ethylenediamine tetraacetic acid (1 mg/mL) was measured with the enzyme-linked immunosorbent assay Mercodia Oxidized-LDL ELISA kit (Mercodia AB, Uppsala, Sweden), in which the wells of the microtiter plates are coated with the capture antibody mAb-4E6 [Holvoet et al., 2001]. No antioxidant were added to the plasma samples before blood collection.

3. Result

Serum serological markers (hs-C-RP), levels were estimated in 90 patients with ACS, (60 AMI & 30 UA) compared with 30 healthy control group, age and sex matched. The results reflect that patients with Q-MI have a higher CRP value than Non-Q-MI and unstable angina (see figure 1) but statistically there was no significant differences between the groups (p=0.39074), but significant differences when compared ACS patients with control groups (p<0.001). As shown in table (1).
Fig. (1): average of CRP in ACS patients and healthy control.

Table: (1) Serum hs-CRP in ACS and Control Groups.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>UA</th>
<th>Non-Q-MI</th>
<th>Q-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30</td>
<td>30</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Mean</td>
<td>2.29</td>
<td>5.76</td>
<td>7.97</td>
<td>11.26</td>
</tr>
<tr>
<td>SEM</td>
<td>0.15</td>
<td>0.16</td>
<td>0.21</td>
<td>0.82</td>
</tr>
<tr>
<td>Range</td>
<td>0.66-4.71</td>
<td>3.73-8.32</td>
<td>6.35-12.33</td>
<td>9.74-31.73</td>
</tr>
<tr>
<td>Comparison with control</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Comparison within the groups</td>
<td>P=0.39074</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oxidized LDL was estimated by ELISA technique in the sera of patients at admission (n=90). The mean of Oxidized LDL of control, UA, non-Q-MI, and Q-MI are shown in table (4-9). There was a highly significant difference between controls and disease groups (P<0.001). Also there was a significant difference in the mean of Oxidized LDL among disease groups (P<0.001), with the highest level seen in the Q-MI group. See figure. (2).

![Bar chart showing mean Oxidized LDL levels in different groups](chart.png)

**Figure. (2) Average of sera Oxid- LDL levels in patients at admission, and controls group.**

**Table: (2) Serum Oxid LDL in ACS and Control Groups.**

<table>
<thead>
<tr>
<th>Oxidized LDL( Oxi LDL)</th>
<th>Control</th>
<th>UA</th>
<th>Non-Q-MI</th>
<th>Q-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>N</td>
<td>Mean</td>
<td>SEM</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>72.20</td>
<td>0.68</td>
<td>62.90-78.60</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>280.67</td>
<td>2.95</td>
<td>257.60-326.40</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>312.77</td>
<td>4.88</td>
<td>265.00-362.92</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>343.20</td>
<td>3.29</td>
<td>299.00-380.08</td>
</tr>
</tbody>
</table>
Table (2) shows the results of the laboratory tests in the three groups of patients. A significant positive correlation between Ox-LDL and C-RP in (Q-MI), but data showed a positive correlation in Non-Q-MI & UA patients. See fig(3A), (3B) positive correlation between Ox-LDL and C-RP, & (3C).

Figure (3): Correlation between Serum Ox-LDL Level & C-RP in UA (A), Ox-LDL Level & C-RP in Non-Q-MI patients (B), and Ox-LDL Level & C-RP in Q-MI patients (C).
Table (3): Correlation Coefficient ($r$) and significant value ($p$) of Serum C-RP vs. Ox-LDL in ACS.

<table>
<thead>
<tr>
<th>Correlation C-RP &amp; Ox-LDL</th>
<th>Type</th>
<th>$r$</th>
<th>$P$</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA</td>
<td>Positive</td>
<td>0.081</td>
<td>0.869</td>
<td>Non significant</td>
</tr>
<tr>
<td>Non-Q-MI</td>
<td>Positive</td>
<td>0.277</td>
<td>0.286</td>
<td>Non significant</td>
</tr>
<tr>
<td>Q-MI</td>
<td>Positive</td>
<td>0.384</td>
<td>0.021</td>
<td>Significant</td>
</tr>
</tbody>
</table>

**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 16.0.

**4. Discussion**

Many inflammatory markers can be used as predictive markers for the risk of coronary heart diseases like CRP: 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 (16) which also showed that our lived patients have elevated level of CRP in circulation, and in patients with AMI is higher than unstable angina, (23) noted that primary cytokines (eg, IL-1ß or TNF-) stimulate production of "messenger" cytokine, IL-6, which induces expression of hepatic genes encoding acute-phase reactants found in blood, including CRP.our result also agreement with (24) who said that Greater early blood CRP moderately increases long-term risk of recurrent cardiovascular events or death, and may be a valuable prognostic predictor in patients after ACS. Our results also agreement with other results done by (31) who showed that C-reactive protein and a family history of myocardial infarction were positively associated with subsequent venous thrombosis.

Our data agreement with results done by (26) who showed that high sensitive C-reactive protein levels were higher in acute coronary syndrome patients compared to control also showed that ACS is associated with greater inflammation in the presence of myocardial necrosis than in cases of angina without necrosis.and agreement with (22) who showed that CRP level were found significantly high in patients with AMI as compared to healthy controls ($p<0.01$). Our findings suggest that early CRP is a valuable predictor in patients with ACS. However,. Moreover, admission electrocardiogram, a widely available measurement, was suggested that many simple clinical measurements were good predictors of prognosis of ACS. But, it was uncertain which clinical measurement was the most valuable or most cost-effective in clinical use since no study had compared their independent prognostic value under the same conditions. Further studies are needed to compare the prognostic values of common clinical markers or joint multiple markers in the same study.

There are several possible explanations for the prognostic value of CRP in patients with
ACS. It has been shown that CRP is related to the dysfunction of endothelial cells and the progression of atherosclerosis. Pasceri et al., 2000 found that CRP induced a significant increment of adhesion molecule expression in human endothelial cells, indicating the direct proinflammatory effect of CRP (29). Second, CRP has a role in the progression of atherosclerosis by decreasing the production of nitric oxide and prostacyclin produced by endothelial cells (34, 35). Moreover, CRP can amplify the immune response through complement activation,(28, 37). Pasceri et al., 2001 which has the effect of expanding the infarct size (29). Barrett et al., 2002 an animal study showed directly harmful effects on ischaemic myocardium (17). A significantly enlarged infarct size was found when human CRP was injected into rats after ligation of the coronary artery (19). In addition, elevated CRP might independently affect the coagulation system and increase mortality (18). When an ACS occurs, serum CRP concentration apparently increases and reaches a peak at 72 h (33, 20) CRP obtained within 72 h from the onset of symptoms is a reflection of the acute response of tissue injury. A higher level of CRP was related to more severe damage caused by the cardiovascular events and further damage caused by CRP itself (32). The early phase of the inflammatory response was also related to the ventricular function and remodeling (27). Ischaemia and reperfusion injury,(17) which can cause long-term. The present study demonstrates that plasma levels of oxidized LDL are significantly elevated in ACS patients compared with control groups, our results are agreement with other results done by (Paul et al., 2008 and Yamagishi et al., 2007) suggesting that their increases are independent of plaque instability (30, 36) also our results agreement with results done by (Maurizio et al., 2006) who said that Ox-LDL levels are higher in unstable patients and correlate with the presence of angiographically documented complex plaques (25). Ox-LDL might be markers of destabilization of CAD..also our data agreement with other results done by( Johannes Hulthe and Björn Fagerberg, 2002) who showed Ox-LDL was associated with both subclinical atherosclerosis and inflammatory variables (21). Statistically our data also demonstrate a significant positive correlation between Ox-LDL and C-RP in (Q-MI).but data showed a positive correlation in Non-Q-MI &UA patients, see table (3).
References

16- Armstrong E. J., David A. Morrow and Marc S. Sabatine. (2006): Inflammatory Biomarkers in Acute Coronary SyndromesPart II: Acute-Phase Reactants and Biomarkers of
25- Maurizio Anselmi a,, Ulisse Garbin b, Pierfrancesco Agostoni a, Massimiliano Fusaro a, Anna Fratta Pasini b, Cristina Nava b, Dritan Keta a, Marco Turri a, Piero Zardini a, Corrado Vassanelli a, Vincenzo Lo Cascio b, Luciano Cominacini b. (2006): Plasma levels of oxidized-low-density lipoproteins are higher in patients with unstable angina and correlated with angiographic coronary complex plaques; Atherosclerosis 185:114–120.

26- Mehmet Yunus Emiroglu, MD¹, Özlem Batukan Esen, MD⁵, Mustafa Bulut, MD¹, Hekim Karapinar, MD³, Meier CA, Bobbioni E, Gabay C, Assimacopoulos-Jeannet F, Golay A, Dayer JM( 2010 ):IL-1 receptor antagonist serum levels are increased in human obesity: a possible link to the resistance to leptin? J Clin Endocrinol Metab 87:1184–1188.


31- Petter Quist-Paulsen, Inger Anne Næss, Suzanne C. Cannegieter, Pål R. Romundstad, Sverre C.  


