STUDY OF SERUM LEVELS OF URIC ACID IN CORONARY ARTERY DISEASE AND DIABETES MELLITUS

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ABSTRACT

Coronary Artery Disease (CAD) leads to Angina and Myocardial Infarction (MI). Premature mortality on Coronary Heart Disease (CHD) is more common in diabetic atherosclerosis. In the present study serum Uric Acid level was estimated in patients of CAD with DM, CAD without DM, DM without CAD and CAD with DM and other risk factors compared to healthy normal subjects. The level of Uric Acid was significantly increased in all four groups of patients as compared to control group.

Conclusion: On the basis of our results we conclude that high circulating uric acid levels may be indicator that the body is trying to protect itself from harmful effects of free radicals by increasing the production of endogenous antioxidants like uric acid. Hence uric acid may act as non conventional marker to predict the risk of Coronary Vascular Disease (CVD) complication in Diabetes Mellitus (DM).

Keywords: Coronary Artery Disease, Diabetes Mellitus, and Uric Acid.

INTRODUCTION

Coronary Artery Disease (CAD) leads to Angina and Myocardial Infarction (MI). Premature mortality on Coronary Heart Disease (CHD) is more common in diabetic atherosclerosis (1).

Cardiovascular diseases (CVD), comprising coronary heart disease (CHD) are currently the leading cause of death globally, accounting for 21.9 per cent of total deaths, and are projected to increase to 26.3 per cent by 2030. The factors that coalesce to increase the risk of developing atherosclerotic Coronary Heart Diseases were demonstrated in Framingham in the mid - 20th century and have subsequently been shown to be pervasive across ethnicities and regions of the world. These are not new risks, but the ubiquity of smoking, dyslipidaemia, obesity, diabetes, and hypertension has been gradually escalating, and is thought to be the driving influence behind the epidemic of heart disease faced today (2).

Of the risk factors, diabetes, and its predominant form, type 2 diabetes mellitus (T2DM), has a distinctive association with Coronary Heart Disease. Those with diabetes have two- to four-fold higher risk of developing coronary disease than people without diabetes, and cardiovascular diseases accounts for an overwhelming 65-75 per cent of deaths in people with diabetes. More significantly, however, the age- and sex-adjusted mortality risk in diabetic patients without pre-existing coronary artery disease was found to be equal to that of non-diabetic individuals with prior myocardial infarction (MI). These remarkable findings regarding higher risk of mortality have led to suspicion that common precursors predispose to diabetes and Coronary Heart Disease, with subsequent implications that insulin resistance, visceral adiposity, and excess inflammation (2).

However, a great controversy arose as to whether elevated uric acid was an independent risk factor for Coronary Artery Disease or it was merely a marker of co-existing conditions such as hypertension, abdominal obesity, diabetes...
mellitus, hyperlipidaemia, inflammation, impaired renal function and diuretic treatment (3). The contradictory data obtained in the studies have been analysed and reviewed by independent research groups. Although different potential mechanisms explaining the associations between high serum uric acid and CAD have been proposed, a well-established pathophysiological link is still missing (4-6). The concentration of uric acid, as well as other risk factors for the development of CAD, is strongly influenced by different genetic factors and lifestyle habits. Traditionally, elevated serum uric acid (SUA) is linked to gout. Recent investigations have shown that there may be a relationship between hyperuricemia, ischemic heart disease and metabolic syndrome, which is characterized by obesity, dyslipidaemia, diabetes and hypertension. Although a direct relationship between Serum uric acid and cardiovascular disease is difficult to prove due to confounding factors like hypertension and diabetes, Strasak et al have recently demonstrated that Serum uric acid is an independent predictor of mortality due to congestive heart failure and stroke (7).

**MATERIALS AND METHODS**

The present study was carried out in the Department of Biochemistry, Dr. D. Y. Patil Education Society’s Medical College and Hospital, Kolhapur. This study was approved by Institutional ethical committee. In this study a total number of 200 subjects between age 40 yrs to 60 yrs matched with age and sex were included. They were distributed in controls and four study groups.

<table>
<thead>
<tr>
<th>Controls</th>
<th>Normal Healthy controls- 100 cases</th>
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<tbody>
<tr>
<td>Group- I</td>
<td>Patients with CAD and DM- 25 cases</td>
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<tr>
<td>Group- II</td>
<td>Patients with CAD – 25 cases</td>
</tr>
<tr>
<td>Group- III</td>
<td>Patients with DM – 25 cases</td>
</tr>
<tr>
<td>Group- IV</td>
<td>Patients with CAD and DM + Other risk factors- 25 cases</td>
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</tbody>
</table>

All controls were from the same age groups as patients, not showing any clinical signs and symptoms suggestive of CAD. They were having normal blood pressure (BP), ECG, blood sugar level and apparently no other cardiac risk factors. Group-I contained patients diagnosed to have CAD (based on angiography) with confirmed DM and were receiving treatment for the same. Group-II contained patients with CAD but no DM. Group-III contained Type II DM patients receiving treatment for DM, and were not showing any complications of DM, and had normal ECG and BP. Group- IV contained patients with CAD and DM along with other risk factors (such as smoking, hypertension, family history of Coronary Artery Diseases, obesity etc.)

Sample collection-3ml of venous blood sample was collected in plain bulb and was allowed to clot. Serum was separated by taking necessary precautions to avoid haemolysis. This serum was used for the estimation of uric acid. Uric acid was estimated of Dynamic extended stability with lipid clearing agent modified Trinder method, End point (8).

**Inclusion Criteria:** A) Control group: 100 age matched healthy subjects were included in the control group. The subjects were selected after screening for any prior history of cardiovascular disease or any other disease. B) Coronary Artery Disease Patients: Angiographically proven patients by the cardiologists with relevant coronary artery disease showing greater than 50% stenoses in at least one major coronary artery at the time of diagnostic catheterization were enrolled in this study. Each subject was screened by a complete history, physical examination and laboratory analysis. C) Diabetic Patients with Coronary Artery Disease: Clinically diagnosed patients whose fasting blood glucose level was above 125 mg/dl.
Exclusion Criteria:- The patients with hemodynamically significant valvular heart disease undergoing catheterization, surgery or trauma, known cardiomyopathy, known cancer, abnormal hepatic and renal function, past or concurrent history of any disease and taking any medication that could influence the oxidant and antioxidant status and endothelial functions were excluded from the study group.

RESULT-

Showing the levels of Uric Acid in (mg/dl) in control subjects and different study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Uric Acid (mg/dl)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>4.6 ± 2.43</td>
</tr>
<tr>
<td>Group I (CAD with DM)</td>
<td>6.0 ± 2.7 #</td>
</tr>
<tr>
<td>Group II (CAD with out DM)</td>
<td>6.4 ± 3.06 #</td>
</tr>
<tr>
<td>Group III (DM with out CAD)</td>
<td>5.2 ± 3.04 ♣ ♦</td>
</tr>
<tr>
<td>Group IV (CAD with DM with other risk factors)</td>
<td>6.8 ± 2.62 * ♦ $</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD
* P<0.001 Group IV as compared to control
# P<0.05 Group I and II as compared to control
♣ P<0.05 Group III compared to control
♦ P< 0.05 Group IV as compared to Group I
♣ P< 0.05 Group III as compared to Group II
$ P< 0.001 Group IV as compared to Group III

The level of Uric Acid was significantly increased in all four groups of patients as compared to control group. Similarly significant rise in the serum uric acid level was observed when Gr. III was compared with Gr. II and Gr. IV was compared with Gr. I and III.

DISCUSSION

Serum uric acid (or more correctly, its mono anion uric acid at physiological pH values) has been thought to be, in humans, a metabolically inert end product of purine metabolism without physiological significance (except gouty diathesis). However, serum uric acid has been recently associated with insulin resistance (9, 10). Furthermore, in non diabetic subjects an elevated level of uric acid has been shown to be an independent predictor of coronary heart disease and total mortality (11-14). Elevated serum uric acid has been found to be closely associated with dyslipidaemia, obesity, hypertension, diabetes, smoking and inflammation (15).

The topical role of uric acid and its relation to cardiovascular disease, renal disease, and hypertension is rapidly evolving. Its important role both historically and currently in the clinical clustering phenomenon of the metabolic syndrome, type 2 diabetes mellitus (T2 DM), atheroscleropathy, and non-diabetic atherosclerosis is of great importance. The association between high serum uric acid and incidence of was Coronary Artery Disease reported more than 50 year ago (16). Since then numerous clinical and epidemiological studies have explored the association more precisely. Such studies confirmed that elevated uric acid was predictor of cardiovascular disease. However, a great controversy arose as to whether elevated uric acid was an independent risk factor for Coronary Artery Disease.

In the present study the level of uric acid was significantly increased in all four groups of patients as compared to control group. Similarly significant rise in the serum uric acid level was observed when Gr. III was compared with Gr. II and Gr. IV was compared with Gr. I and III. Hyperuricemia could play a role in the pathogenesis of atherosclerosis. Overwhelming evidence suggests that hyperuricemia is linked to obesity, hypertension, reduced HDL cholesterol, hypertriglyceridemia, hyperinsulinemia and reduced insulin sensitivity (9, 10).

Elevated levels of serum uric acid are due to either an increase in uric acid production or a decrease in its excretion.

The mechanism by which uric acid may cause Coronary Vascular Disease has been explored...
using cell culture and animal models. It appears that uric acid must enter the endothelial and vascular smooth muscle cells via a specific organic anion exchanger, where it activates a variety of intracellular signaling molecules involved in inflammation and proliferation. In the endothelial cells there is a decrease in nitric oxide levels and an inhibition of endothelial proliferation, whereas in vascular smooth muscle cells there is activation of proliferative and inflammatory pathways. Local activation of the rennin-angiotensin system has also been shown. Low nitric oxide may also have a central role in the induction of insulin resistance, as insulin requires nitric oxide for its action (by stimulating blood flow to the skeletal muscle) (17).

Despite the consensus that hyperuricemia is a significant Coronary Vascular Disease marker, there are controversies regarding a causative role for uric acid in Coronary Vascular Disease and/or metabolic syndrome. Prospective clinical studies are necessary to investigate whether a reduction in uric acid levels prevents Coronary Vascular Disease or metabolic syndrome (17).

Uric acid is one of the major endogenous water-soluble antioxidants of the body (18). There is accumulating evidence that increased oxidative stress is closely related to diabetes and its vascular complications (19). Thus, high circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the production of endogenous antioxidants, eg. uric acid. Interestingly, uric acid prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress. (18) There is also some evidence that uric acid may have the direct role in the atherosclerotic process, because human atherosclerotic plaque contains more uric acid than do control arteries (20). Inflammation is one of the features of atherosclerosis, (21) and uric acid crystals may induce inflammatory responses that are reduced by lipoproteins which have an ability to bind uric acid crystals (22).

Hyperuricemia via purine metabolism may also promote thrombus formation (23, 24). Increased level of Uric Acid in the current study might be responsible for the induction of inflammatory process of atherosclerosis as well as to promote thrombus formation. Increased uric acid production may also be an attempt by the body to overcome the oxidative stress associated with diabetes and its vascular complications.

**CONCLUSION**

In the present study the level of serum uric acid was significantly increased in all four groups of patients as compared to control groups. High uric acids could be a marker of sodium retention coupled with impaired hemodynamic reserves and/or disturbed blood flow. Increased oxidative stress is closely related to diabetes and its vascular complications. Thus high circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the production of endogenous antioxidants like uric acid. Hyperuricemia may also promote thrombosis.

**REFERENCES**

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