

SERUM URIC ACID CONCENTRATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS DURING DIET OR GLIBENCLAMIDE THERAPY

Isam Hamo Mahmood¹

ABSTRACT

Objective: To investigate serum uric acid concentration in patients with type 2 diabetes mellitus.

Methodology: This is a case control study conducted in Al-Wafa Diabetic Center in Mosul over a period of one year starting from January 1, 2005 to January 1, 2006. Serum glucose concentration and uric acid concentration were measured in both control and patient's groups (group 1 patients on diet therapy, group 2 patients on glibenclamide therapy and group 3 involve naturopathic patients).

Results: Serum glucose concentration was high in the diabetic groups as compared with the control group ($P < 0.001$). Serum uric acid concentration was lower in the diabetic groups as compared with the control group but do not reach a significant level ($P > 0.2$) except in group-3 ($P < 0.05$). A negative correlation was reported between hyperglycemia and uric acid concentration of the different groups.

Conclusion: Serum uric acid concentration is slightly reduced in type 2 diabetic patients particularly in the complicated patients with peripheral neuropathy and this may be due to the oxidative stress that decreases the antioxidant capacity of the body involving uric acid.

KEY WORDS: Type 2 diabetes mellitus, Fasting Blood Sugar, Uric acid, Oxidative stress.

Pak J Med Sci May - June 2007 Vol. 23 No. 3 361-365

INTRODUCTION

Over recent years there has been renewed debate about the nature of the association between raised serum uric acid concentration and cardiovascular disease.¹ Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls.² However, hyperuricaemia 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.³⁻⁵ About one quarter of hypertensive patients have co-existent hyperuricaemia⁶ and elevated serum uric acid is a consistent feature of the insulin resistance syndromes, which are also characterized by elevated plasma insulin level, blood glucose concentration, serum triglyceride concentration, raised body mass index and waist hip ratio.^{3,7} Hyperuricaemia has been described as a strong predictor of well defined cerebrovascular complications (stroke) in patients with type 2 diabetes.⁸

An important observation was that uric acid may function as an antioxidant, which is of great importance in plasma.^{9,10} The plasma concentration of uric acid is almost 10-fold

1. Dr. Isam Hamo Mahmood,
Head of Pharmacology,
Department College of Medicine,
University of Mosul,
Mosul - Iraq.

Correspondence

Dr. Isam Hamo Mahmood,
E-mail: isam_abdulaziz@yahoo.com

- * Received for Publication: June 19, 2006
- * Revision Received: December 7, 2006
- * Accepted: December 28, 2006

higher than other antioxidants, such as vitamin C and E.¹¹ Moreover; uric acid has much higher antioxidant capacity,¹² Urate (the soluble form of uric acid in the blood) can scavenge super oxide, hydroxyl radical, and singlet oxygen and can chelate transition metals.^{9,10} Peroxynitrite is a particularly toxic product formed by the reaction of super oxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitro tyrosine formation) of proteins. Uric acid can also block this reaction.¹³ There is currently a great interest in the potential role of increased oxidative stress in the development of diabetes mellitus and its complication.¹⁴⁻¹⁶

As uric acid is an antioxidant,¹² and is increased in oxidative stress,¹⁷ the present study was designed to measure serum uric acid concentration in non - complicated and complicated type 2 diabetic patients with peripheral neuropathy treated with diet or glibenclamide.

PATIENTS AND METHODS

This study was carried out after being submitted to the local ethic committee of Nineveh Health Administration for official approval. It included 120 individuals; comprising of four groups thirty diabetic patients on diet therapy (group 1), 30 diabetic patients treated with oral hypoglycemic drug glibenclamide (group 2), 30 diabetic patients with diabetic neuropathy diagnosed by the presence of the symptoms (pain, paresthesia, numbness) and confirmed by EMG tests of the nerves treated with glibenclamide (group 3), and 30 healthy control (group 4).

The patients were recruited from Al-Wafa diabetic center in Mosul. The 4 groups were comparable for age, gender and number of individuals to exclude the effect of this parameter on the trial outcome. The patients included in the study are those belonging to type 2 diabetic patients on diet or hypoglycemic agent (glibenclamide), those with history of diabetic neuropathy as in group 3, and those with no history of other diabetic complications such as nephropathy, hypertension, cardiac ischemic

disease and peripheral vasculopathy. The following patients were excluded from study, patients taking drugs other than glibenclamide (such as antihypertensive agents, aspirin or vitamin supplements), those with history of smoking, pregnant women and those with current illness (such as hepatic, cardiac or renal disease).

Biochemical analysis: After an overnight fast, blood was taken from a forearm vein. The blood was clotted and immediately centrifuged to separate serum which was used for the determination of FBS and serum uric acid concentrations. FBS was measured using a glucose oxidase method¹⁸ which is available as a kit manufactured by Biomaghreb. Serum uric acid was assessed by uricase enzymatic method,¹⁹ using Biomaghreb uric acid kit (Morocco). The body mass index was calculated as the weight in kilograms divided by the squared height in meters (Kg/m²)²⁰

Statistical Methods: Paired t-test was used to compare the results of various parameters among the studied groups. Linear regression analysis (Person correlation coefficient, r) was performed for determining the degree of association between different parameters. All values expressed as mean±SD, and P values of ≤0.05 were considered to be statistically significant.

RESULTS

Clinical and biological data of healthy and diabetic subjects are summarized in Table-I. Diabetic patients and control have matched ages as shown by the non-significant differences between groups when compared with control group (P > 0.05). The number of male and female was identical. BMI was statistically high when compared with control group (P < 0.005). FBS was high in the diabetic group as compared with the control group (P < 0.001). Serum uric acid concentration was lower than control but they do not reach a significant level (P > 0.2) except in Group-3 (P < 0.05).

Comparison of uric acid between the different groups other than the control group

Table-I: Clinical and biological data of healthy and diabetic subjects.

Groups	Age (y)	Sex	BMI (kg/m ²)	FBS (mmol/L) (μmol/L)	Uric acid of disease (y)	Duration
On diet (Group-1)	50.37± 6.30	M 18F 12	30.16±4.77	10.58±3.78	338.87± 73.6	4.4± 2.62
On Glibenclamide (Group-2)	50.66± 5.9	M 18 F 12	30.85± 4.23	10.76±3.93	327.58± 95.65	7.33± 4.26
With Neuropathy (Group-3)	51.3± 6.08	M 18F 12	30.37± 4.56	12.61± 3.46	313.3± 54.77	9.27± 4.3
ControlGroup-4 (Shift to the bottom: 1,2,3,4)	50.7±7.1	M 18 F 12	24.96±4.2	4.97±0.95	359.47± 83.47	————

showed non - significant differences between uric acid of the glibenclamide and diet groups ($P>0.5$), naturopathic group and diet groups ($P>0.1$), and naturopathic group and glibenclamide group ($P>0.5$).

Table-II shows the relationship between uric acid and FBS and BMI of the different groups. Negative correlations were obtained except for BMI in the glibenclamide and naturopathic groups where no relationship was obtained ($r= 0.06$).

The correlation between serum uric acid and FBS or serum uric acid and BMI were obtained statistically from the following equation:

$$\text{Correlation Coefficient (r)} = \frac{\sum xy - (\sum x)(\sum y) / n}{\sqrt{[\sum x^2 - (\sum x)^2 / n][\sum y^2 - (\sum y)^2 / n]}}$$

This equation calculate the closeness of relationship (linear relationship) between 2 variables (x and y), which are in the present study uric acid and FBS or uric acid and BMI. The P values were calculated from the following equation: $t = r \sqrt{n-2} / \sqrt{1-r^2}$ This equation represent a test for a linear relation between two variables, x and y. Degree of freedom = n-2 P value is then obtained from the t- table, which involves a number of t values and their P values and degrees of freedom.

DISCUSSION

Although there was a trend towards lower urate in our patients with NIDDM, this was not a statistical significance in the non - complicated constitute patients. Uric acid is a physiological free radical scavenger.²¹ In humans, uric acid is the main plasma antioxidant followed by vitamin C. Uric acid stabilizes vitamin C in plasma and protects it from oxidation.²² The significance that reduction in uric acid concentration in the neuropathic patients is more than in the non complicated patients obtained in the present study may be due to the fact these patients possess higher FBS compared to non - complicated group. The higher serum glucose concentration may increase fractional excretion of urate caused by an effect of glucose at the renal tubule.

The potent antioxidant properties of urate have been recognized for many years by free radical biologists, and urate appears to function as an antioxidant in vivo.⁹ Type 2 diabetes mellitus is associated with oxidative stress and increased free radical formation.²³⁻²⁵ Oxidative stress causes reduction of the antioxidant status of the body.²⁶⁻²⁸ This may explain the

Table-II: Correlation between serum uric acid concentration and FBS or BMI of the different groups

Group	Uric acid (μmol/L)	FBS (mmol/L)	Correlation Coefficient (r)	Uric acid (μmol/L)	BMI (kg/m ²)	Correlation Coefficient (r)
Diet (Group-1)	338.87±73.6	10.58±3.78	-0.19P>0.1	338.87±73.6	30.16±4.77	-0.16P>0.2
Glibenclamide (Group-2)	327.58±95.65	10.76±3.93	-0.3P>0.05	327.58±95.65	30.85±4.23	0.06P>0.5
Neuropathic (Group-3)	313.3±54.77	12.61±3.46	-0.53P<0.005	313.3±54.77	30.37±4.56	0.06P>0.5
Control (Group-4)	359.47±83.47	4.97±0.95	-0.21, P>0.05	359.47±83.47	24.96±4.2	-0.56P<0.005

reduction of serum uric acid in the present study as uric acid is also regarded as one of the total antioxidant substance present in the body.²⁹ The insignificant difference between serum uric acid concentration between the three patient groups in the present study may suggest that glibenclamide is devoid of any effect on uric acid excretion. It was found that some drugs may have hyperuricaemia properties in addition to their therapeutic effects. A number of studies have shown that fenofibrate can significantly decrease serum uric acid levels.^{30,31} There is some evidence that atorvastatin exerts a hypouricemic action in addition to its hypolipidemic capacity.³²⁻³⁴ A number of newer agents have been shown to lower serum uric acid levels including sibutramine, troglitazone, and losartan.³⁵

The negative correlation obtained in the present study between serum uric acid concentration and FBS may reflect the role of hyperglycemia in the genesis of oxidative stress in the diabetic patients. It was found that hyperglycemia can induce oxidative stress via glucose auto oxidation and the subsequent formation of advanced glycation end products, disruption of the polyol pathway, altered eicosanoid metabolism and decreased antioxidant defenses.^{36,37}

The poor correlation obtained in the present study between uric acid concentration and BMI of the diabetic patients may suggest a non effect of the increased BMI of the diabetic patients on uric acid concentration and the increased body BMI did not affect the VD of uric acid and consequently its concentration in the serum.

Many studies revealed hyperuricaemia in type 2 diabetic patients in the presence of cardiovascular diseases such as stroke.³⁸ It is impossible to recognize whether the increase in serum urate is a predisposing risk factor or can instead be considered the effect of stroke itself or both. Other investigators reported that the alleged great risk of cardiovascular events or death attributable to hyperuricaemia in some studies challenges the antioxidant properties shown by this molecule under different

experimental conditions and the antioxidant capacity of uric acid is an independent factor that ameliorate the clinical prognosis of patients with acute ischemic stroke.³⁹ The increase in serum uric acid in subjects with cardiovascular disease might therefore reflect a compensatory mechanism to counter the oxidative stress that occurs in these conditions.¹⁷ The present study concluded that uric acid is slightly reduced in patients with type 2 diabetes mellitus particularly in the complicated patients with peripheral neuropathy and this may be due to the oxidative stress that decreases the antioxidant capacity of the body involving uric acid.

REFERENCES

1. Waring WS, Webb DJ, Maxwell SRJ. Uric acid as a risk factor for cardiovascular disease *J Med* 2000;93:707-13.
2. Torun M, Yardin S, Simsek B, Burgaz S. Serum uric acid levels in cardiovascular diseases. *J Clin Pharm Ther* 1998;23:25-9.
3. Agamah ES, Srinivasan SR, Webber LS, Berenson GS. Serum uric acid and its relation to cardiovascular disease risk factors in children and young adults from a biracial community: the Bogalusa Heart Study. *J Lab Clin Med* 1999;118:241-9.
4. Lee J, Sparrow D, Vokonas PS, Lardsberg I, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. *Am J Epidemiol* 1995;142:288-94.
5. Patten RL, Hewitt D, Waldman GT, Jones G, Little JA. Association of plasma high density lipoprotein cholesterol with clinical chemistry data. *Circulation* 1980;62:1V 31-41.
6. Tykarski A. Evaluation of renal handling of uric acid in essential hypertens hyperuricaemia related to decreased urate secretion. *Nephron* 1991;59:364-8.
7. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, et al. Relationship of uric acid concentration to cardiovascular risk factors in young men. Role of obesity and central fat distribution. *Int J Obes Relat Metab Disord* 1996;20:975-80.
8. Lehto S, Niskanen L, Ronnema T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin dependent diabetes mellitus. *Stroke* 1998;29:635-9.
9. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant and radical causing aging and cancer: a hypothesis. *Proc Natl Acad Sci USA* 1981;78:6858-62.
10. Simie MG, Jovanovich SV. Antioxidation mechanisms of uric acid. *J Am Chem Soc* 1989;111:5778-82.

11. Becker BF. Towards the physiological function of uric acid. *Free Radic Biol Med* 1993;14:615-31.
12. Buettner GR. The pecking order of free radicals and antioxidants: lipid peroxidation, α -tocopherol, and ascorbate. *Arch Biochem Biophys* 1993;300:535-43.
13. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. *Arch Biochem Biophys* 2000;376:333-37.
14. Ziegler D, Christoph GH, Nourooz-Zadeh J. Oxidative stress and antioxidant defense in relation to the severity of diabetic polyneuropathy and cardiovascular autonomic neuropathy. *Diabetes Care* 2004;27:2178-83.
15. Ceriello A. New insights on oxidative stress and diabetic complications may lead to a causal antioxidant therapy. *Diabetes Care* 2003;26:1589-96.
16. Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes* 1991;40:405-12.
17. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: A reaction to atherosclerosis. *Atherosclerosis* 2000;148:131-9.
18. Lott JA, Turner K. Evaluation of trinder's glucose oxidase method for measuring glucose in serum and urine. *Clin Chem* 1975;21:1754-60.
19. Gochman N, Schmitz JM. Automated determination of uric acid with use of an uricase-peroxidase system. *Clin Chem* 1971;17:1154-9.
20. Cantrill JA. Diabetes Mellitus. In: Walker R, Edwards C (Eds). *CliniPharmacy and Therapeutics*, 2nd edition. Churchill Livingstone, London 1999;633-52.
21. Pasaoglu H, Sancak B, Bukan N. Lipid peroxidation and resistance to oxidation in patients with type 2 diabetes mellitus. *Tohoku J Exp Med* 2004;203:211-8.
22. Grootveld M, Halliwell B. Measurement of allantoin and uric acid in human body fluids. *Biochem J* 1987;243:803-8.
23. Maritim AC, Sanders RA, Watkins JB. Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Mol Toxicol* 2003;17:24-38.
24. Montonem J, Knekt P, Jarvinen R, Reunanen A. Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes Care* 2004;27:362-6.
25. Palanduz S, Ademoglu E, Gokkusu C, Tamer S. Plasma antioxidants and type 2 diabetes mellitus. *Research Communications in Molecular Pathology and Pharmacology* 2001;109:309-18.
26. Ahmed M, Khan MA, Khan AS. Naturally occurring antioxidant vitamin levels in patients with type 11 diabetes mellitus. *J Ayub Med Coll Abbottabad* 2003;15:54-7 (Abstract).
27. Memisogullari R, Taysi S, Bakan E, Capoglu I. Antioxidant status and lipid peroxidation in type 11 diabetes mellitus. *Cell Biochem Funct* 2003;21:291-6.
28. Yamada H, Yamada K, Waki M, Umegaki K. Lymphocyte and plasma vitamin C levels in type 2 diabetic patients with and without diabetes complications. *Diabetes Care* 2004;27:2491-2.
29. Fouad T. Antioxidant, nature and chemistry. The Doctor's Lounge-net2005 <http://www.thedoctorslounge.net/medlounge/articles/antioxidants/antioxidants11.htm>.
30. Desager JP, Hullhoven R, Harvengt C. Uricosuric effect of fenofibrate in healthy volunteers. *J Clin Pharmacol* 1980;20:560-4.
31. Harvengt C, Heller F, Desager JP. Hypolipidemic and hypouricemic action of fenofibrate in various types of hyperlipoproteinemia. *Artery* 1980;7:73-82.
32. Marais AD, Firth JC, Bateman ME. Atrovastatin: an effective lipid modifagent in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 1997;17:1527-31.
33. Giral P, Bruckert E, Jacob N. Homocysteine and lipid lowering agents: a comparison between atrovastatin and fenofibrate in patients with mixed hyperlipidemia. *Atherosclerosis* 2001;154:421-37.
34. Milionis HJ, Kakafika AI, Tsouli SG, Athyros VG, bairaktari ET, Seferiadis KI, et al. Effects of statin on uric acid homeostasis in patients with primary hyperlipidemia. *Am Heart J* 2004;148:635-40.
35. Alderman M, Alyer KJV. Uric acid: role in cardiovascular disease and effects of losartan. *Curr Med Res Opin* 2004;20:369-79.
36. Ceriello A. New insights on oxidative stress and diabetic complications may lead to a causal antioxidant therapy. *Diabetes Care* 2003;26:1589-96.
37. Greene DA, Stevens MJ, Obrosova I, Feldman EI. Glucose induced oxidative stress and programmed cell death in diabetic neuropathy. *Eur J Pharmacol* 1999;375:217-23.
38. Waring WS, Webb DJ, Maxwell SRJ. Uric acid as a risk factor for cardiovascular disease. *Q J Med* 2000;93:707-13.
39. Chamorro A, Obach V, Carver A, Revilla M, Deulofeu R. ApontPrognostic significance of uric acid serum concentration in patients with acute stroke. *Stroke* 2002;33:1048. <http://stroke.ahajournals.org/cgi/content/full/33/4>