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Study of Serum Uric Acid in Relation to Diabetic Neuropathy in Type 2 Diabetic Patients

Mohamed M. Awad[1], Ahmed Lotfy Elsayed[1], Walaa samy[2], Farid Fawzy[1]
Departments of [1]Internal Medicine and [2]Medical Biochemistry,
Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Ahmed Lotfy Elsayed, **Email:** ahmed.abdelkareem@medicine.zu.edu.eg

ABSTRACT

Background: Diabetic peripheral neuropathy (DPN) considered a potential complication correlated with diabetes type 1 and type 2 (T2DM).

Objective: The present study was aimed for better control of T2DM complications such as diabetic DPN and to assess the relationship between serum uric acid (SUA) level and DPN.

Patients and Methods: This cross-sectional study was carried out in Internal Medicine Outpatient Clinics, Zagazig University Hospital and El Ahrar Teaching Hospital. The study included 50 patients; aged between 42 and 78 years, divided into two groups, diabetic group without neuropathy (DM) and diabetic group with peripheral neuropathy.

Results: The findings revealed that there was a statistically insignificant difference between DM, and DPN groups and gender, age, weight, height, BMI. There was a significant difference between the two studied groups and duration of diabetes and SUA. There was a statistically insignificant difference between DM and DPN groups and type of medication, systolic BP, diastolic BP, Hemoglobin A1c, and fasting blood glucose.

Conclusion: It could be concluded that elevated SUA level increased the chance of developing peripheral neuropathy in a person with type 2 diabetes (T2DM). Many animal experiments and large-scale clinical observations and experiments are needed to confirm this observation.

Keywords: Diabetes Mellitus, neuropathy, Serum uric acid.

INTRODUCTION

Diabetes mellitus type 2 (T2DM) incidence was expected to reach 7090 cases in every 100,000 by the next decade. Regarding the gender, both males and females were with equal incidences while the mean age of T2DM was around 55 years. DM comes in the ninth place in the highest cause of mortality **(1).**

Egypt comes ninth in the leading countries of T2DM incidences, the prevalence of T2DM grows fast during the past two decades caused by risk factors especially obesity **(2).**

Uric acid considered a metabolic product of degradation of purines (guanine & adenine), and nucleic acids, formed in intestines, liver, and endothelium **(3).** Reference uric acid levels are 3.4-7.0 mg/dL (male) and 2.4-6.0 mg/dL (female) **(4).**

Recent reports found that studies revealed that inflammation and oxidative stress could be causative agents of insulin resistance. Insulin resistance was induced by SUA that promotes oxidative stress and elevates reactive oxygen species (ROS) level **(5)**.

Some implications for the improvement of novel treatments for diabetic peripheral neuropathy can be provided from the identification of the associations of diabetic peripheral neuropathy (DPN) with modifiable risk factors. In addition, recognizing risk factors of diabetic peripheral neuropathy is also necessary for screening and prevention of diabetic neuropathy **(5, 6).**

This present study was aimed for better control of type 2 diabetes complications such as diabetic neuropathy and to investigate relationship between SUA and DPN.

PATIENTS AND METHODS

This cross-sectional study included a total of 50 Type 2 diabetic patients, aged from 42 to 78 years, attending at Internal Medicine Outpatient Clinics, Zagazig University Hospitals and El Ahrar Teaching Hospital.

The included subjects were divided into two groups; **Group A (Diabetic group without neuropathy)** consisted of 25 patients, 13 males and 12 females and their average age was (58.04±6.49) ranged from 49-70 years and **Group B (**Diabetic group with peripheral neuropathy**)** consisted of 25 patients, 11 males and 14 females and their average age was (58.84 ± 8.56) ranged from 42-75 years.

All the cases with the following criteria were enrolled in the study; Type 2 diabetic patient more than 18 years, Gender both male and female, patients newly diagnosed with microvascular complications such as nephropathy, and controlled group type 2 diabetic patient without microvascular complications.

The patients with following criteria were excluded from the study; pregnant and lactating female patients, causes of retinopathy or nephropathy other than diabetes mellitus, exclusion of any drug that affects serum uric acid level, and lymphoproliferative, myeloproliferative, and haematological disorder.

All cases were subjected to full history taking (age, sex, time since diagnosis of diabetes, and type of medication), general examination, laboratory investigation (FBG, HbA1c, Serum uric acid).

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Ethical Consideration:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Written informed consent of all the participants' parents was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data were collected, and analyzed using SPSS software package (Version 20.0. Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median. Comparisons between groups for categorical variables were assessed using Chi-square test. Student t-test was used to compare two groups for normally distributed quantitative variables. Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

RESULTS

The current results regarding cases in DM group showed that the mean age was 57.7 years, 42.9% of cases were males while females represented 57.1%. The mean weight was 89.8 Kg, while the mean height was 170.01 cm. The mean BMI was 31.05 (kg/m^2). On the other hand, the DPN group cases showed that the mean age was 56.6 years. Regarding gender, 62.9% of cases were males, and 37.1% were females. The mean weight was 90.1 Kg, and the mean height was 171.3 cm. The mean BMI was 30.4 (kg/m^2). Regarding DM group, 24 cases got oral medication, while 11 cases received insulin. The mean duration of diabetes was 3 years, the mean systolic blood pressure (SBP) was 133.3 mmHg, while the mean diastolic blood pressure (DBP) was 83.3 mmHg. The mean HbA1c was 8.1 %, the fasting blood glucose was 184.9 mg/dl. The mean 2 hours post prandial was 280.7 mg/dl, and the mean serum uric acid was 5.58 mg/dl, Creatinine mean level was 0.837 mg/dl. Concerning DPN group, 12 cases got oral medication, while 17 cases received insulin. The mean HbA1c was 8.34 %, the fasting blood glucose was 201.1 mg/dl. The mean DM duration was 6 years, the mean systolic blood pressure was 133.7 mmHg, while the mean diastolic blood pressure was 82.86 mmHg. The mean 2 hours post prandial was 292.57 mg/dl, and the mean serum uric acid was 9.24 mg/dl, creatinine mean level was 0.897 mg/dl. (Table 1).

In the current study, diabetes duration and SUA levels were significantly higher in diabetic neuropathy group compared to diabetic patients without neuropathy. However, the two groups were comparable regarding demographic and clinical characteristics (Table 1).

Table (1): Basic characteristics between groups.

Variable	Total (n=70)	DPN (n=35)	DM (n=35)	P
Age (years)	57.16 ± 8.4	56.6 ± 8.1	57.71 ± 8.76	.583
Sex, n (%)				.094
Males	37 (52.9%)	22 (62.9%)	15 (42.9%)	
Females	33 (47.1%)	13 (37.1%)	20 (57.1%)	
Weight (kg)	89.97 ± 7.54	90.11 ± 7.68	89.83 ± 7.52	.875
Height (cm)	170.63 ± 5.22	171.26 ± 5.42	170.01 ± 5.01	.317
BMI (kg/m^2)	30.73 ± 2.69	30.41 ± 2.74	31.05 ± 2.65	.324
WC (cm)	109.69 ± 7.92	109.31 ± 7.79	110.06 ± 8.15	.698
SBP (mmHg)	133.93 ± 17.42	133.71 ± 17.67	134.14 ± 17.43	.919
DBP (mmHg)	83.34 ± 10.02	82.86 ± 9.87	83.83 ± 10.28	.688
Comorbidities, n (%)				
Smoking	23 (32.9%)	12 (34.3%)	11 (31.4%)	.799
Hypertension	40 (57.1%)	23 (65.7%)	17 (48.6%)	.147
Dyslipidemia	25 (35.7%)	15 (42.9%)	10 (28.6%)	.213
CV diseases	7 (10%)	4 (11.4%)	3 (8.6%)	.690
DM medication, n (%)				.228
Insulin (μIU/mL)	28 (40%)	17 (48.6%)	11 (31.4%)	
Oral	31 (44.3%)	12 (34.3%)	19 (54.3%)	
Both	11 (15.7%)	6 (17.1%)	5 (14.3%)	
Diabetes duration (years)#	4 (0.8 - 20)	6 (0.8 - 20)	3 (0.8 - 15)	**.001**
FBS (mg/dl)	195.34 ± 5.55	201.1 ± 7.57	183.89 ± 5.94	.149
2h-PP (mg/dl)	286.66 ± 49.73	292.57 ± 29.66	280.74 ± 63.77	.323
HbA1c (%)	8.17 ± 1.19	8.34 ± 1.11	8.01 ± 1.26	.255
Uric acid (mg/dl)	7.41 ± 2.31	9.24 ± 1.22	5.58 ± 1.54	**<0.001**
Creatinine (mg/dl)	0.861 ± 0.145	0.897 ± 0.167	0.837 ± 0.159	.128

Median (IQR). Other quantitative data were expressed as mean ± SD.

Table 2 showed that there was a significant positive correlation between SUA and diabetes duration among DPN patients (table 2).

Table (2): Correlation between uric acid and other parameters among the two studied groups.

Variable	DPN		DM	
	r	p	R	p
Age	-0.199	.252	.310	.070
BMI	.050	.777	.114	.514
WC	.082	.641	.072	.680
Diabetes duration	**.372**	**.038***	.138	.147
SBP	.131	.452	.168	.335
DBP	.264	.125	.067	.703
HbA1c	-0.074	.673	-0.007	.968

The present results showed that older patients and elevated SUA were significantly associated with the development of DPN.

Table (3): Regression analysis to determine the associated factors with diabetic neuropathy.

	OR	S.E.	Sig.	95% Confidence Interval
Age	.166	.004	**.030**	.019 - 0.233
Male gender	2.750	.520	.052	0.992 - 7.623
Weight	.210	.019	.461	0.024 - 0.583
Height	.144	.019	.477	0.053 - 0.322
BMI	.219	.050	.416	0.141 - 0.593
Waist circumference	.056	.007	.544	0.009 - 0.108
Duration of Diabetes	.155	.007	.059	0.029 - 0.310
Inulin medication	.389	.531	.076	0.138 - 1.103
FBG	.134	.001	.260	0.001 - 0.401
2 hours post prandial	.106	.001	.356	0.003 - 0.284
HbA1C	.065	.045	.584	0.011 - 0.305
Uric acid	.784	.011	**.000**	0.130 - 1.086

DISCUSSION

The elevated prevalence of DM has increased complications accompanied DM including diabetic peripheral neuropathy. This complication had a potential effect on the microvasculature that also had burdens on the health, social, and financial aspects of the patients [7]**.** Uric acid is a metabolic product of purine. The increase of UA production in the body or/and the decrease in excretion of UA can cause increase SUA level [8, 9].

The current results showed that there was insignificant difference between DPN and DM groups regarding gender, age, weight, height, and BMI.

In similar study by **Kiani *et al.*** [10]**,** they reported that DM group showed that the mean age was 55.8 years, females represented 61.9%. The mean BMI was 27.6. Also, the DPN group case found that the mean age was 54.6 years. Regarding gender, 61.9% were females. The mean BMI was 29.3. The results showed that there was insignificant difference between DPN and DM groups and gender, age, and BMI. Also, the mean (SD) age of cases was 64.74 (11.29) years, and males represented 55.87% in a study conducted on 247 cases with DM [11]. A previous study showed that the mean DM duration was 10 years, the males represented 56% of cases, and the mean age was 64 years [12].

Regarding DM group, 24 cases got oral medication, while 11 cases received insulin. The mean DM duration was 3 years, the mean SBP was 133.3 (mmHg), while the mean DBP was 83.3 (mmHg). The mean HbA1c %was 8.1, the fasting blood glucose was 184.9 mg/dl. The mean 2 hours post prandial was 280.7 mg/dl, and the mean serum uric acid was 5.58 mg/dl, creatinine mean level was 0.837 mg/dl.

Concerning DPN group, 12 cases got oral medication, while 17 cases received insulin. The mean HbA1c was 8.34 %, the fasting blood glucose was 201.1 mg/dl. The mean DM duration was 6 years, the mean SBP was 133.7, while the mean DBP was 82.86. The mean 2 hours post prandial was 292.57 mg/dl, and the mean serum uric acid was 9.24 mg/dl, creatinine mean level was 0.897 mg/dl. In the current study, we found that DM duration and SUA were significantly higher in DPN compared to DM.

The results from a previous study showed that regarding DM without neuropathy showed that 40.4% got oral medication, while 28.5% cases received insulin. The mean DM duration was 9.1 years, the mean SBP was 131, while the mean DBP was 80. The mean HbA1c was 7.9. The mean serum uric acid was 4.36, Creatinine median level was 1. Concerning DPN group, 33.3% got oral medication, while 40.4% received insulin. The

mean HbA1c was 8.1. The mean DM duration was 9.7 years, the mean SBP was 134.4, while the mean DBP was 80. The mean serum uric acid was 4.7, Creatinine median level was 1. The SUA were significantly higher in DPN compared to DM ($p<0.05$) [10].

Behradmanesh *et al.* [13] reported that 60 cases with T2D were conducted in the study, the mean age was 57 years, 43.3% of cases were females, and the mean SUA was 4.5 mg/dL.

Papanas *et al.* [14, 15] had two reports concerning the assessment of SUA in DM with peripheral neuropathy and with and without sudomotor impairment. They have revealed that SUA levels were higher in cases with DPN compared to DM without peripheral neuropathy in the first study regarding NSS-NDS characteristics [14]. The cases with DPN with sudomotor impairment had elevated SUA as reported in the second study [15]. SUA was found to have a significant role in diabetic long-term complications including peripheral neuropathy also it may contributes in DNP progression and development [10].

The present study reported that there was a remarkable variation in DM duration, and SUA between the groups. There was statistically insignificant difference between DPN, and DM and type of medication, systolic BP, diastolic BP, hemoglobin 1 C, fasting blood glucose. The current findings revealed a remarkable positive correlation between SUA and diabetes duration among DPN patients.

A previous studies showed that there was a significant difference between DPN and DM without neuropathy regarding SUA ($P<0.001$) as SUA levels were higher in DPN than DM without neuropathy, the other data did not show any significant difference ($P>0.05$). They also revealed a remarkable correlation between DPN and DM concerning SUA [15].

Another report found that SUA is negatively related to islet β cell function in diabetic patients, suggesting that SUA is correlated with diabetes [9, 16].

The present results showed that older patients and elevated SUA were significantly correlated with the development of DPN.

In study by **Fayazi *et al.*** [17], a total of 230 patients with type 2 diabetes were examined. The mean SUA level in the DPN group was significantly higher compared to DM without neuropathy (6.72 ± 1.75 vs. 4.57 ± 1.49 mg/dL). With increasing the SUA, the odds of developing neuropathy increased by 2.2 times (OR = 2.2). The chance of developing polyneuropathy in patients with retinopathy was 3.3 times higher than in the control group.

It was reported that SUA may be related with the presence, development, and severity of diabetic peripheral neuropathy [15].

Xia *et al.* [18] found that the SUA increased levels were correlated with higher age, compared with normal SUA levels ($p = 0.005$).

The correlation between DPN and SUA was mediated by several mechanisms which were reported by several studies. SUA serves as an antioxidant during the vascular passage, and on the contrary it has a reverse action in vascular smooth myocytes as it promotes the release and production of NO forming vascular impairment and DPN progression [17].

Some researchers have suggested that UA is closely related to DN that occurs shortly after hyperuricemia in patients with type 1 diabetes mellitus (T1DM), which can independently predict its occurrence [16].

Elevated SUA level increased the chance of developing DPN in cases with T2DM. SUA levels higher than 5.25 mg / dL expose cases with T2DM to developing DPN [17].

CONCLUSION

It could be concluded that elevated SUA level increased the chance of developing peripheral neuropathy in a person with type 2 diabetes (T2DM). Many animal experiments and large-scale clinical observations and experiments are needed to confirm this observation.

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REFERENCES

1. **Khan M, Hashim M, King J *et al.* (2020):** Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health, 10: 107–111.
2. **Hegazi R, El-Gamal M, Abdel-Hady N *et al.* (2015):** Epidemiology of and Risk Factors for Type 2 Diabetes in Egypt. Ann Glob Health, 81: 814–820.
3. **El Ridi R, Tallima H (2017):** Physiological functions and pathogenic potential of uric acid: A review. J Adv Res., 8: 487–493.
4. **Chen D, Sun X, Zhao X *et al.* (2020): A**ssociations of serum uric acid and urinary albumin with the severity of diabetic retinopathy in individuals with type 2 diabetes. BMC Ophthalmol., 20: 467-72.
5. **Yu S, Chen Y, Hou X *et al.* (2016):** Serum Uric Acid Levels and Diabetic Peripheral Neuropathy in Type 2 Diabetes: a Systematic Review and Meta-analysis. Mol Neurobiol., 53: 1045–1051.
6. **Chen C, Lü J, Yao Q (2016):** Hyperuricemia-Related Diseases and Xanthine Oxidoreductase (XOR) Inhibitors: An Overview. Med Sci Monit Int Med J Exp Clin Res., 22: 2501–2512.
7. **Tikkanen-Dolenc H (2020):** Physical activity and type 1 diabetes: impact on diabetic complications. BMC Endocr Disord., 105: 17-23.
8. **Komendarek-Kowalska M (2017):** The assessment of renal function in patients with newly diagnosed hypertension - the role of hyperuricemia as a risk factor for chronic kidney disease - preliminary study. Pol Merkur Lek Organ Pol Tow Lek., 42: 193–196.
9. **Mortada I (2017):** Hyperuricemia, Type 2 Diabetes Mellitus, and Hypertension: an Emerging Association. Curr Hypertens Rep., 19: 69-73.
10. **Kiani J, Habibi Z, Tajziehchi A *et al.* (2014):** Association between serum uric acid level and diabetic

peripheral neuropathy (A case control study). Casp J Intern Med., 5: 17–21.

11. **Lai Y, Chen Y, Ku P *et al.* (2021):** Association between uric acid level and incidence of albuminuria in patients with type 2 diabetes mellitus: A 4.5-year cohort study. Medicine (Baltimore), 100: 41-46.
12. **De Cosmo S, Viazzi F, Pacilli A *et al.* (2015):** Serum Uric Acid and Risk of CKD in Type 2 Diabetes. Clin J Am Soc Nephrol., 10: 1921–1929.
13. **Behradmanesh S, Horestani M, Baradaran A *et al.* (2013):** Association of serum uric acid with proteinuria in type 2 diabetic patients. J Res Med Sci., 18: 44–46.
14. **Papanas N, Papanas N, Demetriou M *et al.* (2011):** Increased Serum Levels of Uric Acid Are Associated with Sudomotor Dysfunction in Subjects with Type 2 Diabetes Mellitus. Exp Diabetes Res., 2011:346051.
15. **Papanas N, Katsiki N, Papatheodorou K *et al.* (2011):** Peripheral neuropathy is associated with increased serum levels of uric acid in type 2 diabetes mellitus. Angiology, 62: 291–295.
16. **Gul A, Harford A, Zager P (2017):** Mendelian randomization to establish the causality of uric acid with diabetic nephropathy in type 1 diabetics. Kidney Int., 91: 1005–1007.
17. **Fayazi H, Yaseri M, Mortazavi S *et al.* (2022):** The relation between serum uric acid levels and diabetic peripheral neuropathy in type 2 diabetes in Guilan, north of Iran. BMC Endocr. Disord., 22: 1-8.
18. **Xia Q, Zhang S, Yang S *et al.* (2020):** Serum uric acid is independently associated with diabetic nephropathy but not diabetic retinopathy in patients with type 2 diabetes mellitus. J Chin Med Assoc., 83: 350-356.