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Association between serum uric acid level and diabetic peripheral neuropathy (A case control study)

Abstract

Background: The role of uric acid is well known for the development of nephropathy and retinopathy in diabetic patients. The aim of this study was to evaluate the serum uric acid levels in patients with or without diabetic neuropathy (DPN).

Methods: Forty-two patients with DPN (case group) and 42 patients without DPN (control group) matched with regard to age, gender, body mass index (BMI) and duration of their disease were entered into the study. The diagnosis of DPN was based on the nerve conduction studies on sural, peroneal and tibial nerves in lower limbs. Serum uric acid was measured in these two groups.

Results: The mean age of the patients in the case group was 54.6 ± 6.9 and in the control group was 55.8 ± 5.8 years ($p=0.389$). The demographic characteristics of the patients in these two groups were equal, but only the history of diabetic foot ulcer was higher in patients with DPN ($p<0.05$). The mean serum uric acid was 4.70 ± 0.96 in diabetic patients with DPN and 4.36 ± 0.89 mg/dl in patients without DPN ($p=0.019$).

Conclusion: The results show the higher level of serum uric acid level in diabetic patients with diabetic neuropathy. Further studies are required to determine the role of uric acid in the development and progression of DPN.

Keywords: Diabetes Mellitus, Neuropathy, Uric Acid

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Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, which is occasionally the initial manifestation of type 2 diabetic patients (1). The factors involved in the pathogenesis of diabetic neuropathy have not been understood completely, and multiple hypotheses have been proposed but they are commonly accepted to be a multifactorial process (2). Development of symptoms depends on various factors, such as duration of hyperglycemia and other risk factors such as dyslipidemia, hypertension, smoking, increased height, and exposure to other neurotoxic agents such as ethanol. The probable etiologic factors include polyol pathway, non-enzymatic glycation, free radical and oxidative stress (3). In addition to these factors, it seems that some other etiologies influence the pattern and presentation of clinical diabetic neuropathy. In this field, the role of the factors such as hyperuricemia is doubtful. The role of serum uric acid in coronary heart disease, vascular disease, peripheral arterial disease, and stroke was shown in some studies (4-7). Regarding the microvascular complications of diabetes, the role of uric acid in the onset and progression of diabetic nephropathy or albuminuria was shown in some studies (8-10). Also, the increased uric acid level was reported in diabetic foot patients with retinopathy (11). Higher serum uric acid levels in type 2 diabetic patients with sudomotor dysfunction or with peripheral neuropathy were shown in two studies (12, 13).

Because of the obscurity in this field, the aim of this study was to evaluate the serum uric acid level in patients with and without diabetic peripheral neuropathy.

Methods

From October 2012 and January 2013, 42 patients with diabetic peripheral neuropathy and 42 subjects without peripheral neuropathy were entered into the study. All patients had diabetes type 2 and were matched with regard to age, gender, duration and body mass index (BMI). The patients were selected from 600 patients with diabetes type 2 in Hamedan Diabetes Center, Hamedan University of Medical Sciences, Iran (14). We used the standard Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) criteria for screening of diabetic neuropathy in this population (15, 16). The patients with age less than 30 and more than 70 years, other causes of neuropathy, the use of any medication that alters serum uric acid level (such as allopurinol, thiazides, salicylate, levodopa, ethambutol, pyrazinamide, niacin or cyclosporine and glucocorticoids), history of hepatic or renal dysfunction ($Cr > 1.5$), malabsorption or malnutrition and alcohol abuse were excluded from the study.

After signing an informed consent for each patient, first, the subjects completed a questionnaire including general information, smoking status, duration of diabetes, type of medication and history of foot ulcer. Then, the height, weight and blood pressure were recorded. For the diagnosis of peripheral diabetic neuropathy, we performed a nerve conduction study. Biochemical parameters including serum creatinine, HbA1c and uric acid were measured in the fasting state. The study was approved by the Research Ethics Review Committee of Hamedan University of Medical Sciences, Hamedan, Iran.

Screening for peripheral diabetic neuropathy: NSS (Neuropathy Symptom Score) and NDS (Neuropathy Disability Score) criteria were used for the screening (15-17). NSS questionnaire included questions regarding the type of the sensation, location of the symptoms, the time of the symptoms, waking up from the sleep and factors that relieve symptoms. NDS contains neurologic examination parameters such as the ankle reflex and perceptions of pinprick, cold and vibration. Each parameter takes a score of 0 to 2. Total NSS and NDS score is the sum of these scores. The criteria for the existence of DPN were a NDS score of at least 6,

irrespective of NSS score, or a NDS score of 3-5 in combination with a NSS score of at least 5 (15-17).

Nerve conduction studies were performed on sural, peroneal and tibial nerves in lower limbs while amplitude, conduction velocity and latency were measured. The obtained values were compared with normal values (18). Diagnosis of DPN was based on the recommended protocol. The case definition criterion for confirmation of DPN was an abnormality (≥ 99 th or ≤ 1 st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve (19).

The severity of DPN was assessed by a combination of neuropathy symptoms, signs, nerve conduction studies abnormalities as mild, moderate and severe (20). Serum uric acid and creatinine were measured by enzymatic colorimetry using an autoanalyzer (Selectra-2, Italy) and relevant commercial kits (Pars Azmoon, Tehran, Iran). HbA1c was assessed by color reflectometer using an analyzer and kit (Nycocard, England).

Data analysis: SPSS Version 16 was used to perform the statistical analysis. To determine the normal distribution of variables, Kolmogorov Smirnov test was used. Data with normal distribution were expressed as mean and standard deviation and data without normal distribution were expressed as median and inter-quartile range. For comparison between these two groups, t-test and Mann-Whitney test were used. To compare qualitative variables between the two groups, chi square test was used. P-values less than 0.05 were considered to be significant.

Results

General characteristics and biochemical parameters of the case and control groups are shown in table 1. The mean age of the patients in the case group was 54.6 ± 6.9 and in the control group was 55.8 ± 5.8 years ($P=0.389$). Twenty six patients in each group were females (61.9%). Only the history of diabetic foot ulcer was higher in patients with DPN ($P=0.003$). Other variables did not have significant difference in two groups (table 1). The mean serum uric acid level was significantly higher in case group (4.70 ± 0.96 vs. 4.36 ± 0.89) ($P=0.019$). In the control group, 19 patients had mild DPN, 11 patients had moderate DPN and 12 patients had severe DPN. Uric acid levels in these three groups were as follows respectively: 4.28 ± 0.95 mg/dl, 4.94 ± 0.89 mg/dl and 5.13 ± 0.82 mg/dl.

Table 1. General characteristics and biochemical parameters of the case and control groups

	With DPN (n= 42)	Without DPN (n=42)	P.Value
Female, n (%)	26 (61.9)	26 (61.9)	1.000
Age (years)	54.6±6.9	55.8±5.8	0.389
BMI (Kg/m ²)	29.3±4.1	27.6±3.9	0.056
Duration of Diabetes (years)	9.7±4.2	9.1±5.2	0.583
Medication, n (%)			
Oral agent	14 (33.3)	17 (40.4)	
Insulin	17 (40.4)	12 (28.5)	0.517
Both	11 (26.1)	13 (30.9)	
Smoking (%)	6 (14.2)	3 (7.1)	0.290
History of diabetic foot ulcer (%)	8 (19)	0 (0)	0.003
History of hypertension (%)	27 (64.2)	20 (47.6)	0.124
Systolic blood pressure (mm/Hg)	134.4±16.7	131.0±17.3	0.373
Diastolic blood pressure (mm/Hg)	80 (80-90)*	80 (80-90)*	0.640
Serum creatinine (mg/dl)	1 (0.9-1.2)*	1 (0.9-1.2)*	0.831
HbA1c %	8.1±1.3	7.9±1.5	0.524
Uric acid (mg/dl)	4.70±0.96	4.36±0.89	0.019

*Median and inter-quartile range. Others as mean±SD

Discussion

The results of this study showed that the uric acid level was significantly higher in diabetics with peripheral diabetic neuropathy. The role of uric acid in the development of complications of diabetes has been investigated in several studies. Some studies proposed uric acid as a mediator in the prediction of the development of albuminuria in diabetes. Hovind et al. studied 277 patients with type 1 diabetes that showed uric acid level soon after onset of type 1 diabetes was independently associated with the risk for later development of diabetic nephropathy (8). Another study showed that elevated serum uric acid levels was a strong predictor of the development of albuminuria in patients with type 1 diabetes (9). Also, the contribution of high-normal range uric acid concentration in disturbance of renal function in patients with type 1 diabetes was demonstrated in one study (10). Existing studies focusing on diabetic retinopathy are scarce. Feldman et al. did not find any significant difference in uric acid levels between those with or without retinopathy, but Mohora et al. who compared two groups of diabetic foot patients, with and without retinopathy showed higher concentrations of uric acid in diabetic foot patients with retinal disease (11, 21). Another study demonstrated the association of hyperuricemia with smaller retinal arteriolar

caliber and larger venular caliber in a high risk Chinese population for diabetes (22). Two recent studies that have been published by Papanas et al. were evaluated the serum uric acid levels in type 2 diabetic patients with and without peripheral neuropathy and with and without sudomotor dysfunction (12, 13). In the first study, they showed that serum uric acid increased in 64 patients with neuropathy versus 66 matched patients without neuropathy according to NSS-NDS criteria (13). Also, in another study, they showed significantly higher serum uric acid levels in type 2 diabetic patients with sudomotor dysfunction (12).

We added electro diagnostic tests to NSS-NDS criteria for better documentation of peripheral neuropathy. In the clinical point of view, while the main etiologic factor in the pathogenesis of diabetic neuropathy is hyperglycemia and its consequences, it seems that the other factors may decrease residual risk. Uric acid and many unknown factors may play roles in this context. Since the role of uric acid in other long term complications of diabetes was suggested in some studies, its contribution for the development or progression of diabetic neuropathy is probable. In the present study, we tried to match those factors that affect serum uric acid level such as BMI and renal function in case and control groups. The advantage of our study is the confirmation of the

peripheral neuropathy by electrodiagnostic method as the minimal criteria for the diagnosis of DPN (20). Variations in serum uric acid level and the effect of diet on its level may be the limitations of our study. Although further studies are needed to clarify the specific role for uric acid in the pathogenesis of diabetic neuropathy, the results of the present study raised the possible role of uric acid in this process. Proving this hypothesis will expand our understanding about the pathogenesis of diabetic neuropathy. Whether changes in serum uric acid level may cause changes in progression of diabetic neuropathy needs further studies. In conclusion, the result of our study shows the probable role of serum uric acid levels in the development of peripheral diabetic neuropathy.

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Conflict of interest: There was no conflict of interest.

References

- Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 1998; 15: 508-14.
- Greene DA, Sima AA, Stevens MJ, Feldman EL, Lattimer SA. Complications: Neuropathy, pathogenetic consideration. *Diabetes Care* 1992; 15: 1902-25.
- Feldman EL, Stevens MJ, Greene DA. Pathogenesis of diabetic neuropathy. *Clin Neuro sci* 1997; 4: 365-70.
- Moriarty 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; 10: 136-43.
- Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. *Curr Med Res Opin* 2004; 20: 951-4.
- Shankar A, Klein BE, Nieto FJ, Klein R. Association between serum uric acid level and peripheral arterial disease. *Atherosclerosis* 2008; 196: 749-55.
- Lehto S, Niskanen L, Rönnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with noninsulin dependent diabetes mellitus. *Stroke* 1998; 29: 635-9.
- 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: 1668-71.
- Jalal DI, Rivard CJ, Johnson RJ, et al. 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; 25: 1865-69.
- Rosolowsky ET, Ficociello LH, Maselli NJ, et al. 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; 3: 706-13.
- Mohora M, Virgolici B, Coman A, et al. Diabetic foot patients with and without retinopathy and plasma oxidative stress. *Rom J Intern Med* 2007; 45: 51-7.
- Papanas N, Demetriou M, Katsiki N, et al. Increased Serum Levels of Uric Acid Are Associated with Sdomotor Dysfunction in Subjects with Type 2 Diabetes Mellitus. *Exp Diabetes Res* 2011: 1-5.
- Papanas N, Katsiki N, Papatheodorou K, et al. Peripheral neuropathy is associated with increased serum levels of uric acid in type 2 diabetes mellitus. *Angiology* 2011; 62: 291-5.
- Kiani J, Moghimbeigi A, Azizkhani H, Kosarifard S. The prevalence and associated risk factors of peripheral diabetic neuropathy in Hamedan, Iran. *Arch Iran Med* 2013; 16: 17-9.
- Young RJ, Zhou YQ, Rodriguez E, et al. Variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetic polyneuropathy. *Diabetes* 1986; 35: 192-7.
- Skljarevski V, Malik RA. Clinical Diagnosis of Diabetic Neuropathy In: Veves A, Malik RA. *Diabetic Neuropathy*. Totowa, New Jersey: Humana Press, 2007; pp: 277-8.
- Cabezas-Cerrato J. The prevalence of clinical diabetic polyneuropathy in Spain: a study in primary care and hospital clinic groups. *Diabetologia* 1998; 41: 1263-9.
- Pease ws, lew HI, Johnson Ew. *Johnsons practical Electromyography*. 4th ed. Philadelphia, PA: Lippincott williams & wikins 2007; pp: 240-53.

19. England JD, Gronseth GS, Franklin G, et al. 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; 64: 199-207.
20. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33: 2285-93.
21. Feldman T, Weitzman S, Biedner B. Retinopathy and serum uric acid in diabetics. *Harefuah* 1995; 128: 681-3. [In Hebrew]
22. Yuan Y, Ikram MK, Jiang S, et al. Hyperuricemia Accompanied with Changes in the Retinal Microcirculation in a Chinese High-risk Population for Diabetes. *Biomed Environ Sci* 2011; 24: 146-54.