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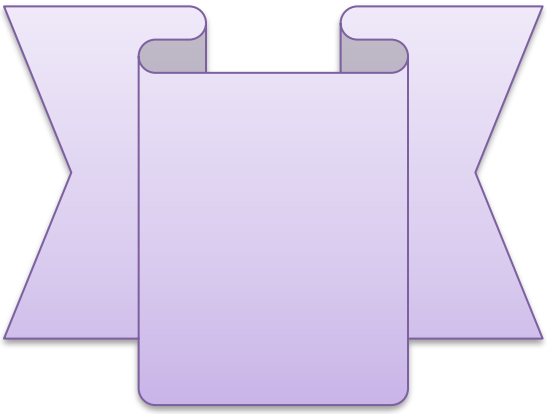

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Original Article

Relation between Serum Uric Acid and Peripheral Neuropathy in Cases of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Peripheral neuropathy is a common sequel of diabetes mellitus type 2, and may occur as an initial manifestation of diabetes. The role of uric acid in diabetic neuropathy as a microvascular complication of diabetes type 2 has been reported in numerous studies.

Aim of the Work: The objective of the study is to assess the relationship between serum uric acid levels and diabetic neuropathy in cases with diabetes mellitus type 2.

Patients and Methods: A case-controlled study included 168 cases with type 2 diabetes mellitus, conducted at internal medicine and neurology departments. Two groups of diabetic patients [type 2 DM] each one was 84 in number; 1st one diabetic with peripheral neuropathy and 2nd group was diabetics without peripheral neuropathy. All patients submitted to history taking, general and neurological examination, biochemical study, and electro-physiological examination.

Results: The serum uric acid mean level was a statistically significant higher in the 1st group in comparison with the 2nd group [4.71 ± 0.97 vs. 4.35 ± 0.9]. The severity of polyneuropathy in the 1st group showed that 38 patients had mild diabetic peripheral neuropathy [DPN], while 22 patients had moderate DPN and 24 patients had severe DPN. Uric acid levels in these three subgroups were respectively as follows: [4.6 ± 0.8] mg/dl, [4.9 ± 0.5] mg/dl and [5.3 ± 0.6] mg/dl. Regarding the relation of severity of peripheral polyneuropathy to serum uric acid level, there was a statistically significant relation between mild and moderate poly-neuropathy and a statistically significant relation between Mild to severe polyneuropathy. The logistic regression model revealed that an increase in uric acid level is an important indicator for a more severe degree of peripheral neuropathy.

Conclusion: The severity of diabetic polyneuropathy is increased with the increase of uric acid serum level.

Keywords: Diabetic peripheral neuropathy; Electrophysiological study; Serum uric acid.

INTRODUCTION

Peripheral neuropathy is considered the most common sequel of diabetes mellitus type 2, which can affect >30% of diabetic patients type 2 DM and can occur as an initial manifestation of diabetes [1].

Currently, the management of diabetic neuropathy is just symptomatic and not curative, and despite good control of blood sugar, the microvascular complication continues to occur. So, we have to detect and identify other elements that lead to the progress of diabetic neuropathy [2-3].

The pathogenesis of neuropathy in diabetics is not completely understood until now. Numerous hypotheses have been anticipated but they are frequently believed to be a multi-factorial procedure [4].

Symptoms occurrence rest on numerous factors, like hyperglycaemic duration and further risk factors like smoking, hypertension, dyslipidemia, increased height, and neurotoxic agents' exposure such as ethanol. Oxidative stress, free radical, non-enzymatic glycation, and polyol can be considered as probable causative factors [5].

The role of hyperuricemia is uncertain, while its role in vascular disease, stroke, and coronary heart disease was revealed in some studies [6-9]. The role of hyperuricemia in diabetic nephropathy, diabetic foot, retinopathy, and sudomotor dysfunction as a microvascular complication of diabetes in type 2 diabetic patients was reported in several studies [10-15].

Detection of the modifiable risk factors which can occur with diabetic polyneuropathy can improve the management and early prevention of diabetic neuropathy [1].

The objective of the study was to assess the relationship between serum uric acid levels and diabetic neuropathy in cases with diabetes mellitus type 2.

PATIENTS AND METHODS

A case-control study included 168 diabetic patients conducted at internal medicine and neurology departments, during the period from February 2021 to January 2022.

Two groups of diabetic patients [type 2 DM]; 1st one 84 diabetics with peripheral neuropathy and 2nd group, 84 diabetics without peripheral neuropathy; both groups are compared as regards to gender, age, body mass index, and duration of diabetes.

Exclusion criteria: Cases with a history of hepatic, renal impairment, malnutrition, malabsorption syndrome, alcoholic or patient receiving drugs affecting serum uric acid [like thiazides, allopurinol, salicylate, ethambutol, cyclosporine, levodopa, pyrazinamide, niacin, or glucocorticoids].

All patients submitted to history taking, general and neurological examination, biochemical study, and electrophysiological examination. The diagnosis of polyneuropathy was set on **Hanewinkel *et al.*** [16] criteria [bilateral symmetrical distal sensory and motor impairment; it was presented with tingling, pain, numbness, and motor weakness].

The severity of polyneuropathy was graded into mild, moderate, and severe using a total neuropathy symptom score [17] which consists of five questions. Every question takes point for calculation of the score where mild= 3-4 points, moderate =5-6 points, and severe 7-9 points.

[1] Tingling, burning, and numbness [2 points] or aching, cramping, and fatigue in lower limbs [1 point].

[2] Symptoms in feet [2 points] or calf [1 point].

[3] Symptoms increased at night [2 points] or equally along the day and night [1 point].

[4] Symptoms wake the patient from sleep [1 point].

[5] Symptoms decreased by walking [2 points] or standing [1 point].

Electrophysiological study: was done using Nihon Kohden device; Model UT- 0800 J. Box Board two-channel, For JB-942BK. Made in Tokyo, Japan.

Motor conduction study was done by bipolar electrical stimulation of peroneal and tibial nerves at the level of ankle and the knee and recording the evoked response from the extensor digitorum brevis and abductor halluces

respectively and measuring conduction velocity, terminal latency, and amplitude of the evoked response. Sensory conduction study of sural [antidromic] was done by bipolar electric stimulation on the back of the leg and recording the evoked response from the area behind and below the lateral malleolus and measuring terminal latency and amplitude of the evoked response. Then compared with normal values of tibial, peroneal, and sural nerves which were ≥ 3.6 mv, 3.1 mv and 4 UV for amplitude respectively, and for conducting velocity were ≥42.9 m/s, 48.4 m/s, and 34.4 m/s respectively also for latency were ≤ 6.1 ms, 4.9 ms and 4.5 ms respectively. The diagnosis of poly-neuropathy is based on the abnormality of any element of nerve conduction in 2 separate nerves, one of which is the sural nerve [18].

Lab work: serum creatinine, HbA1c, and uric acid level were assessed in fasting state [3.5 - 7.2 mg/dl].

Ethics approval and consent to participate: The study was accepted by the local Ethics committee of Damietta Faculty of Medicine Al-Azhar University. Registration Number: IRB00012367-21-02-016. Issuance and Expiration Date: 23/02/2021 valid until 22/02/2023, Damietta Faculty of Medicine IRB, Al-Azhar University. Before contribution in the study, the study process was explained for each person. Also, verbal and written consent was obtained from of the contributors, and was approved by the ethical committee as the study practice does not contradict with any medical circumstances and there are no effects on the health of contributors.

Statistical Analysis: The statistics were prepared, arranged, and statistically analyzed using a statistical package for social science [SPSS] version 18 [SPSS Inc., USA, Chicago, Illinois]. Numerical data were existed as mean ± SD [standard deviation], while categorical data were presented as frequency and percent. P-value < 0.05 was considered significant for interpretation of results. Comparison between groups was done by independent samples [t] test for two means and one-way analysis of variance for more than two means with the least significant differences as post-Hoc analysis. Comparison was carried out by ANOVA with post hoc test Turkey Multinomial logistic regression.

RESULTS

Each group was 84 in number, as regard to demographic and laboratory results of both groups are described in table [1]. The mean age in the 1st group was 54.6 ± 6.9 and the 2nd group was 55.8 ± 5.8 years without significant difference. The mean level of serum uric acid was a statistically significant higher in the 1st group in comparison with the 2nd group [4.71 ± 0.97 vs. 4.35± 0.9].

Neurophysiological findings of the studied groups were shown in table [2]. As regards the severity of polyneuropathy in the 1st group, 38 patients had mild diabetic peripheral neuropathy [DPN], 22 patients had moderate DPN and 24 patients had severe DPN. Uric acid levels in these three subgroups were as follows respectively: 4.6 ± 0.8 mg/dl, 4.9 ± 0.5 mg/dl and 5.3 ± 0.6 mg/dl. Regarding the relation of severity of peripheral polyneuropathy to serum uric acid level, there was a statistically significant relation between mild and Moderate polyneuropathy [P1 < 0.08], and a statistically significant relation between mild to severe polyneuropathy [P3 <0.001]. While there was a statistically non-significant relation between moderate to severe peripheral polyneuropathy [P2 < 0.320] [table 3]. The logistic regression model revealed that Uric acid level increases [β = 0.402, p <0.001] is an important indicator for a more severe degree of peripheral neuropathy. [table 4, figure 1].

Table [1]: Demographic and laboratory findings of the studied groups

	1st group [n = 84]	2nd group [n = 84]	P. value
Female, NO [%]	52[61.9]	52[61.9]	1.00
Age	54.6±6.9	55.8±5.8	0.4
BMI [Kg/m2]	29.3 ± 4.1	27.6±3.9	0.056
Diabetic duration[years]	9.1±5.2	9,7±4.2	0.58
Smoking [%]	12 [14.2]	6[7.1]	0.29
Hypertension [%]	54[64.2]	40[47.6]	0.12
Serum creatinine [mg/dl]	1 ± 0.2	0.9± 0.3	0.8
Hba1c %	8 ±1.4	7.8±1.6	0.52
Uric acid [mg/dl]	4.8±0.98	4.37±0.90	0.02

Table [2]: Neurophysiological finding of the studied groups

		1st group [n = 84]		2nd group [n = 84]		Test	P-value
		Mean	S. D	Mean	S. D		
Right common peroneal nerve	Distal latency [ms]	5.07	0.68	4.4	0.46	5.20	**<0.001***
	Amplitude [mv]	3.4	0.9	3.9	0.61	2.34	**<0.023***
	Conduction velocity [m/s]	45.7	8.09	53.05	4.56	4.59	**<0.001***
Left common peroneal nerve	Distal latency [ms]	5.14	0.7	4.21	0.55	6.99	**<0.001***
	Amplitude [mv]	3.24	0.76	3.87	0.54	3.93	**<0.001***
	Conduction velocity [m/s]	45.4	8.35	54.91	2.59	6.17	**<0.001***
Right posterior tibial nerve	Distal latency [ms]	5.58	0.56	4.74	0.28	7.89	**<0.001***
	Amplitude [mv]	3.98	0.63	4.49	0.86	2.85	**0.006***
	Conduction velocity [m/s]	46.3	6.5	48.48	5.49	1.57	**0.13**
Left posterior tibial nerve	Distal latency [ms]	5.59	0.54	4.8	0.26	8.21	**<0.001***
	Amplitude [mv]	3.97	0.63	4.65	0.84	3.92	**<0.001***
	Conduction velocity [m/s]	46.14	6.57	50.11	5.07	2.78	**0.007***
Right sural nerve	Latency [ms]	5.65	0.42	3.5	0.63	70.186	**<0.001***
	Amplitude [uv]	3.7	1.53	8.4	2.25	57.415	**<0.001***
Left sural nerve	Latency [ms]	5.66	0.43	3.47	0.61	73.193	**<0.001***
	Amplitude [uv]	4.39	3.70	8.4	2.44	21.287	**<0.001***

Table [3]: Relation of serum uric acid level to the severity of Peripheral neuropathy

Peripheral neuropathy	S. Uric acid [Mean ± SD]	Test	Post hoc test
Mild	4.6 ± 0.8	F= 7.86	**P1 < 0.08***
Moderate	4.9 ± 0.5		**P2 < 0.320**
Sever	5.3 ± 0.6	P <0.01	**P3 <0.001***
Total	4.9 ± 0.7		**-------**

P1; Mild and Moderate relation, P2; Moderate to severe relation, P3; Mild to Severe relation* Significant value p< 0.05. F [ANOVA]

Table [4]: Correlation between the severity of peripheral neuropathy and serum uric acid level

	Coefficients				
	Unstandardized Coefficients		Standardized Coefficients	t	Significance
	B	Std. Error	Beta		
Uric acid	0.456	0.115	0.402	3.973	**< 0.001**
[Constant]	-0.383-	0.564	4.9 ± 0.7	-0.679-	0.499

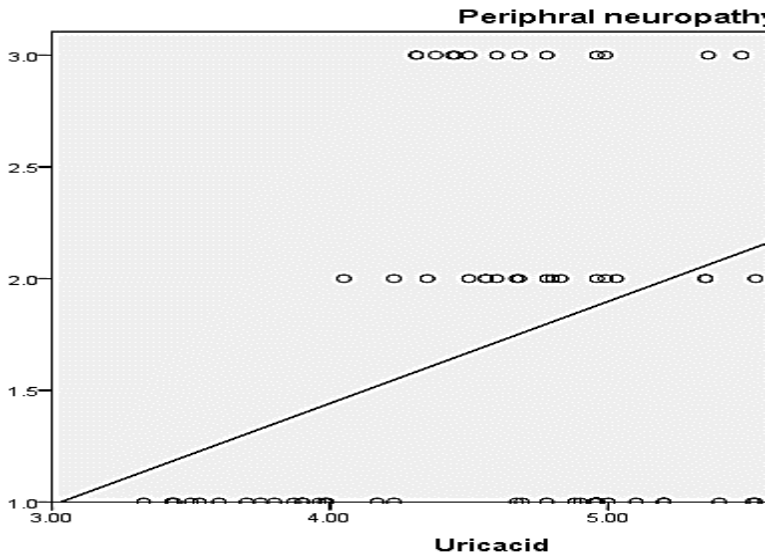

Figure [1]: Correlation between the severity of peripheral neuropathy and serum uric acid level

DISCUSSION

In the present study, the group of diabetic polyneuropathy showed significant increased serum uric acid in comparison with the diabetic group without polyneuropathy. Also, the serum uric acid was increased as the increase in the severity of neuropathy. These findings agree with **Kiani *et al.*** [19] who emphasized the role of serum uric acid in diabetic neuropathy, as the level of serum uric acid was higher in the diabetic neuropathy group in comparison with the diabetic group without neuropathy and recommend further studies to clarify the role of hyperuricemia in diabetic polyneuropathy. Also, **Kaewput *et al.*** [20], in his multicentre nation-wide cross-section study that conducted on 7511 diabetic patients type 2, and concluded that the increased uric acid in serum must be measured as a risk factor of diabetic poly-neuropathy. **Yu *et al.*** [21] showed a meta-analysis of 12 small cross-sectional studies for evaluation of serum uric acid relationship to diabetic's neuropathy of T2DM. They reported that increased serum uric acid linked to the development of diabetic peripheral neuropathy of T2DM. **Abraham *et al.*** [22] in their study reported that uric acid has correlated with the severity of diabetic polyneuropathy assessed by clinical and neurophysiological examination, while **Lin *et al.*** [23] mentioned a significant correlation between serum uric acid and diabetic poly-neuropathy in their study.

The current study supposed that the increased serum uric acid has a role in diabetic neuropathy. The role of serum uric acid in the development of other diabetic complication was studied in several conditions such as diabetic retinopathy [13, 24]; Also, in diabetic nephropathy, **Hovind *et al.*** [25] has reported the uric acid is a risk factor of development diabetic nephropathy from his study on 277 patients with diabetes type one. In pseudo motor neuropathy, **Papanas *et al.*** [14] reported that increased serum uric acid was associated with pseudo motor neuropathy among patients with type 2 diabetes mellitus. This also agrees with the report of **Xiong *et al.*** [26] the pathogenesis of T2DM is complex, including serval interacting factors.

Hyperuricemia is strictly related to the development of chronic complications of diabetes. Many studies have shown that uric acid is associated with complications through oxidative stress, inflammation, endothelial dysfunction, and other effects. Where the oxidant reacts with uric acid-producing free radicals and promotes oxidative damage of the cells [27]. Also, the uptake of uric acid by cells leads to stimulation of the production of local thromboxane and expression of platelet-derived growth factors [28].

Conclusion: The severity of diabetic poly-neuropathy is increased with the increase of uric acid serum level.

Conflict of Interest and Financial Disclosure: None.

REFERENCES

1. Yu S, Chen Y, Hou X, Xu D, Che K, Li C, *et al*. Serum Uric Acid Levels and Diabetic Peripheral Neuropathy in Type 2 Diabetes: a Systematic Review and Meta-analysis. Mol Neurobiol. 2016 Mar;53[2]:1045-1051. doi: 10.1007/s12035-014-9075-0.

2. Kwai NC, Nigole W, Poynten AM, Brown C, Krishnan AV. The Relationship between Dyslipidemia and Acute Axonal Function in Type 2 Diabetes Mellitus In Vivo. PLoS One. 2016 Apr 14;11[4]:e0153389. doi: 10.1371/journal.pone.0153389.

3. Steiner G. How can we improve the management of vascular risk in type 2 diabetes: insights from FIELD. Cardiovasc Drugs Ther. 2009 Oct; 23[5]:403-8. doi: 10.1007/s10557-009-6190-7.

4. Greene DA, Sima AA, Stevens MJ, Feldman EL, Lattimer SA. Complications: neuropathy, pathogenetic considerations. Diabetes Care. 1992 Dec;15[12]:1902-25. doi: 10.2337/diacare.15.12.1902.

5. Feldman EL, Stevens MJ, Greene DA. Pathogenesis of diabetic neuropathy. Clin Neurosci. 1997;4[6]:365-70. PMID: 9358981.

6. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities [ARIC] Study. Ann Epidemiol. 2000 Apr;10[3]:136-43. doi: 10.1016/s1047-2797[99]00037-x.

7. Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. Curr Med Res Opin. 2004 Jun;20[6]:951-4. doi: 10.1185/030079904125003971.

8. Shankar A, Klein BE, Nieto FJ, Klein R. Association between serum uric acid level and peripheral arterial disease. Atherosclerosis. 2008 Feb;196[2]:749-55. doi: 10.1016/j.atherosclerosis.2006.12.029.

9. Lehto S, Niskanen L, Rönnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in

patients with non-insulin-dependent diabetes mellitus. Stroke. 1998 Mar;29[3]:635-9. doi: 10.1161/01.str.29.3.635.

10. Kushiyama A, Tanaka K, Hara S, Kawazu S. Linking uric acid metabolism to diabetic complications. World J Diabetes. 2014 Dec 15; 5[6]:787-95. doi: 10.4239/wjd.v5.i6.787.

11. Jalal DI, Rivard CJ, Johnson RJ, Maahs DM, McFann K, Rewers M, Snell-Bergeon JK. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study. Nephrol Dial Transplant. 2010 Jun;25[6]:1865-9. doi: 10.1093/ndt/gfp740.

12. Rosolowsky ET, Ficociello LH, Maselli NJ, Niewczas MA, Binns AL, Roshan B, Warram JH, Krolewski AS. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol. 2008 May; 3[3]:706-13. doi: 10.2215/CJN.04271007.

13. Mohora M, Vîrgolici B, Coman A, Muscurel C, Găman L, Gruia V, Greabu M. Diabetic foot patients with and without retinopathy and plasma oxidative stress. Rom J Intern Med. 2007;45[1]: 51-7. PMID: 17966443.

14. Papanas N, Demetriou M, Katsiki N, Papatheodorou K, Papazoglou D, Gioka T, *et al*. Increased serum levels of uric acid are associated with sudomotor dysfunction in subjects with type 2 diabetes mellitus. Exp Diabetes Res. 2011; 2011:346051. doi: 10.1155/2011/346051.

15. Papanas N, Katsiki N, Papatheodorou K, Demetriou M, Papazoglou D, Gioka T, Maltezos E. Peripheral neuropathy is associated with increased serum levels of uric acid in type 2 diabetes mellitus. Angiology. 2011 May;62[4]: 291-5. doi: 10.1177/0003319710394164.

16. Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. Eur J Epidemiol. 2016 Jan;31[1]:5-20. doi: 10.1007/s10654-015-0094-6.

17. Meijer JW, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Diabet Med. 2002 Nov;19[11]:962-5. doi: 10.1046/j.1464-5491.2002.00819.x.

18. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, *et al.*; American Academy of Neurology; American Association of Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2005 Jan 25;64[2]: 199-207. doi: 10.1212/01.WNL.0000149522.32823.EA.

19. Kiani J, Habibi Z, Tajziehchi A, Moghimbeigi A, Dehghan A, Azizkhani H. Association between serum uric acid level and diabetic peripheral neuropathy [A case control study]. Caspian J Intern Med. 2014 Winter;5[1]:17-21.

20. Kaewput W, Thongprayoon C, Rangsin R, Jindarat S, Narindrarangkura P, Bathini T, Mao MA, Cheungpasitporn W. The Association between Serum Uric Acid and Peripheral Neuropathy in Patients with Type 2 Diabetes Mellitus: A Multicenter Nationwide Cross-Sectional Study. Korean J Fam Med. 2020 May;41[3]:189-194. doi: 10.4082/kjfm.18.0205.

21. Yu S, Chen Y, Hou X, Xu D, Che K, Li C, *et al*. Serum Uric Acid Levels and Diabetic Peripheral Neuropathy in Type 2 Diabetes: a Systematic Review and Meta-analysis. Mol Neurobiol. 2016; 53[2]:1045-51. doi: 10.1007/s12035-014-9075-0.

22. Abraham A, Breiner A, Barnett C, Katzberg HD, Lovblom LE, Perkins BA, Bril V. Uric acid levels correlate with the severity of diabetic sensorimotor polyneuropathy. J Neurol Sci. 2017;379:94-98. doi: 10.1016/j.jns.2017.05.053.

23. Lin X, Xu L, Zhao D, Luo Z, Pan S. Correlation between serum uric acid and diabetic peripheral neuropathy in T2DM patients. J Neurol Sci. 2018;385:78-82. doi: 10.1016/j.jns.2017.11.034.

24. Feldman T, Weitzman S, Biedner B. [Retinopathy and serum uric acid in diabetics]. Harefuah. 1995 Jun 1;128[11]:681-3, 744. Hebrew. PMID: 7557663.

25. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. Diabetes. 2009;58[7]:1668-71. doi: 10.2337/db09-0014.

26. Xiong Q, Liu J, Xu Y. Effects of Uric Acid on Diabetes Mellitus and Its Chronic Complications. Int J Endocrinol. 2019 Oct 13;2019:9691345. doi: 10.1155/2019/9691345.

27. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids. 2008 Jun;27[6]:608-19. doi: 10.1080/15257770802138558.

28. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, *et al*. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003 Jun;41[6]:1183-90. doi: 10.1161/01.HYP.0000069700.62727.C5.

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