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Biochemistry

STUDY OF SERUM URIC ACID AND C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE

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ABSTRACT

Aim: Present study was done to evaluate relationship between Serum uric acid (SUA), C- reactive protein (CRP) and Coronary artery disease (CAD).

Material and Methods: In the present study SUA and serum levels of CRP were compared between 100 cases of CAD and 100 age and gender matched controls. Unpaired t-test and Pearson correlation coefficient (r) were used to assess the correlation between SUA and CRP in CAD Case group. Results: The mean SUA and CRP levels are significantly higher in CAD cases compared with normal controls. The highly significant positive correlation is found between serum uric acid and CRP levels in CAD patients. The correlation is stronger in females than males.

Conclusion: Chronic low grade inflammation and hyperuricemia is positively associated with CAD and the relationship is not independent of each other.

KEYWORDS : Coronary Artery Disease (CAD), SERUM URIC ACID (SUA), C - reactive protein (CRP).

INTRODUCTION

Coronary artery disease is caused due to the obstruction of the arteries that provide oxygen and nutrients to the heart. It is caused by atherosclerosis. This restricts blood flow to the heart. The complete blockage of the coronary artery leads to heart attack. According to Global and Regional Projection of mortality and burden of disease, Coronary artery disease (CAD) will remain the leading cause of death for the next twenty years (Mathers & Loncar, 2006).

Uric acid is the end product of purine metabolism in human beings. In spite of the expectation that the antioxidant properties of uric acid might play a protective role against cardiovascular disease, studies have reported association with greater risk of coronary artery disease, higher blood pressure, and an adverse cardiovascular risk profile (Alderman & Aiyer, 2004; Bos, Koudstaal, Hofman, Witteman, & Breteler, 2006; Fang & Alderman, 2000; Kim et al., 2009; Liese et al., 1999; Meisinger, Koenig, Baumert, & Döring, 2008; Perlstein et al., 2006; Sinan Deveci et al., 2010; Sundström et al., 2005). A possible association of serum uric acid (SUA) with risk of CAD has been noted in several studies (BENEDEK, 1967; Gertler, Garn, & Levine, 1951; Jacobs, 1972; Kagan, Gordon, Rhoads, & Schiffman, 1975; Kohn & Prozan, 1959; Shoshkes, 1976; Welborn et al., 1969). Other reports have not established these findings (Allard & Goulet, 1973; Higgins, Higgins, Lockshin, & Canale, 1969; Medalie, Kahn, Neufeld, Riss, & Goldbourt, 1973) or noted that the association disappears when controlling for relative weight or use of diuretics (Bengtsson & Tibblin, 1974; Gordon, Sorlie, & Kannel, 1971; Group, 1976; Isomäki, 1969; Klein et al., 1973; Myers, Epstein, Dodge, & Mikkelsen, 1968; Shurleff, 1974; Yano, Rhoads, & Kagan, 1977). C-reactive protein (CRP) is an inflammatory marker produced and released by the liver under the stimulation of cytokines such as TNF-α, IL-1 and IL-6. It plays an important role in the process of atherothrombosis (Li et al., 2004; Pasceri, Willerson, & Yeh, 2000).

CRP has been considered as active participate in both atheromatous lesion formation and plaque disruption (Nyandak, Gogna, Bansal, & Deb, 2007; Pasceri et al., 2000). CRP has emerged as a powerful risk estimator for cardiovascular disease (Ridker, 2003; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997; Yeh & Willerson, 2003). It is higher among people who are physically inactive (Ford, 2002; Geffken et al., 2001; Reuben, Judd-Hamilton, Harris, & Seeman, 2003; Wannamethee et al., 2002) and those with worse cardiorespiratory fitness (Church et al., 2002; LaMonte et al., 2002) and in obese (Hak et al., 1999).

There are lots of striking similarity between SUA and CRP as markers of coronary risk. A very few combined study have been done till date. Thus this comprehensive study is being done to record any association between SUA and CAD, CRP and CAD and relationship between SUA and CRP in CAD.

MATERIALS AND METHOD

The present study was conducted in the Department of Biochemistry, Government Medical College Nagpur with the help of Medicine Department. The study was approved by institutional Ethics Committee for research work.

Study design: Hospital based cross sectional study with Comparison Groups.

Sample size estimation: From the study of **Deveci OS et al** (Sinan Deveci et al., 2010)**.**

- SD_1 in CAD cases= 121
- SD_2 in controls= 83.2
- Difference of means of serum uric acid in two groups= 56.5
- α-Error= 5%
- β-Error= 10 %
- Power= 90%
- Minimum sample size needed for study in each arm= 72
- Sample size was calculated using MedCalc Statistical software (MedCalc, 2018).

Study population: From Oct 2013 to Sept 2015, one hundred patients with Coronary Artery Disease were studied. Coronary Artery Disease patients were acute Myocardial infarction patients admitted in the ICU of Medical College.

The criteria to select patient in our study consisted of the patients with acute myocardial infarction diagnosed by physician on the basis of the definition approved by American College of Cardiology Committee (ACC) and European Society of Cardiology (ESC).

This included typical rise and gradual fall of troponin level and /or severe increase and decrease of CK-MB associated with at least one of the following parameters:

1) Gradual appearance of pathological Q wave on electrocardiogram strip (ECG) or

2) EKG changes indicating ischemia on the ECG strip (ST segment elevation)

STUDY GROUPS
The study subjects were divided into two groups.

A: Control subjects (n=100)
One hundred normal subjects without CAD

B: CAD Cases (n=100)
One hundred newly diagnosed CAD patients.

INCLUSION CRITERIA
One hundred newly diagnosed cases of acute myocardial infarction more than or equal to twenty years of age admitted in the ICU of Medical College Hospital.

EXCLUSION CRITERIA
Patients with inflammatory diseases like gout, rheumatoid arthritis, inflammatory bowel disease, renal disease, hypothyroidism, diabetes, anaemia, stroke, malignancy, bacterial infections and smokers were excluded from the study.

CLINICAL DATA RECORDING
After explaining all details, informed consent was taken from each subject for participation in this study. History and examination of patient was recorded on preformed questionnaire which included detailed history and clinical examination.

SPECIMEN COLLECTION AND PRESERVATION
Blood samples were collected from peripheral veins of case and control subjects under aseptic conditions. Enrolment was voluntary and written consent was obtained from each participant. Fasting blood samples were taken. Four ml blood sample in plain tube and one ml in sodium fluoride and oxalate bulb were collected. Estimation of fasting blood sugar was done to rule out diabetes. After one hour of collection samples were centrifuged; serum and plasma of a subject were separately taken in the new tubes. Serum uric acid, CRP, blood urea, serum creatinine and fasting blood sugar were estimated on XL300 - Erba Mannheim – A Fully Automatic Random Acess Clinical Chemistry Analyzer**.** Serum was preserved at 2-8 degree Celsius.

PARAMETERS WERE ESTIMATED WITH FOLLOWING METHODS

S.No	PARAMETER	METHOD
1	Serum uric acid	Uricase-pap method
2	C Reactive Protein	CRP Latex Turbidimetry
3	Blood Urea	Enzymatic method – Urease Berthelot ;end point method
4	Serum Creatinine	Initial rate method using alkaline picrate.
5	Plasma Glucose	Enzymatic method- Glucose Oxidase and Peroxidase- End point

STATISTICAL ANALYSIS
- Serum uric acid (SUA) and C Reactive Protein (CRP) were presented as mean ± SD.
- Statistical data was recorded on Microsoft Excel programme.
- Unpaired t-test was performed to compare Serum uric acid (SUA) and CRP between CAD case and control groups.
- Pearson correlation coefficient (r) was calculated to assess the correlation between Serum uric acid and CRP in CAD Case group.
- Both the tests were two sided. P value <0.05 was considered as statistically significant. The p value < 0.001 was considered as highly significant and the p value > 0.05 was taken as non-significant (NS).
- Statistical software Microsoft Excel was used for statistical analysis.
- The p value calculator downloaded from www. socscistatistics. com was used for calculating p value for Pearson's correlation.

Results and Discussion

Table- 1 Distribution of Serum Uric Acid and CRP in CAD patients and controls without CAD

PARAMETERS	CONTROLS (Mean ± SD)	CASES (Mean±SD)	P-VALUE
Serum uric acid in both males and females(mg/dl)	4.65 ± 0.77	5.756 ± 0.32	< 0.001
Serum uric acid in males (mg/dl)	4.92 ± 0.59	5.65 ± 0.28	< 0.001
Serum uric acid in females (mg/dl)	4.11 ± 0.8	5.96 ± 0.305	< 0.001
CRP levels in both males and females (mg/L)	2.62 ± 0.59	17.66 ± 6.41	< 0.001
CRP levels in males (mg/L)	2.72 ± 0.55	16.97 ± 6.95	< 0.001
CRP levels in female (mg/L)	2.43 ± 0.64	19.06 ± 4.95	< 0.001

* p<0.05 is considered significant; SD – Standard deviation

In our study the mean level of serum uric acid in both males and females taken together in control group is 4.65 ± 0.77 mg/dl and in case group is 5.756± 0.32 mg/dl with p value < 0.001. The serum uric acid level is significantly higher in CAD cases compared with normal controls. Morris London et al (Lim et al., 2010; London & Hums, 1967) and M. Torun et al (Torun, Yardım, Simsek, & Burgaz, 1998) have reported significantly higher uric acid level in CAD patients. The Rotterdam Study has reported uric acid as a strong risk factor for myocardial infarction and stroke (Bos et al., 2006). In the study by Culleton et al (Culleton, Larson, Kannel, & Levy, 1999) published in the year 1999, reported that uric acid was not a causal risk factor for cardiovascular events because uric acid was not independent of hypertension. In a substudy of LIFE (Hoieggen et al., 2003) published in 2004, baseline serum uric acid level was reported to be significantly associated with increased rate of fatal or non-fatal myocardial infarction. The high level of SUA in ischemia is due to excess production of uric acid by xanthine oxidase enzyme which, causes oxidative stress and promotes the oxidation of Low density lipoprotein cholesterol (LDL-c) and the peroxidation of lipid (Akpek et al., 2011; Braunwald, 2008; Wasserman, Shnell, Boursi, & Guzner-Gur, 2010). Also,hyperuricemia leads to decline in the production of nitric oxide and causes endothelial dysfunction and myocardial microvascular disease and local inflammation.

The mean level of serum uric acid in male in case group is 5.65 ± 0.28 mg/dl. The mean level of serum uric acid in females in case group is 5.96 ± 0.305 mg/dl. The mean serum uric acid level is slightly higher in females as compared with males in CAD cases (Tuttle, Short, & Johnson, 2001). Study published in the year 2001 have reported that the uric acid level was correlated with the CAD severity score in women; however, such relationship was not established for men. According to the National Health and Nutrition Examination Survey I data (Fang & Alderman, 2000) published in the year 2000, cardiovascular mortality is increased 1.77-fold in men and 3.0-fold in women who had uric acid levels in the upper quartile.

The mean level of C-reactive protein in both males and females taken together in control group is 2.62 ± 0.59 mg/L and in case group is 17.66 ± 6.41 mg/L with p value < 0.001. The CRP levels is significantly higher in CAD cases compared with normal controlsl (Arroyo-Espliguero et al., 2004; Yilmaz et al., 2007). and (Sharma, Garg, Veerwal, & Dwivedi, 2008) have reported significantly higher CRP level in CAD patients than in normal controls. The main biological function of CRP is the nonspecific defence against the infectious agents and removal of apoptotic and necrotic cells. As, myocardial tissue necrosis is associated with myocardial infarction which, may lead to the increased level of CRP. CRP directly participate in the inflammatory process of atherosclerosis & localizes in atherosclerotic plaque (Inoue et al., 2005; Ishikawa et al., 2003). C-reactive protein also increases the production of matrix metalloproteinase (MMP) thus, makes the plague vulnerable for rupture and hence may lead to acute myocardial infarction (Abe et al., 2006; Montero et al., 2006; Williams, Zhang, Game, He, & Huang, 2004). Prothrombotic state generated by CRP is due to tissue factor release from mononuclear cells (Cermak et al., 1993; Paffen, Vos, & Bertina, 2004). CRP promotes endothelial, and smooth muscle cells proliferation (Cirillo et al., 2005).

The mean level of C-reactive protein in males in case group is 16.97 ± 6.95 mg/L and in females in case group is19.06 ± 4.95 mg/L. The mean CRP levels is slightly higher in females as compared to that in males in CAD cases. Significantly higher CRP level in females as compared with males have been reported by Ross Arena et al (Arena, Arrowood, Fei, Helm, & Kraft, 2006).

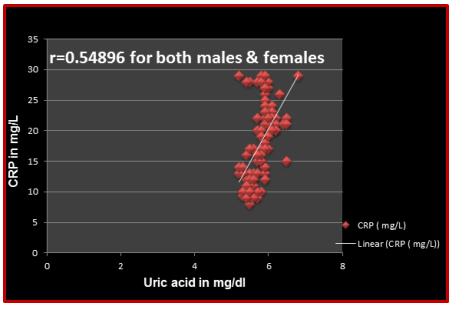
Table -2: The Pearson Correlation coefficient between Serum Uric Acid and CRP in CAD cases

Pearson correlation coefficient between CRP & SUA	Value of Pearson correlation coefficient	P value
In both genders	0.54896	< 0.001
In males	0.52878	< 0.001
In females	0.62259	< 0.001

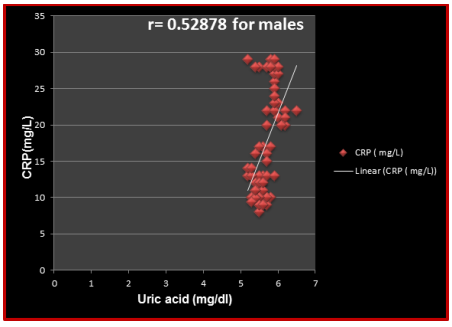
* p<0.05 is considered significant.

The Pearson correlation coefficient 'r' between CRP and serum uric acid in both males and females taken together in CAD cases is found to be 0.54896 ; with p- value < 0.001. It has been postulated that uric acid is involved in sterile (i.e., non-infectious) inflammation by activating the release of inflammatory cytokines, mainly CRP and TNF-α. Such systemic inflammation may later lead to the development of atherosclerosis and subsequently CAD. These findings are in favour of the experimental data in mice reporting that uric acid represents a major proinflammatory damage-associated molecular pattern (DAMP) (Kono, Chen, Ontiveros, & Rock, 2010). Similar findings have been reported by Frohlich et al (Fröhlich et al., 2000), Saito et al (Saito et al., 2003) and In CHIANTI study (Ruggiero et al., 2006). The in vitro studies have manifested that uric acid enters the vascular smooth muscle cells and stimulates pro-inflammatory response, leading to increased cell proliferation and production of CRP and other inflammatory mediators (Johnson, Rodriguez-Iturbe, Kang, Feig, & Herrera-Acosta, 2005; Kanellis et al., 2003). The pearson correlation coefficient 'r' between CRP and serum uric acid is more stronger for females than males in CAD cases in the present study.

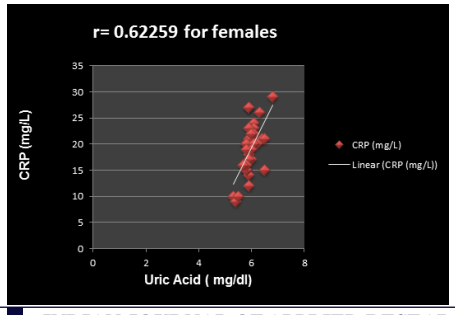
Graph-1: The correlation between Serum Uric Acid levels and CRP levels in both male & female patients with CAD



Graph-2: The correlation between Serum Uric Acid levels and CRP levels in male patients with CAD



Graph-3: The correlation between Serum Uric Acid levels and CRP levels in female patients with CAD



SUMMARY AND CONCLUSIONS

This study entitled 'Study of Serum uric acid and C-reactive protein in Coronary artery disease ' was a hospital based cross sectional study with comparison groups, conducted in the Department of Biochemistry at tertiary health care centre with the help of Medicine Department during the period of two years. The Study population consisted of age and sex matched one hundred newly diagnosed CAD patients in case group and one hundred normal subjects in control group. The study was carried out to evaluate the relationship between CRP and CAD, Serum Uric Acid and CAD, CRP and Uric Acid together in CAD. The concentrations of serum uric acid was estimated from the serum samples of both the cases and controls by colorimetric methods. The serum CRP levels was measured by Latex Turbidimetry. Statistical analysis was performed using student's unpaired t-test and the p value was calculated. The relationship between the quantitative variables in CAD group were evaluated by Pearson correlation coefficient.

CONCLUSIONS

In the present study, we have following findings:

1. The mean serum uric acid level is significantly higher in CAD cases compared with normal controls.
2. The mean serum uric acid level is slightly higher in females as compared with males in CAD cases.
3. The mean CRP level is significantly higher in CAD cases compared with normal controls.
4. The mean CRP level is slightly higher in females as compared with males in CAD cases.
5. The highly significant positive correlation is found between serum uric acid and CRP levels in CAD patients.
6. The positive correlation between serum uric acid and CRP is stronger in females than males.

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