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Original Research Article

EARLY NERVE CONDUCTION ABNORMALITIES AND THEIR ASSOCIATION WITH SERUM URIC ACID IN TYPE 2 DIABETES: A CROSS-SECTIONAL STUDY IN NORTHERN INDIA

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ABSTRACT

Background: Diabetic peripheral neuropathy (DPN) is a prevalent complication of type 2 diabetes mellitus (T2DM), often leading to significant morbidity. Emerging evidence suggests that elevated serum uric acid (SUA) levels may contribute to the development of DPN. **Aim:** To find the association between SUA levels and nerve conduction study (NCS) parameters in T2DM patients, comparing those with controlled and uncontrolled SUA levels.

Materials and Methods: A case control study was conducted on 70 T2DM patients without symptomatic neuropathy. The patients were categorized into two groups based on SUA levels: controlled (n=39; 3.4-7.2 mg/dl) and uncontrolled (n=31; >7.2 mg/dl). NCS parameters like latencies, amplitudes and conduction velocities were recorded for motor nerves (median and tibial) and sensory nerves (median and sural) on the right upper and lower limbs. SUA levels were measured using an enzymatic uricase method with Beckman Coulter automated analyzers.

Results: Patients with uncontrolled SUA levels exhibited significant impairments in nerve conduction parameters. Specifically, reductions were observed in amplitude and conduction velocity of median motor nerve and tibial motor nerve. Additionally, increased latencies were noted in median and sural sensory nerves. These findings indicate a correlation between elevated SUA levels and impaired nerve conduction in T2DM patients.

Conclusion: Elevated SUA levels are associated with significant impairments in both motor and sensory nerve conduction parameters in T2DM patients, suggesting a potential role of hyperuricemia in neuronal dysfunction. Monitoring and managing SUA levels may be crucial in early detection and prevention of DPN, highlighting the importance of comprehensive diabetic care strategies.

Keywords: Type 2 diabetes mellitus (T2DM), diabetic peripheral neuropathy (DPN) serum uric acid (SUA), nerve conduction study (NCS), motor nerve, and sensory nerve.

INTRODUCTION

Globally, around 422 million people have diabetes mellitus, with a rising prevalence across all income levels and a global target to halt its rise by 2025.[1,2] Diabetic neuropathy, a major complication affecting nearly 50% of type 2 diabetes patients, results in sensory deficits, motor impairments and contributes significantly to disability.[3,4,5]

Annual neuropathy screening is advised for all diabetes patients—starting at diagnosis for T2DM and five years post-diagnosis for T1DM.[6,7]

Nerve conduction studies (NCS) are the gold standard for detecting early nerve damage in T2DM patients, often preceding clinical symptoms.[4,5,8] Routine use of NCS may aid in preventing long-term diabetic neuropathy complications.[4,9]

Serum uric acid (SUA) levels ≥7.3 mg/dL have been linked to insulin resistance, diabetes, and abnormal nerve conduction studies in long-standing T2DM, possibly due to oxidative stress and inflammation.[4,5,8,10,11] This underscores SUA's potential as a biomarker for early detection and therapeutic targeting to prevent neuropathy in T2DM [5,8]. For this study, serum uric acid levels >7.2 mg/dL were considered uncontrolled, based on standard laboratory reference values.

Gaining insight into these associations may lead to improved therapeutic approaches that target uric acid, aiming to protect nerve function and lessen the impact of diabetic peripheral neuropathy (DPN) in diabetic patients.[5,9]

Therefore, by comparing nerve conduction parameters in T2DM patients with controlled and uncontrolled SUA levels, the present study aims to elucidate the impact of hyperuricemia on peripheral nerve health. The findings may not only enhance our understanding of neuropathic progression in diabetes but also support the integration of SUA monitoring in comprehensive diabetes management strategies.

MATERIALS AND METHODS

Selection of subjects

The study was a cross-sectional study conducted in the Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences (Dr. RMLIMS), Lucknow in collaboration with Department of General Medicine, Department of Neurology and Department of Biochemistry, Dr. RMLIMS, Lucknow, Uttar Pradesh. Ethical clearance was obtained from the institutional ethics committee of Dr. RMLIMS, Lucknow, before the commencement of the study.

A total of 80 patients of type II diabetes mellitus without symptomatic neuropathy with 39 controlled 31 uncontrolled serum uric acid level attending OPD of department of General Medicine of Dr. RMLIMS, Lucknow were selected by Simple Random Sampling without replacement.

Those who satisfied the inclusion/ exclusion criteria were included in the study after taking written informed consent. The total duration of the study was 18 months.

SUBJECT SELECTION

Inclusion Criteria

Patients of diagnosed type 2 diabetes mellitus without clinical peripheral neuropathy, within the age limit of 20 to 60 years were included.

Exclusion Criteria

Patients with any muscular disorder, neuromuscular transmission disorders such as myasthenia gravis, history of lumbosacral radiculopathy, other metabolic or endocrine disease (hypothyroidism, hyperthyroidism); diagnosed case of type 1 diabetes mellitus and type 2 diabetes mellitus with symptoms of diabetic peripheral neuropathy; pregnancy; patient taking drugs affecting serum uric acid level such as diuretics, cyclosporine, allopurinol, estrogen, cytotoxic drugs, ethambutol, levodopa and pyrazinamide ; presence of factors resulting in neuropathy such as vitamin B12 deficiency, alcohol abuse, cancer, and peripheral nerve damage, demyelinating disease; terminally ill patients like cardiac failure, severe liver or kidney damage; patients having underlying disease like chronic or acute infections, blood disorders, arthritis; patients with concurrent major psychiatric illness and/or concurrent major medical illness and patient having peripheral edema were excluded.

Statistical Analysis

Data was entered in the Microsoft word excel sheet and analyzed by using Statistical Package for Social Sciences (SPSS), version 21.0. Continuous data was summarized as Mean ± SD (standard deviation). Shapiro Wilk test was used for normality. Parametric test was applied on normal data, otherwise non-parametric test was applied. Groups were compared by independent Student's test and the results were validated with non-parametric Mann-Whitney U test. Pearson correlation analysis was used to assess correlation between the variables. p value <0.05 was considered statistically significant. R- Statistical software will be used for the analyses.

Assessments

A Case Record Form (CRF) was designed as per the study protocol which was filled accordingly. It included demographic details, patients name, age, sex, a detailed history, associated comorbid conditions, family history, investigations related to diagnosis. Polyneuropathy was examined by nerve conduction study (NCS). HbA1C and serum uric acid were also recorded.

Recording of Nerve Conduction Study (NCS)

Nerve conduction study (NCS) was performed in the Neurophysiology laboratory of the Department of Physiology, Dr. RMLIMS, Lucknow, using the Neuro MEP.NET system (Neurosoftware version 4.4.9.0). Supramaximal stimulation was applied to obtain reliable and reproducible evoked responses in both motor and sensory nerve conduction studies. The presence of neuropathy was documented by evaluating the latencies, amplitudes, and conduction velocities for motor nerves in both median and tibial nerves and for sensory nerves in both median and sural nerve on right upper and lower limbs of body.

Biochemical parameters

Blood samples were collected after an overnight fasting for 10–12 h. A 6 mL blood sample was collected into three separate tubes: plain (3 mL),

EDTA (2 mL), and fluoride (1 mL). Serum and plasma were separated by centrifugation at 3500 rpm for 15 min.

Fasting blood sugar (FBS) and post-prandial sugar (PPS) were measured in plasma using the hexokinase enzymatic. Glycated haemoglobin (HbA1c) levels were quantified using a Bio-Rad D10 analyzer with HPLC. An enzymatic uricase method for serum uric acid quantification using Beckman Coulter automated analyzers.

- **HbA1C: -** (normal < 5.7, Prediabetic 5.7-6.4, Diabetic >6.4)
- **Serum Uric Acid level**:-(normal range 3.7-7.2 mg/dl)

RESULTS

Demographic profile

Figure 1 shows that, age of patients ranged from 23 to 60 years. Majority of patients were in the age group of 41–60 years (n = 60; 86.3%). There were only 10 (13.8%) cases each in age group less than ≤40 years, respectively. The mean age of patients was 50.09±8.27 years.

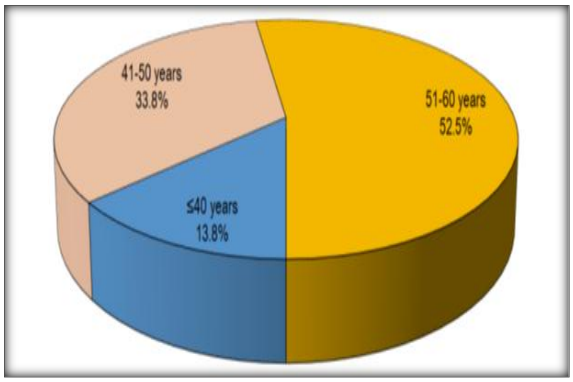

Figure 1: Distribution of study population according to age

Figure 2 shows that majority of cases were male 47 (67.5%) and 23 (32.5%) were female. The sex ratio of study population was 2.07.

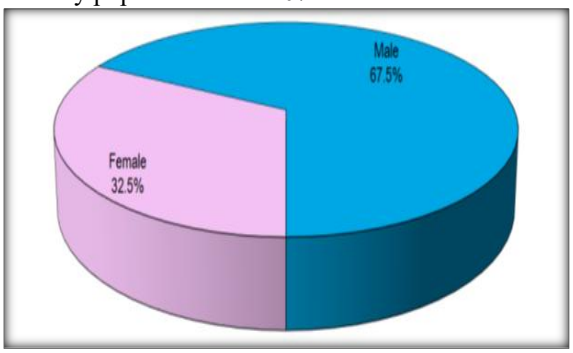

Figure 2: Distribution of study population according to gender

Figure 3 shows that duration of diabetes ranged from2 to 14 years; mean duration of diabetes was 7.04±2.88 years.

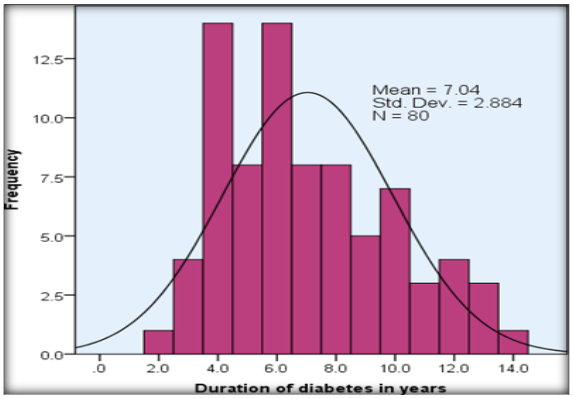

Figure 3: Duration of diabetes in study population

Distribution of study population according to S. Uric acid levels

Table 1 shows that out of 70 type 2 DM patients, 43 (61.3%) patients had uric acid in normal range (3.4-7.2 mg/dl) while rest 27 (38.8%) had uncontrolled (raised) uric acid (>7.2 mg/dl).

Table 1: Distribution of Study Population according to S. Uric acid levels

SN	S. Uric acid levels		No.	%
1-	Control Uric acid	3.4-7.2 mg/dl	39	55.7
2-	Uncontrol Uric acid	>7.2 mg/dl	31	44.3
			70	100.0

Distribution of Study Population according to Glycaemic status

The study population was categorized based on their HbA1c levels into three groups: Normal, pre-diabetic and diabetic. The distribution of participants across these categories is depicted in Table 2. Out of the total study population, 18 individuals (22.5%) had HbA1c levels below 5.7, classifying them as normal. A larger proportion, 28 individuals (35.0%), fell into the pre-diabetic category with HbA1c levels ranging from 5.7 to 6.4. The highest proportion of participants, 34 individuals (42.5%), were classified as diabetic with HbA1c levels above 6.4.

Table 2: Distribution of Study Population according to Glycemic status

SN	HbA1c level		No.	%
1-	Normal	HbA1c <5.7	16	22.5
2-	Pre-diabetic	HbA1c 5.7-6.4	24	35.0
3-	Diabetic	HbA1c >6.4	30	42.5

Table 3: Association of Serum Uric acid with Nerve Conduction Parameters

		Normal Uric acid (n=39)		Raised Uric acid (n=31)		Statistical significance	
		Mean	±SD	Mean	±SD	't'	'p'
Motor							
Median Nerve	Latency	3.73	±0.76	4.01	±0.59	-1.735	0.087
	Amplitude	7.43	±2.70	5.71	±2.41	2.905	0.005
	Velocity	46.08	±7.39	41.58	±6.02	2.845	0.006
Tibial Nerve	Latency	4.34	±0.87	4.43	±1.07	-0.411	0.682
	Amplitude	6.66	±2.82	5.11	±2.47	2.503	0.014
	Velocity	42.78	±6.08	38.52	±5.28	3.207	0.002
Sensory							
Median Nerve	Latency	2.61	±0.42	2.91	±0.41	-3.196	0.002
	Amplitude	31.71	±13.17	23.80	±14.33	2.529	0.013
	Velocity	48.80	±7.48	43.08	±6.45	3.505	0.001
Sural Nerve	Latency	2.37	±0.45	2.71	±0.55	-2.974	0.004
	Amplitude	14.70	±5.79	8.95	±4.95	4.570	<0.001
	Velocity	51.29	±9.16	41.69	±9.57	4.489	<0.001

Table 3 shows that on comparing the right motor nerve conduction parameters of patients with uncontrolled uric acid and controlled uric acid, it was observed that type 2 DM patients with uncontrolled uric acid had significantly lower upper limb median nerve amplitude, velocity and lower limb tibial nerve amplitude & velocity.

On comparing the right sensory nerve conduction parameters of patients with uncontrolled uric acid and controlled uric acid, patients with uncontrolled uric acid had significantly higher upper limb median latency and ulnar latency. Rest of the parameters of the patients with uncontrolled serum uric acid were lower than those having controlled serum uric acid.

DISCUSSION

The present study reveals that type 2 diabetes mellitus (T2DM) patients with elevated serum uric acid levels exhibit significant impairments in motor nerve conduction parameters compared to those with normal uric acid levels. Specifically, there is a notable reduction in median nerve amplitudes and velocities, as well as tibial nerve amplitudes and velocities.

These findings align with previous research indicating a correlation between elevated serum uric acid levels and diabetic peripheral neuropathy (DPN). Grundy et al. (2005),[12] observed that higher uric acid levels were associated with decreased motor and sensory nerve amplitudes and conduction velocities in T2DM patients. Similarly, Kaewput et al. (2020),[13] reported that elevated serum uric acid levels were independently associated with an increased risk of peripheral neuropathy in T2DM patients. Conversely, Zhang et al. (2023),[14] found that lower serum uric acid levels were a risk factor for DPN, particularly affecting the motor conduction velocity of the tibial nerve. This discrepancy suggests a complex relationship between uric acid levels and neuropathy, warranting further investigation.

The observed impairments in nerve conduction parameters among patients with elevated uric acid levels may be attributed to the pro-oxidative effects of uric acid at higher concentrations, leading to neuronal damage. This oxidative stress could exacerbate the progression of neuropathy in T2DM patients. Therefore, monitoring and managing serum uric acid levels might be crucial in preventing or mitigating peripheral neuropathy in this population.

The present study's findings indicate that patients with elevated serum uric acid levels exhibit significant impairments in motor nerve conduction parameters compared to those with normal uric acid levels. Specifically, there is a notable reduction in upper limb median amplitude and velocity, lower limb tibial amplitude and velocity. Additionally, these patients demonstrate increased latencies in upper limb median, as well as lower limb tibial nerves.

These observations align with previous research that has explored the relationship between serum uric acid levels and peripheral nerve function. For instance, Lin et al. (2018),[15] reported that higher uric acid levels are associated with decreased motor and sensory nerve amplitudes and conduction velocities in patients with type 2 diabetes mellitus (T2DM). Their study found significant negative correlations between serum uric acid levels and nerve conduction parameters, suggesting that elevated uric acid may contribute to the development of diabetic peripheral neuropathy (DPN).

Furthermore, a study by Abraham et al. (2019),[16] demonstrated that higher uric acid levels correlate with diminished sensory nerve function in healthy individuals. Their research expanded the evidence of uric acid's negative influence on peripheral nerves, even in the absence of underlying conditions such as diabetes. The discrepancies in these findings may be attributed to differences in study populations, underlying health conditions, and the multifaceted role of uric acid as both an antioxidant and a pro-oxidant. While elevated uric acid levels have been linked to oxidative stress and subsequent neuronal damage, uric acid also possesses antioxidant properties that may offer neuroprotection under certain circumstances. Therefore, the relationship between serum uric acid levels and peripheral nerve

function appears to be complex and context-dependent.

The present study's findings indicate that patients with elevated serum uric acid levels exhibit significant alterations in sensory nerve conduction parameters compared to those with normal uric acid levels. Specifically, increased latencies were observed in the upper limb median and lower limb sural nerves. Additionally, most other parameterswere lower in patients with elevated serum uric acid.

These results align with previous research that has demonstrated a relationship between elevated serum uric acid levels and peripheral neuropathy. For instance, a study by Lin et al. (2018),[15] found that higher serum uric acid levels were significantly associated with diabetic peripheral neuropathy in type 2 diabetes mellitus patients, with negative correlations observed between uric acid levels and nerve conduction velocities. Similarly, Abraham et al.(2019),[16] reported that elevated uric acid levels correlated with reduced sensory nerve function in healthy individuals, suggesting a potential detrimental effect of uric acid on peripheral nerves.

Finally, the present study underscores the significant association between elevated serum uric acid levels and deteriorated motor and sensory nerve conduction parameters in T2DM patients. These findings underscore the importance of regular monitoring and managing uric acid levels to potentially prevent or mitigate peripheral neuropathic complications as part of comprehensive diabetic care to identify individuals at higher risk for peripheral neuropathy. Further research is warranted to elucidate the precise mechanisms by which uric acid influences peripheral nerve function and to determine optimal therapeutic strategies.

Limitations

Since it was a single-centred study with a small sample size with short duration, the results cannot be generalized. The study did not include follow-up assessments, limiting the ability to track physiological changes over time.

CONCLUSION

Elevated SUA levels were associated with significant impairments in both motor and sensory nerve conduction parameters, suggesting a potential role of hyperuricemia in neuronal dysfunction through oxidative stress and neurotoxic mechanisms.

Hence, the study highlights that diabetic neuropathy (DN) is a major clinical challenge where nerve conduction studies (NCS) are essential for diagnosis and management. Serum uric acid (SUA) is identified as a potential biomarker for type 2 diabetes mellitus (T2DM) and neuropathy, emphasizing the need to understand its metabolism and excretion and the importance of monitoring uric acid levels as part of comprehensive diabetic care to mitigate the risk of neuropathy and improve patient outcomes.

A comprehensive approach, including early identification and targeted interventions for hyperuricemia may help mitigate neural complications.

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