

# Association of Lp(a) with CRP in patients of Rheumatoid Arthritis

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## ABSTRACT

**Aim:** To measure the Lp(a) levels and correlating them with CPR levels in patients of rheumatoid arthritis.

**Method:** The total number of hundred subjects was included in this study. Fifty (25 males and 25 females) diagnosed cases of RA were taken as patient group while fifty (22 males and 28 females) healthy subjects were taken as control group. The samples were collected from RA patients coming to Rheumatology OPD Shaikh Zayed Hospital Lahore.

**Results:** The patient group (both males and females) showed significantly higher ( $P < 0.001$ ) CRP and Lp(a) as compared to the control group (both male and female). Pearson co-efficient of correlation of Lp(a) was calculated with age, BMI and CRP. It was found that Lp(a) has a positive correlation with CRP in patients of Rheumatoid Arthritis.

**Conclusion:** The RA patients who had raised CRP also showed raised Lp(a) levels. These patients with raised Lp(a) are more prone to develop cardio vascular defects thus Lp(a) levels may be integrated and monitored as independent CV risk factor into existing screening tests and follow up of RA patients.

**Keywords:** Rheumatoid arthritis, CRP, Lp(a).

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## INTRODUCTION

The inability of traditional CV risk factors such as diabetes mellitus, hypertension, dyslipidemia, higher BMI, higher waist to hip ratio to explain the increase CVD mortality in RA patients has prompted exploration of other mechanisms that increases atherogenesis among RA patients, particularly increased systemic inflammation<sup>1</sup>. As the inflammation in RA is not confined to the joints only it is also present in vessel wall and recent studies have also demonstrated impaired endothelial dysfunction in RA, even at early stage of disease. The systemic release of TNF- $\alpha$  and cytokines IL-1, IL-6 leads to endothelial dysfunction<sup>2</sup>.

Galarraga. Bet al in a large cross sectional study found for the first time that systemic inflammation is independently associated with microvascular dysfunction in patient with RA. When the endothelial function is impaired it results in pro-inflammatory and pro-coagulant endothelium that leads to atherosclerosis and thrombosis.<sup>3</sup> Lp(a) was first detected in human plasma by Berg in 1963<sup>4</sup>. It is a complex cholesterol rich particle composed of a lipid moiety and two disulphide linked sub units. Apoprotein B100 (apo-B) and Apoprotein a (apo-a). The lipid part and apo B-100 of Lp(a) are shared with low density lipoprotein (LDL)<sup>5,6</sup>.

The presence of apo(a.) influences to a mainly metabolic and physiochemical properties of Lp(a)<sup>7,8</sup>. It appears from certain clinical studies that LP(a) levels are not affected by LDL receptor activity<sup>9,10</sup> suggesting that apo (a) introduces a charge on steric interaction which affects binding potential of apo B in LP(a) for LDL receptor LP(a) levels are particularly affected by apo (a) synthetic rate and affected only to a minor extent by age, sex and environmental factors because of its strong genetic impact<sup>11</sup>.

Lawn, Scanu and their collaborator reported a similarity between the apo (a) and plasminogen genes both having coding sequences for loop structures which are stabilized by interchain disulphide bonds so called Kringle (K) domains. The plasminogen gene contains coding sequence for 5 different K domains (K1-K5) out of these 2 are present in apo (a) gene K4 and K5<sup>12,13,14</sup>. This structural homology renders Lp(a) with the capacity to bind to the fibrin and to membrane proteins of endothelial cells and monocytes and thereby to inhibit binding of plasminogen and plasmin (fibrinolytic enzyme) generation. The inhibition of plasmin generation and accumulation of Lp(a) on the surface of fibrin and cell membrane favours deposition of fibrin and cholesterol at the site of vascular injury so these mechanisms may constitute the basis of athero-thrombotic mode of action of Lp(a). This Competitive inhibition of binding of plasminogen with Lp(a) also suggested that Lp(a) and LDL particles are sensitive to oxidative process. Phagocytosis of

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oxidized Lp(a) and LDL particles results in the formation of foam cells<sup>15</sup>.

Sotirios.T et al suggested that Lp(a) binds pro-inflammatory oxidized phospholipids, so atherogenicity of Lp(a) may be mediated by these pro-inflammatory oxidized phospholipids.<sup>16</sup> In a large scale prospective data a broad range of individuals are found to show continuous association between Lp(a) and CHD<sup>17</sup>.

CRP is one of the most sensitive acute phase reactants in humans and its elevated serum levels are a precise index of inflammatory activity.<sup>18</sup> It is demonstrated that concentration of CRP in the serum is related to disease activity.<sup>19</sup> In a recent study a positive correlation was seen between LP(a) levels and serum CPR levels in patients of Rheumatoid Arthritis.<sup>20</sup> It is also found that there is an inverse association between elevated CRP and HDL-C levels<sup>21</sup>. In some other studies a positive association between Lp(a) with acute phase response has been demonstrated<sup>22,23</sup>.

The present study was aimed to correlate Lp(a) levels with CPR in patients of RA. It is seen that traditional cardiovascular risk factors and CRP (due to generalized inflammation in RA) cannot be used to evaluate the cardiovascular risk in RA patients<sup>24</sup> so if Lp(a) levels are included in addition with other cardiovascular risk factor screening, it can be helpful in development of new guideline for the treatment and to save pts from early cardiovascular threats.

## MATERIALS & METHODS

A total number of hundred subjects were included in this study. Out of these, fifty (25 females and 25 males) diagnosed cases of RA were taken as patients and fifty (22 males and 28 females) healthy subjects were taken as controls. The patients were taken from the Rheumatology clinic of Shaikh Zayed Hospital, Lahore. A 5 ml blood sample from each subject and control after 12 hours fast was drawn. It was placed in plain tube, and allowed to clot for 20 to 30 minutes and then centrifuged. Clear serum thus obtained was preserved at -20°C in eppendroff tubes for later analysis of hs-CRP and LP(a). Quality control was maintained by using control sera manufactured by Human; both normal (N) and pathological (P) controls were used. The hs-CRP method was based on a particle enhanced turbidimetric immunoassay (PETIA) technique.

**CRP <3mg/l taken as low and CRP>10mg/l as high levels<sup>25</sup>:** The quantitative total human lipoprotein alpha Lp(a) was done by solid phase capture sandwich ELISA assay using a microwell format.

**Reference range:** normal value of Lp(a) is

<30mg/dl<sup>26</sup>

Excess Lp(a) was defined as serum Lp(a) conc>30mg/dl<sup>27</sup>

Statistical analysis was done on SPSS (latest version). Results of hs-CRP and Lp(a) were expressed as mean±SD. The association between CRP and Lp(a) was assessed by coefficient of correlation and the significance was seen by using probability table for coefficient of correlation (r). A 'p' value of less than 0.05 was considered statistically significant.

## RESULTS

The mean age, weight, height and BMI of male patients and controls is given in table 1 while table 2 shows mean age, weight, height and BMI of female patients. The mean CRP level in male and female patients was found to be significantly higher (P<0.01) as compared to mean CRP levels of controls (Table 3 and 4). The mean Lp(a) level in male control group was significantly higher (P<0.001) than the male control group (Table 3), similarly in female control group the mean Lp(a) level was significantly higher than the control group (P<0.001) (Table 4).

Pearson coefficient of correlation was calculated for Lp(a) with hs-CRP. Lp(a) showed highly significant (P<0.01) correlation (r=0.56) with CRP in male patient group and female patient group. No significant correlation was seen in male and female control groups (Table 5)

Table 1: Comparison of Age, Weight, Height, BMI in Male Patient and Control Groups. Mean±SD is given. Figure in parenthesis Indicates Number of Cases in Each Group

Parameters	Patients (25)	Control (22)
Age (Yr)	40.45±7.93	42.55±5.20
Weight (Kg)	69.36±6.33	68.68±3.15
Height (m)	1.61±0.02	1.60±0.04
BMI (Kg/m <sup>2</sup> )	26.82±2.48	26.75±1.56

\*p<0.05 significantly higher as compared to controls

Table 2: Comparison of Age, Weight, Height, BMI in female Patient and control Group. Mean±SD is given. Figure in parenthesis Indicates Number of Cases in Each Group

Parameters	Patients (28)	Control (25)
Age (Yr)	44.00±10.22	42.93±8.11
Weight (Kg)	68.24±6.79	66.71±3.65
Height (m)	1.61±0.02	1.59±0.05
BMI (Kg/m <sup>2</sup> )	26.36±2.55	26.57±1.93

\*p<.05 significantly higher as compared to controls

Table 3: Comparison of CRP and LPa in Male Patient and Control Groups. Mean ± SD is given. Figure in parenthesis Indicates Number of Cases in Each Group

Parameters	Patients (25)	Control (22)
CRP (mg/l)	28.73±24.33***	2.24±1.53
LPa (mg/dl)	48.16±15.63***	22.15±8.46

\*\*\*p< 0.001 significantly higher as compared to control  
 Table 4: Comparison of CRP and LPa in female patient and control Groups. Mean±SD is given. Figure in parenthesis indicates number of cases in each group

Parameters	Patients (25)	Control (28)
CRP (mg/l)	38.72±30.09***	2.28±3.11
LPa (mg/dl)	53.01±16.61***	26.66±7.88

\*\*\*p<.001 significantly higher as compared to controls

Table 5: Correlation of Lp(a) with CRP in Male and Female Patients and Control groups. Coefficient of correlation (r) is Given. Figure in parenthesis Indicate Number of Cases in Each Group

	Patient		Control	
	Male (25)	Female (25)	Male (22)	Female (28)
LPa with CRP	0.561**	0.567**	0.008	-0.118

\*p<.05 significant positive correlation and \*\*p<.01 highly significant positive correlation

## DISCUSSION

The current study “Association of Lp(a) and CRP in patients of rheumatoid arthritis” was done to measure Lp(a) levels and correlate them with the CRP levels in RA patients. This was done to assess the relationship of the degree of inflammation (predicted by CRP levels) and cardiovascular risk (predicted by Lp(a) levels) in patients of rheumatoid arthritis. Along with this Lp(a) was correlated with the lipid profile of these patients.

When a comparison of CRP level was made between patients and controls it was observed that both male and female patients had significantly higher CRP levels (p<0.001) as compared to their respective control groups (Table 3&4). Jonathen *et al.* reported the similar results showing raised CRP levels among RA patients<sup>28</sup>. Ridher PM and Cook. N (2004) had emphasized the fact that patients with raised CRP (CRP>10 mg/dl) are considered to be at greater cardiovascular risk<sup>29</sup>. This concept is consistent with findings in current study because both male and female patient groups showed significantly higher CRP levels.

Lp(a) was within normal range in both male and female control groups (Table 3 & 4), while male and female patient group had significantly higher (p<0.001) Lp(a) as compared to their respective control groups. These results are in agreement with the results reported by Ranatappa D *et al.* (1991) and Ankur G and Barry F (2009)<sup>22,30</sup>. All of these researchers reported high levels of Lp(a) in RA patients. Considering the strong association between raised Lp(a) levels (due to its (atherogenicity and thrombogenicity) and cardiovascular risk, it is suggested that Lp(a) may be evaluated as cardiovascular risk factor in RA patients.

A positive strong correlation (p<0.001) was seen between Lp(a) and CRP in both male and female patient group (Table 5 ), which is in agreement with the studies conducted by Dursun D *et al.* (2004) and Panagiotist. H *et al.* (2005)<sup>17,31</sup>. It is observed that Lp(a) rises with the systemic inflammation in RA patients.

## CONCLUSIONS

The following conclusions may be derived from the results of the study:

1. The patients of rheumatoid arthritis (both male and female) had raised CRP levels (more than 10mg/l) and raised Lp(a) levels (more than 30mg/dl).
2. A significant positive correlation was observed between Lp(a) and CRP levels of these patients. Therefore it can be concluded that patients who had raised CRP and Lp(a) levels are more prone to develop cardiovascular defects. Lp(a) should be integrated and monitored as independent CV risk factor into existing screening tests and treatment algorithms of RA patients.

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