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SERUM URIC ACID LEVELS IN TYPE II DIABETES MELLITUS

Dr .M Satya Pratik[1], Dr. A. Raghuram Bhargavi[2], N.Madhu Naveen Reddy[3], Dr. K. Varsha Reddy[4]
[1,2,3]Assistant Professor, Department of General Medicine, Malla Reddy Institute of Medical Sciences.
[4]Associate Professor, Department of General Medicine, Malla Reddy Institute of Medical Sciences

Corresponding Author: Dr. K. Varsha Reddy[4]

ABSTRACT
Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin or to a combination of insulin resistance and inadequate insulin secretion to compensate for the resistance. Increased levels of uric acid have been associated with insulin resistance and with established Type II Diabetes Mellitus. Uric acid is an independent predictor of Type II Diabetes Mellitus in general population. Uric acid and its changes during follow up were related to corresponding changes in fasting and post prandial glucose and insulin levels.
Objective: To investigate Serum Uric Acid levels, HbA1c levels in patients with Type II Diabetes mellitus and compare with normal subjects.

Methodology: The present study is a case control study conducted at Malla Reddy Institute of Medical Sciences, over a period of 1 year. 100 participants were divided into 2 different groups, Cases and Controls. Cases included 50 patients with Type II Diabetes Mellitus and controls included 50 matched participants who didn't have Type II Diabetes mellitus, both the groups fulfilling the inclusion criteria and exclusion criteria. Serum uric acid, blood sugar levels, HbA1c levels were measured in both controls and patients.

Results: The mean serum uric acid in cases was 3.4mg/dl where as the mean serum uricacid in controls was 4.86 mg/dl. The mean serum uric acid in males (cases) was 3.5 mg/dl and in females (cases) was 3.4 mg/dl. The serum uric acid levels were low in cases, compared to controls (mean in cases 3.4890 mg/dl compared to 4.8600 mg/dl in controls). The HbA1c levels negatively correlated with serum uric acid, i.e.; as HbA1c increased, serum uric acid levels decreased (p value < 0.001; highly negatively correlated).

Conclusion: Serum Uric Acid levels were low in patients with Type 2 Diabetes Mellitus, particularly in those who had poor glycemic control. This may be due to increased excretion of serum uric acid during hyperglycemia and glycosuria.

Keywords: Serum uric acid, Type 2 Diabetes Mellitus, HbA1c.

INTRODUCTION

Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin or to a combination of insulin resistance and inadequate insulin secretion to compensate for the resistance. [1] The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. [2]

Uric acid is the end product of purine metabolism in humans. Humans convert the major purine nucleosides, adenosine and guanosine to uric acid through intermediates. It is then excreted unchanged via the renal system and the gastrointestinal system as humans lack the enzyme uricase. [3]

Uric acid acts as a pro-oxidant, particularly at increased concentration. It provides for more than half of body's anti-oxidant capacity. Serum Uric Acid is thus a marker of oxidative stress. [4]

Glucotoxicity due to both acute and chronic hyperglycaemia induces both an oxidative stress and reductive stress through pseudohypoxia with the accumulation of NAD^+ and NADH in the vascular intima. [5] This redox stress consumes the naturally occurring local antioxidant such as: SOD, GPX and Catalase. Once these local intimal

antioxidants are depleted, uric acid can undergo the paradoxical antioxidant- prooxidant switch or the urate-redox shuttle. [6]

Serum uric acid has been shown to be associated with production of Tumor Necrosis Factor alpha (TNF-α), which are both related to the development of diabetes. Uric acid decreases endothelial nitric oxide production and leads to endothelial dysfunction and insulin resistance. Consequently, uric acid induces vascular inflammation and artery damage, which in turn leads to increased risk of diabetes and atherosclerosis. [7]

Increased levels of uric acid have been associated with insulin resistance and with established Type II Diabetes Mellitus. Dehghan et al and Chien et al studies have demonstrated that uric acid is an independent predictor of Type II Diabetes Mellitus in general population. Uric acid and its changes during follow up were related to corresponding changes in fasting and post prandial glucose and insulin levels. [8]

The present study is being done to study the levels of Serum Uric Acid in Type II Diabetes Mellitus and the correlation between Serum Uric Acid levels and Glycemic control (HbA1c) in Type II Diabetes Mellitus.

MATERIALS AND METHODS

This is a prospective study was conducted patients presenting to Out Patient and In Patient Department, Department of General Medicine with Type II Diabetes Mellitus at Malla Reddy Institute of Medical Sciences. 100 subjects presenting to the Department of General Medicine were randomly taken and divided into two groups, each comprising of 50 subjects each.

The first group consisted of 50 subjects who had Type II Diabetes Mellitus and fulfilled the inclusion and exclusion criteria as discussed below. They were labelled as cases.

The second group comprised of 50 subjects, who were matched to the subjects in the first group and fulfilled the inclusion and exclusion criteria. The subjects belonging to the second group did not have Type II Diabetes Mellitus. They were labelled as controls.

INCLUSION CRITERIA

1. Individuals in the age group 20-70 years suffering from Type II Diabetes Mellitus, which is defined as fasting glucose concentration ≥ 126mg/dl.
2. Includes both men and women.
3. Diagnosed Type II Diabetes Mellitus patients taking oral hypoglycaemic medications or insulin for treatment.

EXCLUSION CRITERIA

1. Individuals having Type I Diabetes Mellitus.
2. Diagnosed hypertensive individuals.
3. Individuals known to have cardiovascular disease.
4. Individuals who had stroke.
5. Patient with pre-existing renal disease.
6. Individuals with dyslipidemia.
7. Individuals diagnosed as suffering from gout.
8. Patients on drugs which alters serum uric acid levels.
9. All other conditions which alter the levels of serum uric acid.

INVESTIGATIONS

1. Random Blood Sugar
2. Fasting Blood Sugar
3. Post Prandial Blood Sugar
4. Serum Uric Acid
5. HbA1c

Results

TABLE 1: AGE DISTRIBUTION ACROSS MALES AND FEMALES

AGE	SEX					
	MALE		FEMALE		TOTAL	
	NO	%	NO	%	NO	%
32 - 41	7	7	6	6	13	13
42 - 51	11	11	16	16	27	27
52 - 61	24	24	11	11	35	35
62 - 71	13	13	12	12	25	25

The given table depict the age distribution, Males of the age group 32 to 41 were 7, 42 to 51 were 11, 52 to 61 were 24 and 62 to 71 were 13. Women of the age group 32 to 41 were 6, 42 to 51 were 16, 52 to 61 were 11, 62 to 71 were 12. This when compared with overall, subjects of the age group 32 to 41 were 13, 42 to 51 were 27, 52 to 61 were 35, 62 to 71 were 25.

TABLE 2: MEAN SERUM URIC ACID IN CASES, CONTROLS

	Total	Mean Serum Uric Acid
Cases	50	3.489
Controls	50	4.86
Males (cases)	27	3.5
Females (cases)	23	3.4

The mean serum uric acid in cases was 3.4mg/dl where as the mean serum uricacid in controls was 4.86 mg/dl. The mean serum uric acid in males (cases) was 3.5 mg/dl and in females (cases) was 3.4 mg/dl. This is depicted in the table and graph below. The graph compares mean serum uric acid in case, controls, males and females.

TABLE 3: MEAN FASTING BLOOD SUGAR, MEAN POST PRANDIAL BLOOD SUGAR, MEAN RANDOM BLOOD SUGAR, HBA1C LEVELS INCASES AND CONTROLS

		Number	Mean
FBS	**CASES**	50	220.02
	CONTROLS	50	79.04
PPBS	**CASES**	50	322.5
	CONTROLS	50	91.22
RBS	**CASES**	50	270.44
	CONTROLS	50	84.98
HbA1c	**CASES**	50	9.066
	CONTROLS	50	5.016

The *Mean Fasting Blood Glucose* in cases was 220 mg/dl, controls 79.04 mg/dl. The *Mean Post Prandial Blood Glucose* in cases was 322.5 mg/dl, controls was 91.22 mg/dl. The *Mean Random Blood Glucose* in cases was 270.44 mg/dl and in controls was 84.98 mg/dl. The *Mean HbA1c* in cases was 9.06% and that in controls was 5.016%.

TABLE 4: MEAN AGE, FASTING BLOOD SUGAR, POSTPRANDIAL BLOOD SUGAR, RANDOM BLOOD SUGAR, HbA1C LEVELS, SERUMURIC ACID

		Age	FBS	PPBS	RBS	HbA1c	Serum Uric Acid
Cases	**Minimum**	32	135	203	116	6	2.21
	Maximum	80	408	570	486	14.4	4.6
	Mean	55.62	220.02	322.5	270.44	9.066	3.489
Males	**Minimum**	32	135	203	116	8.78	3.56
	Maximum	78	368	487	440	14.4	4.6
	Mean	54.85	210.25	308.59	259.74	8.78	3.556

Females	**Minimum**	32	140	242	166	6	2.21
	Maximum	80	408	570	486	14.3	4.5
	Mean	55.73	231.47	338.82	283	9.4	3.4

Mean *Fasting Blood Sugar* in cases was 220.02; in males was 210.25 mg/dl and in females was 231.47 mg/dl. The *Mean Post Prandial Blood* sugar in cases was 322.5 mg/dl; in males was 308.59 mg/dl; in females was 338.82 mg/dl. The *Mean Random Blood Sugar* in cases was 270.44 mg/dl; in males was 259.74 mg/dl and in females was 283 mg/dl. The *HbA1c* in cases was 9.066%; in males was 8.78%, in females was 9.4%.

TABLE 5: TABLE SHOWING CORRELATION BETWEEN HbA1c ANDSERUM URIC ACID IN CASES

			SERUM URIC ACID	**HbA1c**
SERUM URIC ACID		Pearson CorrelationSig. (2-tailed)	1	**-.737**** **.000**
	N		100	100
HbA1c		Pearson CorrelationSig. (2-tailed)	**-.737**** **.000**	**1**
	N		100	100

** Correlation is significant at the 0.01 level (2-tailed).

r = -0.737 and p < 0.001; highly negatively correlated

The *Pearson Correlation Co-Efficient* was calculated to check the relation between Serum Uric Acid and HbA1c. It was deduced that HbA1c in cases negativelycorrelated with Serum Uric Acid. The *p value* of the statistical analysis was < *0.001* and it was statistically significant.

TABLE 6: GROUP STATISTICS SHOWING VARIOUS VALUES INCASES AND CONTROLS

GROUPING	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**
CASES	50	55.2600	11.27904	1.59510
AGE				
CONTROLS	50	53.3800	10.78148	1.52473
CASES	50	220.02	60.88882	8.61098
FBS				
CONTROLS	50	79.0400	6.99843	.98973
CASES	50	322.50	78.62446	11.11918
PPBS				
CONTROLS	50	91.2200	5.35777	.75770
CASES	50	270.44	67.98504	9.61454
RBS				
CONTROLS	50	84.9800	7.59025	1.07342
CASES	50	9.0660	2.32586	.32893
HbA1c				
CONTROLS	50	5.0160	.58532	.08278

SERUM URIC ACID	CASES	50	3.4890	.59689	.08441
CONTROLS		50	4.8600	.78792	.11143

DISCUSSION

According to the study serum uric acid levels were low in cases (2.21 mg/dl to 4.6 mg/dl) compared to controls (3.5 mg/dl to 7 mg/dl). It also shows that HbA1c was *negatively correlating* with serum uric acid levels in cases and controls; i.e.; as the HbA1c levels increased the serum uric acid levels decreased.

A large prospective study in Israel by Herman & Goldbourt, [9] which had 10000 men aged 40 years and over. It was shown that pre-diabetic subjects had higher uric acid levels than non-diabetics, and that overt diabetics had lower uric acid levels than non-diabetics. Their finding of a negative association between serum glucose and uric acid concentrations is similar to or study as shown. However they were not able identify the cause of hypouricemia in their case study.

Dr S R Meena, [10] of Kota Rajasthan performed a similar study over 100 patients, which included 50 cases and 50 controls. The cases include 40 patients with Type II diabetes Mellitus and 10 with impaired glucose tolerance. Their study showed that serum uric acid was lower in patients in the diabetic group when compared with controls. Serum uric acid was 3.32 ± 0.882 in diabetic group compared to 4.74 ± 1.51 in controls which was statistically significant (p value < 0.001). They concluded that Serum uric acid concentration is slightly reduced in patients with Type II Diabetes Mellitus and this may be due to increased excretion of uric acid during hyperglycemia and glycosuria.

A study was performed by S. Bo et al in Italy, to evaluate the relation between uric acid and metabolic parameters, creatinine clearance and albumin excretion rate in a cohort of Type II Diabetic patients. They showed that hypouricemia in Type II Diabetes Mellitus is associated with worse metabolic control, hyperfilteration and a late onset or decreased progression to overt nephropathy. [11]

Derek G. Cook et al in their study showed that at higher levels of glucose, serum uric acid decreased. [12] The relationships between serum uric acid, serum glucose and diabetes were examined in a survey of 7735 middle-aged men drawn at random from general practices in 24 British towns. There was a positive relationship between serum glucose and serum uric acid concentrations up to about 8.0 mmol/l; at higher levels of glucose, serum uric acid decreased. It probably reflects the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyperglycaemia and glycosuria.

Gotfredsen et al[13] in their study showed that serum uric acid was less in patients with Type 2 Diabetes mellitus when compared to their controls, concluded that it was due to the increased glucose concentration in the renal tubules causing hyperfilteration of uric acid. Uric acid metabolism was investigated in 69 insulin treated male diabetic outpatients and in 23 healthy male subjects. Compared with normal, the diabetics had significantly lower mean serum uric acid concentrations (0.34 ± 0.08 (SD) mmol/l versus 0.23 ± 0.06 mmol/1, $p < 0.001$). 17% of the diabetic patients had serum concentrations below the normal mean—2 SD.

We compared our study with the works done by Gotfredsen et al[13] The comparison revealed that Serum Uric Acid was low in patients who had Type II Diabetes Mellitus when compared with the controls; which was similar to the results in our case.

The study done by Magoula I [14] also included 10 patients, who had impaired glucose tolerance. The Serum Uric Acid in these patients (6.19 ± 1.13) was higher when compared to controls (4.74 ±1.51). They proposed that patient with Type II Diabetes Mellitus had hypouricemia due to glycosuria causing uricosuria, but the factors causing increased Serum Uric Acid in patients with Impaired Glucose Tolerance was uncertain.

CONCLUSION

Thus it can be concluded that as shown in our thesis Serum Uric Acid and HbA1c have an inverse relation. This is possibly due to increased Glucose in the nephrons, which impairs the reabsorption of Uric Acid and thereby causing decreased levels of Serum Uric Acid when compared to the controls. Our study also correlates with various other studies which also show decreased Serum Uric Acid levels when compared to controls in uncomplicated Type II Diabetes Mellitus.

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