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# ORIGINAL ARTICLE

## SERUM URIC ACID LEVELS IN TYPE-2 DIABETES MELLITUS AND ITS ASSOCIATION WITH CARDIOVASCULAR DISEASE

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**ABSTRACT: BACKGROUND:** Cardiovascular disease is the leading cause of morbidity and mortality especially in diabetic patients. The association between increased serum uric acid (SUA) levels and cardiovascular risk has been reported for decades. Several large studies have provided conflicting results regarding the clinical significance of elevated SUA levels in cardiovascular disease (CVD). The aim of this study was to investigate the relationship between SUA and CVD in diabetic patient. **OBJECTIVES:** To estimate the level of serum uric acid in Type 2 Diabetes mellitus. To establish the association of elevated serum uric acid concentration as a risk factor for CAD in type–2 diabetes patients. To establish the association of uric acid level in relation to other risk factors of coronary artery disease in type-2 diabetes patients. **METHODS:** This is a cross sectional study conducted is people with type 2 diabetes mellitus. Clinical and biochemical parameters like serum uric acid, lipid profile, fasting blood sugar and post prandial blood sugar were compared between subjects with and without coronary artery disease. Statistical analysis included usage of students test and chi square test. **RESULTS:** Among males in hyperuricemia group, 24.5% were obese, 51.5% were smoker, 20% were alcoholic 28.5% were hypertensive and 84.3% had coronary artery disease as compared to patient with normal uric acid group 10% were obese, 37.2% were smokers, 30% were alcoholic, 17. 2% were hypertensive and 26% had coronary artery disease. This shows increased incidence of hypertension, coronary artery disease and obesity in patient who have increased uric acid. Biochemical profiles in patient with hyperuricemia and patient with normal uric acid is as follows. FBS (184.8 Vs. 152.4mg%), PPBS (274.9 Vs. 258.6mg%), TC (207.3 Vs. 181.6mg%), TGL (185.7 Vs. 148.6mg%), LDL (136.7 Vs. 127.1mg%), HDL (40.05 Vs. 40.87mg%). There was significant elevation of total cholesterol, triglycerides and LDL in study group. Mean fasting blood sugar was 175.8 in patient with CAD as compared to 169.58 in patient without CAD. Total cholesterol was 206.68 Vs. 182.4mg%, triglycerides was 174.3 Vs. 152.3mg% and LDL was 135.6 Vs. 120.7mg%. **CONCLUSION:** The mean values of serum uric acid were elevated in diabetics with coronary artery disease. Elevated uric acid may be an epiphenomenon due to associate other coronary artery disease risk factors. Our study also found out that significant elevation of triglycerides in both the groups with and without coronary artery disease. Which is more significant patient with CAD. It also has been observed that elevated uric acid is associated with hypertriglyceridemia. When there is elevated serum uric acid in diabetics that can be considered as a marker of coronary artery disease.

**KEYWORDS:** Diabetes mellitus, serum uric acid, cardiovascular disease.

**INTRODUCTION:** Type-2 Diabetes Mellitus has assumed an epidemic in India for the past few decades. Diabetes mellitus is a metabolic disorder that is associated with cardiovascular complications. The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that is characterized by central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension.[(1)].

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Hyperuricaemia or elevated serum uric acid level (SUA) is a biochemical entity that is gaining increasing importance as a cardiovascular risk factor.[2,3,4]

Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes.[5,6] Further potentially important biological effects of uric acid relate to endothelial dysfunction by inducing anti proliferative effects on endothelium and impairing nitric oxide production and inflammation.[7,8]

Some evidences suggest that uric acid may exert a negative effect on cardiovascular disease by stimulating inflammation, which is clearly involved in the pathogenesis of cardiovascular disease.[9,10]

Here an attempt has been made to study the level of serum uric acid level in Type 2 diabetes mellitus & the correlation between elevated serum uric acid level and its association with cardiovascular disease.

**MATERIALS AND METHODS:** Our study included about 140 patients. Our study included the patients in 2 groups, all of them were diabetic. One group was patients without any evidence of coronary heart disease clinically or electrocardiographically. They were considered as control group. Those patients who had clinical and electrocardiographic evidence of myocardial infarction were another group. There were totally 70 patients in control group and 70 patients in the study group. 97 patients were males and 43 patients were females.

**CASE SELECTION:** The study was done with a random selection of patients suffering type-2 diabetes mellitus from wards, OPDs, review OPDs. All the studied patients were ambulant, clinically stable with no evidence of congestive heart failure due to post myocardial infarction state or free from other major chronic diseases.

**CLINICAL PARAMETERS:** Following clinical parameters such as duration of diabetes, age of onset of the diabetes, history of hypertension, prior history of CAD or cerebrovascular accident, smoking, alcoholism was assessed.

Body mass index was calculated by measuring the weight and height of the patients and using the formula BMI = weight in kg/height in m.$^2$ Normal BMI ranges from 18.5 to 25. 25-30kg/m$^2$ is considered as overweight, and >30kg/m$^2$ were considered to be obese. Our study population was small framed individuals most of whom had normal body mass index in the range of 18.5 to 25.0 kg/m$^2$. Only small group of patients formed the group of overweight patients.

Supine and standing BP was measured in all patients to rule out autonomic imbalance and none of the patients in our study group had any clinical evidence of autonomic neuropathy.

**EXCLUSION CRITERIA:** Those patients who were already suffering from chronic diseases such as tuberculosis, or chronic leg ulcers were not included in our study. As our study was analysis of serum uric acid level with the association of coronary artery disease and its associated risk factors, the patients taking the drugs that significantly alter the serum uric acid level were also excluded. Patients who are already suffered from the ischemic event, most of them were on low dose aspirin, which do not affect the serum level of uric acid significantly.

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The patients suffering from any form of renal failure either acute or chronic were also excluded from the study. Other patients who were suffering from volume overload or volume depletion were also excluded from the study as these conditions may significantly affect the serum uric acid level.

**Biochemical Parameters:** As a screening procedure for early renal involvement of kidneys by diabetic nephropathy, urine spot protein/ creatinine ratio was done in all patients.

Our primary end point results were the analysis of serum uric acid level in association with the coronary artery disease and its associated risk factors. Therefore basic biochemical parameters like blood urea and serum creatinine were done in all patients to rule out overt renal failure.

Fasting and postprandial blood sugar estimation was done to assess the glycemic status of the individuals. All the patients were also investigated for complete lipid profile, which include total cholesterol, triglycerides, VLDL, LDL, and HDL. Total cholesterol was estimated by Allantoin et al method and triglycerides by enzyme calorimetric test and HDL by precipitation method were directly measured and VLDL was calculated by TGL/5 and LDL was calculated by Total cholesterol – (VLDL+HDL). Triglyceride level has to be estimated only when there is gross elevation of triglycerides more than 400mg/dl. None of our patients had such a higher value.

Serum uric acid level also estimated by using Trinder method (ERBA diagnostic kit) in the fasting state, as purine rich diet may influence the serum uric acid levels significantly.

Single channel ECG was taken in all patients to assess whether the patients suffer from any ischemia or not. Those patients who had old myocardial infarction pattern or normal ECG were included. The patients who suffered only from ischemia were not included in our study. The patients who had nonspecific changes or the evidence of other cardiac diseases were also excluded from the study.

**OBSERVATIONS AND RESULTS:** The analysis was separately done for males and females in which each subgroup was analyzed for the presence of hyperuricemia and coronary artery disease risk factors and compared with the coronary artery disease patients with patients who had no evidence of coronary artery disease and the associated risk factors. The analysis was done using the standard error of the difference between the means.

Mean and S. D. of age of control groups is 59.94±7.69.

$Z = 0.22$, $P > 0.05$, not significant.

Age is not significant difference among study and control groups.

$X^2=0.004$, $P > 0.05$, not significant.

Sex is also not significant difference among study and control groups.

While analysis in the females showed the same results as in males, the incidence of coronary artery disease in patients with elevated uric acid level was remarkably significant. There was no alcoholism in female patients. Obesity and hypertension was found more in association with elevation of uric acid level.[11]

The mean age of diabetics in this group is 57.3 years in normal uric acid group while it is 62.3 years in hyperuricemia group.

There was significant difference among males and females in the mean age showing that females had highly elevated uric acid at an earlier age in diabetes than males. And there was no

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significant difference in serum uric acid levels in males and females because most of the females were in postmenopausal period.

Comparison between the biochemical values in both the groups showed important differences as follows.

Mean blood sugar was higher in hyperuricemia group than normouricemic group (184 vs. 152mgs% of fasting value). There was also significant elevation of total cholesterol triglycerides and low density lipoprotein in the hyperuricemic group when compared to the normouricemic group.

Analysis of the results in females also showed the significant difference in all the biochemical values except the postprandial blood sugar, which was not significantly different with that to the normouricemic group. All these factors prove that the patients with multiple risk factors have a significant elevation in the uric acid level. Probable mechanism of elevation of uric acid in relation to the multiple risk factors denotes the complex interaction of these risk factors with uric acid metabolism.[12]

According to a study by Dr. Wun et al, serum uric acid was significantly associated with body mass index, history of hypertension, serum triglyceride and serum creatinine, but was not related to the control of diabetic status. Females were more likely to have more elevated serum uric acid levels than in males.[13]

Bouvenet G et al in the analysis of 1000 cases in relation to the association of serum uric acid and serum lipids have found that blood triglycerides and blood cholesterol in males were found significantly higher in patients with hyperuricemia than normouricemic control subjects.[14] Present study also confirms this result even though association of serum cholesterol is less strong than serum triglycerides, which is highly significant.

**Clinical profile in coronary artery disease groups:** Comparison of risk factors between the normal ECG group and old infarction group revealed a positive association with the age, smoking and hypertension both in males and females.

| Clinical parameter | With CAD | | Without CAD | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Obesity | 21 | 30 | 16 | 22.85 |
| Smoking | 36 | 51.4 | 26 | 37.14 |
| Alcohol | 23 | 32.8 | 27 | 38.57 |
| Hypertension | 41 | 58.5 | 27 | 38.57 |

Table 1: Clinical Profile of Patient with and Without CAD

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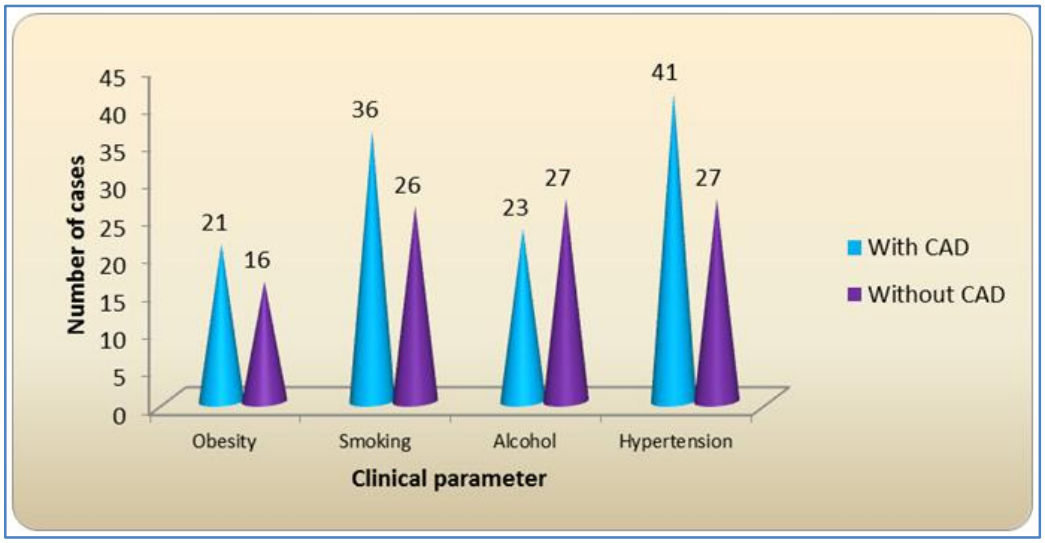


**Graph 1: Cone graph showing clinical profile of patient with and without CAD**

The above table shows the percentage of risk factors between the groups of CAD and no CAD. Smoking was 51% Vs 37% and alcoholism was 32% Vs 38.5% in the CAD group and no-CAD group. 58% of patients with CAD were hypertensive and 38.5% of no CAD group were hypertensive.

| Biochemical Profile | Patients with CAD | Patients without CAD | t test |
|---|---|---|---|
| BS-F | 175.83±48.6 | 169.58±39.62 | 0.69 |
| BS-PP | 274.46±54.42 | 267.68±46.8 | 0.76 |
| TC | 203.68±39.62 | 182.42±_40.62 | 2.81 |
| TGL | 174.31±46.8 | 152.36±_31.2 | 2.96 |
| LDL | 135.15±5.2 | 120.7±38.6 | 2.05 |
| HDL | 39.15±5.2 | 37.68±_5.92 | 1.42 |

Table 2: Biochemical Profile of Males with CAD and Without CAD

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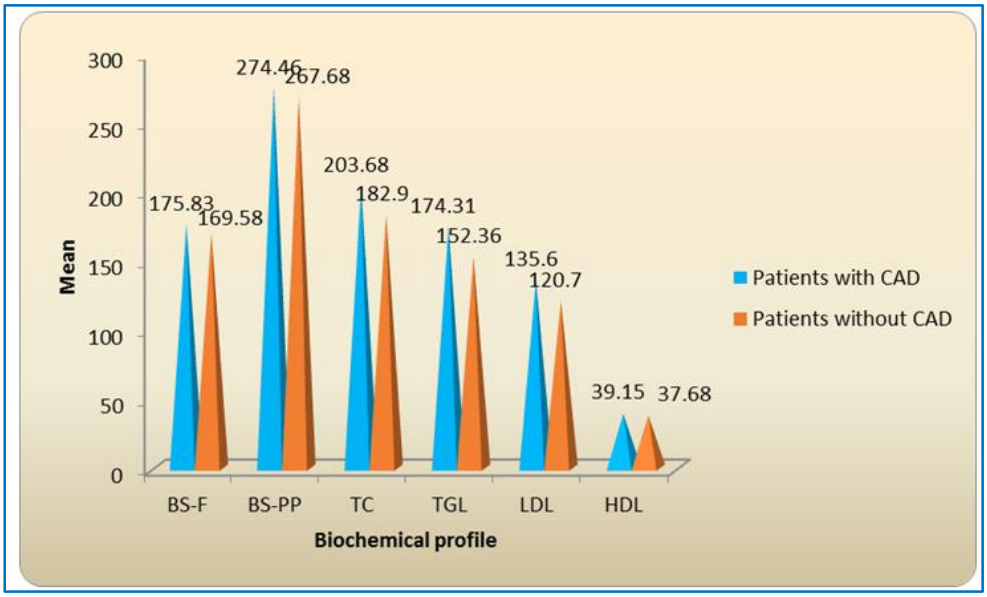


**Graph 2: Cone graph showing biochemical profile of Males with CAD and Without CAD**

Mean fasting blood sugar was 175.83 vs. 169.58mg%, total cholesterol was 203.68 vs. 182.42mg%, Triglycerides was 174.3 vs. 152. Mg%, and low density lipoprotein cholesterol was 135.6 vs. 120.7mg%. There was no significant association between the high density lipoprotein cholesterol levels.

| Biochemical profile | Patients with CAD | Patients without CAD | t test |
|---|---|---|---|
| BS-F | 172.65±31.25 | 167.48±20.28 | 0.64 |
| BS-PP | 273.24±54.42 | 266.62±42.8 | 0.46 |
| TC | 202.24±36.56 | 184.92±42.5 | 1.42 |
| TGL | 169.6±32.41 | 156.24±42.8 | 0.86 |
| LDL | 134.2±31.6 | 121.6±34.6 | 1.13 |
| HDL | 39.45±5.2 | 38.92±5.78 | 0.14 |

Table 3: Biochemical profile of Females with and without CAD

In females the mean fasting blood sugar was 172.65 vs. 167.4mg%, total cholesterol was 202.2 vs. 184.92mg%, triglycerides was 169.6 vs. 156.2mg% and low density lipoprotein cholesterol 134.2 vs. 121.6mg%

According to Cadeddu et al in their study of hyperuricemia and cardiac risk factors, there was strict correlation of hyperuricemia and hypertriglyceridemia.[15]

Recent studies suggest that one of the important, independent risk factor of coronary artery disease as hypertriglyceridemia, which is also proved in our present study.

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Comparison between the risk factors of coronary artery disease and hyperuricemia in males and females showed some statistical correlation for biochemical profile mainly.

This study shows no statistical significance for age, body mass index and glycemic control for coronary artery disease but it was significantly correlated with hyperuricemia. Lipid profile was significantly correlated for both coronary artery disease and hyperuricemia, except for a weak correlation for low density lipoprotein, cholesterol, and high density lipoprotein cholesterol in this subgroup.

In females also coronary artery disease was not significantly associated with age, body mass index and glycemic control. There was correlation between total cholesterol, Triglycerides and low density cholesterol and high density lipoprotein cholesterol for both the groups except for total cholesterol in hyperuricemia group, which was not statistically significant for hyperuricemia. High density lipoproteins were relatively higher in both coronary artery disease group as well as hyperuricemia group.

Overall comparative analysis between the risk factors for coronary artery disease and hyperuricemia showed no statistical correlation for age, sex and body mass index. Glycemic control, even though statistically significant it was poor in both subgroups. Total cholesterol showed no statistical significance but hypertriglyceridemia was present in both groups. (>150mg %).

| Parameters | Patients with and Without coronary artery disease | Patients with and without hyperuricemia |
|---|---|---|
| Age | >0.05 | >0.05 |
| Sex | >0.05 | >0.05 |
| BMI | >0.05 | >0.05 |
| BS –Fasting | >0.05 | <0.001 |
| BS-Postprandial | >0.05 | <0.001 |
| TC | >0.05 | >0.05 |
| TGL | <0.01 | <0.001 |
| LDL | >0.05 | >0.05 |
| HDL | <0.02 | >0.05 |

Table 4: Comparison between the Risk Factors

Low density lipoprotein cholesterol was also not significant in our study in both groups. Low levels of high density cholesterol was not associated in our study. To summarize, the results in our study, there is significant association between the risk factors for coronary artery disease as well as hyperuricemia. There was significant elevation of uric acid in association with presence of coronary artery disease. Considering all these factors it can be concluded that presence of hyperuricemia in type-2 diabetes indicates increased incidence of coronary artery disease and seems to be a marker for coronary artery disease.

**DISCUSSION:** Except for very few studies much has not been studied about the serum uric acid level as an important measure of this important dysmetabolic syndrome called as type-2 diabetes mellitus. “In the absence of gout presence of hyperuricemia in patients with type-2 diabetes mellitus is an important marker as well as added risk factor for atherosclerosis”.

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Even though there are many controversial arguments about elevated serum uric acid as a risk factor there some of the studies, which proved it. As well as there are few studies, which considered it as marker in combination with other risk factors particularly elevated levels of triglycerides, which is also an important risk factor in acceleration of atherosclerosis according to various studies recently[16]. Our study also proved a significant association of elevated serum uric acid with hypertriglyceridemia.

A study by Pearl A et al (J Ed Cyst 1993 Aug: 17 (3-4): 233-7) found out uric acid as a free radical scavenger by estimating the relationship between the serum urates and the Molar Equivalent Serum Anti-oxidant (MESA) in diabetic and normal individuals and found a linear relationship between serum uric acid and MESA. Significant differences between the two groups were both mean MESA values and mean uric acid values.[17]

According to another recent study conducted in Lomo Medical Clinic, The Heart of Africa, Cardiovascular center, Kinshasa, Congo by Longo- Mbenza B et al with the background of "uric acid stabilizes the platelet aggregation and enhances thrombotic tendency" suggested hyperuricemia as a strong predictor of myocardial infarction and stroke and all causes of mortality. (Int J Cardiol 1999 Sept; 30; (1): 17-22).

Tkac l et al in a similar study like our present study with 91 type-2 diabetics, in which 57 patients had clinical and ECG evidence of old myocardial infarction was compared with a control group of 34 diabetics without any evidence of coronary heart disease. There were significantly higher mean serum uric acid values in the whole group with the Ml. Biserial regression analysis showed the persistent significance between the serum uric acid level, even after elimination of age and serum creatinine levels.[18]

The author favored the view that uric acid is rather a marker than true risk factor of atherosclerosis in type-2 diabetes mellitus (Vnitr Lek 1990 Aug; 36 (8): 763-8).

As there are many references with regard to newly emerging risk factors to coronary heart disease like Hypertriglyceridemia, Lipoprotein (a), small dense LDL, our present study has thrown light on hypertriglyceridemia as an important risk factor for coronary heart disease, which was also independently associated with elevation of serum uric acid level.[19,20]

Diabetic dyslipidemia is major problem adding to the atherogenicity in type-2 diabetes mellitus in our patients both in the control group as well as infarction group. A comparison between the serum lipids in Indians with our study population and American population is as follows.

| Lipids | Indians | Present study | | Americans |
|---|---|---|---|---|
| | | Males | Females | |
| TC | 192.2+31.8 | 203.7+39.62 | 202.24+54.4 | 177+25.3 |
| TGL | 174.1+18.1 | 174.3+46.8 | 169.6+32.4 | 85.9+45.8 |
| LDL-C | 126.8+28.5 | 135.5+31.2 | 134.2+31.6 | 119.5+22.3 |
| HDL-C | 36.2+7 | 39.15+5.2 | 39.45+5.2 | 40.3+8.2 |
| TC/HDL | 5.53+1.42 | 5.15+0.89 | 5.12+0.89 | 4.55+0.88 |
| LDL/HDL | 3.56+0.96 | 3.46+0.81 | 3.40+0.85 | 3.09+0.88 |

**CONCLUSION:** Mean serum uric acid level in diabetic population in our study was comparable to normal range in the general population.

There was no significant difference in serum uric acid between the diabetics without any evidence of coronary heart disease and the general population.

When there is elevated serum uric acid in diabetics that can be considered as a marker of coronary heart disease in diabetics.

Elevated uric acid may be an epiphenomenon due to associate other coronary heart disease risk factors.

Our study also found out that significant elevation of Triglycerides in both the groups with and without coronary heart disease which is more significant in patients with coronary heart disease. It also has been observed that elevated uric acid is associated with hypertriglyceridemia.

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