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Uric Acid and Vascular Complications in Type 2 Diabetes Mellitus

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Original Research Article

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Abstract: Uric acid is a risk factor for vascular disease and many experimental and epidemiological data have suggested a possible role for hyperuricemia in inducing endothelial dysfunction, which is involved in diabetes mellitus type 2. It has been associated with various complications like nephropathy, neuropathy, cardiovascular morbidity, retinopathy and other vascular complications etc. The aim of our study was to ascertain the role of serum uric acid in vascular complications of type 2 DM. 1000 patients with type 2 Diabetes Mellitus diagnosed according to ADA criteria from outpatient of diabetic clinic were taken up in the study. These were divided into 2 subgroups depending upon presence or absence of complications as AI (with vascular complications) and AII (without vascular complications). 380 diabetics were without complications, 150 had diabetic neropathy, 70 had diabetic nephropathy, 220 had cardiovascular morbidity, 60 had diabetic retionopathy or cataract while 120 had other complications like gastroparesis, triopathy, frequent UTI, perineal infections, NASH etc. The mean serum uric acid in diabetics without complication (4.43$\pm$1.40 mg/dL) was significantly less as compared to mean serum uric acid in those having cardiovascular morbidity due to diabetes (p=.014), those with diabetic retinopathy (p=.004). The mean serum uric acid in those with diabetic neuropathy (p=.027) was significantly lower as compared to those with diabetic retinopathy. The mean serum uric acid value in diabetic nephropathy (p= .005), cardiovascular morbidity due to diabetes (p<.001) and diabetic retinopathy (p<.001) was significantly higher as compared to controls while in those with other complications (p=.031) was significantly lower as compared to those having diabetic retinopathy. The association of uric acid with a particular complication was not clear .Though hyperuricemia is not directly responsible for vascular injury and simply represents a surrogate marker for high levels of damaging oxidative stress involved in pathogenesis of various complications of DM type 2.

Keywords: Uric acid, type 2 Diabetes Mellitus, diabetic neropathy, diabetic retionopathy

INTRODUCTION

Diabetes mellitus (DM) is one of the most common non-communicable diseases globally [1]. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030[2]. India is ranked second in the world in diabetes prevalence. In 2011, International Diabetes Federation estimated that India has 61.3 million people living with diabetes [3].

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy and nephropathy) and macrovascular complications [coronary heart disease (CHD), peripheral arterial disease (PAD), cerebrovascular disease]. Nonvascular complications include problems such as gastroparesis, infections, and skin changes [1].

The risk of chronic complications increases as a function of the duration and degree of hyperglycemia; they usually do not become apparent until the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis [1].

Table-1: Chronic Complications of Diabetes Mellitus

MICROVASCULAR
Eye disease
Retinopathy (nonproliferative/proliferative)
Macular edema
Neuropathy
Sensory and motor (mono- and polyneuropathy)
Autonomic
Nephropathy
MACROVASCULAR
Coronary heart disease
Peripheral arterial disease
Cerebrovascular disease
Other
Gastrointestinal (gastroparesis, diarrhea)
Genitourinary (uropathy/sexual dysfunction)
Dermatologic
Infectious
Cataracts
Glaucoma
Periodontal disease
Hearing loss

Uric acid is a risk factor for vascular disease and many experimental and epidemiological data have suggested a possible role for hyperuricemia in inducing endothelial dysfunction, and particularly impaired NO bioavailability and role for uric acid in the development of endothelial dysfunction [4].

Recently, Kim *et al.* [5] suggested that elevated serum uric acid was associated with diabetic nephropathy. Zoppini *et al*. [6] found that elevated serum uric acid concentrations independently predicted cardiovascular mortality in type 2 DM. However, Ong *et al*. [7] revealed that serum uric acid did not predict cardiovascular or all-cause mortality in type 2 DM. Various types of study populations and study designs might have contribution to these disparate findings, as shown in table 4[8]. Thus, the aim of our study was to ascertain the role of serum uric acid in vascular complications of type 2 DM.

Serum uric acid seems to be a graded marker of risk for the development of CHD or CVA and stroke compared with patients with normal uric acid levels and especially those in the lower 1/3 of its normal physiological range[9]. Study by Strasak *et al.* investigated the association between increased uric acid concentrations in serum and mortality from cardiovascular causes in more than 80,000 Austrian men followed for a median of 13.6 years, and found increased uric acid was associated with increased risk of death from CHD, congestive heart failure (CHF), and stroke[10].

Ito *et al*. [11] showed the incidence of coronary heart disease was significantly higher in the patients with hyperuricemia than in those without during the follow-up observation period. They suggested that high uric acid levels clearly predicted the incidence of diabetic macroangiopathies in the patients with type 2 DM. Rathmann *et al.*[12] reported that high uric acid levels was associated with coronary heart disease in 4,047 patients with type 2 diabetes mellitus according to a cross-sectional study.

Tseng *et al.* [14] reported that the serum uric acid level was elevated, along with increased urinary albumin excretion in the smaller study population with type 2 diabetes using a cross-sectional design. Considering the conflicting data about uric acid in type 2 diabetes, the present study has been designed to evaluate serum uric acid levels in type 2 DM and its different complications.

Table-4: Characteristics of 9 articles focusing on relationship of SUA and macrovascular disease, microvascular disease, mortality in type 2DM [8]

Lead author's nam	Publication year	No of subjects	Study Population	Mean age	men (%)	Complications
Tapp[13]	2003	11247	Australian	≥25	51.4	PVD NA Neuropathy
Tseng[14]	2004	508	Chinese	63.8±10.6	41.3	PVD
Cai [15]	2006	526	Chinese	55.9	60.2	Retinopathy
Zoppini [6]	2009	2726	Italian	67.3±9.6	55.3	CHD-M All cause M
Ong [7]	2010	1,268	Australian	64.1±10.5	48.6	CHD-& All-cause Mortality
Kim [5]	2011	504	Korean	57.3±13.9	47.4	Nephropathy
Ito [11]	2011	1,213	Japanese	64.0±12.0	59.0	CHD PVD CVD Retinopathy Nephropathy Neuropathy
Zoppini [16]	2012	1449	Italian	66.1 ± 9.9	61.3	Nephropathy
Panero[17]	2012	1540	Italian	68.9	NA	All cause CHD Mort Non CHD Mortality

MATERIAL AND METHODS

1000 patients with type 2 Diabetes Mellitus diagnosed according to ADA criteria from outpatient of diabetic clinic were taken up in the study.

EXCLUSION CRITERIA

- Subjects who were taking drugs like diuretics, antihypertensive or, lipid-lowering agents, hyper or hypouricemic agents, excess vitamin supplements and hormone replacement for menopause.
- Subject with any clinical suspicion of malignancy, severe chronic obstructive pulmonary disease, acute inflammatory disease, immunological disorders.
- End stage renal disease, liver disease, hypo or hyperthyroidism.
- Acute infectious disease, fever, urinary tract infection.
- Pregnant women will be excluded.
- Patients with cerebrovascular disease (defined as angina, myocardial infarction, coronary or peripheral revascularization procedures, and stroke), kidney disease, and peripheral and autonomic nervous tissue disease and eye changes due to causes other than diabetes are excluded.

STUDY GROUPS

The subjects were divided into two groups 1000 diagnosed cases of type 2 DM were taken. These were divided into 2 subgroups depending upon presence or absence of complications as-

- AI (with vascular complications)
- AII (without vascular complications)

Complications were decided based on complains, signs and symptoms, physical examination and investigations like microproteinuria for nephropathy, retinal examination for retinopathy, ECG and echocardiography for cardiovascular morbidity

RESULTS

The mean age of patients was 55.82 ± 1.29 years (range 32-88years). 53% were males and 47% were female Depending on the diabetic complications, the patients were grouped into 2 subgroups- patients AI (patients having complications) and patient AII (patients not having complications). Complications in patient AI were as depicted in table 2.

380 diabetics were without complications, 150 had diabetic neropathy, 70 had diabetic nephropathy, 220 had cardiovascular morbidity, 60 had diabetic retionopathy or cataract while 120 had other complications like gastroparesis, triopathy, frequent UTI, perineal infections, NASH etc. Maximum diabetics had cardiovascular morbidity (22%). Fig 1 shows the percentage of diabetics according to complications. Diabetic retinopathy presents the last among complications.

Table-2: D**istribution of patient's ii according to diabetic complications**

Complications	Number of patients	M	F	age range (yrs)
Healthy Controls	1000	530	470	30-85
Diabetics without Complication	380	180	200	32-75
Diabetic Neuropathy	150	90	60	35-80
Diabetic Nephropathy	70	50	20	40-80
Cardiovascular Morbidity	220	130	90	32-82
Diabetic Retinopathy	60	30	30	58-88
Others	120	50	70	32-82

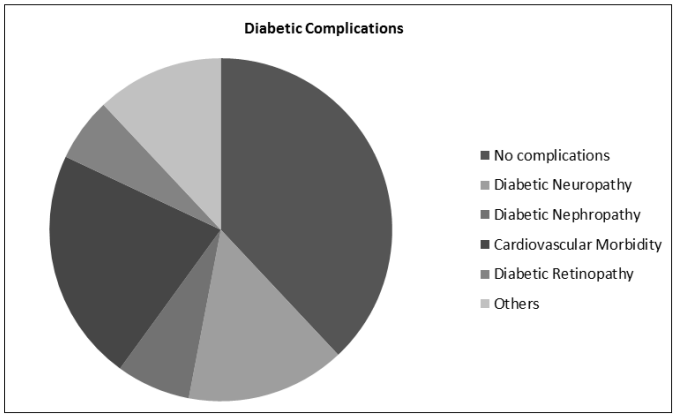

Fig-1: Distribution of patients according to complications

Table-3: **Blood pressure and kidney function tests in patients and controls (mean ± s.e.)**

Parameters	PATIENTS (n=100)	CONTROLS (n=100)	p value	Significance
Systolic B.P. (mm of Hg)	134.46 ± 1.51	114.18 ± 0.73	<.001	HS
Distolic B.P. (mm of Hg)	86.66 ± 1.18	76.18 ± 0.73	<.001	HS
Blood urea (mg/dL)	42.51 ± 3.50	23.70 ±0.68	<.001	HS
Serum creatinine (mg/dL)	1.07 ± 0.06	0.84 ± 0.01	<.001	HS

Mean systolic B.P. (134.46 ± 1.51mm of Hg) and diastolic B.P. (86.66 ± 1.81mm of Hg) was higher in patients as compared to healthy controls. Blood urea and serum creatinine in patients were also higher. These parameters were in normal range but still higher than the control group (p<.0001 (table 3).

The comparison of BMI, blood pressure and renal function in patients with complications is shown in table 4.

Table-4: **Comparison of bmi, blood pressure and renal function in patients with complications with those without complications (mean ± s.e.)**

Parameters	Subgroup A I	Subgroup A II
BMI (Kg/m^2)	25.70 ± 0.58*/**	28.01 ± 0.63*
Systolic B.P. (mm Hg)	137.55 ± 1.91*/**	129.42 ± 2.27*
Diastolic B.P. (mm Hg)	89.03 ± 1.47*/**	82.79 ± 1.18*
Blood urea (mg/dL)	48.18 ± 5.34*/**	33.26 ± 1.19*
Serum creatinine (mg/dL	1.19 ± 0.09*/**	0.88 ± 0.04

* Significant with respect to controls

** Significant with respect to subgroup A II

Patient subgroup An I had significantly higher BMI, B.P., and blood urea and serum creatinine with respect to patient subgroup A II and with respect to healthy controls as well.

Table-5: **Comparison of mean of serum uric acid levels and endothelial function in patients with complications with those without complications (mean ± s.e.)**

Parameters	Subgroup A I	Subgroup A II
Serum uric acid (mg/dL)	9.24 ± 0.33*/**	4.43 ± 0.03*
Serum NO (µmol/L)	40.65 ± 2.51*/**	63.16 ± 2.34
Serum hs-CRP (mg/L)	3.47 ± 0.18*/**	1.13 ± 0.10*

* Significant with respect to controls
** significant with respect to subgroup A II

Patient subgroup A I had significantly higher mean serum uric acid levels (9.24 ± 0.33 mg/dL) and mean serum hs-CRP levels (3.47 ± 0.18 mg/L) as compared to patient subgroup A II. (table 5, figure 2)

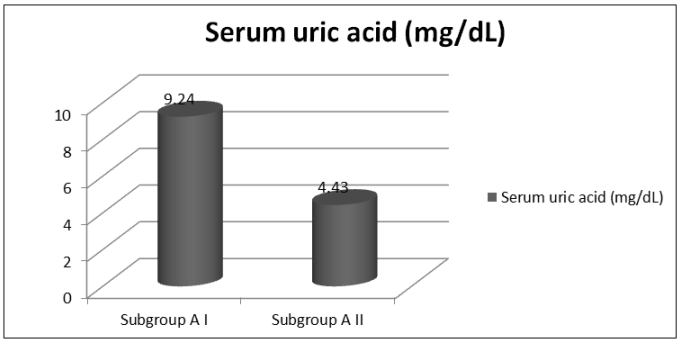

Fig-2: **Comparison of serum uric acid levels in patients with complications and without complications**

Finding one way variance of serum uric acid in different complications showed F= 12.727, and the results were highly significant (p<.001). The mean and range of serum uric acid in various complications of diabetics are shown in table 6. The mean serum uric acid in diabetics without complication (4.43±1.40 mg/dL) was significantly less as compared to mean serum uric acid in those having cardiovascular morbidity due to diabetes (p=.014), those with diabetic retinopathy (p=.004). The mean serum uric acid in those with diabetic neuropathy (p=.027) was significantly lower as compared to those with diabetic retinopathy. The mean serum uric acid value in diabetic nephropathy (p= .005), cardiovascular morbidity due to diabetes (p<.001) and diabetic retinopathy (p<.001) was significantly higher as compared to controls while in those with other complications (p=.031) was significantly lower as compared to those having diabetic retinopathy.

Figure 3 shows the variation of uric acid in the complications of diabetics, diabetics without complications and controls.

Table-6: **variation of serum uric acid in different complications (mean ± s.d.)**

	Mean uric acid (mg/dL)	Range
Controls	3.41±0.81	2-5.4
Diabetics without complications	4.43±1.40 a	2.0-8.4
Diabetic neuropathy	4.61±1.57	2.0-6.6
Diabetic nephropathy	5.77±2.03 a	2.8-8.8
Cardiovascular morbidity	5.91±3.02 a,b	2.4-15.0
Diabetic retinopathy	7.12±3.91 a,b,c,d	4.5-14.7
Other diabetic complications	4.56± 2.0	2.1-8.2

a significant w.r.t. controls
b significant w.r.t. patients without complications
c significant w.r.t. diabetic neuropathy
d significant w.r.t. other complications

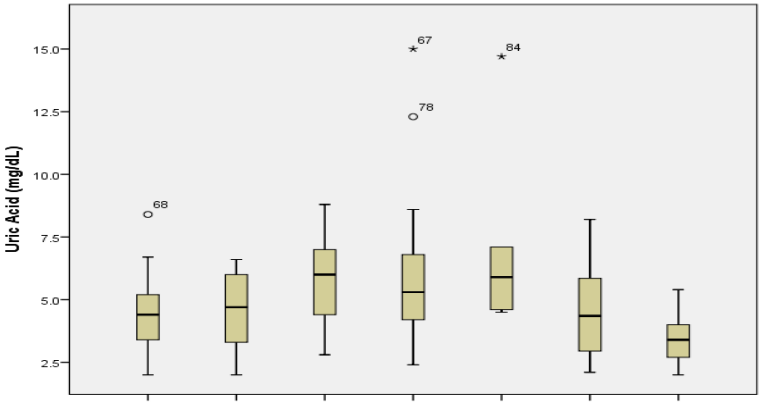

Fig-3: **Variation of uric acid in vascular complications of diabetes**

Subgroup A II	Diabetic neuropathy	Diabetic nephropathy	CVS morbidity	Diabetic retinopathy	others	Controls

Dividing serum uric acid into 4 quantiles according to uric acid distribution among diabetes and finding the relationship between serum uric acid and various complications is shown in table 7. The quantiles were 1st quantile (<3.4 mg/dL), 2nd quantile (3.4-4.7mg/dL), 3rd quantile (4.8-5.9 mg/dL), 4th quantile (≥6mg/dL). The results were not statistically significant (p=.172). Maximum percentage of complications in 4th quantile (hyperuricemia and high normal) were in diabetic nephropathy (57.1%) followed by diabetic retinopathy (50%).

Table-7: **Percentage of patients with complications according to uric acid quantiles**

Complications	1st quantile (<3.4 mg/dL)	2nd quantile (3.4-4.7 mg/dL)	3rd quantile (4.8-5.9 mg/dL)	4th quantile (>6.0 mg/dL)
Diabetics without complications	8(21.1%)	14(36.8%)	11 (28.9%)	5 (13.2%)
Diabetic neuropathy	4 (26.7%)	3 (26.7%)	3 (20%)	4 (26.7%)
Diabetic nephropathy	1 (14.3%)	2 (28.6%)	0	4 (57.1%)
Cardiovascular morbidity	4 (18.2%)	2 (9.1%)	8 (36.4%)	8 (36.4%)
Diabetic retinopathy	0	3 (50%)	0	3 (50%)
Others	3 (33.3%)	3 (25%)	3 (25%)	2 (16.7%)

DISCUSSION

The incidence of type 2 DM is increasing as a result of change in life style, dietary pattern and obesity[1]. Despite significant progress in diagnosis, treatment and prevention, diabetes particularly continues to remain the leading cause of hyperlipidemia, endothelial dysfunction, coronary artery disease, metabolic syndrome and represents global socioeconomic burden. Serum uric acid is implicated as one of the potential risk factors associated with all above[18]. The probable mechanism by which uric acid may endanger organ damage is through endothelial dysfunction, whereby it may affect cardiovascular function and structure[19].

Uric acid is most abundant antioxidant in plasma, reacts directly with NO in a rapid irreversible reaction resulting in the formation of 6-aminouracil and depletion of NO which is an EDRF. The reduction in endothelial NO level leads to endothelial dysfunction, producing the development of arterial stiffness and cardiovascular disease[20].

Depending upon the presence and absence of complications, patients were further divided into two subgroups. Among diabetics 62 % had complications evident by their complains, signs and symptoms and investigations. 38 % were apparently normal without manifested complications. Among complications, diabetic neuropathy was present in 15% of diabetics, diabetic nephropathy in 7%, cardiovascular morbidity in 22 %, diabetic retinopathy in 6% and other complications like UTI, perineal infections, gastroparesis, triopathy in 12% (table 2, figure 1).

Our study demonstrated significantly higher systolic (134.46 ± 1.51 mm of Hg) and diastolic B.P.(86.66 ± 1.18 mm of Hg) in diabetic patients, as compared to 114.18 ± 0.73 mm of Hg and 76.18 ± 0.73 mm of Hg of controls (p<.001) (table 3). This is consistent with the results of study by Dudekala *et al*. [21], where they showed systolic B.P. to be 124.98 ± 12.23 mm of Hg and diastolic B.P.to is 82.32 ± 11.23 mm of Hg. In the study done by Huang *et al*. [22] patients had systolic B.P. of 131.7 ± 17.7 mm of Hg and diastolic B.P. of 75.3 ± 10.8 mm of Hg. Ling *et al*. [23]

showed B.P. as 133.00 ± 0.53/ 80.60 ± 0.29 mm of Hg in their study? The systolic B.P. in diabetics with complications subgroup (137.55 + 1.91 mm of Hg) was significantly higher to that of diabetics without complications subgroup (129.42 ± 2.27 mm of Hg). Similarly diastolic B.P. in diabetics with complications subgroup (89.03 ± 1.47 mm of Hg) was also significantly higher as that of diabetics without complications subgroups (82.79 ± 1.18 mmof Hg) (table 4). Tomic *et al.* [24] in 2003 evaluated increase in prevalence of retinopathy with higher systolic B.P. Ramachandran *et al*. [25] has shown that high B.P. is significantly associated with diabetic vascular complications (retinopathy, nephropathy and cardiovascular disease). Wijesuriya *et al.* [26] showed high BP. was significantly associated with both micro and macro vascular complications. In their study, high systolic and diastolic B.P. was significantly associated with retinopathy, nephropathy, neuropathy, IHD and CVA. It also showed that high B.P. is significantly associated with the development of vascular complications including diabetic nephropathy. Oplez *et al.* [27] in1998 showed that systolic B.P. is an important predictor of the progression of diabetic nephropathy [27].

Comparing mean serum uric acid levels in diabetics with complications and without complications, uric acid was significantly raised in diabetics with complications and was in hyperuricemic range (9.24 ± 0.33 mg/dL) as compared to 4.43 ± 0.03 mg /dL in diabetic without complications (table 5, figure 2). Causevic *et al*. [28] showed diabetic patients who hyperuricemic are appearing to be at increased risk for developing diabetic complications, especially renal and cardiovascular disease. Study done by Hayden and Tyagi reported that elevation of uric acid > 4 mg/dL should br considered a "red flag" in the patients who are at a risk for cardiovascular disease [9]. In a study done in Thai Chuengsamarna *et al.* [29] found odds ratios between uric acid levels and several chronic vascular complications. Prevalence of chronic vascular complications in type 2 DM patients, namely coronary arterial disease, cerebrovascular disease, diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy was significantly correlated with increase of uric acid level [2.29 (1.01–5.2), 16.01 (4.74–54.09), 9.99 (4.4–22.8), 4.43 (1.3–15.1), 4.37 (1.5–12.9)], and concluded elevated uric acid levels were significantly associated with diabetic chronic micro/macro-vascular complications [29].

Classifying vascular complications into each disease, mean serum uric acid level in neuropathy were comparable with those of controls, while mean uric acid in other complications were significantly higher as compared to controls. Uric acid values in cardiovascular morbidity and in retinopathy were significantly high in comparison to diabetics without complications also (table 6, figure 3). Maximum percentage of complications in 4th quantile (hyperuricemia and high normal) were in diabetic nephropathy (57.1%) followed by diabetic retinopathy (50%) (Table 7) but its association with a particular complication was not clear. Xu *et al*. [8] showed the association between uric acid and chronic complications was statistically significant both in macrovascular group (the pooled ORs (95% CI) was 1.03 (1.00-1.06)) and microvascular group (1.47 (1.11-1.94)). Findings suggested a significantly positive correlation with each 0.1 mmol/l increase in serum uric acid leads to a 28% increase for the risk of vascular complications in type 2 DM and a 9% increase for the risk of mortality. Several studies supported serum uric acid was an essential predictor for diabetic macrovascular complications including stroke, cardiovascular heart disease(CHD) and peripheral vascular disease [30,31-33] Epidemiological research showed consistent results of a significant correlation between serum uric acid concentration and nephropathy in type 2 DM[32,34-36]. As regards to retinopathy, it has been established that serum uric acid increase positively related with the progression of retinopathy in cross-sectional studies [37-38] As for the neuropathy, studies presented controversial results [39, 34]. A recent study documented a significantly positive association between higher serum uric acid concentration and neuropathy (P<0.001)[40], while other indicated a non-significant relationship. Previous studies have indicated that elevated serum uric acid level increases the risk of all-cause and CHD-mortality dealing with type 2 DM alone or mixed with the general population [6, 41] Uric acid although one of the major antioxidants in circulation can induce oxidative stress in a variety of cells including vascular smooth muscle cells and thus, mediate progression of cardiovascular disease [42].

Uric acid reacts preferentially with peroxynitrite anion, which is a short-lived oxidant species formed by the reaction between NO and superoxide radical, occurring particularly in the vascular endothelium. Peroxynitrite is capable of inducing cell death or abnormal functioning, thus contributing to various forms of endothelial dysfunction. The relationship between uric acid and NO has also been characterized by another reactive product nitrosated uric accid, identified by mass spectrometry under aerobic conditions, which results from the reaction with NO donors, but not with peroxynitrite. Thus uric acid may act as a vehicle of NO, suggesting that its elevated levels may represent a favourable response to oxidative stress in endothelial dysfunction[31].

In overt contrast with the above data, since 2005 experimental and clinical studies have suggested that elevated uric acid levels are associated with a

reduction in NO levels with ensuing endothelial dysfunction. Uric acid reduces NO levels in endothelial cell cultures, blocks acetylcholine-induced vasodilatation of aortic rings, and reduces circulating nitrites in experimental animals. Further, rat studies have shown that hyperuricemia-induced hypertension and vascular disease are partially reversed by the supplementation of the NOS substrate, L-arginine. Gersch *et al.* have demonstrated that uric acid reacts directly with NO in a rapid irreversible reaction resulting in the formation of 6- aminouracil, with consequent depletion of NO. This reaction occurs preferentially with NO, even in the presence of peroxynitrite and hydrogen peroxide, and is partially blocked by glutathione, showing a potential mechanism by which uric acid could deplete NO under conditions of oxidative stress, when intracellular glutathione is depleted[20].

There is increased vascular cell apoptosis and inflammatory necrosis due to increased oxidative stress through ischemia-reperfusion in diabetes resulting in with increased purine metabolism by xanthine oxidase. Thus, these leads to increase in serum uric acid levels due to increased oxidative-redox stress and antioxidant "Prooxidant Paradox of Urate Redox Shuttle" where an antioxidant uric acid gets converted to a pro-oxidant. Due to hyperinsulinemia, leptin may induce hyperuricemia, and also insulin increases sodium reabsorption and is tightly linked to urate reabsorption. Additionally, low density lipoproteins such as LDL-cholesterol are capable of being modified and retained within the intima through a process of oxidative modification through free radicals, hypochlorous acid, peroxynitrite, and selected oxidative enzymes such as xanthine oxidase, myeloperoxidase and lipoxygenase [43] Increased visceral fat accumulations provide excessive free fatty acid in the portal vein, which accelerates the overproduction of very low-density lipoprotein and this causes hypertriglyceridemia. This also accelerates the de novo purine synthesis by NADPH produced in the pentose phosphate pathway which increases the uric acid production[44].

This urate redox shuttle is influenced by on its surrounding environment such as timing (early or late in the disease process), location of the tissue and substrate, acidity (acidic – basic or neutral ph), the surrounding oxidant milieu, depletion of other local antioxidants, the supply and duration of oxidant substrate and its oxidant enzyme. In the accelerated atherosclerotic vulnerable plaque the intima has been shown to be acidic, depleted of local antioxidants with an underlying increase in oxidant stress and ROS and associated with uncoupling of the eNOS enzyme and a decrease in the locally produced naturally occurring antioxidant: eNO and endothelial dysfunction.

CONCLUSION

In conclusion our study shows, instead of its controversial role in pathogenesis of type 2 DM, uric acid may play an important role in diagnosis, prognostic and therapy monitoring. Serum uric acid is involved in pathobiochemisty of endothelial dysfunction in type 2 DM. Maximum percentage of complications in 4th quantile (hyperuricemia and high normal) were in diabetic nephropathy (57.1%) followed by diabetic retinopathy (50%) but its association with a particular complication was not clear .Though hyperuricemia is not directly responsible for vascular injury and simply represents a surrogate marker for high levels of damaging oxidative stress involved in pathogenesis of various complications of DM type 2.. Thus indeed, hyperuricemia is a significant predictor of disease state and progression of diabetes (establishment of complications). The assessment of uric acid is widely available at low cost, which may be an advantage for widespread determination of this marker.

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