



## Study of Serum Uric Acid, C-Reactive Protein and Atherogenic Index in Coronary Artery Disease

Authors

**Dr Suresh Kumar Sabar<sup>1</sup>, Prof. Dr. Manmath Kumar Mandal<sup>2</sup>,  
Dr Upendra Kumar Das<sup>3</sup>**

<sup>1</sup>Senior Resident, Biochemistry, VSS Institute of Medical Science and Research (VIMSAR), Burla, Odisha, India, Email: [dr.sureshsabar@rediffmail.com](mailto:dr.sureshsabar@rediffmail.com), Phone no: 919437701361

<sup>2</sup>Professor & HOD, Biochemistry, VIMSAR, Burla, Odisha, India

<sup>3</sup>Associate Professor, Biochemistry, SCB Medical College, Cuttack, Odisha, India

Corresponding Author

**Prof. Dr Manmath Kumar Mandal**

Professor & HOD, Biochemistry, VIMSAR, Burla, Odisha, India

Email: [manmathk.mandal@gmail.com](mailto:manmathk.mandal@gmail.com), Phone no: 919437080136

### Abstract

Coronary Artery Disease (CAD) or Ischemic Heart Disease (IHD) is the leading cause of death worldwide. Coronary artery disease has a number of well determined risk factors which include smoking, family history, hypertension, obesity, Diabetes, lack of exercise, stress and blood lipids. While the prevalence and mortality due to CHD is declining in the developed nations, there has been an alarming increase over the past two decades in the prevalence of CHD and cardiovascular mortality in India and other south Asian countries. A few studies have shown that serum uric acid has a role in the development of cardiovascular morbidity. The aim of the present study was to evaluate the level of serum uric acid, serum C - reactive protein and atherogenic index in patients with coronary artery disease. This study was conducted by taking 41 cases of coronary artery disease and 35 number of age and sex matched healthy controls. Results showed increased level of serum uric acid and atherogenic index ( $P < 0.005$ ) and decreased value of serum HDL- cholesterol ( $P < 0.005$ ) which were statistically significant. Also, we found a strong positive correlation between the atherogenic index and serum uric acid. There were many positive result for elevated C-reactive Protein. Thus, serum uric acid, atherogenic index and CRP can be helpful for risk assessment and can be used as prognostic markers for patients with ischemic heart disease.

**Keywords:** Coronary artery disease (CAD), Atherogenic index (AI), C-reactive protein(CRP), Uric acid. Ischemic Heart Disease (IHD).

### Introduction

Coronary artery disease is a form of ischemic heart disease occurs when there is imbalance between myocardial oxygen supply and demand<sup>1</sup>. Most common cause of myocardial ischemia is atherosclerosis of epicardial coronary arteries; sufficient to cause a regional reduction in

myocardial blood flow & inadequate perfusion of the myocardium supplied by the involved coronary artery. The term coronary artery disease recognizes the clinical condition resulting from rupture of unstable coronary plaque with subsequent overlying thrombus formation and blood flow restriction resulting in cardiac chest

pain; typical ECG changes or elevation of serum cardiac biomarkers. Coronary artery disease causes more death and disability and incurs greater economic cost than any other illness in the developed world. In developing countries it is growing among low income groups rather than in high income groups (who are adopting more healthful life styles). At present incidence of coronary artery disease is increasing in developing countries.

There are several risk factors for the development of coronary artery disease such as high TG, low HDLc, high LDLc, Hypertension, Age, Sex & Smoking<sup>2</sup>. High (AIP) atherogenic index of plasma (TG/HDL- cholesterol) predict high BP, diabetes and vascular events<sup>3</sup>. Epidemiological studies have identified a strong association between raised serum uric acid concentration and increased cardiovascular risk<sup>4</sup>. Elevated serum uric acid is highly predictive of mortality in patients with coronary artery disease. Various studies have shown the association between increased uric acid concentration with oxidative stress, endothelial dysfunction, inflammation, subclinical atherosclerosis and increased risk of cardiovascular events<sup>5</sup>.

C-reactive protein (CRP) is the classical acute phase reactant<sup>6</sup> the serum level of which has long been known to increase after myocardial infarction<sup>7</sup>. Earlier works suggest that measurement of CRP may be useful in the diagnosis and management of myocardial infarction. Increase in CRP production is a non specific response to most form of cell death, tissue injury, infection or inflammation and it is clear that myocardial necrosis is a potent stimulus.

Other studies shows that body mass index (BMI) as well as C-reactive protein are associated with acute coronary syndrome<sup>8</sup>.

The present study was carried out to evaluate the level of serum uric acid, C-reactive protein and atherogenic index and also to correlate the association of serum uric acid and atherogenic index in coronary artery disease.

## Materials & Methods

Informed consent was obtained from individuals before enrollment of the study & approval from ethical committee was obtained.

The present study was undertaken in the Department of Biochemistry, VSS institute of Medical science and research (VIMSAR), Burla on diagnosed coronary artery disease patients attending the outpatient Department and getting admitted to the Department of Medicine and Cardiology between September 2011 to September 2013. The study included 41 coronary artery disease patients between 30 to 60 years of age. 35 number of age and sex matched healthy individuals were taken as control. Clinically established/ confirmed coronary artery disease cases, hypertensives, obese persons & smokers were included in the study. Cases with diabetes mellitus, nephropathy, chronic alcoholism & pregnant ladies were excluded.

Blood pressure and BMI were measured. Routine biochemical investigations were carried out in both the study groups by standardized protocols using Cobas Integra 400, fully automated high throughput Chemistry analyzer

Sample collection and preparation: After an overnight fast, 5ml fasting venous blood was collected for following tests and routine tests like fasting plasma glucose, serum urea, serum creatinine, serum protein, serum albumin, lipid profile and serum uric acid were carried out.

Serum uric acid was estimated by Caraway method. Special tests like C-Reactive protein was estimated by Rapid slide latex method & atherogenic index by formula  $AI = \log_{10} \frac{TG}{HDL}$  were carried out.

T test was done to evaluate the statistical significance of difference between two mean and 'p' value were determined. Correlation test was used to find out the relationship between two quantitative variables. The extent of relationship between the variables was measured in terms of correlation co-efficient (r). 'p' value <0.05 were considered statistically significant.

**Observation**

**Table-I** Distribution of Cases According to the Type of Coronary Artery Disease

Type	No. of Cases	Percentage
STEMI	20	48.78%
NSTEMI	10	24.39%
UA	6	14.63%
SA	5	12.19%

**Table-II** Clinical Parameters in The Groups Studied

PARAMETERS	CONTROL(n=35)		Case (n=41)		't' value	'p' value
	MEAN±SD	Range	MEAN±SD	Range		
AGE(Years)	45.5±10.1	30-60	45.9±9.3	30-60	3.40	>0.05
AC (inch)	34.1±1.3	32-36	36.2±2.4	32-44	4.71	<0.0001
BMI (Kg/m <sup>2</sup> )	21.7±1.5	19.2-23.8	29.6±1.8	25.8-32.2	20.4	<0.0001
SBP(mm Hg)	120±10.8	90-136	144±13.2	110-162	7.82	<0.0001
DBP(mm Hg)	80±6.6	70-88	98 ± 7.7	80-110	10.7	<0.0001

**Table-III** Comparison of Urea & Creatinine in Study Groups

Parameters	Controls(35)		Cases(41)		't' value	'p' value
	Mean±SD	Range	Mean±SD	Range		
Uric acid	5±1.5	2.5-7.0	7.7±1.7	4-12	7.3	<0.0001
AI	0.15 ±0.03	0.10-0.21	0.33±0.16	0.11-0.67	6.2	<0.001

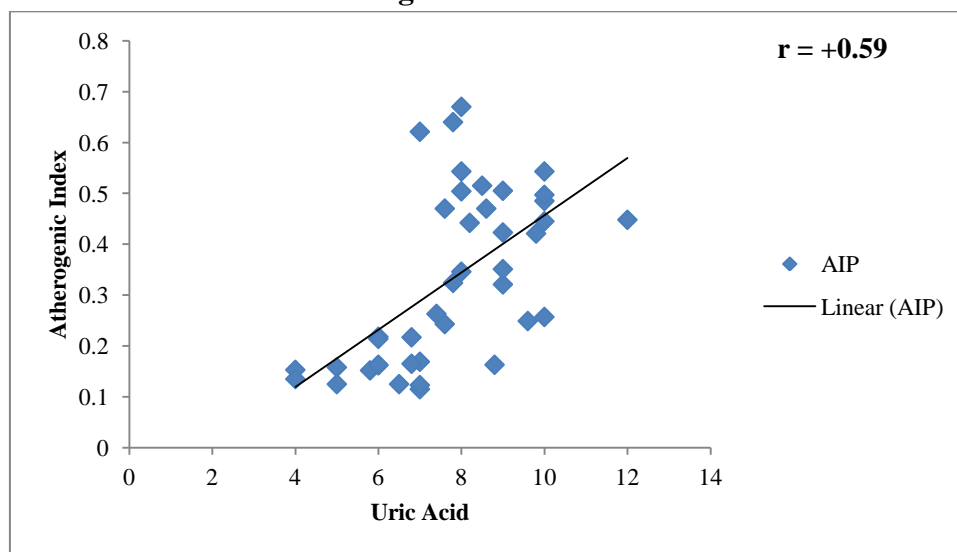
**Table-IV** Comparison between Serum Uric Acid and Atherogenic Index in Study Group

PARAMETERS (mg/dl)	CONTROLS (n=35)		CASES (n=41)		't' VALUE	'p' VALUE
	MEAN±SD	RANGE	MEAN±SD	RANGE		
UREA	32±8.44	15-40	33±8.44	20-40	0.22	>0.05
CREATININE	1.0±0.24	0.7-1.4	1.4±0.24	1-1.4	0.45	>0.05
Protein	6.8±0.48	6.2-7.6	6.8±0.51	6.1-7.8	0.45	>0.05
Albumin	4.5±0.28	4.2-5	4.4±0.27	4.0-4.8	0.35	>0.05

**Table –V** Correlation Of Serum Uric Acid With Atherogenic Index

Serum uric acid (mean±SD)	Atherogenic index	Correlation coefficient
7.7±1.7	0.33±0.16	+0.59

**Correlation of Serum Uric Acid with Atherogenic Index**



**Figure-1**

**Table VI** Comparison of Elevated CRP Levels Among Cases and Controls

Test for CRP	CONTROLS	CASES
POSITIVE	0	30
NEGATIVE	35	11

**Discussion**

A considerable progress has been made delineating the role of plasma lipids and lipoprotein in the development of atherosclerosis and coronary artery disease during the past two decades. Close association of hyperlipidemia and coronary artery disease has been well documented by a number of workers (Kannel et al., 1971<sup>9</sup>; Kaukola et al.,1980<sup>10</sup>) Some workers have found hyperuricemia in the patients of manifested coronary artery disease while others have found raised C- Reactive protein as common abnormality. Our study was carried out to evaluate the serum uric acid, CRP and atherogenic index in the patients of coronary artery disease.

In the present study group the number of coronary artery disease patients were 41 and the number of healthy controls were 35.

According to the TABLE I the different types of the coronary artery disease patients selected for this study were ST-segment elevated myocardial infarction (STEMI), non ST- segment elevated myocardial infarction (NSTEMI), Stable Angina And Unstable Angina. The largest group was that of STEMI 49% followed by NSTEMI 24% then Unstable Angina 15% and Stable Angina 12%. The study done by Kristina Orth Gomer et al<sup>11</sup> showed that 52% of the patients had STEMI ,26% of the the patient were NSTEMI,22% had Angina. This was very much closer to our study.

TABLE II summarizes the clinical parameters studied in both the groups. Mean age for controls was 45.5±10.1 SD with a range of 30-60 years and for cases was 45.9±9.3 with a range of 30-60 years. BMI (Body mass index) for controls was 21.7±1.5 Kg/m<sup>2</sup> with a range of 19.2-23.8 .and for cases was 29.6±1.8 kg/m<sup>2</sup> with a range of 25.8-32.2 kg/m<sup>2</sup>. The mean body mass index of cases is significantly higher than the controls (p<0.0001).

AC (Abdominal Circumference) for control group was 34.1±1.3 inch with a range of 32-36 inch and for cases it was 36.2±2.4 inch with a range of 32-44 inch. (p<0.0001).Pan WH et al<sup>12</sup> studied that hyperuricemia is associated with the increasing BMI even in apparently younger subjects. Our study is consistent with this study.

Hypertension is strongly associated with hyperuricemia. According to Cannon PJ et al<sup>13</sup> serum uric acid is elevated in hypertension and present in 25% of untreated hypertensive subjects, 50% of the subject taking diuretics and greater than 75% of the patients were with malignant hypertension.

Potential mechanism involved with the association of hyperuricemia and hypertension includes as follows

- i. Decreased renal blood flow stimulating the urate reabsorption.
- ii. Microvascular disease resulting in local tissue ischemia.
- iii. Ischemia is associated with increased lactate production that blocks the uric acid secretion in the proximal tubule.
- iv. Ischemia induces xanthine oxidase activities.

Lin KC et al<sup>14</sup> were able to demonstrate that blood pressure level can predict for cardiovascular disease incidence synergistically with serum uric acid levels.

Table III shows comparison of serum urea, serum creatinine, Total protein and albumin among the cases and control groups.

Serum urea in controls was 32± 8.44 mg/dl with a range of 15-40 mg/dl and for cases 33±8.44 mg/dl with a range of 20-40 mg/dl. Serum urea level was higher in cases as compared to the controls which was statistically not significant (p>0.05) Serum creatinine in control group was 1.0±0.24 mg/dl with a range of 0.7-1.4 mg/dl and for cases 1.4±0.24 with a range of 1-1.4 mg/dl. Serum creatinine was higher in cases as compared to the controls which was statistically not significant (p>0.05).

Serum protein in controls are  $6.8 \pm 0.48$  gm/dl with a range of 6.2-7.6 gm/dl and for cases  $6.8 \pm 0.51$  gm/dl with a range of 6.1-7.8 gm/dl. Serum protein in cases was higher as compared to controls which was statistically not significant ( $p > 0.05$ ). Serum Albumin in control group was  $4.5 \pm 0.28$  gm/dl with a range of 4.2-5 gm/dl and for cases  $4.4 \pm 0.27$  gm/dl with a range of 4-4.8 gm/dl. Serum Albumin was higher in controls as compared to cases which was statistically not significant ( $p > 0.05$ ).

TABLE IV shows the comparison of uric acid and atherogenic index among the study groups. The mean uric acid in the cases was  $7.7 \pm 1.7$  mg/dl, whereas in controls it was  $5 \pm 1.5$ . Thus serum uric acid level was significantly higher ( $< 0.0001$ ) in cases as compared to the controls.

The mean atherogenic index ( $\text{LOG}_{10} \text{ TG/HDL-C}$ ) of case was  $0.33 \pm 0.16$  whereas in control it was  $0.15 \pm 0.03$ . The Atherogenic index of cases as compared to the control is significantly higher. ( $p < 0.001$ ) Studies by Johnson R J, et al also showed that patients of CAD had hyperuricemia.<sup>15</sup> Study by T Souli SG, showed that more severe the blood pressure elevation, the higher the serum uric acid level. About 75% persons with malignant hypertension have hyperuricemia.<sup>16</sup> In our study we found patient having hyperuricemia irrespective of history of diabetes mellitus. This finding is consistent with the study of Tuomilhto et al in which there was no significant association between serum uric acid level and diabetic status.<sup>17</sup>

Hyperuricemia is very common in patient with heart failure. Several studies notably those by Anker, Coats and others demonstrated a very powerful association of serum uric acid and mortality. (Levy F, Anker S, Swan JW et al).<sup>18</sup> Killip classification is an indicator of severity of heart failure. In a study by Bickel C et al<sup>19</sup> out of 294 subjects with CAD, there were 116 deaths during 10 yrs of follow up. The 12 subjects with serum uric acid more than normal limit died during first 3 yrs while subjects within normal level were alive at 9 yrs.

The relation of serum uric acid to the cardiovascular disease outcome was continuous and independent of other risk factors. One mg/dl increase in serum Uric acid was associated with a 26% increase in mortality as found by the study by Bickel C et al.<sup>19</sup>

TABLE V shows the correlation between the atherogenic index and the serum uric acid. It shows that serum uric acid level has positive correlation with atherogenic index in patient of coronary artery disease ( $r = +0.59$ ).

Our study is consistent with Alderman et al<sup>20</sup> where he studied 100 number of coronary artery disease and found that hyperuricemia was positively correlated with increased triglyceride level and decreased HDL<sub>C</sub> level. A much larger trial (1967) confirmed the initial interest in serum uric acid and cardiovascular disease with publication of epidemiologic Framingham study. This classical paper by Kannel et al<sup>9</sup> noted that an elevated serum uric acid was also associated with increased risk of CAD for men aged 30-59. In addition to the important finding of elevated cholesterol level  $> 250$  mg/dl being associated with CAD there also appeared a definite association of elevated serum uric acid which was associated with an increase in the incidence rate of CAD. Hyperuricemia is associated with endothelial cell damage, dysfunction, decreased endothelial nitric oxide bioavailability and increased reactive oxygen species.

Johnson RJ et al<sup>15</sup> have nicely demonstrated that hyperuricemia predict cardiovascular events in general population, hypertensive population and patient with preexisting cardiovascular disease. Furthermore hyperuricemia predicts the future hypertension. Tamkoshi k et al<sup>21</sup> have shown a statistically significant positive correlation between CRP, Body mass index (BMI), Total cholesterol, triglycerides, LDL<sub>C</sub>, Uric acid, systolic blood pressure, diastolic blood pressure and significant negative correlation of CRP with HDL<sub>C</sub> in a study of 3692 Japanese aged 30-60 yrs. TABLE VI shows the elevated level of C-reactive protein among the study group. Out of 41 numbers



of cases 30 (73%) were having elevated CRP. But on the other hand none of the controls was having elevated CRP. This observation is very much consistent with the finding of Kushner et al.<sup>22</sup> They noted a lag period of 22 hour for increase of C-Reactive Protein to occur in some but not in all patients.

Pietila et al<sup>23</sup> reported on increase in CRP in 40 numbers of patients with coronary artery disease along with CK-MB. They found 32 out of 40 numbers of patients had an increase in CRP 20 hours after the onset of symptoms. Coronary artery disease induces an acute phase inflammatory reaction that is characterized by an increase in CRP. Peak CRP concentration correlates with infarct size. CRP is synthesized by liver as a part of the acute phase response stimulated by the pro-inflammatory cytokine interleukine-6. It was shown by Newman et al,<sup>24</sup> in patients undergoing angioplasty for CAD that the interleukin-6 is released from the myocardium and can be detected in the blood circulation.

Now a day's differential diagnosis of coronary artery disease from other causes of chest pain is a common clinical problem. Even when the diagnosis is established there are many difficulties like recognition of myocardial necrosis in patients with known ischemic heart disease, recognition of intercurrent complications in the post infarct period, prognosis in the immediate post infarct period, and the assessment of patient for discharge from coronary care unit to the ward and from ward to home.

So in such a difficult situation measurement of CRP along with other cardiac biomarkers like Troponin, CK-MB and Uric acid is very much helpful for the clinician to take further steps in the management of patients with coronary artery disease.

### Conclusion

Present study reveals that high serum uric acid level was associated with the coronary artery disease. Elevated uric acid is highly predictive of morbidity in these patients. C-Reactive protein

can be used for the risk assessment and prognostic marker in patients with coronary artery disease. There is positive correlation between uric acid and atherogenic index in patients with coronary artery disease

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