Association of Serum Uric Acid and Neuropathy in Pre-diabetic and Diabetic subjects in North Indian Population

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***Abstract*- Background:** Diabetes is a metabolic condition with inappropriate hyperglycemia either due to deficiency of insulin secretion or resistance to insulin or both. It is also associated with disturbances concerned with protein, carbohydrate, and lipid metabolism. Thus we had estimated the Level of serum Uric Acid and it's association with neuropathy in pre-diabetics and diabetics from northern India.

Method: This is an observational study and total 79 subjects were enrolled as per American Diabetic Association (ADA) Guidelines 2010. Out of 79 subjects, 16 subjects were Pre-Diabetic and 63 subjects were Diabetic. Serum uric acid was estimated by using MERK Kit with the help of semi-automated analyzer. Estimation of Neuropathy was done by Nerve Conduction Studies.

Result:

- The Serum uric acid level of Diabetic group was lower as compared to Pre diabetic group. ($p<0.001$)
- In diabetics upper extremity sensory nerve conduction velocity were significantly lowered as compared to prediabetic, while in lower extremity the difference was statistically not significant.
- In lower extremity motor nerve conduction velocity was significantly lower in diabetics than prediabetics. We concluded that motor abnormalities more in diabetics as compared to prediabetics.
- Serum uric acid of Pre diabetics negatively (inverse) and significantly correlated with neuropathy in left Sural nerve (Velocity) ($r=-0.60$, $p<0.05$). In prediabetic subjects serum uric acid level was higher and neuropathy was not observed.

Conclusion: In prediabetics serum uric acid level might be useful for prediction of diabetes. Though the neuropathy was more common in diabetics but it also affect the prediabetics.

***Index Terms*-** Diabetes, Prediabetes, Serum Uric Acid, Nerve conduction velocity, Neuropathy

I. Introduction

Diabetes is a metabolic disorder with inappropriate hyperglycemia either due to deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both.

International Diabetic Federation data shows that world Diabetes & Pre-diabetes prevalence in 2007 is 5.7% and 7.5% respectively. In India Diabetes Mellitus prevalence ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas[3]. Uric acid is formed by the breakdown of purins and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine. An elevated level of uric acid was found in pre-diabetic individuals, and in offspring of conjugal diabetic parents. However, conflicting results on uric acid concentrations have been reported in diabetic patients.[7-9] Although some studies have demonstrated the role of Uric Acid in the progression of pre-diabetes to diabetes. Still, the role of Uric Acid in the pathogenesis and the development of the diabetic complications are controversial.[10,11]

Neuropathy is common complication of diabetes mellitus leading to great morbidity.[15] It is well known that neuropathy has a metabolic component in its pathophysiology[17,18] Hence early metabolic aberrations as seen in Pre-Diabetics(IGT) may also lead to changes in the nerve conduction. Studies in the Caucasian population have shown that IGT is associated with dysfunction in peripheral nerves.[19,20]

Present study was first time designed to look for the presence of neuropathy and it's association with serum uric acid in pre-diabetic and diabetic patients, in North Indian population. Emphasis was given on Pre-diabetics so that complications can be identified and managed in early stage.

II. Material and Method

This is an observational study conducted in the department of physiology in collaboration with department of pathology at King George's Medical University, Lucknow. Total 79 subjects were enrolled in study based on well defined inclusion and exclusion criteria. Out of 79 subjects, 16 subjects were Pre-Diabetic and 63 subjects were Diabetic. Subjects with conditions, which may affect metabolic parameters (such as polycystic ovary syndrome or thyroid dysfunctions in history or present), pregnancy, chronic diseases, infection, and coronary artery disease, were excluded from study.

Definition

Pre-diabetic and diabetic patients were defined as per the American Diabetic Association (ADA) Guidelines 2010.

The subjects having impaired fasting blood glucose level 100-125mg/dl or 2 hours oral glucose tolerance test with 75 gm of glucose, 140-199 mg/dl were defined as Pre-diabetic patients.

Diabetic patients were defined as those having fasting blood glucose ≥126 mg/dl or 2 hours oral glucose tolerance test with 75 gm of glucose, ≥ 200 mg/dl.

Biochemical analysis

After ethical approval from institutional ethical committee of King George's Medical University, Lucknow and obtaining informed consent total 5 ml. venues blood sample was drawn from each participant. 2 ml. blood was collected in fluoride vial and 3 ml. blood was taken in plain vial. Serum and plasma was separated, aliquoted and stored at -80 C. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) estimation was done by glucose oxidaseperoxidase method (Merck Kit). Serum uric acid was estimated by using MERK Kit with the help of semi automated analyzer (Microlab 300, Merck) on the same day of sample collection.

Nerve Conduction Study

A detailed questionnaire was completed for each of the 79 participating subjects. Information was obtained, including age, gender, smoking history, history of alcohol consumption, duration of DM, history of hypertension or cardiovascular diseases, and symptoms related to peripheral neuropathy. NCV examinations was performed according to the standard method.

Diabetic Peripheral Polyneuropathy will be defined as a positive NCV and a positive neurologic physical exam in patients with a clinical MNSI score ≥ 3 and who also had accompanying neurologic symptoms such as paraesthesia, numbness, pain, and tingling sensation and there will be no apparent etiology of peripheral polyneuropathy besides diabetes.

The presence of polyneuropathy was documented by evaluating the latencies, amplitudes, and conduction velocities for motor nerves in both median, and peroneal nerves and for sensory nerves in both median and sural nerve.

The motor or mixed nerve is stimulated at least at two points along its course and Compound Muscle Action Potential (CMAP) is recorded. The surface recording electrodes are placed in belly tendon montage; keeping the active electrode close to the motor point and reference to the tendon. Ground electrode is placed between stimulating and recording electrodes. A biphasic action potential with initial negativity is thus recorded.

The measurements for motor nerve conduction study include the onset latency, duration, and amplitude of CMAP and nerve conduction velocity. **Onset Latency:** Time from the stimulus artifact to the first negative deflection of CMAP. Measure of conduction in the fastest conducting motor fibers. It also includes neuromuscular transmission time and the propagation time along the muscle membrane which constitute the residual latency. **Amplitude**: Measured from base line to the negative peak (base-to-peak) or between negative and positive peaks (peak-to peak). The amplitude correlates with the number of nerve fibers. **Duration of CMAP**: Measured from the onset to the negative or positive peak or the final return of waveform to the base line. Duration correlates with the density of small fibers. Motor nerve conduction velocity is calculated by measuring the distance in millimeter between two points of stimulation, which is divided by the latency difference in millisecond.

Principles of sensory nerve conduction:

The sensory conduction can be measured antidromically, In which nerve is stimulated at a proximal point and nerve action potential is recorded distally. The recommended filter setting for sensory conduction is 10 Hz to 2kHz, sweep speed 1-2 milisecond/division and gain 1-5μV/division.

III. Statistical Analysis

Continuous data were summarized as Mean ± SD (standard deviation). Groups were compared by independent Student's t test and the results were also validated with non parametric Mann-Whitney U test. Discrete (categorical) observations were summarized in % and compared by chi-square ($\chi 2$) test. Pearson correlation analysis was used to assess association between the variables. Diagnostic evaluation of S. uric acid was done by ROC (receiver operating characteristic) curve analysis. A two-sided ($\alpha=2$) $p<0.05$ was considered statistically significant. SPSS (version 18.0) and STATISTICA (version 6.0) software were used for the analyses.

IV. Result

The age of Pre-diabetic and diabetic groups were ranged from 28-66 yrs and 32-77 yrs respectively with Mean ± SD 49.50 ± 11.57 yrs and 55.14 ± 10.79 yrs, respectively. The mean age of Diabetic group was comparatively higher than Pre diabetic group. Further, in both the groups, the age (%) of males was higher than females. The mean level of both FBS and PPBS were comparatively higher in Diabetic group than Pre diabetic group. On comparing, the difference in mean age and % age of males and females were statistically not significant between the two groups. The mean Serum uric acid level of Diabetic group was significantly ($p<0.001$) lower as compared to Pre diabetic group **(Table 1)** The diagnostic accuracy (cut off value) of S. uric acid levels for pre diabetics and diabetics were evaluated via ROC curve analysis.**Table 2 and figure 1**. The cut off value (criterion) of S. uric acid was ≤7 mg/dl and at this value it is discriminating diabetics with 77.78% sensitivity (95% CI=65.5-87.3) and 100.00% specificity (95% CI=79.2-100.0).

Nerve conduction velocity

It was observed that in 31(50%) diabetic patients sensory nerve conduction studies were non recordable. 50% diabetic patients showed sensory neuropathy While it was observed only in 12% prediabetics.

The mean level of Sensory-Left Median Latency was significantly ($p<0.01$) higher in Diabetic group while Amplitude and Velocity lowered significantly ($p<0.01$) as compared to Pre diabetic group.

Similarly, the mean level of Sensory-Right Median Latency was also significantly ($p<0.01$) higher in Diabetic group while had significantly ($p<0.01$) lower Velocity as compared to Pre diabetic group. However, Sensory-Right Median Amplitude did

not differed significantly (p>0.05) between the two groups i.e. found to be statistically the same.

In contrast, Left-Sural Latency, Amplitude and Velocity were almost similar (p>0.05) between the two groups.

Similarly, Right-Sural Latency, Amplitude and Velocity were also statistically not different between the two groups (p>0.05).

However, Motor-Right Median (wrist) Latency was significantly (p<0.01) higher in Diabetic group than Pre diabetic group while Amplitude and Velocity were similar (p>0.05).

The Motor-Left Median (wrist) Latency was also significantly (p<0.01) higher in Diabetic group than Pre diabetic group while Amplitude and Velocity not differed significantly (p>0.05) between the two groups.

The L-Common peroneal (ankle) Amplitude was significantly (p<0.001) lower in Diabetic group as compared to Pre diabetic group while Latency and Velocity were almost similar (p>0.05) between the two groups.

The R-Common peroneal (ankle) Amplitude and Velocity lowered significantly (p<0.01) in Diabetic group as compared to Pre diabetic group while latency was similar (p>0.05) between the two groups. **(Table-3)**

Correlation:

Table 4 showed that the S. uric acid of Pre diabetics negatively (inverse) and significantly correlated with neuropathy L-Sural Velocity (r=-0.60, p<0.05). However, other neuropathy parameters/variables did not (p>0.05) shows any association with Serum uric acid.

In contrast**,** Serum uric acid of Diabetics did not (p>0.05) shows any association with any of the neuropathy parameters/variables.

However, the S. uric acid of all (Pre diabetics + Diabetics) showed significant inverse association with Left-Sural Velocity (r=-0.42, p>0.05) while significant and direct association with Left-Sural Latency (r=0.50, p<0.01).

Table 1: Distribution of age, gender, FBS, PPBS and Serum Uric Acid inpre-diabetic and diabetic patients

Characteristics	**Pre diabetic (n=16)**	**Diabetic (n=63)**	**p value**
Age (yrs)	49.50 ± 11.57	55.14 ± 10.79	0.069
Gender: Male Female	 11 (68.8%) 5 (31.3%)	 49 (77.8%) 14 (22.2%)	0.451
FBS (mg/dl)	111.50 ± 10.56	142.66 ± 44.39	0.007*
PPBS (mg/dl)	168.75 ± 17.34	216.04 ± 52.89	0.001*
Serum uric acid (mg/dl)	10.84 ± 2.84	5.79 ± 1.87	p<0.001**

*- p<0.01, values are in % (Categorical data) and mean±SD (Continuous data),
FBS (Fasting Blood Sugar), PPBS (Postprandial Blood Sugar)

Table 2: Diagnostic accuracy of S. uric acid level for diabetic from pre diabetic

Variables	**Criterion (cut off value)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**AUC**	**p value**	**+LR**	**-LR**	**+PV**	**-PV**
S. uric acid	≤ 7 mg/dl	77.78 (65.5-87.)	100.0 (79.2-100.0)	0.947	p<0.001	-	0.22	100.0	53.3

+LR: Positive likelihood ratio; -LR- Negative likelihood ratio;+PV: Positive predictive value; -PV: Negative predictive value

Fig. 1: Diagnostic accuracy of Serum uric acid for pre diabetics and diabetics

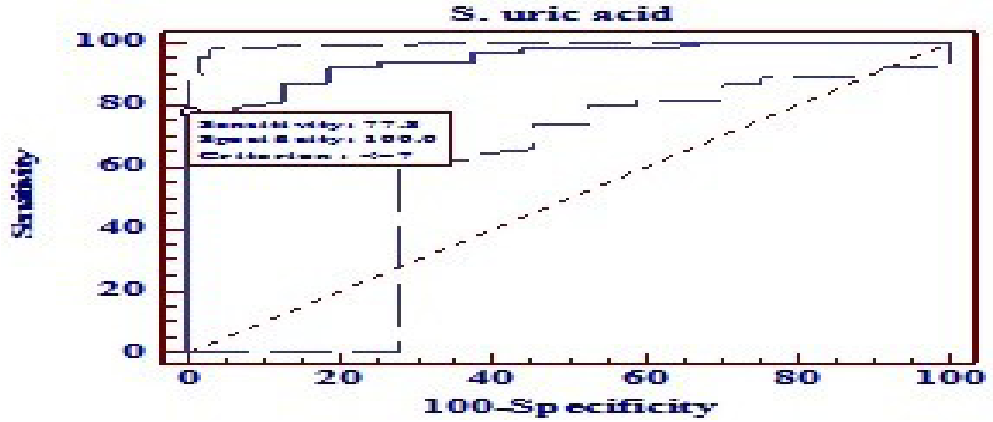

Table 3: Nerve conduction velocity parameters summary (Mean ± SD) of two groups

Parameters	Variables	N	Pre diabetic	N	Diabetic	t value	p value
S-L Median	Latency (ms)	16	2.43 ± 0.28	32	2.77 ± 0.40	3.05	0.004
	Ampl (µv)	16	43.17 ± 13.76	32	30.73 ± 12.29	3.18	0.003
	Velocity (m/s)	16	51.14 ± 7.05	32	45.58 ± 6.38	2.75	0.009
S-R Median	Latency (ms)	16	2.36 ± 0.30	33	2.78 ± 0.43	3.46	0.001
	Ampl (µv)	16	38.28 ± 16.98	33	31.80 ± 12.96	1.48	0.146
	Velocity (m/s)	16	53.38 ± 7.20	33	45.96 ± 7.06	3.43	0.001
Left -Sural	Latency (ms)	14	1.99 ± 0.29	30	1.82 ± 0.28	1.83	0.074
	Ampl (µv)	14	19.56 ± 5.18	30	22.60 ± 8.31	1.25	0.218
	Velocity (m/s)	14	50.05 ± 4.97	30	50.72 ± 7.56	0.30	0.763
Right-Sural	Latency (ms)	14	1.91 ± 0.27	32	1.90 ± 0.23	0.12	0.906
	Ampl (µv)	14	19.49 ± 5.82	32	24.98 ± 11.12	1.74	0.089
	Velocity (m/s)	14	51.19 ± 6.73	32	49.33 ± 5.64	0.97	0.337
M-R Median (wrist)	Latency (ms)	16	3.09 ± 0.32	61	3.78 ± 0.74	3.60	0.001
	Ampl (mv)	16	8.99 ± 3.62	61	7.70 ± 3.21	1.39	0.168
	Velocity (m/s)	16	53.76 ± 5.13	61	50.58 ± 6.16	1.90	0.062
M-L Median (wrist)	Latency (ms)	16	3.11 ± 0.49	58	3.88 ± 1.10	2.73	0.008
	Ampl (mv)	16	8.65 ± 4.16	58	8.81 ± 8.41	0.08	0.940
	Velocity (m/s)	16	54.08 ± 5.64	58	51.32 ± 7.07	1.44	0.155
Left-Common peroneal (ankle)	Latency (ms)	15	3.88 ± 0.94	38	7.34 ± 15.65	0.85	0.399
	Ampl (mv)	15	4.53 ± 1.60	38	2.63 ± 1.70	3.72	0.001
	Velocity (m/s)	15	48.53 ± 5.65	38	44.73 ± 6.44	2.00	0.051
Right-Common peroneal (ankle)	Latency (ms)	15	3.79 ± 0.48	40	7.48 ± 15.33	0.93	0.359
	Ampl (mv)	15	4.45 ± 1.82	40	2.91 ± 1.75	2.87	0.006
	Velocity (m/s)	15	50.06 ± 8.56	40	43.48 ± 7.86	2.70	0.009

*S-L Median-Sensory Left Median, S-R Median-Sensory Right Median, M-R Median- Motor Right Median, M-L- Median-Motor Left Median

Table 4 : Correlation of S. uric acid levels with neuropathy

Neuropathy parameters	Variables	Pre diabetic (n=14)	Diabetic (n=13)	Total (n=27)
		S. uric acid	S. uric acid	S. uric acid
S-L Median	Latency	-0.25	0.29	-0.22
	Amplitude	0.04	-0.17	0.24
	Velocity	0.06	0.05	0.25
S-R Median	Latency	0.27	-0.21	-0.15
	Amplitude	0.14	-0.26	0.25
	Velocity	-0.21	0.35	0.26
Left-Sural	Latency	0.21	0.44	0.50**
	Amplitude	0.09	-0.09	0.00
	Velocity	-0.61*	-0.32	-0.42*
Right-Sural	Latency	-0.21	0.22	0.06
	Amplitude	0.20	-0.17	-0.21
	Velocity	-0.33	0.15	0.07
M-R Median (wrist)	Latency	0.09	-0.05	0.01
	Amplitude	-0.03	-0.06	-0.03
	Velocity	-0.48	0.13	0.07
M-L Median (wrist)	Latency	0.09	0.35	0.06
	Amplitude	0.13	-0.24	-0.04
	Velocity	-0.05	-0.23	-0.22
Left-Common peroneal (ankle)	Latency	0.07	0.46	0.03
	Amplitude	0.45	-0.36	0.32
	Velocity	0.29	-0.04	0.28
Right-Common peroneal (ankle)	Latency	-0.07	0.09	-0.05
	Amplitude	0.42	0.11	0.33
	Velocity	0.22	-0.01	0.33

*S-L Median-Sensory Left Median, S-R Median-Sensory Right Median,
M-R Median- Motor Right Median, M-L- Median-Motor Left Median

V. Discussion

In our study S. uric acid level of diabetic group was significantly lower than prediabetic ($p<0.001$).These findings were consistent with the previous study, demonstrated that diabetics have lower serum uric acid levels and that prediabetics have higher levels than non-diabetics.[7,29-33]The reduced urate level in severe hyperglycemia has been attributed to the uricosuric effect of glycosuria, which might be an explanation of the low uric acid concentration among overt diabetic patients.[34] Furthermore, uric acid concentration might be influenced by the changes in plasma glucose and insulin concentrations.[35] Thus, uric acid fluctuations during prediabetes and diabetes have so far been regarded as a secondary metabolic phenomenon. In other previous study it was also reported that serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis α, both of which are related to development of diabetes.[36] Elevated serum uric acid levels may reflect prediabetes status particularly at the renal level. Higher insulin level associated with prediabetes can reduce renal excretion of uric acid.[37] Insulin can stimulate urate anion exchanger and it increases renal urate reabsorption[38]. The cut off value of Serum uric acid in our study was ≤7 mg/dl and at this value it is discriminating diabetics with77.78% sensitivity and 100.00% specificity. Result of the study supports the previous report based on 475 overweight or obese individual with impaired glucose tolerance, they found that having a serum uric acid level within the top tertile (≥6.4mg/dl) was associated with two-fold increase in the risk of type-2 diabetes compared with the lower tertile (<5.2mg/dl)[39]. Although it was multifactorial cause but as per our study findings, it may be concluded that high Serum uric acid in prediabetics can be considerd as a predictor of diabetes .

Neuropathy is most common complication of diabetes mellitus[13]. As Pre-Diabetes (IGT) is a forerunner of diabetes and prevalence of nerve conduction abnormalities in the IGT stage calls for early screening of these subjects for complications. Nerve conduction studies (NCS) are gold standard and the most consistent indicator of nerve damage even in subclinical (largely asymptomatic) neuropathy.

The early detection of abnormal glucose metabolism is particularly important, as treatments will probably be most effective if administered early in the course of neuropathy, when abnormalities of peripheral nerves are more likely to be reversible.

In our study mean level of Sensory Right and Left Median Latency were significantly ($p<0.01$) higher in Diabetic group as compared to Pre diabetic group, but velocity of the same nerves were significantly ($p<0.01$) lower in Diabetic group as compared to Pre diabetic group.

Motor Right and Left Median nerve latency were significantly ($p<0.01$) higher in Diabetic group as compared to Pre diabetic group but velocity decreases in Diabetic group as

compared to Pre diabetic group, but statistically not significant ($p>0.05$).

Right and Left Common peroneal Amplitude and velocity were significantly ($p<0.001$) lower in Diabetic group as compared to Pre diabetic group but latency increases in Diabetic group as compared to Pre diabetic group, but not statistically significant ($p>0.05$). No significant changes were observed in sural nerve on both side.

The major finding of the our study was that the prediabetic subjects exhibited minimal changes in nerve conduction abnormalities in comparision to diabetic subject. Result of our study shows decreased sensory conduction velocity in both median and right sural nerve. Motor conduction velocity in median and common peroneal (both side) were decreased in diabetic subject in comparision to prediabetic subjects. Thrainsdottir et al,[40] had shown that increased basal membrane thickening was associated with sensory peripheral neuropathy in IGT and diabetic subjects. This may be one of the reasons for slower MCVs in the IGT subjects in this study.

In our study serum uric acid of Pre diabetics negatively (inverse) and significantly correlated with neuropathy L-Sural Velocity ($r=-0.60$, $p<0.05$). However, other neuropathy parameters/variables did not ($p>0.05$) shows any association with S. uric acid levels. S. uric acid of Diabetics did not ($p>0.05$) shows any association with any of the neuropathy parameters/variables.

VI. Conclusion

It has been documented that neuropathy often is subclinical, therefore, if such a patient does not show signs of neuropathy on the clinical neurological assessment, referral for a nerve conduction studies may be ancillary tools to detect incipient neuropathy. As per our study findings in diabetics nerve conduction velocity was lowered as compared to prediabetics. Though the neuropathy was more common in diabetics but it also affect the prediabetics. It is important to evaluate the patients in prediabetic stage so that prevention and early intervention can be possible. This can be possible by evaluation of serum uric acid level in prediabetics. As per our study uric acid level might be useful for prediction of diabetes.

Disclosure of Interest: None

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