The Effect of Uric Acid as a Predisposing Factor on Polyneuropathy in Patients with Type 2 Diabetes Mellitus

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Abstract: *Background*: Since serum uric acid is a controllable and modifiable factor in diabetic patients, identifying the risk factors and accelerating the incidence of neuropathy in these patients plays an important role, and can reduce its level, and the patient's disability, as well as additional therapeutic costs for the patient and the health system in the country.

Method: In this retrospective cohort study conducted at the Golestan Hospital in 2015-2017, the study population was 100 type 2 diabetic patients based on NCS of 54 patients with polyneuropathy. First, the demographic data on clinical examinations, lab tests, and uric acid levels in these patients were recorded on a checklist. Then, in 2017, patients were reassessed for clinical investigations and lab tests, and all data entered on the previous checklist. Finally, all the data were analyzed using the SPSS v23.

Results: The mean age of patients with polyneuropathy was 51.77 years, and there was a significant relationship between age, BMI and duration of diabetes with neuropathy, but there was no significant difference in gender, smoking and hypertension. The mean serum level of uric acid in the two years ago was 3.85 mg/dl, and at the time of the study, it was 4.18±1.55 mg/dl. There was no significant difference in serum levels of this substance after two years of follow up in patients with polyneuropathy (P=0.139). The incidence of polyneuropathy was reported by NCS findings of 54%. In other words, 54% of diabetic patients developed diabetic polyneuropathy for two years.

Conclusion: Polyneuropathy is a common complication in diabetic patients, and the serum levels of uric acid over time cannot have a significant effect on the incidence of this disorder.

Keywords: Diabetes Mellitus, Polyneuropathy, Uric Acid.

INTRODUCTION

Diabetes mellitus is a common metabolic disease that is also complex in carbohydrate metabolism, which affects millions of people around the world, and the number of people infected is increasing. Patients with diabetes are always more likely to have several clinical manifestations and cardiovascular, renal, ocular and, especially, neurological complications [1]. Diabetic neuropathy is a known microvascular disease in type II diabetes that is associated with chronic hyperglycemia and is defined as the presence of peripheral nerve dysfunction in diabetes after the rejection of other causes [2]. The incidence of polyneuropathy is reported in 10.5% of diabetic patients, which is present in 10% of patients at the time of diabetes diagnosis [1]. It is known as one of the most important factors to cause chronic hyperglycemia [2, 3]. However, other causes as vascular damaging factors such as obesity,

hyperlipidemia, hypertension and cigarette [3-6], and clinical atherosclerosis such as coronary artery disease and peripheral vascular disease (PAD) [5-7], as well as genetic polymorphisms as an additional factor are also involved in the pathogenesis of type II diabetic neuropathy [8]. The role of uric acid in coronary artery disease and peripheral vascular disease and stroke has been shown in some studies [9]. This has been attributed to the role of uric acid in elevated blood pressure and metabolic syndrome and kidney disease [10]. Also, in type II diabetic patients with neuropathy, higher levels of uric acid have been reported, and the association between serum uric acid levels and clinical severity of neuropathy has been shown [9]. Since previous studies [9, 10] were cross-sectional and case-control, in a Systematic Review and Meta-analysis study [11], it was advised to conduct cohort studies to illustrate this association better. Thus, for the first time, we investigated the relationship between increasing uric acid levels in diabetic patients and their association with diabetic neuropathy in the form of a cohort study. We aimed to reduce the incidence of potentially severe

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complications that could have a significant impact on patients if such a connection could be found and if a modification was made at the lowest possible cost.

MATERIALS AND METHODS

This study was a retrospective cohort study conducted at the Golestan Hospital's Diabetes Research Center in 2015. In this study, 100 types of II diabetic patients at the Research Center for Diabetes in the year 2015.

Inclusion Criteria

In this study, inclusion criteria included having type II diabetes, the presence of uric acid test over the past 2 years, referring to the Research Center for Diabetes of Golestan Hospital affiliated to the Jundishapur University of Ahvaz, and the signed written informed consent to participate in the study.

Exclusion Criteria

In this study, exclusion criteria included diabetic foot ulcer and NDS> 6 according to examinations of the year 2015, and factors causing neuropathy, such as a decrease in B12 and thyroid hormone deficiency, cancer, and age> 70 years.

Data Collection Method

This study was a retrospective cohort study conducted at the Golestan Hospital's Diabetes Research Center in 2015. In this study, 100 type II diabetic patients at the Research Center for Diabetes in year 2015, who participated in a research project and information from these patients was available in a questionnaire including age, gender, height, weight, blood pressure and blood samples of these patients, including HbA1c and the level of the uric acid. After obtaining satisfaction of these patients, the information about the patient questionnaire was recorded and the measurement of uric acid and new HbA1c from a blood sample of 96 patients from the laboratory of the Research Center for Diabetes of Ahvaz Jundishapur University, was measured. It should be noted that all patients had a neurological examination on two occasions (2 years before and in 2017) and NDS scores were evaluated. Then, the subjects underwent NCS of the tibial peroneal, and sural nerves of the lower limb and amplitude, conduction velocity and distal latency were also evaluated. In this study, the normal rate of these findings was evaluated according to the following table:

	Distal latency (ms)	Conduction Velocity (m/s)	Amplitude (mv)
Peroneal	6.5 ≥	44 ≤	2 ≤
Tibial	5.8 ≥	41 ≤	4 ≤
Sural	4.4 ≥	40 ≤	6 ≤

In this study, neuropathy was also evaluated based on NDS Score. The NDS score, which included neural examination, including ankle reflexes, a feeling of cold and heat dissipation, feeling the pain of the needle and understanding the diapazon, were completed in both 2015 and 2017 at both times. In this score, which was performed based on examinations of both feet, patients were given a score of 1 to 5 for each foot, and the sum of these scores was called NDS. A score higher or equal to 6 was called as a neuropathy. The patient rating was based on a clinical examination and based on the following table:

NDS items	Description
Vibration sensation (128 Hz tuning fork)	0= present, 1= reduced/absent
Temperature sensation (cold tuning fork)	0= present, 1= reduced/absent
Pin-prick	0= present, 1= reduced/absent
Ankle reflex	0= normal, 1= present with reinforcement, 2= reduced/absent

Finally, diabetic neuropathy was diagnosed using NCS findings and NDS criteria, and a supplementary questionnaire was completed for the years 2015 and 2017. All data were entered into the SPSS v 23 and analyzed.

Data Analysis and Statistical Analysis

In order to analyze the results, descriptive statistical methods, including frequency distribution tables and central tendency and dispersion indices such as mean and standard deviation were used to describe the variables studied. To compare the quantitative values between two groups, an independent t-test was used, and the Chi-square test was used to compare qualitative values. Meanwhile, the relative risk index (RR) along with the corresponding confidence intervals was calculated. The significance level of the tests was less than 0.05. The software used to analyze the data is SPSS 23.

RESULTS

This study was performed on 100 patients with diabetes mellitus after determining an average age of

Table 1:   Baseline Characteristics of the Patients Studied (n = 100)

Variables		values
Age categories, years, n (%)	<19	1 (1%)
	19 – 25	6 (6%)
	25 – 30	51 (51%)
	30 – 35	29 (29%)
	> 35	13 (13%)
History of smoking, n (%)	Yes	2 (2%)
	No	98 (98%)
Blood pressure, mmHg (mean ± SD)	Systolic	12.99 ± 11.63
	Diastolic	81.5 ± 7.1
Duration of diabetes onset categories, years, n (%)	< 5	33 (33%)
	6 -10	31 (31%)
	11 – 15	20 (20%)
	> 15	16 (16%)

51.61 ± 2.24 years. In this study, 53 patients (53%) were female. After performing an age categorization, most of the patients (45 (45%) were at the ages of more than 35 years. Also, the mean systolic blood pressure in the patients was 12.99 ± 11.63 mmHg, and the mean diastolic blood pressure was 81.5 ± 7.1 mmHg (Table **1**). In the study of blood pressure records, 22 patients (22%) had high blood pressure. The duration of the onset of diabetes was another variable that was evaluated in patients. The results showed that the mean duration of diabetes in the study was 123.17 ± 69.32 months (Table **1**). It has also been observed that 33 patients have been diagnosed with diabetes mellitus in less than 5 years (Table **1**).

The mean HbA1c level was 8.46 ± 1.6% in the past two years, as well as during the study. The mean HbA1c level was 8.58 ± 1.76% (P = 0.615). The uric acid level in patients two years before the start of the study and during the study, was 85.3 mg/dl and 91.3 mg/dL, respectively (P = 0.761). NDS scores were evaluated in patients two years ago and at the time of the study. The results showed that the mean NDS score was 2.03 ± 1.89 in the past two years and 3.48 ± 3.04 during the study, which showed a significant increase in NDS score (P = 0.000). Also, 32 patients (32%) had a 2-fold increase in NDS score over these two years (Figure **1**).

Based on NDS scores, cases with greater than or equal to 6 were considered to be neuropathies. In this study, two years ago, it was observed that none of the patients had scores greater than 6, but at the time of the study, 29 patients had scores greater than 6.
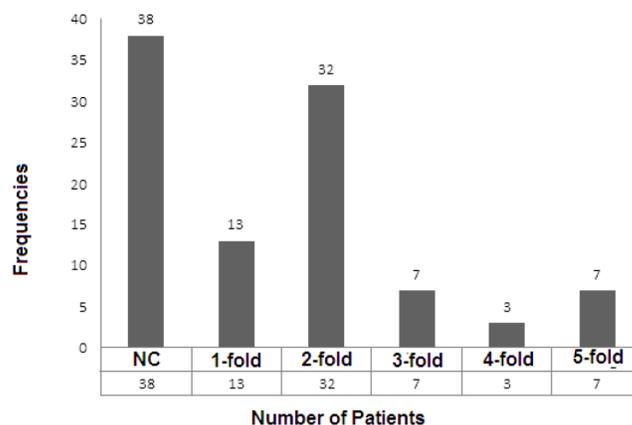
Figure 1: change in NDS scores in the past 2-year and during the study.

Finally, the involvement of more than 2 nerves in patients was considered polyneuropathy and the results showed that among 100 patients with diabetes mellitus 54 patients (54%) had polyneuropathy. There was no significant difference between the three levels of uric acid (2015 and 2017), and the presence of polyneuropathy in the past two years, at the time of the study, as well as there was no significant difference between this period and the relationship between the incidence of polyneuropathy and uric acid levels (Table **2**).

In a study on the association between NDS scurry and uric acid levels, there was no significant relationship between the increased NDS scores in patients and the increased uric acid levels at different study times (Table **3**).

In the present study, the mean age of patients with polyneuropathy was 52.55±8.8 years, and in the

Table 2: **The Relationship between the Incidence of Polyneuropathy and Uric Acid Levels Two Years Ago, at the Time of the Study**

Uric acid Levels	Polyneuropathy*	Mean ± SD	P-values
2015	Yes	3.99±1.68	0.273
	No	3.68±1.02	0.273
2017	Yes	4.11±1.65	1.39
	No	3.68±1.14	1.39
Difference	Yes	0.12±0.51	0.360
	No	0.000	0.76

*It should be noted that this polyneuropathy is based on the diagnosis of polyneuropathy in 2017, and the amount of uric acid in these patients was 2015, 2017 and the difference between these two times was measured.

Table 3: **The Relationship between NDS Scurry and Uric Acid Level**

Year	NDS' score	Mean± SD	P-valuee
Uric acid level in 2015	<5	3.75±1.12	0.309
	6≤*	4.07±1.96	
Uric acid level in 2016	<5	3.83±1.18	0.408
	6≤	4.1±1.98	
Difference between the two time	<5	0.08±0.65	0.709
	6≤	0.03±0.63	

*It should be noted that this score is more than 6 related to scurvy patients in the year 2017. In other words, patients who had more than 6 and less than 5 in 2017 had scurvy levels of uric acid in 2015.

patients without polyneuropathy, it was 48.30±8.36 year. This difference was statistically significant (P = 0.016). The duration of diabetes in patients with neuropathy was 139.61 ± 74.67 months, and in the patients without polyneuropathy was 81.13 ± 46.71 months (P = 0.000). BMI was significantly higher in the group with neuropathy. Also, in the study of the relationship between gender, smoking, hypertension and also the increase in HbA1c levels with the occurrence of polyneuropathy, there was no significant relationship between these variables and the incidence of this neuropathic disorder.

DISCUSSION

Diabetic neuropathy is one of the common side effects of diabetes, which is a disorder of the functioning of the peripheral nervous system of the body and is associated with high mortality and an increased economic burden on diabetic care. This type of disorder is a late complication in diabetic patients and is an early complication in type II diabetic patients.

The lack of timely diagnosis of diabetes and its complications can be a cause for the relatively high incidence of this complication in recent studies [18].

This study was performed on 100 patients with diabetes mellitus, and based on NCS, 54 patients were with polyneuropathy. In the study of patients with polyneuropathy, it was observed that the mean age was 51.77 years and there was a significant relationship between age, BMI and duration of diabetes with neuropathy, but there was no significant difference in gender, cigarette smoking and hypertension. In the study by Boya *et al*. [19], the mean age of patients with diabetic neuropathy was 58.4 years, and patients without neuropathy were 55 years old. In women with neuropathy, female gender was higher. Also, the duration of diabetes was 14.5 months in patients with neuropathy and 11.6 months in other patients, which showed no significant difference. In the study by Kargarian Marvesti *et al*. [20], it was reported that among patients with diabetic neuropathy, 69.3% were female, and the mean age was 64 years. Duration of diabetes was 76.6 months. A study by Prikhozhan *et al*. [21] concluded that diabetic neuropathies of less than 30 years of age occur mainly in women and neuropathies of more than 50 years occur mainly in men, and the cases between the two did not have the association with the gender of patients. In another study by Aaberg *et al*. [20], among the patients with diabetic neuropathy, 59% were women, and 41% were

men. The mean of the onset of neuropathy was 63 years for men and 67 years for women. There was a significant difference between the age of onset of neuropathy and the gender of the patients. In another study by Pop-Busui et al. [21], the mean age of patients with diabetic neuropathy was 68 years, 52.6% were male, HbA1c levels were more than 7 in 52.6% of patients and obesity was seen in 51.8% of patients. All of them had a significant relationship with neuropathy. In the study of patients' data, the reason for not finding a relationship between age and gender, BMI, HTN, and HbA1c are probably the lowest level of the statistical population of the patients. So that all of the above studies were performed on more than 300 patients, while, since it was carried out in the form of a cohort project, as well as limiting the number of people was important for us, it was done on fewer patients.

In this study, the mean serum level of uric acid in the two years ago was 3.85±1.42 mg/dl, and at the time of the study, it was 3.91 ± 1.45 mg/dl. The results showed that serum levels of this substance did not significantly correlate with the incidence of polyneuropathy in patients. In the study of Mirzapur et al. [22], the mean level of uric acid in nondiabetic patients was 4.88 mg/dl, in patients with diagnosed diabetes, it was 4.74 mg/dl, and in patients with undiagnosed diabetes, it was 4.73 mg/dl. In the study of Kiani et al. [22], the mean serum uric acid level in patients with DPN was 4.7 mg/dl, and in patients, without DPN it was 36.4 mg/dl, and a significant relationship was seen between serum uric acid levels and the incidence of diabetic polyneuropathy (P = 0.019). In another study by Chuengsamarn et al. [23], the mean uric acid level in diabetic patients was mg/dl. The study found that increased levels of uric acid could lead to microvascular complications such as neuropathy in diabetic patients. So that the incidence of these complications at level 2.7- 6.2 was without risk; at the level of 7.3-8, this level reached OR = 4; at the level of 8.1-8.5 reached 6.7 and at the level of 8.6-13.1, this risk reached 5.8 times higher. Another study by Lu et al. [22] reported that the serum level of uric acid in patients with normal glucose tolerance was 289.58 mol/L, in patients with impaired glucose tolerance it was 301.9 mol/L, in patients with diabetes mellitus it was 314.47 mol/L. It was found that the level of this substance in diabetic patients' serum was significantly higher than that of healthy people. Two other studies by Wei and Wu [38] and Sang [39] also reported that uric acid levels in diabetic patients were significantly higher than healthy subjects, probably due to an association with metabolic disorders related to

diabetes. The two studies also indicated that a level (more than 7 mg / DL) higher than normal uric acid has a significant relationship with the incidence of diabetic neuropathy and increases the risk of this complication. In the study by Kishalay Jana et al. [23], the mean serum uric acid level was 7.6 ± 0.76 for DPN patients and 4.8 ± 0.82 for patients without DPN. (P0.05). In a study by Yu et al. [23], 12 out of 1388 DM12 with DPN and 4,748 DMMS without DPN showed a clear increase in uric acid in diabetic patients (P = 0.0004). In reviewing the studies, uric acid increases significantly in diabetic patients, which is not visible due to the fact that all patients in the current study have diabetes. On the other hand, it was observed that a high level of uric acid has a significant relationship with the incidence of diabetic neuropathy. In the present study, this finding was not proved, probably due to several reasons. First, in the present study, 98% of patients had uric acid levels below 6.5, which is considered to be normal levels of uric acid. Secondly, the number of patients in this study was lower than in other studies. Thirdly, in this study, patients with a clear neuropathy who had already been proven were excluded. These causes may have had an effect on the inactivation of uric acid levels on the incidence of neuropathy.

In this study, the incidence of polyneuropathy reported based on NCS findings was 54%. In other words, 54% of diabetic patients developed diabetic polyneuropathy for two years. In the study by Kargarian Marvesti et al. [23], the incidence of neuropathy was 41.6%. However, in the study by Muller [24], the incidence of lightheadedness in patients with type 2 diabetes was 20-40%. In his research done in Korea, Sung Hyun [25] reported an incidence of diabetic neuropathy between 14.1% and 54.5%. In the study of diabetes control in Asia in 230 diabetes care centres in 12 Asian countries, the incidence of this nerve lesion was 34% [26]. Another national study in South Korea, conducted on patients with diabetes mellitus, reported a 44.7% increase in neuropathy in these patients [25]. In Iran, in a meta-analysis study conducted by Sobhani et al., the incidence of diabetic neuropathy in Iranian patients was 53% [26]. In another study in Hamadan, Olfatifar et al. [18], the incidence of neuropathy in patients with type 2 diabetes mellitus was 57.34%, and in patients with type 1 diabetes, it was 37.65%. Another study by Yazdanpanah et al. [45] suggested that the prevalence of neuropathy was 52.5%, of which 17.5% had peripheral polynucleotides, 22.5% had Carpal tunnel syndrome, and 12.5% of them had both. Other results showed that the distal motor-sensory symmetric

polyneuropathy is the most common, and carpal tunnel syndrome is the most common mononeuropathy. In the study, it is observed that the incidence of neuropathy in Iranian studies is more than other countries, and the prevalence of neuropathy in this study is in line with internal investigations. Probably the high prevalence of neuropathy in Iranian patients is due to weakness in controlling the serum glucose levels in or a demographic characteristic in these patients so that the incidence of this complication in the Iranian population is more than other populations.

In this study, NRS scores were 3.03 patients two years ago and 3.48 at the time of the study. Only 38% of patients had a stable score within two years, and other patients showed more scores. About 29% of patients also had neuropathy, according to NDS criteria, and no significant correlation was observed between neuropathy by NPS score and serum uric acid levels. In a study by Kisozi *et al*. [25] in which diabetic patients were classified according to NDS and severity of neuropathy, 70.6% of patients had no neuropathy and had NDS less than 5 and 29.4% had neuropathy (NDS larger than or equal to 6). Of these, 53.4% had moderate neuropathy, and NDS ranged from 8-7%, 30.2% had mild neuropathy (NDS = 6), and 16.4% had severe neuropathy (NDS between 9 and 10 %). Another study by Gibbons *et al*. [25] found that NDS scores were 0.2% in healthy subjects, 0.4% in diabetic patients without neuropathy and 6.3 in diabetic neuropathy patients. It was also observed that with increasing neuropathy severity, NDS increased. Abbott *et al*. [26] argued that score NDS in diabetic patients with neuropathy is more than those without this sign. In patients with neuropathy, it increased with increasing NDS so that with NDS over 8, the painful neuropathy occurred in patients. In reviewing the studies, it is observed that the NDS score is a good score for choosing patients with diabetic neuropathy so that with increasing this score, the severity of neuropathy is elevated in patients. Of course, it should be noted that several patients in this study, were with polyneuropathy by the NCS, but NDS in these patients was reported to be less than 6, and only 29% had NDS of more than 6. The event may be due to the fact that Cut Off's level of this score can be reduced to diagnose neuropathy in diabetic patients so that in the lower scores, neuropathy diagnosis can be made for patients.

STUDY LIMITATIONS

The low number of patients and the absence of basic NDS from patients and in 2015, and the absence of uric acid test between 2 years and the lack of a similar cohort study to compare the results were some of the limitations of this study.

Studies with more sample size and more cohort studies as well as futuristic cohort studies are suggested to be pursued more appropriately.

CONCLUSION

The results of this study showed that polyneuropathy is a common complication in diabetic patients. And the distal motor-sensory symmetric polyneuropathy is the most common type. Carpal tunnel syndrome is the most common mononeuropathy. The incidence of neuropathy in Iranian studies is more than other countries, and probably it is due to weakness in controlling the serum glucose levels in these patients. The serum levels of uric acid over time cannot have a significant effect on the incidence of this disorder. Also, in the diagnosis of neuropathy, NCS is more valuable than NDS.

DECLARATION

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethic code: IR.AJUMS.REC.1396.813).

In this study, we obtained a conscious, informed consent from patients to enter the study, and completely keeping all information about patients secretly in the information sheets was one of the other measures to comply with ethical considerations in this research project. On the other hand, no additional costs were incurred for patients.

Consent for Publication

This manuscript has not been published and is not under consideration for publication elsewhere in whole or in part. No conflicts of interest exist in the submission of this manuscript, and the manuscript has been approved for publication by all listed authors.

Availability of Data and Material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing Interests

None of the authors has any financial and personal relationships with other people or organizations that could potentially and inappropriately influence this work

and its conclusions. Authors declared no competing interest in publishing this paper.

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