SERUM URIC ACID AS A MARKER OF CORONARY ARTERY DISEASE IN TYPE-2 DIABETES MELLITUS

CROSS SECTIONAL STUDY

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CERTIFICATE

This is to certify that this dissertation titled "**SERUM URIC ACID AS MARKER OF CORONARY ARTERY DISEASE IN TYPE- 2-DIABETES MELLITUS"**submitted by **DR. J.PREM GEOVANNI**. to the faculty of General Medicine, **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine is a bonafide research work carried out by him under our direct supervision and guidance

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DECLARATION

I**, Dr. J.PREM GEOVANNI.** solemnly declare that the dissertation titled "Serum uric acid –coronary artery disease marker in type-2 diabetes mellitus**"** has been prepared by me. This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of MD degree (branch I) General Medicine

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CONTENTS

INTRODUCTION

Type – 2 Diabetes Mellitus is an epidemic in India for the past few decades. Diabetes mellitus is a very important risk factor associated with two to four fold increased incidence of Coronary heart disease.

Even though disease of small blood vessels is specific to diabetes mellitus large vessels disease is very common in treated diabetes and accounts for about 70% of all the deaths.

Hyperuricemia is one the component of Syndrome – X in Type-2 diabetes mellitus. But exact pathogenesis role of uric acid in coronary heart disease is not known. Uric acid was recognized as atherosclerosis marker in type-2 DM and it was correlated with the presence of CHD independently of hypertension and nephropathy.

Combination of risk factors in coronary disease play role in morbidity and mortality in patients with coronary heart disease of type-2 diabetes mellitus among which diabetic dyslipidemia plays major role.

AIM OF THE STUDY

1. To establish the association of elevated serum uric acid concentration as a marker of coronary artery disease in type -2 diabetic patients.
2. To establish the association of uric acid level in relation to other risk factors of coronary artery disease in type – 2 diabetic patients.

REVIEW OF LITERATURE

During recent year's cardiovascular disease have registered a sharp increase in Indian subcontinent. The risk of coronary heart disease in Indians is three to four times higher than white Americans, six times more than Chinese and twenty times more than in Japanese.

A sharp increase in the incidence of type – 2 diabetes mellitus in Indian is explained by the "westernized" life style such as overeating in combination with obesity and under activity. Strong genetic predisposition is confirmed, probably of polygenic inheritance. Increasing age is an independent risk factor for NIDDM.

NIDDM predisposes to Coronary heart disease by its unique metabolic disturbance affecting homeostasis of the individual. Obesity, systemic hypertension, Hypercholesterolemia is associated with NIDDM, as a result of insulin resistance state. But in Indians who have smaller body frames than western people still had high incidence of NIDDM and CHD.

The four major risk factors for CAD viz hypercholesterolemia, hypertension, diabetes mellitus and cigarette smoking which were present in Framingham's cohort are difficult to explain among Indians with CAD.

CAD in Indians is present with low cholesterol level. In contrast insulin resistance is much more prevalent in Indians. Hyperinsulinemia, impaired fasting glucose, hypertriglyceridemia, abdominal obesity, hypertension and Low HDL commonly referred to as syndrome – X is important in Indian context.

Apart from dyslipidemia nonlipid risk factors for coronary heart disease in NIDDM are Hypertension, aging, male sex, smoking alcohol, body mass index, waist to hip ratio. Evidence is emerging in favor newer risk factors like high Plasminogen activator inhibitor – l (PAI – I), raised fibrinogen levels,presence of lipoprotein(a), low levels of Apo –A, high levels of Apo –B, LDL and IDL and particularly small dense LDL.

NIDDM is associated with following risk factors for atherosclerosis. They have been divided in to two major types – Non lipid risk factors and Lipid risk factors.

NON LIPID RISK FACTORS FOR ATHEROSCLEROSIS IN TYPE-2 DM

Body Mass Index

Obesity is a state of adipose tissue having a body mass index more than 30kg/m^2. Assessment of BMI (weight in kg divided by height in square meters) has the advantage of simplicity and is useful for assessing both undernutrition and overnutirion. It is a widely used means of energy balance, but it does not take into account the differences in frame size. As the Indian population is more of smaller frame than other western countries BMI alone was not sufficient as a marker of risk factor in type – 2 diabetes mellitus of coronary heart disease.

Central Obesity

Central obesity is defined as increased ratio of waist to hip circumference measured at the level of umbilicus and pubic symphysis respectively. It differs in males and females because of difference in body fat content.

Normal W/H ratio in males is <0.85 and in females <0.90. This is the most important factor for insulin resistance in type -2 diabetics. The possible

mediator of insulin resistance in type -2 DM is central obesity lead to elevated free fatty acid levels. This leads to inhibition of insulin stimulated glucose utilization in muscles via “Randle effect”(the inhibition of oxidation of glucose by an excess of fatty acids)which stimulated hepatic glucose output, inhibit hepatic clearance of insulin.

Physical Inactivity

Regular physical activity has been shown to reduce the risk for coronary artery disease events in number of observational epidemiological studies. In 10 year follow up of MRFIT subjects, subjects in both treatment groups who engaged in moderate physical activity had a 27% lower mortality than less active subjects. The mechanism by which increased exercise decreases the risk for coronary artery disease events include improvements in high density lipoprotein cholesterol level, insulin resistance, body weight and blood pressure. Exercise also increases maximal cardiac output and the amount of oxygen extracted from the blood.

Type A Personality and Stress

Type A personalities are highly competitive, ambitious, and in constant struggle with their external environment, whereas type B personalities are passive and less disturbed by the environmental stimuli. The mechanism by which personality types may predispose to increased coronary risks is not known but may include increased cardiovascular reactivity, which may lead to increased endothelial injury and platelet aggregation, and increased sympathetic nervous system activity, which increase the blood pressure and heart rate.

Low Circulating Levels of Anti-Oxidants

Blood concentrations of anti-oxidants may effect the susceptibility of low density lipoprotein cholesterol and lipoprotein (a) to oxidation. Because lipoprotein oxidation is thought to be prerequisite to the recognition of these particles by the scavenger receptors on the macrophages, decreased level of substances that protect against oxidation may improve the atherosclerotic risk.

Hyperglycemia

The major and simplest parameter for the assessment of diabetic status and also an important risk factor for the pathology and pathophysiology of the disease process in diabetes mellitus. The important mechanism underlying in the pathogenesis of long term complications of diabetes mellitus by hyperglycemia is nonenzymatic glycation of the various important proteins and structural and functional enzymes. This leads to increased levels of oxidized LDL which is more atherogenic and when the HDL undergoes nonenzymatic glycation that leads to decreased reverse transport of cholesterol from the vessels wall to the liver ultimately leading to diabetic dyslipidemia and increased incidence of atherogenecity. Nonenzymatic glycation of structural proteins in the vessel wall leads to thickening of basement membrane and hyalinization.

Other important mechanism involved in increased atherogenicity is by

- Enhanced TX-A_2 synthesis
- Decreased PGI_2 synthesis
- Increased secretion of endothelin in vitro
- Increase in arterial endothelial permeability

Tissue Type Plasminogen Activator (t-PA)

t-PA is synthesized in endothelial cells, and is an important anticoagulant. In the presence of endothelial dysfunction, fibrinolysis is retarded in arteries rendering them ripe for fibrin deposition and development of thrombus. Following thrombolysis, there is extensive damage to the endothelial lining. This may also explain the occurrence of reocclusion following successful thrombolytic therapy. Plasma levels of t-PA appear to be inversely related to high density lipoprotein cholesterol levels.

Although counter-intuitive, plasma levels of endogenous t-PA are increased in subjects with atherosclerosis and acute coronary syndrome. Elevated levels of t-PA also found to be an independent predictor of CAD in large European studies. Asian Indians also have high levels of t-PA than Chinese in Singapore. This may be reflection of a state of endothelial activation.

Plasminogen Activator Inhibitor – 1

Plasminogen activator inhibitor – 1 is single chain glycoprotein that forms stable complexes with t-PA and urokinase type plasminogen activator, and inhibit fibrinolytic activity. Its levels are highly correlated with serum

triglyceride levels. Because of its procoagulant effect, high levels of PAI-1 serve as a marker for increased thrombogenesis. Recent studies indicate an inverse relation between PAI-1 and dietary fiber, and the cardio protective effect of high fibre diet may be mediated through lowering the PAI-1 levels. Asian Indians have a higher level of PAI-1 than Chinese in Singapore and whites in UK and the US. High levels of PAI-1 levels are predictive of premature CAD in whites and may contribute to higher rates of CAD among Asian Indians.

Homocysteine

At the cellular level homocysteine down regulates endothelial thrombomodulin function, affects the activation of protein-C and impairs plasmin generation by inhibiting binding of t-PA to the endothelial receptors. Homocysteine augments the deposition of Lp(a) on fibrin surfaces and its pathological effects are exponentially increased with the concomitant presence of elevated Lp(a) and factor V Leiden. Elevated levels of homocysteine are a powerful risk factor for thrombogenesis, atherogenesis, and premature CAD. About 12% to 40% of patients with premature vascular disease have mild moderate hyperhomocysteinemia. The normal plasma

homocysteine level range from 4.4 – 10.8 micromoles/L. and increased risk of CAD starts at a concentration of 10 micromoles/L.

Lipoprotein (a)

High levels of lipoprotein (a) are evolving to be another genetically linked risk factor in thrombogenesis. Apo-A competitively binds to plasminogen receptor and inhibits the conversion of plasminogen to plasmin. The inhibition of naturally occurring t-PA creates a prothrombotic state, resulting in local thrombus formation. It may represent an important link between atherogenesis and thrombogenesis. Lp(a) level more than 20 – 30mg/dl are associated with 2-3 fold increase in the risk of CAD, which increases exponentially with the concomitant presence of low HDL-C and high total/HDL-C ratio, or high homocysteine, all of which are common among Asian Indian.

Fibrinogen, Factor VII and Blood Viscosity

Serum fibrinogen level, coagulation factor VII activity, and blood viscosity are some of the well-studied haemostatic risk factors for CAD. Fibrinogen is a cofactor of platelet aggregation. Fibrinogen levels are higher in patients that develop ACS or CAD deaths. This association is independent

of other coronary risk factors and has the same predictive value as elevated serum cholesterol levels.

Platelet Activity

Platelets play a crucial role in endothelial dysfunction, coagulation, and thrombosis. The participation of platelets in thrombotic process depends on their ability to adhere to an abnormal surface and aggregate to form an initial platelet plug. The activation of platelets stimulates further platelet aggregation and triggers the coagulation cascade. Platelet activity is highest in the early morning hours and enhanced by high fat diet and is reduced by aspirin therapy.

Endothelial Dysfunction

Vascular endothelium is an active site of protein synthesis and may be considered as one of the most important paracrine organ in human body. The endothelial cells synthesize, secrete, modify and regulate connective tissue components, vasodilators, constrictors, anticoagulants, fibrinolytic compounds, and prostanoids, each contributing to the maintenance of the vascular tone, thromboresistance, and physiological homeostasis. There are number of reports indicating endothelial dysfunction in patients with CAD

“risk profile”. Whether Asian Indians suffer from endothelial dysfunction and if it relates to the coronary risk profile has not been studied.

LIPID RISK FACTORS FOR ATHEROGENESIS IN TYPE-2 DM

Dyslipidemia is one of the major contributors to atherosclerosis in diabetes but clustering of risk factors is also more frequent in diabetic patients. Dyslipidemia in type -2 diabetes is as follows.

Triglycerides

Although many mechanisms contribute to the development of hypertriglyceridemia in type-2 diabetes insulin resistance seems to be a common basis. The insulin resistance state impairs the normal suppression of fatty acid release from the adipose tissue in the postprandial state. Thus flux of free fatty acids of the liver increases and overproduction of VLDL from these substrates occurs when hyperinsulinemia is present.

The catabolism of TGL rich lipoproteins is initiated by lipoprotein lipase which hydrolyzes the triglyceride moiety of chylomicrons and the VLDL and releases free fatty acids for energy production in muscle and storage in adipose tissue. The activity of lipoprotein lipase enzyme is lower in type-2 diabetes. In type-2 diabetes, the passage of TGL rich lipoprotein through the lipolytic cascade is delayed for two reasons 1) there is shortage

of catalytic sites on LPL 2) overproduction of TGL saturates the sites that are available. Both mechanisms promote hypertriglyceridemia.

Very Low Density Lipoprotein – C

Insulin is also is involved in another defect of VLDL metabolism. Acute hyperinsulinemia such that after a meal suppresses the production of large buoyant VLDL particles in the liver (VLDL-1) in the nondiabetic people but not in type-2 diabetes patients. VLDL-1 particles are analogous to chylomicrons which should be released only in fasting state when lipids from food are not available, thus insulin functions in nondiabetic people to maintain the balance between intestinally derived and liver derived TGL rich proteins. In type-2 diabetes patients this regulation fails, inappropriate production of VLDL by the liver occurs and the balance favors hypertriglyceridemia.

Low Density Lipoprotein –C

There is an increased transfer of cholesteryl esters from LDL to TGL from VLDL to LDL. The TGL enriched LDL loose their TGL by the

action of hepatic lipase resulting in the formation of small dense LDL. Again nonenzymatically glycated LDL by chronic hyperglycemia of diabetes leads to decreased clearance from the circulation and thereby increased incidence of atherogenecity.

High Density Lipoprotein – C

The high levels of TGL rich lipoproteins and low levels of HDL are interwoven. Hypertriglyceridemia contributes to low levels of HDL in two ways. Because the lipolysis is impaired in type-2 diabetes, there few surface remnants available to be incorporated into the HDL particles. Second the large amount of TGL rich lipoproteins and their prolonged resistance time in circulation increase the exchange (mediated by CETP) of esterified cholesterol from HDL to TGL rich lipoproteins and of TGL and HDL particles. The resultant is enrichment of the HDL particle core with TGL. The enriched HDL has a faster catabolic rate than normal HDL, which leads to lower number of circulating HDL particle

ROLE OF URIC ACID IN NIDDM

Uric Acid Metabolism

It was carl wihelm Scheele in 1776 isolated uric acid from urine. Marcet in 1819 discovered xanthine. Strecker in 1857 showed the presence of uric acid in urine. In 1892, Sir frederirk Hopkins (nobel prize,1929) estimated uric acid. In 1895 , Emil fischer showed that uric acid is derived from purine nucleus.

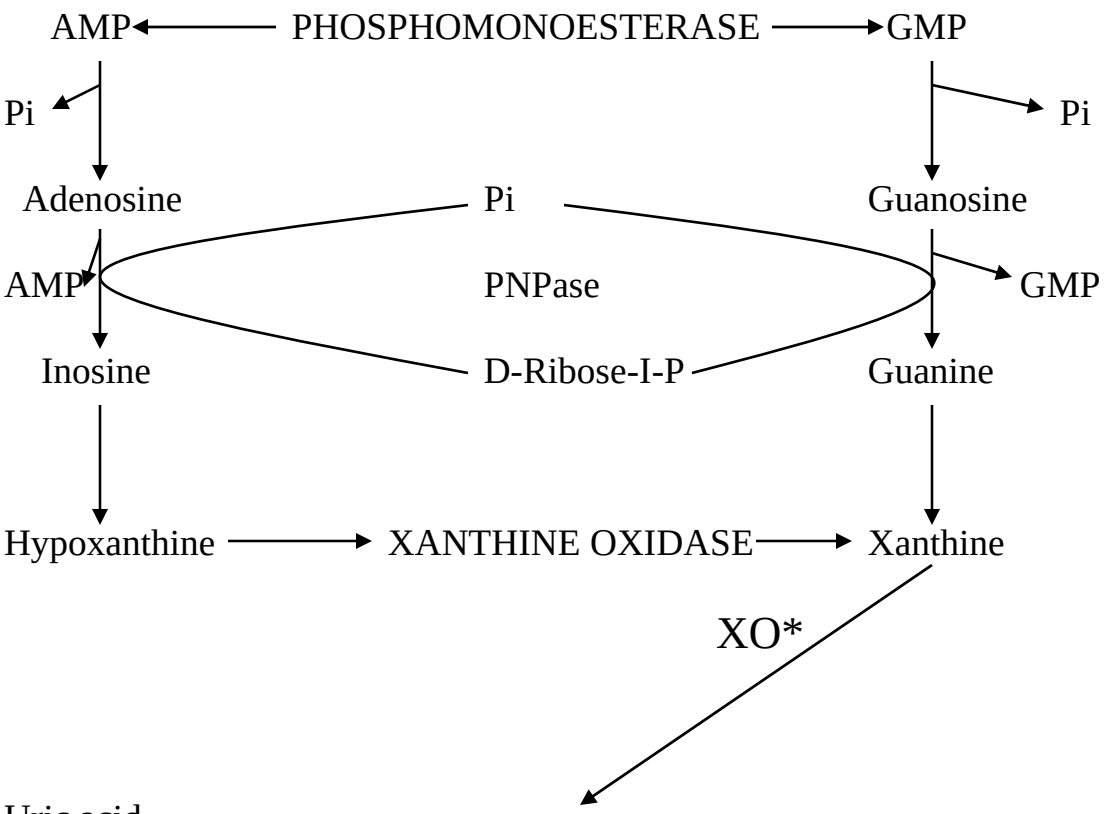
Uric acid is the final breakdown product of purine metabolism. It is a weak acid with pKas of 5.75 & 10.3. Urates the ionized form of uric acid, predominate in plasma, ECF, and synovial fluid, with approximately 98% existing as monosodium urate at pH of 7.4. MSU easily ultra filtered and dialyzed from the plasma.

Although purine nucleotides are synthesized and degraded in all tissues, urate is produced in tissues only contain the enzyme xanthine oxidase primarily liver and small intestine. The amount of urate produced in the body is net result of the amounf produced and the amount excreted.

Serum urate levels vary with age sex. Mean serum uric acid conc. In adult and premenopausal women are 6.8mg and 6.0mg/dl respectively. After menopause, values for women increase to approximate to those of men hyperuricemia is defined as serum urate conc. more than 7.0mg/dl in men and 6.0mg/dl in premenopausal women.

Hyperuricemia reflects defect in insulin action on renal tubules which helps in reabsorption of uric acid.

URIC ACID METABOLISM



XO - Xanthine Oxidase

PNPase - Purine nucleotide phosphorylase

Pi - Inorganic phosphate

AMP - Adenosine monophosphate

GMP - Guanosine monophosphate

FACTORS THAT AFFECT URATE LEVEL IN TYPE -2 DIABETES MELLITUS

Dietary Habits

An increase in serum urate level may occur in type-2 DM in various situations like purine rich diet such as Non-vegetarian diets – liver, anchovies, kidneys, sardines and sweet breads and yeasts.

Exercise

Exercise acutely increases serum urate levels by excessive degradation of skeletal ATP.

Alcohol

Alcohol increases serum urate level by accumulation of organic acids (beta hydroxyl butyrate, aceto-acetate, lactate) that compete with the urate for tubular secretion and accelerated breakdown of ATP by liver is increased. (Beer contains high uric acid)

Obesity

Various mechanisms play role in increase of serum urate by obesity like anabolic effects of tissues because of insulin resistance, increase in de novo biosynthesis of purines decreased excretion and increased breakdown.

Dehydration

Dehydration can impair uric acid excretion by decreased filtration and secretion and sometimes with the acidosis by competition of H+ ions for excretion. Starvation again causes accumulation of organic acids that compete for the excretion of urate for tubular secretion.

Systemic Hypertension

There are various studies regarding association of systemic hypertension with the elevated uric acid levels. Probable mechanism suggested is impaired excretion of urate because of intrinsic renal defect in HT.

Lactic Acidosis and Diabetic Ketoacidosis

Dehydration and prerenal azotemia both can impair filtration and secretion of urate leading to retention and also there may be diminished reabsoption of the uric acid. Again in the setting of acidosis H+ ions compete with uric acid leading to enhanced reabsorption and retention.

Hyperglycemia

Both uric acid and glucose levels are positively related o body mass index. The association of uric acid in relation to glucose reflects the biochemical interaction between serum glucose and purine metabolism. (Deranged carbohydrate metabolism)

Renal Insufficiency

Decreased urate filtration contributes to the hyperuricemia of renal insufficiency. But the correlation between BUN, serum creatinine and serum uric acid concentration is poor because although uric acid excretion per unit of GFR increases progressively with renal insufficiency, the tubular secretory capacity tends to be preserved, the tubular reabsorptive capacity is

decreased and extrarenal clearance of uric acid increases as the renal damage becomes more severe.

Drugs

They mainly act by decreasing the uric acid excretion by competitive inhibition of uric acid excretion.

Salicylates and nicotinic acid directly compete with the urate for tubular secretion.

Diuretics decrease the secretory capacity and increase reabsorption. L-Dopa, pyrazinamide, ethambutol, cyclosporine also decrease the secretion of urate by the tubules.

INTERACTION OF URIC ACID AND LIPOPROTEIN METABOLISM

One of the recent concepts in atherogenic risk factor is association of elevated triglycerides in which insulin resistance seems to be a common basis. Insulin resistance state impairs the normal suppression of fatty acid release from the adipose tissue in the postprandial state. Thus flux of free

fatty acids to the liver increases and overproduction of VLDL from these substances occurs.

There various studies arguing in favor as well as against the serum uric acid level as a significant risk factor for the coronary artery disease.

HYPERURICEMIA IN CORONARY ARTERY DISEASE

There are studies regarding hyperuricemia as one of the risk factor as early as 1977. Jacobs D et al. compared among patients with Myocardial Infarction, ischemia, non-ischemic whites and South African blacks. The difference in serum uric acid levels between the ischemic and infarction groups was highly significant.

Tkac l et al studied 91 type-2 DM, 57 patients with Myocardial infarction were compared with control group of 34 diabetics without clinical or electrolcardiographic signs of ischemic heart disease. Higher mean serum uric acid level in infarction group was associated with increasing age and

serum creatinine levels. It was associated with elevated TGL, BMI and H/o hypertension.

Study of large group of by Persky VW et al concluded, that the association between uric acid and the prevalence of ECG abnormalities and with the mortality appear to be secondary to association between serum uric acid and other risk factors.

Woo J et al study results found positive association between serum uric acid concentration and BMI, WHR, systolic and diastolic BP, urea, creatinine, fasting glucose, 2 hour insulin, TGL, apolipoprotein – B in men. Similar but fewer associations were seen in women with additional positive association with age. The study suggests that serum uric acid may be a marker for the presence of an adverse cardiovascular risk profile.

Wannamethee SG et al concluded in their study that serum uric acid is not a truly independent risk factor for coronary artery disease. Increased serum uric acid appears to be an integral part of the cluster of risk factors associated with the insuline resistance syndrome that include central obesity, increased serum trigluceride and serum cholesterol.

Pearl A et al study concluded high molar equivalent serum antoxidant capacity (MESA) between diabetics and nondiabetics showed, uric acid as a free radical scavenger in NIDDM.

Brand FN et al according to original Framingham heart study concluded that serum uric acid predicted subsequent development of CAD, in general and myocardial infarction in particular, but not angina. In multivariate analysis, including age, systolic BP, serum cholesterol, serum uric acid did not add independently to the prediction of CAD.

Reunanen A et al concluded that any apparent association between the adverse cardiovascular outcomes is probably due to the association of uric acid level with the other risk factors.

Corella D et al study concluded that the prevalence of hyperuricemia varies with the simultaneous presence of other classical cardiovascular risk factors.

Chu NF et al studied the relationship between hyperuricemia and other cardiovascular risk factors among the adult males in Taiwan. From the

study they concluded that hyperuricemia is associated with overweight, hypertension, and hyperlipidemia. There is a significantly positive association between serum uric acid concentration and other cardiovascular risk factors.

Agamah ES et al, identified the significant association of hyperuricemia with high plasma glucose and insulin, total cholesterol level, serum TGL, VLDL, LDL, and HDL was significantly lower.

Rathman W et al assessed the various components of insulin resistance syndrome in biracial cohort of young adults. They concluded BMI showed strongest positive correlation with the uric acid among insulin resistance components. Others are increased fasting insulin, increased TGL and decreased HDL.

STUDIES CONCLUDING URICACID AS A RISK FACTOR

Lin’ova et al in their clinical and biochemical changes in CAD: hyperuricemia as a risk factor, showed positive correlation dependence between cholesterol and uric acid, fats and uric acid. The results provided the grounds to admit hyperuricemia to be of the risk factors for CAD.

Rathmann W et al in their study of association of elevated serum uric acid with CAD and NIDDM found elevated uric acid associated with body weight, hypertention and nephropathy. After adjustment for these hypertension and nephropathy a significant correlation existed between hyperuricemia and CAD was also found in type-2 diabetes in male diabetics independently of hypertension and nephropathy.

Alderman M in his study of uric acid in hypertension and cardiovascular disease found strong, specific, stepwise independent association of increasing uric acid and cardiac morbidity and mortality.

Huizer T et al in their study of urate production by human heart, proved elevated levels of hypoxanthine in coronary sinus venous sample and concluded that xanthineoxidoreductase is probably present in the heart of

patients suffering from CAD, and responsible for the increased urate production during transient myocardial ischemia.

Lehto S et al in their study of “serum uric acid is a strong predictor of stroke in patients with NIDDM concluded that hyperuricemia is a strong predictor of stroke and overall mortality due to any cause.

Longo M Benza B et al in their study of hyperuricemia as risk factor of stroke and coronary artery disease among African concluded, hyperuricemia as a strong predictor of myocardial infarction in men, stroke in both sexes and all causes of mortality in women.

Fang J et al in NHANES I epidemiologic follow up study (1971-92), concluded that hyperuricemia is independently and significantly associated with risk of cardiovascular mortality.

MATERIALS AND METHODS

Our study included about 93 patients, out of which 7 were excluded because they had ischemic changes alone in the ECG. 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 old myocardial infarction were another group. There were totally 38 patients in control group and 48 patients in the study group. 61 patients were males and 25 patients were females.

Case Selection

The study was done with a random selection of patients suffering type-2 diabetes mellitus from wards, OPs, review OPs and diabetic clinic. All the studied patients were ambulant, clinically stable with no evidence of congestive heart failure due to postmyocardial 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. As most of these patients were from the rural areas and semi-urban areas, most of them relatively undernourished.

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 25.0. 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 25.0kg/m^2. Only small group of patients formed the group of overweight patients. There was only one patient with body mass index more than 30kg/m^2.

Lying 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.

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 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.

Table -1 shows the results as follows,

TABLE -1

CLINICAL PROFILES IN MALES WITH AND WITHOUT HYPERURICEMIA

CLINICAL PARAMETERS	PATIENTS WITH NORMAL SUA	PATIENTS WITH HYPERURICEMIA
Age	55.8±10.3	62.7±7.9
Obesity (%)	9	27
Smoking (%)	57	42
Alcohol (%)	20	15
Hypertension (%)	17	23
CAD (%)	37	81

The above table shows increased incidence of hypertension and coronary artery disease and obesity in patients who had elevated serum uric acid than those with normal serum uric acid levels. Smoking and alcohol was not significantly related to the serum uric acid levels.

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 alcoholic in female patients. Obesity and hypertension was found more in association with elevation of uric acid level.

TABLE -2

CLINICAL PROFILE IN FEMALES WITH AND WITHOUT HYPERURICEMIA

CLINICAL PARAMETERS	PATIENTS WITH NORMAL URIC ACID	PATIENTS WITH HYPERURICEMIA
Age	47.7±8.8	50.1±6.3
Obesity (%)	0	19
Hypertension (%)	11	25
CAD/CVA (%)	11	81

The mean age of diabetics in this group is 47.7 years in normal uric acid group while it is 50.1 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 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.

TABLE -3

BIOCHEMICAL PROFILES IN MALES WITH AND WITHOUT HYPERURICEMIA

BIOCHEMICAL PROFILES	PATIENTS WITH NORMAL URIC ACID	PATIENTS WITH HYPERURICEMIA
BS –F	130±59.6	161±42.9
BS –PP	255.4±63.3	269.4±60.2
TC	178.2±42.5	207.5±51.5
TGL	129.2±41.7	179.9±77.9
LDL	114.6±42.1	133.3±44.3
HDL	37.7±4.9	38.5±4.8

Mean blood sugar was higher in hyperuricemia group than normouricemic group (161 vs 130mgs% 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.

TABLE -4

BIOCHEMICAL PROFILE IN FEMALES WITH AND WITHOUT HYPERURICEMIA

BIOCHEMICAL PROFILES	PATIENTS WITH NORMAL URIC ACID	PATIENTS WITH HYPERURICEMIA
BS –F	170.1±38.1	198.8±92.8
BS –PP	281.9±76.3	285.3±83.7
TC	180.4±33.5	203.9±57.0
TGL	145.7±60.1	185.8±75.4
LDL	114.2±32.2	130.0±45.6
HDL	37.1±2.6	40.0±3.8

Analysis of the results in females also showed the significant difference in all the biochemical values except the postprandial blood sugar,

which was not significant 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.

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.

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. 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.

TABLE -5

CLINICAL PROFILE OF MALES WITH AND WITHOUT CAD

CLINICAL PARAMETERS	WITH CAD	WITHOUT CAD
Age	60.6±8.8	55.7±10.4
Obesity (%)	21	26
Smoking (%)	75	58
Alcohol (%)	27	16
Hypertension (%)	35	12

The above table shows the percentage of risk factors between the groups of CAD and no CAD. In males the mean age of diabetes was 60.6 vs 55.7%, smoking was 75 vs 58% and alcoholism was 27 vs 16% in the CAD group and no-CAD group.

TABLE -6

CLINICAL PROFILE IN FEMALES WITH AND WITHOUT CAD

CLINICAL PARAMETERS	WITH CORONARY ARTERY DISEASE	WITHOUT CORONARY ARTERY DISEASE
Age	55.6±7.3	49.8±8.6
Obesity (%)	21	9
Hypertension (%)	36	27
Smoking (%)	7	0

Table -6 shows the mean age of diabetes in females was 55.6 years vs 49.8 years, obesity was 21 vs 9%, hypertension was 36 vs 27%, and smoking 7 vs 0% in CAD and non-CAD group.

Biochemical profile in coronary artery disease group

As a whole both males and females had poor glycemic control, in both the groups there was significant elevation total cholesterol, triglycerides and low density lipoprotein cholesterol.

TABLE -7

BIOCHEMICAL PROFILE OF MALES WITH CAD AND WITHOUT CAD

BIOCHEMICAL PROFILES	PATIENTS WITH CORONARY ARTERY DISEASE	PATIENTS WITHOUT CORONARY ARTERY DISEASE
BS –F	175.3±62.7	166.9±45.3
BS –PP	263.8±61.9	258.3±62.9
TC	201.7±48.3	176.9±45.6
TGL	155.7±7.9	144.6±81.4
LDL	131.5±45.2	111.4±39.8
HDL	39.2±4.9	36.6±4.5

Mean fasting blood sugar was 175.3 vs 166.9mg%, total cholesterol was 201.7 vs 176.9mg%, Triglycerides was 155.7 vs 144.6mg%, and low density lipoprotein cholesterol was 131.5 vs 111.4mg%. There was no significant association between the high density lipoprotein cholesterol levels.

TABLE -8

BIOCHEMICAL PROFILE OF FEMALES WITH AND WITHOUT CAD

BIOCHEMICAL PROFILES	PATIENTS WITH CORONARY ARTERY DISEASE	PATIENTS WITHOUT CORONARY ARTERY DISEASE
BS –F	206.4	165.5
BS –PP	293.9	271.5
TC	285.0	203.8
TGL	190.7	146.7
LDL	129.9	117.3
HDL	39.4	38.5

In females the mean fasting blood sugar was 206.4 vs 165.5mg%, total cholesterol was 285 vs 203.8mg%, triglycerides was 190.7 vs 146.7mg% and low density lipoprotein cholesterol 129.9 vs 110.3mg%.

According to cadeddu et al in their study of hyperuricemia and cardiac risk factors, there was strict correlation of hyperuricemia and hypertriglycerdemia.

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.

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

TABLE -9

COMPARISON OF RISK FACTORS IN MALES

RISK FACTOR	CAD (P VALUE)	HYPERURICEMIA (P VALUE)
Age	>0.05	<0.001
BMI	>0.05	<0.001
BS – F	>0.05	<0.01
BS – PP	>0.05	<0.02
TC	<0.0001	<0.02
TGL	<0.0001	<0.01
LDL	<0.10 (NS)	<0.01
HDL	>0.05	>0.05

This table 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.

TABLE -10

COMPARISON OF RISK FACTORS IN FEMALES

RISK FACTOR	CAD (P VALUE)	HYPERURICEMIA (P VALUE)
Age	>0.05	<0.05
BMI	>0.05	<0.05
BS – F	>0.05	<0.01
BS – PP	>0.05	<0.05
TC	>0.05	>0.05
TGL	>0.05	<0.05
LDL	>0.05	<0.05
HDL	>0.05	<0.05

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%)

TABLE -11

COMPARISON BETWEEN THE RISK FACTORS

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

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”.

Even though there are many controversial argument 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. 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 irate 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.

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.

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).

LIPIDS	INDIANS	PRESENT STUDY		AMERICANS
		MALES	FEMALES	
TC	192.2±31.8	201.7±48.3	203.8±58.6	177±25.3
TGL	174.1±18.1	155.7±47.9	190.7±78.2	85.9±45.8
LDL-C	126.8±28.5	131.5±45.2	129.9±48.2	119.5±22.3
HDL-C	36.2±7	39.2±4.9	39.4±3.7	40.3±8.2
TC/HDL	5.53±1.42	5.15±0.91	5.18±0.89	4.55±0.88
LDL/HDL	3.56±0.96	3.35±0.81	3.28±0.85	3.09±0.88

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.

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 Indians with our study population and American population is as follows.

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 epiphenomenona due to associated 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.

SUMMARY

The study “serum uric acid- A marker of coronary artery disease in type 2- diabetes mellitus” is a cross sectional study conducted on a random selection of patients suffering from type 2 DM from wards, OP’s, review OP’s and diabetology clinic with in GOVT. Rajaji Hospital, Madurai. 93 patients were studied out of which 7 were excluded as they had ischaemic changes in electrocardiogram.

The rest were divided in to two groups , one without any evidence of CAD, clinically and electrocardiographically. The other had evidence of CAD. The following clinical parameters such as duration of diabetes, age of onset, prior history of HT, CAD, CVA, smoking, alcoholism was assesed . BMI calculated, blood pressure was measured in both lying and in standing position to rule out autonomic neuropathy.

Patients who were suffering from chronic disease such as tuberculosis or chronic leg ulcer were excluded . Urine PCR was done to rule out early renal involvement . Basic biochemical parameters like blood urea, serum

creatinine were done. Fasting and postprandial blood glucose was done to assses the glycaemic status and a complete lipid profile was done.

Along with this serum uric acid level was estimated in the fasting state and a single channel ECG was taken in all patients .Those who had old myocardial infarction pattern or normal ECG pattern were included and the rest were excluded.

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. It was also observed that elevated uric acid is associated with hypertriglyceridemia.

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THE **PROFORMA** FOR THE STUDY

" URIC ACID –A MARKER OFCORONARY ARTERY DISEASE IN TYPE 2 DIABETES MELLITUS"

NAME :

AGE :

SEX :

RESEDENTIAL ADDRESS :

SOCIOECONOMIC STATUS :

OCCUPATION :

TYPE 2 DIABETES MELLITUS DURATION: AGE OF ONSET:

HYPERTENSION :

h/o **CAD/STROKE** :

Smoking :

Alcohol :

Type of personality :

Present medication :

Height: Weight: BMI:

Pulse rate: Blood pressure: W/H ratio:

Urine protienuria/24 Hrs urinary protein/spot PCR:

Blood glucose fasting: post prandial:

Blood urea:

Serum creatinine

LIPID PROFILE

Total cholesterol: TGL:

VLDL: LDL:

HDL:

ELECTROCARDIOGRAM:

SERUM URIC ACID:

GLOSSARY

ATP- Adenosine triphosphate

BMI- Body mass index

BUN- Blood urea nitrogen

CAD- Coronary artery disease

DM- Diabetes mellitus

ECF-Extra cellular fluid

ECG- Electrocardiogram

GFR- Glomerular filtration rate

HDL- High density lipoprotein

HT- Hyperytension

IDL- Intermediate density lipoprotein

LDL-low density lipoprotein

MRFIT-Multiple risk factor intervention trial

NIDDM- Non insulin dependantdiabetes mellitus

OP- Out patient

PGI2- prostacyclin

SUA-Serum uric acid

TGL- Triglycerides

TXA2-Thromoxane A 2

VLDL- Very low density lipoprotein

WHR- Weight hip ratio