

## STUDY OF SERUM URIC ACID LEVEL IN DIABETES MELLITUS WITH SPECIAL REFERENCE TO CARDIOVASCULAR RISK FACTORS

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### ABSTRACT

#### BACKGROUND

This study intends to assess the level of serum uric acid in Type 2 diabetes mellitus and to identify whether any association exists between age, sex, anthropometric measurements (BMI, WHR), hypertension, dyslipidaemia, smoking and coronary artery disease with serum uric acid level.

#### MATERIALS AND METHODS

Period of study was from September 2011 to August 2013. It was done in M.K.C.G Medical College with the approval from Berhampur University. It is a descriptive analytical study. A total of 70 cases, who satisfied the inclusion and exclusion criteria were taken up for the study. Thirty age and sex matched subjects were kept as controls. Parameters like fasting and postprandial blood sugar levels, serum lipid profile, blood urea, serum creatinine and serum uric acid were measured. Statistical analysis was done using standard SPSS software. Student 't' values was applied for significance. Significance was considered, if the 'p' value was below 0.01.

#### RESULTS

Males were found to have higher uric acid level when compared to females. The mean uric acid levels in males and females were  $5.83 \pm 1.20$  mg/dl and  $5.01 \pm 1.38$  mg/dl respectively although the difference was not statistically significant. serum uric acid correlated well with body mass index (BMI). The mean uric acid in subjects with BMI >25 was  $6.52 \pm 0.86$  mg/dl and  $4.29 \pm 0.80$  mg/dl in patients with BMI < 25 (statistically significant). Mean serum uric acid levels in patients with abnormal WHR and normal WHR were  $6.47 \pm 0.87$  mg/dl and  $4.25 \pm 0.76$  mg/dl respectively (statistically significant). In the study, uric acid levels were significantly elevated in patients with dyslipidaemia. The mean serum uric acid level in patients with dyslipidaemia was  $6.61 \pm 1.01$  mg/dl and in patients with normal lipid profile was  $4.39 \pm 0.89$  mg/dl. Serum uric acids were also found to be significantly raised in patients with hypertension. The mean uric acid levels in diabetics with hypertension and without hypertension were  $6.71 \pm 0.73$  mg/dl and  $4.80 \pm 1.22$  mg/dl respectively.

#### CONCLUSION

From this study it has been show that Serum uric acid levels were significantly elevated in diabetic population and that the level was independent of age and smoking status. Elevated levels were observed in those with BMI >25, WHR abnormality, dyslipidaemia with high triglycerides, hypertension and CAD.

#### KEYWORDS

CAD, WHR, CVD, hsCRP, OGTT.

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#### BACKGROUND

Diabetes mellitus has emerged as the fastest growing non-communicable disease, both in developing and developed world. The tremendous concern and focus that is given to the disease is because of its potential to cause multiple end organ damage and thereby having significant morbidity and mortality. Diabetes mellitus is an important risk factor associated with increased incidence of cardiovascular

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disease (CVD). Prevalence of CVD has rapidly increased in the past few years. The four major risk factors for CVD are hypercholesterolemia, hypertension, diabetes mellitus and cigarette smoking. Insulin resistance state is associated with diabetes mellitus (DM) and metabolic syndrome (MS).<sup>1</sup>

The four major players in the MS are hyperinsulinemia, hypertension, hyperlipidaemia, and hyperglycaemia. Each member of this deadly quartet has been demonstrated to be an independent risk factor for CVD and capable of working together in a synergistic manner to accelerate both non-diabetic atherosclerosis and the atheroscleropathy associated with MS and Type 2 DM.<sup>2</sup> In a like manner, hyperuricemia, hyperhomocysteinaemia, reactive oxygen species (ROS), and highly sensitive C- reactive protein (hs CRP) are now included in expanded manifestation of metabolic syndrome.



The above quartet does not stand alone but interacts in a synergistic manner resulting in the progression of accelerated atherosclerosis and arterial vessel wall remodeling along with the original players.<sup>2</sup>

The association of serum uric acid level in diabetes mellitus has also been evaluated in various studies. Some have reported positive<sup>3,4,5</sup> while others have found inverse relationship.<sup>6,7,8</sup> The positive association between serum uric acid and cardiovascular diseases such as ischemic heart disease has been recognized since the 1950s,<sup>9</sup> and has been confirmed by numerous epidemiological studies since then. However, whether uric acid is an independent risk factor for cardiovascular mortality is still disputed as several studies have suggested that hyperuricemia is merely associated with cardiovascular diseases because of confounding factors such as obesity, dyslipidaemia, hypertension, use of diuretics and insulin resistance.<sup>10,11,12</sup> Over recent years there has been renewed debate about the nature of the association between raised serum uric acid concentration and cardiovascular disease,<sup>13,14,15</sup> Several studies have identified the value, in populations, of serum uric acid concentration in predicting the risk of cardiovascular events, such as myocardial infarction. This has directed the research towards the potential mechanisms by which uric acid might have direct or indirect effects on the cardiovascular system. It has been difficult to identify the specific role of elevated serum uric acid because of its association with established cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia and obesity.

Here an attempt has been made to study the level of serum uric acid in type 2 diabetes mellitus and the correlation between elevated serum uric acid levels and cardiovascular risk factors like obesity, hypertension, smoking and dyslipidaemia.

### Aims and Objectives

1. To identify the level of serum uric acid in Type 2 diabetes mellitus.
2. To identify whether any association exists between age, sex, anthropometric measurements (BMI, WHR), hypertension, dyslipidaemia, smoking and coronary artery disease with serum uric acid level.

### MATERIALS AND METHODS

A total of 70 cases, who satisfied the inclusion and exclusion criteria above were taken up for the study. Thirty age and sex matched subjects were kept as controls.

### Limitations

- Because of limited resources GTT, HbA1c, leptin levels, C peptide assay, plasma insulin assay could not be done.
- Because of limited resources urinary uric acid excretion and urate clearance could not be done.

### Methods

Selected data was elicited from the patients and controls and recorded in proforma.

### 1. Socio Demographic Data-

- Age.
- Sex.

### 2. Clinical Data-

- Body weight, height, BMI.
- WHR.
- Systolic and Diastolic blood pressure.
- Family history of diabetes.
- Smoking history.
- Ischemic heart disease.
- Fundus examination.
- Neurological examination for peripheral neuropathy.

### 3. Laboratory Data-

- Fasting and postprandial blood sugar levels estimated by using glucosoxidase -peroxidase (GOD / POD) method.
- Serum lipid profile.
- Blood urea estimation was done manually by using diacetyl monoxime method (DAM).
- Serum creatinine estimation was done by using alkaline picrate method.
- Serum uric acid was done by using phosphotungstic acid method.

### Principle

Step 1: Deproteinisation: In a test tube to 1 ml of distilled water, 0.2 ml of serum, 0.4 ml of 2/3 N H<sub>2</sub>SO<sub>4</sub>, 0.4 ml sodium tungstate (10%) were added and sample centrifuged for 5 minutes.

Step 2: To 1 ml of the filtrate add 0.75N NaOH, saturated picric acid 0.5 ml mix well & wait for 15 minutes. Reading is taken at 490 nm calorimetrically.

### Statistical Analysis

Data was entered in Microsoft Excel Spreadsheet and analysed. Significance and values were analysed using standard SPSS software. Student 't' values were applied for significance. Significance was considered, if the 'p' value was below 0.01.

### Definitions Used in the Present Study Diabetes Mellitus

A1C ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.\*

**OR**

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.\*

**OR**

2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.\*

**OR**

In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

\*In the absence of unequivocal hyperglycaemia, result should be confirmed by repeat testing.

**Hyperuricemia**

Hyperuricemia has been defined as >7.0 mg/dL in men and > 6.0 mg/dL in women.

**Body Mass Index (BMI)**

It is estimated by using the formula:

$$BMI = \text{Weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$$

A BMI of

- Less than 18.5 is considered underweight.
- 18.5 - 24.9 is considered normal.
- 25.0 - 29.9 is considered overweight or preobese.
- More than 30 is considered in the obese category
- Class I (BMI 30 to 34.9)
- Class II (BMI 35 to 39.9)
- Class III (BMI > 40).

**Metabolic Syndrome**

The criteria for the metabolic syndrome have evolved since the original definition by the World Health Organization in 1998, reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations.

**NCEP: ATP III 2001**

Three or more of the following-

- Central obesity: Waist circumference >102 cm (M), > 88 cm (F).
- Hypertriglyceridemia: Triglycerides > 150 mg/dL or specific medication.
- Low HDL cholesterol: < 40 mg/dL and < 50 mg/dL for men and women respectively, or specific medication.
- Hypertension: Blood pressure > 130 mm systolic or > 85 mm diastolic or specific medication.
- Fasting plasma glucose >100 mg/dL or specific medication or previously diagnosed type 2 diabetes.

**Waist Hip Ratio**

The waist is measured by taking a circumference that gives the narrowest measurement between the ribcage and the iliac crest. The hip measurement is taken by measuring at a level that gives the maximal measurement of hip over the buttocks. It is a simple method that is unrelated to height, correlates closely with body mass index. Waist hip ratio is an approximate index of intra-abdominal fat mass and total body fat.

Waist hip ratio > 0.9 in women and >1.0 in men is abnormal.

**Conversion of Blood Glucose to Plasma Glucose**

John Neale (1999) described the conversion of blood glucose to plasma glucose by using the formula:

$$\text{Plasma glucose} = \text{Whole blood glucose} \times 1.12$$

**RESULTS**

The total number of subjects included in this study was 100. Among them 70 were cases (type 2 diabetes mellitus) and

30 were controls (nondiabetics). The details of subjects included in this study are given table 1.

Parameters	Cases	Controls
Total No	70	30
Gender	<b>M=47 F=23</b>	<b>M=17 F=13</b>
Age (Yrs.)	42-75	45-74
Mean Age (Yrs.)	58.71	56.56
WHR	0.79-1.2	0.77-1.06
BMI	19.8-29.4	18.9-26.2
FBS(mg/dl)	108-203	85-125
PBS (mg/dl)	150-310	128-180
SUA (mg/dl)	3.1-8.2	2.9-5.7

**Table 1. Details of the Subjects Included in the Study**

**Analysis of Cases and Controls with Respect to Age-** Mean and standard deviation for age of the cases and controls were 58.71 ± 8.08 years and 56.56 ± 7.38 years respectively; there was no significant difference among the cases and controls with reference to the age. The distribution of cases and controls in relation to age is provided in table 2.

Age Groups	Cases	Controls
Mean	58.71	56.56
SD	8.08	7.38
p Value	0.214 (ns)	

**Table 2. Cases and Controls in Relation to Different Age Groups**

P value = 0.214 (not significant)

The age group of the case and control group did not vary significantly.

**Analysis of Cases and Controls with Respect to Gender-** Among 70 cases studied, there were 47 males and 23 females. Among 30 controls, there were 17 males and 13 females. The details are given in table 3.

Sex	Cases		Controls	
	No.	%	No.	%
Male	47	67.14	17	56.67
Female	23	32.86	13	43.33
<b>Total</b>	<b>70</b>	<b>100</b>	<b>30</b>	<b>100</b>

**Table 3. Cases and Controls in Relation to Gender**

P value = 0.367(not significant)

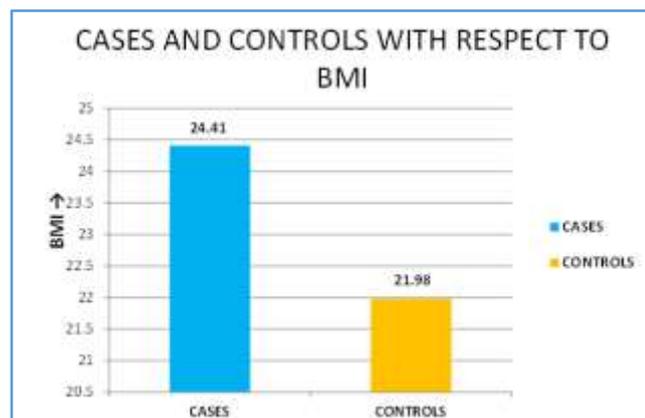
The sex composition of the study and control group did not differ significantly.

**Analysis of cases and controls with respect to B.M.I-** The mean and standard deviation for the cases and controls were 24.41 ± 2.76 kg/m<sup>2</sup> and 21.87 ± 2.26 kg/m<sup>2</sup> respectively. The details are shown in table 4.

BMI	Cases		Controls	
	No.	%	No.	%
<25	39	55.71	24	80.00
>25	31	44.29	6	20.00
<b>Total</b>	<b>70</b>	<b>100</b>	<b>30</b>	<b>100</b>

Mean	24.41	21.98
SD	2.76	2.40
P value	< 0.001	

**Table 4. Cases and Controls with Respect to BMI**



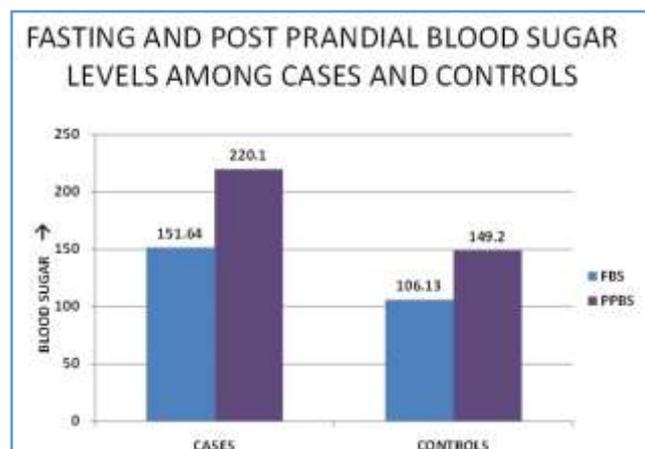
The BMI of the study group was significantly higher than that of the control group.

**Blood Sugar Distribution Among Cases and Controls-**

The details of fasting and post prandial blood sugar distribution among cases and controls are shown in the table 5. The mean and Standard deviation for fasting blood sugar was 151.64 ± 24.65 mg/dl while the mean and Standard Deviation for post prandial blood sugar was 220.1 ± 39.6 mg/dl for cases. The mean and Standard deviation for fasting blood sugar was 106.13 ± 11.41 mg/dl while the mean and Standard Deviation for post prandial blood sugar was 149.2 ± 14.71 mg/dl for controls. This shows that the glycemic status was poor among cases.

Blood Sugar		Cases	Controls	P Value
Fasting (mg/dl)	Mean	151.64	106.13	< 0.0001
	SD	24.65	11.41	
Post Prandial (mg/dl)	Mean	220.1	149.2	< 0.0001
	SD	39.6	14.71	

**Table 5. Fasting and Post Prandial Blood Sugar Levels among Cases and Controls**



p value < 0.0001(significant).

**Analysis of Cases and Controls in Relation to Selected Cardiovascular Risk Factors-**

Details of the analysis of cases and controls in relation to selected cardiovascular risk factors are provided in Table 6.

Risk Factor	Cases		Controls		P Value
	No.	%	No.	%	
Family History					
Yes	14	20.00	7	23.33	0.790 (ns)
No	56	80.00	23	77.67	
Total	70		30		
Smoking (Males)					
Yes	18	38.29	7	41.17	1.000 (ns)
No	29	61.70	10	58.83	
Total	47		17		
Hypertension					
Yes	17	24.28	9	30	0.621 (ns)
No	53	75.72	21	70	
<b>Total</b>	<b>70</b>		<b>30</b>		

**Table 6. Analysis of Cases and Controls in Relation to Selected Cardiovascular Risk Factors**

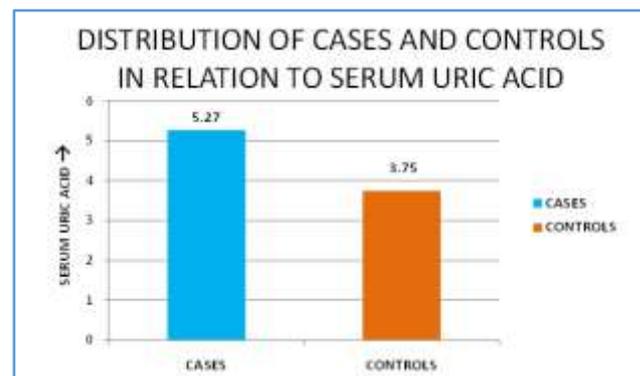
There was no significant difference between cases and controls in relation to selected cardiovascular risk factors.

**Distribution of cases and controls in relation to serum uric acid:**

Mean serum uric acid in the study population was 5.27 ± 1.38 mg/dl. Mean serum uric acid in the control group was 3.75 ± 0.60 mg/dl. The details are shown in the table 7.

Serum Uric Acid	Cases	Controls
Mean	5.27	3.75
SD	1.38	0.60
p Value	< 0.0001	

**Table 7. Distribution of Cases and Controls in Relation to Serum Uric Acid**



P value < 0.0001 (significant). The serum uric acid levels in diabetics were very much high when compared with controls and it was highly significant.

**Analysis of gender distribution with serum uric acid among the cases -**

The mean serum uric acid value in males was 5.83 ± 1.20 mg/dl whereas in females it was 5.01 ± 1.38 mg/dl. The details are shown in table 8.

Serum Uric Acid	Cases		Controls	
	Males	Females	Males	Females
Mean	5.83	5.01	3.76	3.71
SD	1.20	1.38	0.47	0.72
P Value	0.126(Ns)		0.82(Ns)	

**Table 8. Serum Uric Acid Values in Relation to Sex**

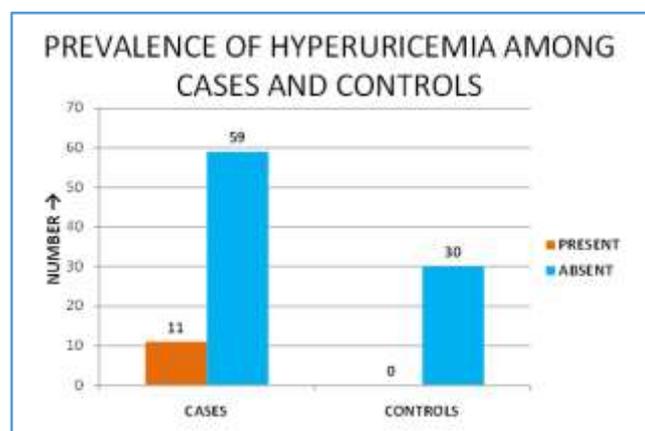
In the study group mean serum uric acid values were higher in males than in females but the difference was not statistically significant (Table 10).

**Analysis of hyperuricemia in cases and controls:**

Hyperuricemia is defined as serum uric acid level  $\geq 7.0$  mg/dl in males and  $\geq 6.0$  mg/dl in females.

Hyperuricemia	Cases				Controls			
	No.	%	Mean	SD	No.	%	Mean	SD
Positive	11	15.71	7.18	0.92	0	0	-	-
Negative	59	84.29	4.91	1.14	30	100	3.75	0.6

**Table 9. Hyperuricemia among Diabetics and Controls**



The mean serum uric acid differed significantly between cases with and without hyperuricemia. P value  $< 0.0001$  (significant).

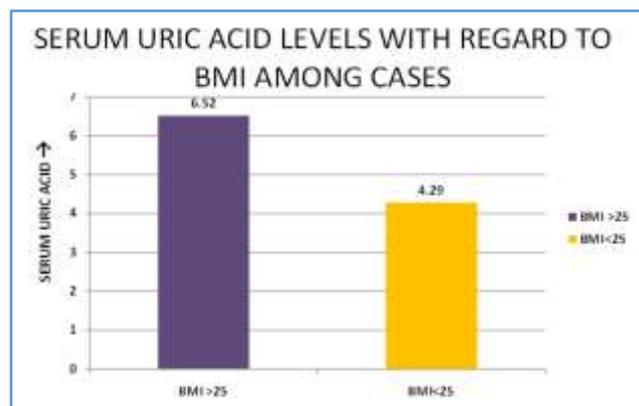
The results are presented in table 9 which indicate that the prevalence of hyperuricemia was more in diabetic patients when compared to controls.

**Serum uric acid values in relation to Body Mass Index (BMI):**

The mean value of serum uric acid was  $6.52 \pm 0.86$  mg/dl in those with BMI  $> 25$ . The mean value of serum uric acid was  $4.29 \pm 0.80$  mg/dl in those with BMI  $< 25$ . The details are shown in table 10.

Serum Uric Acid	BMI $< 25$ N=39	BMI $> 25$ N=31
Mean	4.29	6.52
SD	0.80	0.86
P Value	$< 0.0001$	

**Table 10. Serum Uric Acid Values with Regard to BMI Among Cases**



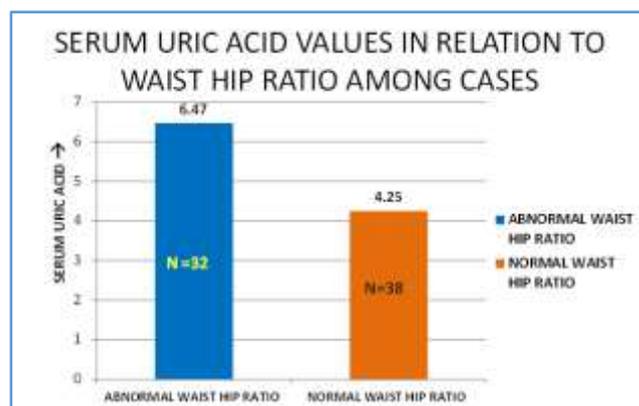
Mean uric acid level was positively correlating with BMI and was significant.

**Serum uric acid value in relation to waist hip ratio (WHR):**

Uric acid level increases with increasing WHR. WHR was considered abnormal if  $\geq 1.0$  in men,  $\geq 0.9$  in females. Thirty-two cases with abnormal WHR had mean uric acid values  $6.47 \pm 0.87$ . Thirty-eight cases with normal WHR had mean uric acid values  $4.25 \pm 0.76$ . The details are shown in table 11.

Serum Uric Acid	Abnormal Waist Hip Ratio (N=32)	Normal Waist Hip Ratio (N=38)
Mean	6.47	4.25
SD	0.87	0.76
P Value	$< 0.001$	

**Table 11. Serum Uric Acid Level with Regard to Waist Hip Ratio**



Mean serum uric acid levels were positively correlating with WHR and difference between two groups is significant.

**Smoking and serum uric acid among the cases (only in males):**

The mean value of serum uric acid level in smokers was  $5.13 \pm 1.69$  mg/dl, while it was  $5 \pm 1.22$  mg/dl among non-smokers (Table 12).

Smoker	Serum Uric Acid	
	Mean	SD
Yes ( n=18)	5.13	1.69
No (n=29)	5	1.22
P Value	0.726(ns)	

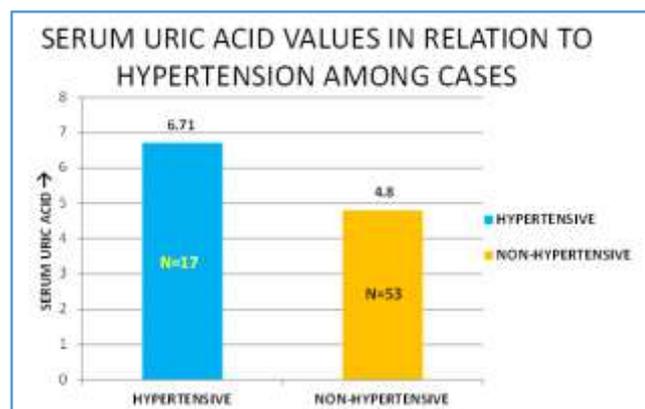
**Table 12. Serum Uric Acid Levels in Relation to Smoking (Only in Males)**

The difference was not statistically significant.

**Serum uric acid values in hypertensive patients:**  
 the total number of hypertensive in the cases group was 17. The mean serum uric acid in the hypertensive group was 6.71 ± 0.73 mg/dl. The mean serum uric acid in the non-hypertensive group was 4.80 ± 1.22 mg/dl. The details are shown in table 13.

Hypertension	Cases	Serum Uric Acid		P Value
		Mean	SD	
Yes	17	6.71	0.73	< 0.0001
No	53	4.80	1.22	

**Table 13. Serum Uric Acid Values in Relation to Hypertension**



**P value < 0.0001**

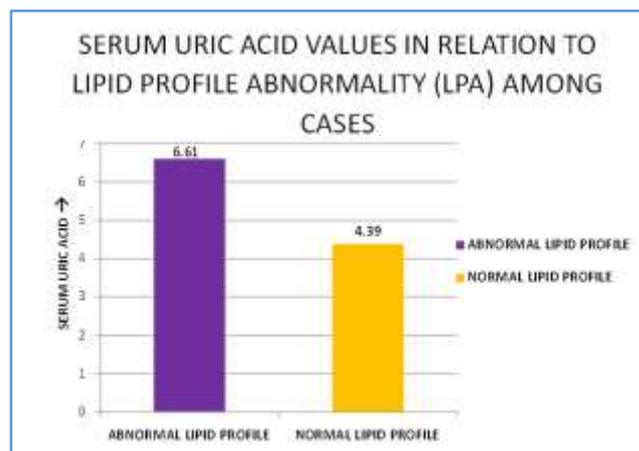
The difference between the two groups was statistically significant.

**Serum uric acid in relation to lipid profile abnormality:**

The mean serum uric acid in patients with lipid profile abnormality was 6.61 ± 1.01 mg/dl. The mean serum uric acid in patients without lipid profile abnormality was 4.39 ± 0.89 mg/dl. The details are shown in table 14.

Lipid Profile Abnormality	Cases	Serum Uric Acid		P Value
		Mean	SD	
Yes	29	6.61	1.01	< 0.0001
No	41	4.39	0.89	

**Table 14. Serum Uric Acid Values in Relation to Lipid Profile Abnormality (LPA)**



P value < 0.0001

The difference between the two groups was statistically significant.

**CAD and Hyperuricemia:**

The number of patients with ischemia were 13. The mean serum uric acid level in ischemia group was 6.52 ± 0.81 mg/dl. Of this only 4 had hyperuricemia. Number of patients with infarction is 6. The mean serum uric acid level in infarction group was 6.98 ± 0.72 mg/dl. Hyperuricemia was present in 3 of them.

CAD	No. of patients	Serum Uric Acid		p value
		Mean	SD	
Ischemia	13	6.52	0.81	0.251(ns)
Infarction	6	6.98	0.72	

**Table 15. CAD VS Serum Uric Acid Values**

CAD	No. of Patients	Total no. with Hyperuricemia	Percentage
Ischemia	13	4	30.76
Infarction	6	3	50.00

**Table 16. CAD and Hyperuricemia**

Percentage of hyperuricemia in infarction (50%) is higher than in ischemia (30.76%).

An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has been recognized for many years. Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls. However, hyperuricemia is also associated with possible confounding factors including elevated serum triglyceride and cholesterol concentrations, blood glucose, fasting and post-carbohydrate plasma insulin concentrations, waist-hip ratio and body mass index. There are certain clinical clustering groups with increased cardiovascular risk, which have associated hyperuricemia.

These are:

- Non-diabetic patient groups with accelerated atherosclerosis,
- T2DM patient groups with accelerated atherosclerosis,
- Congestive heart failure patient groups with ischemic cardiomyopathy, metabolic syndrome patients,

- Renal disease patient groups,
- Hypertensive patient groups,
- African American patient groups,
- Patient groups taking diuretics,
- Patient groups with excessive alcohol usage.

The four major players in the MS are hyperinsulinemia, hypertension, hyperlipidaemia, and hyperglycaemia. Each member of this deadly quartet has been demonstrated to be an independent risk factor for CHD and capable of working together in a synergistic manner to accelerate both non-diabetic atherosclerosis and the atheroscleropathy associated with MS and T2DM.

In a like manner, hyperuricemia, hyperhomocysteinaemia, ROS, and highly sensitive C-reactive protein (hsCRP) each play an important role in expanding the original Syndrome X described by Reaven in the atherosclerotic process. The above quartet does not stand alone but interacts in a synergistic manner resulting in the progression of accelerated atherosclerosis and arterial vessel wall remodeling along with the original players.

In this study serum uric acid levels in diabetes was examined. Uric acid as a marker of CAD in combination with other risk factors which includes Metabolic Syndrome components was examined. A control group consisting of non-diabetics was also examined. Both the groups were age and sex matched. Uric acid levels and age were independent. Yoo et al. (2005) and Becker and Jolly (2006) reported that hyperglycaemia was a remarkable risk factor for hyperuricemia. In a study of 3,681 Japanese adults, it was found that an elevation of serum uric acid concentration in males increased the risk of type 2 diabetes (Nakanishi et al.<sup>16</sup> 2003). It was concluded that hyperuricemia was positively associated with hyperglycaemia.

In the present study males have higher uric acid level when compared to females. The mean uric acid levels in males and females were  $5.83 \pm 1.20$  mg/dl and  $5.01 \pm 1.38$  mg/dl respectively although then difference was not statistically significant. The possible reason may be due to oestrogen promoting uric acid excretion (Sumino et al., 1999).

In the present study serum uric acid correlated well with body mass index (BMI). The mean uric acid in subjects with BMI >25 was  $6.52 \pm 0.86$  mg/dl and  $4.29 \pm 0.80$  mg/dl in patients with BMI < 25. The difference was statistically significant. Waist hip ratio is an important measure of obesity especially central obesity. Waist circumference >102 cm in males and > 88 cm in females is abnormal. In this present study the mean serum uric acid levels in patients with abnormal WHR and normal WHR were  $6.47 \pm 0.87$  mg/dl and  $4.25 \pm 0.76$  mg/dl respectively and the difference was statistically significant. Hyperuricemia has been associated with increasing body mass index (BMI) in recent studies and are even apparent in the adolescent youth.<sup>17,18,19</sup> Leptin levels are elevated and associated with insulin resistance in MS and early T2DM. Bedir A et al.<sup>20</sup> have recently discussed the role of leptin as possibly being a regulator of SUA concentrations in humans and even

suggested that leptin might be one of the possible candidates for the missing link between obesity and hyperuricemia.

In the present study uric acid levels were significantly elevated in patients with dyslipidaemia. The mean serum uric acid level in patients with dyslipidaemia was  $6.61 \pm 1.01$  mg/dl and in patients with normal lipid profile was  $4.39 \pm 0.89$  mg/dl. The difference was statistically significant. Conen et al. (2004) and Schachter (2005) showed the same results. Hyperuricemia and hypertriglyceridemia are suggested to be associated with insulin resistance syndrome (Tai et al., 1999; Bo et al., 2001; Bosello and Zamboni, 2000), and many investigators are studying the mechanisms of the emergence of this syndrome.

The association between insulin resistance syndrome, hyperuricemia, and hypertriglyceridemia are complicated. This might be expected from the fact that uric acid production is linked to glycolysis and that is controlled by insulin. Phosphoribosyl pyrophosphate (PPRP) is an important metabolite in this respect. Its availability depends on ribose-5-phosphate (R-5-P), the production of which is governed by glycolytic flux. Diversion of glycolytic intermediates toward R-5-P, PPRP, and uric acid will follow if there is diminished activity of GA3PDH (glyceraldehyde-3-phosphate dehydrogenase), which is regulated by insulin. Serum triglyceride concentrations may also increase, as might be expected from accumulation of glycerol-3-phosphate. Thus, intrinsic defects in GA3PDH and a loss of its responsiveness to insulin, by causing accumulation of glycolytic intermediates, may explain the association between insulin resistance, hyperuricemia, and hypertriglyceridemia (Leyva et al., 1998). In the present study serum uric acids were significantly raised in patients with hypertension. The mean uric acid levels in diabetics with hypertension and without hypertension were  $6.71 \pm 0.73$  mg/dl and  $4.80 \pm 1.22$  mg/dl respectively. The difference was statistically significant. Lin KC et al.<sup>21</sup> were able to demonstrate that blood pressure levels were predictive for cardiovascular disease incidence synergistically with serum uric acid level. This hypertension was associated with increased renin and a decrease in neuronal nitric oxide synthase in the juxtaglomerular apparatus. Prevention of this hypertension was accomplished by an ACE inhibitor and to a lesser extent L-arginine. These findings indicate an interacting role of the renin-angiotensin system and the NOS enzyme. Hypertension, neural nitric oxide synthase (nNOS) and renin changes were also prevented by maintaining uric acid levels in the normal range with allopurinol or benzbromarone (uricosuric). These above models have provided the first challenging evidence that uric acid may have a pathogenic role in the development of hypertension, vascular disease, and renal disease. The total number of patients with ischemia and infarction in the study group were 13 and 6 respectively. The mean serum uric acid levels in these patients were  $6.52 \pm 0.81$  mg/dl and  $6.98 \pm 0.72$  mg/dl respectively. Total number of hyperuricemic patients (serum uric acid > 7 mg/dl in males and > 6 mg/dl in

females) were 4 in ischemic group and 3 in infarction group. Percentage of hyperuricemia is higher in patients with infarction than in patients with ischemia.

An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has been recognized for many years. Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls. Elevated serum uric acid concentrations are also found in healthy offspring of parents with coronary artery disease, indicating a possible causal relationship. However, hyperuricemia is also associated with possible confounding factors including elevated serum triglyceride and cholesterol concentrations, blood glucose, fasting and post-carbohydrate plasma insulin concentrations, waist-hip ratio and body mass index. About one quarter of hypertensive patients have co-existent hyperuricaemia and, interestingly, asymptomatic hyperuricemia predicts future development of hypertension, irrespective of renal function. Some studies have suggested that the importance of uric acid may be independent of confounding risk factors.

Multivariate analysis of data from the MONICA cohort of 1044 males showed a significant association between raised serum uric acid and cardiovascular mortality, independent of body mass index, serum cholesterol concentration, hypertension, diuretic use, alcohol intake and smoking habits. The Gothenburg prospective study of 1462 women aged 38 to 60 years also found a significant relationship between serum uric acid concentration and total mortality during 12-year follow-up, which was independent of body mass index, serum lipid concentrations, smoking habit, blood pressure and age. In contrast to these findings, several studies have suggested that the relationship between elevated serum uric acid and cardiovascular risk does not persist after correcting for other risk factors. The British Regional Heart Study of 7688 men aged 40 to 59 years showed a significant association between elevated serum uric acid and fatal and non-fatal coronary disease over a mean 16.8 years. However, this relationship disappeared after correcting for other risk factors, particularly serum cholesterol concentration. The Coronary Drug Project Research Group studied 2789 men, aged 30 to 64 years, and found that the association between increased cardiovascular risk and elevated serum uric acid concentration was not significant after consideration of other risk factors, and when thiazide diuretic use was also considered. Higher serum uric acid levels were also observed among diabetics in various studies. In summary, although there is overwhelming evidence that elevated serum uric acid concentrations are strongly associated with increased cardiovascular risk and poor outcome, prospective population studies are often confounded by co-existent risk factors.

## DISCUSSION

An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has been recognized for many years. Observational studies show that serum uric acid

concentrations are higher in patients with established coronary heart disease compared with healthy controls. However, hyperuricemia is also associated with possible confounding factors including elevated serum triglyceride and cholesterol concentrations, blood glucose, fasting and post-carbohydrate plasma insulin concentrations, waist-hip ratio and body mass index.

Diabetes mellitus is strongly associated with hyperuricemia. Higher serum uric acid levels were also observed among diabetics in various population studies. The present study was proposed to assess the uric acid status in patients with diabetes mellitus and to find its association with age, gender, BMI, WHR, smoking, dyslipidaemia, hypertension and CAD.

With rigid criteria patients were selected carefully and evaluated after getting institutional, ethical clearance and informed consent. 70 cases and 30 healthy age and sex-matched individuals were kept as control.

Serum uric acid levels were significantly higher in cases when compared to the control population. BMI >25 significantly correlated with hyperuricemia. Similarly abnormal high WHR positively correlated with hyperuricemia. An elevated serum uric acid level was noticed among those who had hypertension, dyslipidaemia, coronary artery disease and they were significant. Mean serum uric acid in males was high compared to females. Smoking was not significantly associated with higher uric acid levels.

## Factors Contributing to Hyperuricemia in Diabetes are-

- Hyperinsulinemia reduces urinary uric acid excretion and sodium excretion.
- Micro vascular disease in diabetes mellitus causes local tissue ischemia and decreased renal blood flow. Ischemia increases lactate production that blocks urate secretion in proximal tubules.

Meticulous control of blood sugar, hypertension, dyslipidaemia and obesity form an essential component of diabetes management and this will bring down uric acid levels. It is worth to explore uric acid levels in diabetic patients as a marker with other cardiovascular risk factors like obesity, dyslipidaemia, hypertension to detect early cardiovascular complications.

## CONCLUSION

- Serum uric acid levels were significantly elevated in diabetic population.
- The serum uric acid level was independent of age and smoking status (in males).
- Elevated serum uric acid levels were significantly noted among those with BMI >25, WHR abnormality, dyslipidaemia with high triglycerides and hypertension.
- Serum uric acid levels in diabetic patients with CAD were significantly higher.
- Higher serum uric acid level in diabetic population is a marker or risk factor for CAD. Diabetic patients with

raised serum uric acid levels should be carefully monitored for CAD as well as other vascular episodes.

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