Correlation between Serum Uric Acid, C-Reactive Protein and Nerve Conduction Velocity in Prediabetic and Diabetic Subjects

Pushpalata Sachan¹, Radhey Shyam², ML Patel³, RK Garg⁴, Shradha Sing⁵

¹Assistant Professor, Department of Physiology, Career Institute of Medical Sciences, Lucknow, UP, India.
²Assistant Professor, Department of Geriatric and Mental Health, King Georges Medical University, Lucknow, UP, India.
³Associate Professor, Department of Internal Medicine, King Georges Medical University, Lucknow, UP, India.
⁴Professor & Head, Department of Neurology, King George Medical University, U. P. Lucknow, India.
⁵Professor, Department of Physiology, King Georges Medical University, UP Lucknow, India.

Corresponding Author: ML Patel

ABSTRACT

Background: Diabetes is global burden and India is only second to China in prevalence of diabetes. There is clear evidence that the prevalence of diabetes and prediabetes (IGT) is rapidly increasing, especially in urban India. This present study was done to evaluate the correlation between serum uric acid, C-reactive protein and nerve conduction velocity in Prediabetic and Diabetic patients.

Method: This was a cross sectional study carried out over a period of one year. After informed consent and ethical clearance total 79 subjects were enrolled, including 16 Prediabetic and 63 Diabetic subjects, as per American Diabetic Association (ADA) Guidelines 2010. Serum uric acid was estimated by using MERK Kit and C-reactive protein with the help of MISPA instrument based on Nephelometry method. Neuropathy was assessed with the help of nerve conduction study.

Result: Serum uric acid level was significantly (p<0.001) lower in diabetic as compared to prediabetic group, but no any significant difference in C-reactive protein levels between the two groups.

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 velocities were significantly lower in diabetics than prediabetics. This indicates that motor abnormalities more in Diabetics as compared to prediabetics.

Conclusion: This study suggests that low Serum uric acid levels and high CRP levels might play a significant role in progression of pathophysiology of diabetes. Though the neuropathy was more common in diabetics but it also affects the prediabetics.

Keywords: C-reactive protein, Diabetes, Prediabetes, Serum Uric Acid.

INTRODUCTION

International Diabetes Federation (2013) reported that approximately half of all world Diabetics lives in just three countries: China (98.4 million), followed by India (65.1 million) and then USA (24.4 million). [¹] According to ICMR study national estimate of Diabetics was 62.4 million and that of prediabetics was 77.2 million. Prevalence of diabetes in urban ranged from 10.9 to 14.2% while in rural area the range was 3.0 to 8.3%. [²]

C-reactive protein (CRP) is an inflammatory marker, it play an important role in pathogenesis of type 2 diabetes. [³-¹⁰] Number of studies reported that increases in inflammatory parameters are parallel to the stages of glucose intolerance. [¹¹-¹³]
Uric acid, a breakdown product of purine, various studies reported elevated level of purine in prediabetics, however results are conflicting in diabetic patients. [14-16] Few studies suggested the role of Uric Acid in the progression of pre-diabetes to diabetes. Still, it’s role in the pathogenesis and the development of the diabetic complications are controversial.

As various metabolic component play important role in pathogenesis of neuropathy, [17,18] Hence early metabolic changes as seen in prediabetics (IGT) may cause changes in the nerve conduction. It was found that impaired glucose tolerance (IGT) is associated with dysfunction in peripheral nerves. [19,20] Thus we had estimated the Levels of serum Uric Acid and C-reactive protein and nerve conduction velocity in Prediabetic and Diabetic patients from Northern India.

This study was done to evaluate correlation between serum uric acid, C-reactive protein and Nerve Conduction Velocity in prediabetic and diabetic patients.

MATERIALS AND METHODS

This cross sectional study was carried out over a period of one year in the Department of Physiology, in collaboration with Department of Neurology. After informed consent and ethical clearance total 79 subjects were enrolled, including 16 prediabetic and 63 diabetic subjects, as per American Diabetic Association (ADA) Guidelines 2010. Subjects with conditions, which may affect metabolic parameters (such as polycystic ovary syndrome or thyroid dysfunctions), pregnancy, chronic diseases, infection, and coronary artery disease, were excluded from the study.

Subjects were defined as per the American Diabetic Association (ADA) Guidelines 2010. The subjects with impaired fasting blood glucose level 100-125mg/dl or after 2 hours oral glucose tolerance test with 75 gm of glucose, 140-199 mg/dl were defined as prediabetic patients.

Subject having fasting blood glucose ≥126 mg/dl or 2 hours oral glucose tolerance test with 75 gm glucose of ≥ 200 mg/dl were classified as diabetics. A detailed questionnaire was completed for each of the 79 participated subjects. Information was obtained, about age, gender, history of smoking, history of alcohol consumption, duration of DM, history of hypertension or cardiovascular diseases, and symptoms related to peripheral neuropathy.

Biochemical analysis

Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) estimation was done by glucose oxidase peroxidase 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. Estimation of C-reactive protein was done by the commercially available Kit (Agappe Diagnostics Ltd. India) with the help of MISPA instrument based on Nephelometry method.

Nerve Conduction Study (NCV)

NCV examination was performed according to the standard method. Diabetic Peripheral Polyneuropathy will be defined as a positive NCV and a positive neurological physical examination in patients with a clinical MNSI score ≥ 3 and also who 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 nerve 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 closes 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 is the time from the stimulus artifact to first negative deflection of CMAP. Measure of conduction in fastest conducting motor fibres. It also includes neuromuscular transmission time and the propagation time along the muscle membrane which constitute the residual latency.

**Amplitude:** Measured from baseline to the negative peak (base to peak) or between negative and positive peaks (peak to peak). The amplitude correlates with number of nerve fibres.

**Duration of CMAP:** Measured from the onset to negative or positive peak or final return of waveform to baseline. 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.

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 10Hz to 2 kHz, sweep speed 1-2 millisecond/division and gain 1-5µV/division.

**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 accuracy of S. uric acid and C-RP levels were done by ROC (receiver operating characteristic) curve analysis. A two-sided ($\alpha=2$) $p<0.05$ was considered statistically significant.

**RESULTS**

The mean level of both FBS and PPBS were significantly higher in diabetic group than pre diabetic group. (Table.1)

The mean Serum uric acid level of diabetic group was significantly ($p<0.001$) lower as compared to pre diabetic group. The mean CRP was comparatively higher in diabetic group than prediabetic group but statistically not significant. (Table.2)

The cut off value (criterion) of S. uric acid was $\leq 7$ 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). Similarly, the cut off value (criterion) of C-RP level was >6.1 mg/l and at this value it is discriminating diabetics with 66.67% sensitivity (95% CI=53.7-78.0) and 81.25% specificity (95% CI=54.3-95.7). (Table.3)

**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. In upper limb the mean level of Sensory-Left Median (P<0.009) and Right Median conduction velocity was significantly ($p<0.001$) lower in Diabetic group compared to Pre Diabetic group. In contrast in lower limb sensory Right and Left-Sural nerve conduction Velocity were not differ significantly between the two groups. In upper limb Motor-Right Median and Left Median (wrist) conduction velocities were lower in diabetics as compared to prediabetics but difference was statistically not significant ($p$ value 0.062 & 0.015 respectively). In lower limb the motor L-Common Peroneal (ankle) conduction Velocity was not differed significantly($P<0.051$) between the two groups, while in R-Common Peroneal (ankle) it was lowered significantly ($p<0.009$) in diabetic group as compared to pre diabetic group. (Table.4)
Correlation

The S. uric acid of prediabetics negatively (inverse) but strongly correlated with neuropathy L-Sural Velocity (r= -0.60, p<0.05) and R-Sural Velocity also had negative correlation(r= -0.33) with serum uric acid. Both right and left Common Peroneal nerve velocity showed positive correlation with CRP. Median nerve right motor (M-R Median- Motor) velocity had negative correlation with serum uric acid in prediabetics. Other neuropathy parameters or /variables did not (p>0.05) showed any significant association with both serum uric acid and C - reactive protein levels. (Table-5)

In contrast, serum uric acid of diabetics did not showed any association with any of the neuropathy parameters/variables but had negative correlation with L-Sural and positive correlation with sensory right Median nerve (S-R Median). However, C-RP levels of diabetics showed negative and significant correlation with motor left Median (M-L Median) (wrist) Velocity (r= -0.56) and left Sural nerve velocity (-0.39).

Table 1: Distribution of age, gender, FBS and PPBS in Prediabetic and Diabetic patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre Diabetic (n=16)</th>
<th>Diabetic (n=63)</th>
<th>( \chi^2 ) ( \text{/t value} )</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.50 ± 11.57</td>
<td>55.14 ± 10.79</td>
<td>1.34</td>
<td>0.069</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (68.8%)</td>
<td>49 (77.8%)</td>
<td>0.57</td>
<td>0.451</td>
</tr>
<tr>
<td>Female</td>
<td>5 (31.3%)</td>
<td>14 (22.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>111.50 ± 10.56</td>
<td>142.66 ± 44.39</td>
<td>2.77</td>
<td>0.007*</td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td>168.75 ± 17.34</td>
<td>216.04 ± 52.89</td>
<td>3.51</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

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

Table 2: Distribution of Serum uric acid and CRP levels in Prediabetic and Diabetic patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre Diabetic (n=16)</th>
<th>Diabetic (n=63)</th>
<th>( \chi^2 ) ( \text{/t value} )</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum uric acid</td>
<td>10.84 ± 2.84</td>
<td>5.79 ± 1.87</td>
<td>6.60</td>
<td>p&lt;0.001**</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>6.76 ± 5.95</td>
<td>10.51 ± 8.98</td>
<td>1.58</td>
<td>0.117</td>
</tr>
</tbody>
</table>

***, p<0.001, values are in mean ± SD, C-RP (C - reactive protein)

Table 3: Diagnostic accuracy of Serum uric acid and CRP levels for Diabetic and Prediabetic

<table>
<thead>
<tr>
<th>Variables</th>
<th>Criterion (cut off value)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>AUC</th>
<th>p value</th>
<th>+LR</th>
<th>-LR</th>
<th>+PV</th>
<th>-PV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum uric acid</td>
<td>≤ 7 mg/dl</td>
<td>77.78 (65.5-87.3)</td>
<td>100.0 (79.2-100.0)</td>
<td>0.947</td>
<td>p&lt;0.001**</td>
<td>-</td>
<td>0.22</td>
<td>100.0</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>C-RP</td>
<td>&gt;6.1 (Mg/l)</td>
<td>66.67 (53.7-78.0)</td>
<td>81.25 (54.3-95.7)</td>
<td>0.656</td>
<td>0.029</td>
<td>3.56</td>
<td>0.41</td>
<td>93.3</td>
<td>38.2</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001, +LR: Positive likelihood ratio, -LR: Negative likelihood ratio, +PV: Positive predictive value, -PV: Negative predictive value

Table 4: Nerve conduction velocity parameters summary (Mean ± SD) of two groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Variables</th>
<th>N</th>
<th>Pre Diabetic</th>
<th>N</th>
<th>Diabetic</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-L Median</td>
<td>Velocity (m/s)</td>
<td>16</td>
<td>51.14 ± 7.05</td>
<td>32</td>
<td>45.58 ± 6.38</td>
<td>2.75</td>
<td>0.009</td>
</tr>
<tr>
<td>S-R Median</td>
<td>Velocity (m/s)</td>
<td>16</td>
<td>53.38 ± 7.20</td>
<td>33</td>
<td>45.96 ± 7.06</td>
<td>3.43</td>
<td>0.001</td>
</tr>
<tr>
<td>L-Sural</td>
<td>Velocity (m/s)</td>
<td>14</td>
<td>50.05 ± 4.97</td>
<td>30</td>
<td>50.72 ± 7.56</td>
<td>0.30</td>
<td>0.765</td>
</tr>
<tr>
<td>R-Sural</td>
<td>Velocity (m/s)</td>
<td>14</td>
<td>51.19 ± 6.73</td>
<td>32</td>
<td>49.33 ± 5.64</td>
<td>0.97</td>
<td>0.337</td>
</tr>
<tr>
<td>M-R Median (wrist)</td>
<td>Velocity (m/s)</td>
<td>16</td>
<td>53.76 ± 5.13</td>
<td>61</td>
<td>50.38 ± 6.16</td>
<td>1.90</td>
<td>0.062</td>
</tr>
<tr>
<td>M-L Median (wrist)</td>
<td>Velocity (m/s)</td>
<td>16</td>
<td>54.08 ± 5.64</td>
<td>58</td>
<td>51.32 ± 7.07</td>
<td>1.44</td>
<td>0.155</td>
</tr>
<tr>
<td>L-Common peroneal (ankle)</td>
<td>Velocity (m/s)</td>
<td>15</td>
<td>48.53 ± 5.65</td>
<td>38</td>
<td>44.73 ± 6.44</td>
<td>2.00</td>
<td>0.051</td>
</tr>
<tr>
<td>R-Common peroneal (ankle)</td>
<td>Velocity (m/s)</td>
<td>15</td>
<td>50.06 ± 8.56</td>
<td>40</td>
<td>43.48 ± 7.86</td>
<td>2.70</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* 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 5: Correlation of S. uric acid and C-RP levels with neuropathy in both groups

<table>
<thead>
<tr>
<th>Neuropathy parameters</th>
<th>Variables</th>
<th>Pre Diabetic (n=14)</th>
<th>Diabetic (n=13)</th>
<th>Total (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-L Median</td>
<td>Velocity</td>
<td>0.06</td>
<td>0.21</td>
<td>0.05</td>
</tr>
<tr>
<td>S-R Median</td>
<td>Velocity</td>
<td>-0.21</td>
<td>0.21</td>
<td>0.35</td>
</tr>
<tr>
<td>L-Sural</td>
<td>Velocity</td>
<td>-0.61</td>
<td>0.18</td>
<td>-0.32</td>
</tr>
<tr>
<td>R-Sural</td>
<td>Velocity</td>
<td>-0.33</td>
<td>0.01</td>
<td>0.15</td>
</tr>
<tr>
<td>M-R Median (wrist)</td>
<td>Velocity</td>
<td>-0.48</td>
<td>-0.35</td>
<td>0.13</td>
</tr>
<tr>
<td>M-L Median (wrist)</td>
<td>Velocity</td>
<td>-0.05</td>
<td>-0.16</td>
<td>-0.23</td>
</tr>
<tr>
<td>L-Common peroneal (ankle)</td>
<td>Velocity</td>
<td>0.29</td>
<td>0.52</td>
<td>-0.04</td>
</tr>
<tr>
<td>R-Common peroneal (ankle)</td>
<td>Velocity</td>
<td>0.22</td>
<td>0.49</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

DISCUSSION

In our study, the serum uric acid level was significantly higher in prediabetics than diabetics. (p<0.001) These findings were consistent with the previous studies, demonstrated that diabetics had lower serum uric acid level and prediabetics had higher level than non-diabetics. [14,21-25] Low serum uric acid levels in diabetics can be explained by the rationale that severe hyperglycemia has uricosuric effect with glycosuria. [26] Furthermore, uric acid concentration might be influenced by the changes in plasma glucose and insulin concentration. [27] Serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis factor-α, both of which are related to development of diabetes. [28] 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. [29] Insulin can stimulate urate anion exchanger and it increases renal urate reabsorption. [30]

In our study, however the CRP level was comparatively higher in diabetic group than pre-diabetic group, but did not differ significantly. It has been reported that CRP levels were significantly higher in both diabetic men and women as compared to their non-diabetic counterparts. [31] Increased CRP levels have been described in people with type-2 diabetes, [3] as well as in type-1 diabetes. [32]

We believe that increased serum CRP concentration in patients with type 2 diabetes mellitus may partly be explained with its increased synthesis in the liver under the actions of adipocytokines from adipose tissue or might be the reflection of existing atherosclerosis or decreased insulin sensitivity in these patients.

The cut off value of Serum uric acid in our study was ≤7 mg/dl and at this value it is discriminating Diabetics with 77.78% sensitivity and 100.00% specificity. Result of the study supports the previous study that showed, individuals with high serum uric acid level (≥6.4mg/dl) was associated with two-fold increase in the risk of type-2 diabetes compared with those having lower level (<5.2mg/dl) [33] As per our study findings, it may be concluded that low Serum uric acid and high CRP levels might play a significant role in progression of diabetes and these findings can be used at its earlier stage for diagnostic purpose.

The major finding of our study was that the prediabetic subjects exhibited minimal changes in nerve conduction abnormalities in comparison to diabetic subjects. Results of our study showed 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 subjects in comparison to Prediabetic subjects. Thrainsdottir et al, [34] reported that increased basal membrane thickening was associated with sensory peripheral neuropathy in prediabetics (IGT) and diabetic subjects. As prediabetes (IGT) is a forerunner of diabetes and it is a metabolic condition. Thus the metabolic changes can cause nerve conduction abnormalities in diabetics as well as prediabetics.

Nerve conduction studies (NCS) are the gold standard method and the most consistent indicator of nerve damage even in subclinical (largely asymptomatic) neuropathy. The early detection of abnormal glucose metabolism is particularly important. Early treatment probably more effective in prevention of complication so we could reduce the progression of the course of neuropathy, and at that stage abnormalities of peripheral nerves are more likely to be reversible

CONCLUSION

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 affects the prediabetics. It was observed that neuropathy often is subclinical in prediabetics, even if these patients do not
show signs of neuropathy on the clinical neurological assessment. Therefore referral for a nerve conduction studies might be an ancillary tool to detect incipient neuropathy. In our study correlation was found between S. uric acid and C-RP levels with neuropathy in prediabetics. Thus it is important to evaluate the patients in prediabetic stage so that prevention and early intervention can be possible and future complications can be managed in early stage.

REFERENCES


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