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Study of serum uric acid levels in diabetics and its association with metabolic syndrome and cardiovascular morbidity

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Abstract
Introduction: *The incidence of diabetes mellitus is increasing during past few decades due to lifestyle changes in both developing and developed countries. Uric acid being an atherogenic marker presumed to have a role metabolic syndrome, but its role as an independent risk factor for cardiovascular diseases is still a matter of controversy. Here this study aimed to assess serum uric acid levels in diabetics, its association with metabolic syndrome and cardiovascular morbidity.*
Materials and Methods: *200 patients who attended to General Medicine department were included in the study out of which 140(cases) were diabetics and 60 were non diabetics (controls). Age, sex, FBS, PPBS, HBA1c,serum uricacid,ECG,2DEHO,BMI, Waist Hip Ratio(WHR) were estimated, written informed consent was taken from all patients.*
Results: *Mean age for cases & controls was 59.13, 56.97 respectively. Mean BMI for cases and controls was 24.93 & 21.8 respectively. Mean serum uric acids for cases & controls was 5.25 &0.98 respectively.WHR abnormality was seen in 66 out of 140cases, lipid abnormalities were seen in 36 out of 140 cases. Coronary artey disease was seen in 24 of 140 cases of which 8 had hyperuricemia most of them were females.*
Conclusion: *Uric acid was significantly elevated in diabetic population. Significant correlation was noticed between serum uric acid and BMI as well as WHR. Elevated uric acid levels were significantly noticed among those with hypertension, dyslipidemia, coronary artery disease and chronicity of the diabetes*
Keywords: *Diabetes, Metabolic Syndrome, Serum Uric acid, Coronary Artery Disease.*

Introduction

Type 2 diabetes mellitus is an epidemic in India for the past few decades. WHO estimates that, globally, 422 million adults aged over 18 years were living with diabetes in 2014. The largest numbers of people with diabetes were estimated for the WHO South-East Asia and Western Pacific Regions, accounting for approximately half the diabetes cases in the world. Worldwide, the number of people with diabetes has substantially increased between 1980 and 2014, rising from 108 million to current numbers that are around four

times higher. In 2012 there were 1.5 million deaths worldwide directly caused by diabetes. It was the eighth leading cause of death among both sexes and the fifth leading cause of death in women in 2012[1]. The total burden of deaths from high blood glucose 1 in 2012 has been estimated to amount to 3.7 million. 43% of all deaths attributable to high blood glucose occur prematurely, before the age of 70 years – an estimated 1.6 million deaths worldwide. Adults with diabetes historically have a two or three times higher rate of cardiovascular disease (CVD) than adults without diabetes[2]. The risk of cardiovascular disease increases continuously with rising fasting plasma glucose levels, even before reaching levels sufficient for a diabetes diagnosis [3]. Diabetes mellitus is the most important risk factor associated with two to four fold increased incidence of coronary artery disease.

Nearly 120 years have elapsed since serum uric acid was first described as risk factor for cardiovascular disease. The association between uric acid and metabolic syndrome is robust throughout human development. Epidemiological studies have demonstrated a close relationship between serum uric acid (SUA) levels and the presence of metabolic syndrome (and several of its components) among children and adolescents as well as adults [4]. A prospective study from the Framingham Heart Study original ($n = 4883$) and offspring ($n = 4292$) cohorts showed that individuals with higher serum uric acid, including younger adults, had higher future risk of type 2 diabetes.

Serum uric acid levels have an association with surrogate markers of atherosclerosis in a number of studies. Surrogate markers of atherosclerosis shown to have an association with hyperuricemia include carotid intima-media thickness (CIMT) [5, 7], In particular, there is evidence that uric acid has direct effects on key processes involved in endothelial function and vascular remodeling [8]. As noted above, uric acid has both prooxidant and antioxidant activity. When acting an antioxidant, it chelates metals and scavenges oxygen radicals [9,10]. As a prooxidant, uric acid oxidizes lipids [11], reduces nitric oxide availability in endothelial cells[12], and increases reactive oxygen species [13]. Furthermore, as a prooxidant, high levels of serum uric acid cause increased lipid oxidation. The resultant inflammation would be expected to disrupt reverse cholesterol transport, a function that is important to reduce cardiovascular risk[14]. Oxidants also cause endothelial dysfunction by reacting with and removing NO, thereby preventing vasodilation of the endothelium. Decreased NO and increased reactive oxygen speciesmay promote a proinflammatory state that causes endothelial dysfunction and contributes to atherosclerosis and Coronary artery disease [15].

Apart from the well known causal associations of hyperuricemia leading to gout and of metabolic syndrome leading to diabetes, both hyperuricemia and metabolic syndrome are associated with hyperinsulinemia. The metabolic syndrome is currently defined as having at least three of five characteristic signs (abdominal obesity, impaired fasting glucose, hypertriglyceridemia, low HDL-cholesterol, and elevated blood pressure)[16]. The proxy measures of visceral fat obesity, principally, WC, WHR or WHtR are used as a surrogate of body fat centralization and have been use for cardiovascular risk evaluation because of their association with cardiometabolic parameters and outcome[17,18]. In patients with manifest atherosclerosis, both presence of more than three metabolic risk factors and the presence of a high waist circumference are associated with increased risk of future type 2 diabetes[19]. Moreover, hyperuricemia has been associated with metabolic syndrome in studies[20] of both healthy individuals and patients. It may also precipitate cardiovascular diseases for which the metabolic syndrome is a strong risk factor.

One mechanism linking the association between hyperinsulinemia with hyperuricemia is a decrease of renal excretion of uric acid. Insulin can also enhance renal tubular sodium reabsorption [21], which in turn can reduce renal excretion of uric acid. Whatever the mechanisms of insulin on the

renal tubules, be it direct stimulation of tubular ion exchange or acceleration of cellular metabolism [22], insulin can modify the handling of uric acid by the kidney, thus leading to hyperuricemia.

A large epidemiological study[23] of Japanese adult men showed that an elevation of serum uric acid levels increased the risk of type 2 diabetes. Dehghan et al.[24] demonstrated that serum uric acid is a strong and independent risk factor for diabetes in a 10-year follow-up study. Other studies[25] demonstrated a significant linear regression between serum uric acid levels and incident type 2 diabetes. However, diabetic patients who continue to be hyperuricemic appear to be at increased risk of developing diabetic complications, especially renal and cardiovascular disease [25]. Hence an attempt has been made to study the level of serum uric acid level in Type 2 diabetes mellitus & the correlation between elevated serum uric acid level and the component of metabolic syndrome like obesity, hypertension, dyslipidemia. and its association with cardiovascular morbidity

Aims and Objectives

Assessment of serum uric acid levels in patients with type2 Diabetes mellitus and its association with Age, Sex, Anthropometric measurements (BMI,WHR), Hypertension, Dyslipidemia & Coronary artery disease(CAD) with serum uric acid level, correlating this association between diabetics and non diabetics

Materials and Methods

200 Patients who attended to department of General Medicine were included in the present study out of which 140 diabetics (cases), 60 were non diabetics (controls) in a period of 1 yr

Criteria for the diagnosis of diabetes as per ADA2017 guidelines for diabetes.

Selected socio- demographic, clinical, laboratory data were elicited from the patients and controls and recorded in proforma with written informed consent was taken from both.

Age, sex, BMI, WHR, BP, ECG, Blood urea, serum creatinine, serum uric acid, 2D ECHO were estimated.

Inclusion criteria: Patients with type 2 diabetes mellitus (patients were taken irrespective of their glycemic control and their duration of diabetes)

Exclusion criteria: Patients with renal failure, Pregnancy & lactating mothers, Patients who were on long term diuretics & steroid, Patients who had hepatic & metabolic disorders.

Controls: Subjects who were above 40 years and had normal blood sugar and who met the above exclusion criteria.

Results

200 patients were included in the present study out of them 140 were diabetics, 60 were non diabetics. Table 2 shows relations of age with cases and controls. Mean age for cases & controls was 59.13 &, 56.97 P = 0.0551 (Not Significant) respectively. Table 3 shows relation of gender between cases and control P=0.7901 (not significant). Table 4 shows relation of BMI, Mean BMI for cases and controls was 24.93 & 21.8 respectively P=0.0002 (Significant). Table 5 shows relation between serum uric acid between diabetics and controls. Mean serum uric acids for cases & controls was 5.25 &0.98 respectively P value: 0.0001 (significant). Table 6 shows are Hyperuricemia is defined as SUA level ≥ 8 mg/dl in males and ≥6 mg/dl in females. 30 cases had hyperuricemia while none in controls*P = 0.0001 (Significant). This table clearly shows that the prevalence of hyperuricemia is more in diabetic patients when compared to controls. Table 7 Uric Acid with regard to BMI among cases, Mean uric acid level was positively correlated with BMI P = 0.0001 (Significant). Table 8: Waist Hip Ratio and Hyperuricemia, Uric acid level increases with increased WHR P = 0.0001 (Significant). The WHR abnormality was considered in 66 cases based on, WHR above 1.0 for men, above 0.8 for women and correlated with uric acid level was significant. Table 9: Uricacid Values in relation to Smoking , the mean value of serum uric acid

among smokers was 5.03±1.69 when compared to non smokers 5.32±1.42, P = 0.0001 (Significant) but the difference was not significant statistically. Table 10: Serum Uric Acid values in relation to Hypertension, The mean serum uric acid level in the hypertensive group (6.45±1.15) was significant more than non hypertensive group (4.83±1.43) in the cases P = 0.0001 (Significant). Table 11: Serum Uric Acid in relation to lipid profile abnormality, the mean serum uric acid level in patients with lipid profile abnormality was 6.67±0.94, while it was 4.75±1.44 in patients without lipid profile abnormality and it was highly significant P = 0.0001 (Significant). Table 12: shows the number of patients with CAD – 16.Of these 8 had hyperuricemia out of which 5 were females. Female patients were more involved in CAD than males in relation to hyperuricemia. Table 13 shows Duration of Diabetes And Hyperuricemia, Uric acid level increases with increasing duration of diabetes and it was statistically significant. P Value = 0.001 (Significant)

Table 1: Demographic characters

	Cases	Controls
Total No.	140	60
Gender	M=86;F=54	M=36; F=24
Age (Years)	43 to 72	41 to 75
Mean age (Years)	59.13	56.97
BMI	19.6-29.4	18.4-26.0
WHR	0.73-1.14	0.76-1.12
FBS (mg/dl)	105-172	86-120
PPBS (mg/dl)	157-302	139-181
SUricAcid (mg/dl)	2.8-8.3	2.9-5.3

Table 2: Cases and Controls in relation to age

Age Group		Cases		Controls
	No	%	No	%
40-50	28	20	12	20
51-60	42	30	20	33.33
61-70	52	37.14	22	36.66
71-80	18	12.85	6	10
Mean	59.13		56.97	
S.D.	9.11		8.41	
P=O.0551				

Table 3: Cases and Controls in relation to Gender

Sex		Cases		Controls
	No	%	No	%
Male	86	61.43	36	60
Female	54	38.57	24	40
Total	140	100	60	100

Table 4: Cases and Controls in relation to BMI P=

BMI	No	%	No	%
< 25	68	48.57	48	80
≥ 25	72	51.42	12	20
Total	140	100	60	100
Mean	24.93		21.8	
S.D.	3.13		2.3	

Table 5: Serum Uric Acid level in diabetics and controls*

	Case		Controls	
Serum Uric Acid	Mean	S.D.	Mean	S.D.
	5.25	1.59	3.91	0.98

Table 6 : Hyperuricemia in Cases and Controls

Hyperuricemia	No	Cases %	Mean	S.D	No	Controls %	Mean	S.D
+	30	21.4	7.16	0.5	0	-	-	-
-	110	78.67	4.73	1.21	60	100%	3.91	0.98

Table 7: Uric Acid with regard to BMI among cases

BMI	No.	Mean	S.D.
< 25	68	4.13	1.23
> 25*	72	6.13	1.45

Table 8 : Waist Hip Ratio and Hyperuricemia

WHR Abnormality	No.	Uric acid	SD
Yes*	66	5.93	1.37
No	74	4.63	1.3

Table 9: Uricacid Values in relation to Smoking

Smoking	No.	Mean	S.D.
Yes*	38	5.03	1.69
No	102	5.32	1.42

Table 10: Serum Uric Acid values in relation to Hypertension

HTN	No.	Mean	S.D.
Yes*	36	6.45	1.15
No	104	4.83	1.43

Table 11: Serum Uric Acid in relation to lipid profile abnormality

Lipid Profile abnormality	No.	Mean	S.D.
Yes*	36	6.67	0.94
No	104	4.75	1.44

Table 12: CAD and Hyperuricemia

No. of Patients with CAD	Total no. of Hyperuricemia	Sex	%
24	8	3M + 5F	33%

Table 13: Duration of Diabetes And Hyperuricemia

DOD	No.	Mean	S.D.
2-4 years	24	4.31	1.08
5-8 years	74	5.01	1.891
9-12 years*	42	6.87	1.03

Discussion

Diabetes is the most common risk factor for cardiovascular disease, and it is present in nearly 25% adults and increases in prevalence with age. Hyperuricemia is one of the components of metabolic syndrome. "In the absence of gout the presence of hyperuricemia in patients with type 2 diabetes mellitus is an important marker as well as an added risk factor for atherosclerosis. In this study the relation between serum uric acid level and diabetes was examined.

Seum uric acid levels were significantly elevated in diabetics than in control group indicating that hyperuricemia had a role in insulin resistance and predicting diabetes which was in agree with study done by Krishnan E et.al [26]

Uric acid is a marker for CAD in combination with other risk factors among diabetics. Though uric acid level and age was independent it is possible that duration of the illness may have an impact on uric acid levels as seen in the present study. In the present study females have higher uric acid level when compared to males. The mean uric acid value in males was 5.06 ± 1.64 while in females it was 5.93 ± 1.13, and the difference was statistically significant in this study. The possible reasons for such difference may be attributable to increased BMI and increased WHR among women.

In the present study serum uric acid correlated well with body mass index (BMI) indicated that body mass index strongest positive correlation with the uric acid among insulin resistant components. In this study patient with higher waist hip ratio had higher uric acid level when compared with low waist hip ratio. Elevated triglycerides is the most important risk factor in acceleration of atherosclerosis. There is a significant relationship between serum uric acid and dyslipidemia. In the present study dyslipidemia was noticed as a risk factor in those with CAD, who had significantly elevated serum uric acid levels. Hence this study shows that prevalence of metabolic syndrome increases as serum uric acid levels increases which is in agree with study done by H.K Choi et.al [27].

Patients with Poor metabolic control and longer duration of diabetes were more susceptible to develop various complications including hyperuricemia. Our study also shows that higher level of serum uric acid was seen in patients with longer duration of diabetes when compared with shorter duration of diabetes.

An increased levels of serum uric acid levels in diabetics further increases the risk of CAD. Uric acid >4 mg/dl should be considered as a "Red flag" in those patients at risk for cardiovascular disease which was present in 78% of the study population [28]. In this study 78.57% of diabetic patients have serum uric acid level >4 mg/dl, while only 30% of the control have serum uric acid >4mg/dl. In these patients the clinician should strive to utilize global risk reduction programme to reduce the complications of atherogenic process.

A large body of evidence links uric acid with metabolic syndrome of insulin resistance, obesity, hypertension and dyslipidemia. In this study relationship between obesity, hypertension, dyslipidemia and hyperuricemia was statistically significant.

Conclusion

Uric acid was significantly elevated in diabetic population. Significant correlation was noticed between serum uric acid and BMI as well as WHR. Elevated uric acid levels were significantly noticed among those with hypertension, dyslipidemia, coronary artery disease and chronicity of the diabetes. Uric acid level above 4 mg/dl in diabetic population (considered as a "Red flag" sign) was a marker or risk factor for CAD, which was present in 78% of study population.

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