“CORRELATION BETWEEN SERUM URIC ACID LEVEL AND DIABETIC PERIPHERAL NEUROPATHY: A CASE CONTROL STUDY”

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ABSTRACT

Background: It is known to all that uric acid is a key reason for the progression of retinopathy and nephropathy in diabetic patients. This study focuses to evaluate the of serum uric acid levels in patients with and without diabetic peripheral neuropathy (DPN). Methods: Sixty patients with DPN (experimental group) and 60 patients without DPN (control group) were selected and matched with regard to age, sex, body mass index (BMI) and the duration of their different diseases were entered into the study. DPN was diagnosed by nerve conduction studies of lower limbs nerves i.e. sural, tibial and peroneal. We also collect the data of serum uric acid, creatinine and HbA1c level in two separate group. Results: Results shows that the demographic characteristics of the two separate group were same but the history of diabetic foot ulcer was higher in experimental group (p<0.05) when compare to control group. The patients mean age of the experimental group was 55.6±5.3 years and in the control group was 56.8±6.1 years (p=0.401). The serum uric acid level in experimental group was 7.6±0.76 (mg/dl) and in case of control group it was 4.8±0.82 mg/dl (p=0.048). Serum creatinine and Glycated hemoglobin (HbA1C) level also high in case of experimental group than control group of patients. Conclusion: The results indicated that higher level of serum uric acid level is form in diabetic patients with diabetic neuropathy. More research is required to study the role of serum uric acid for the progression of DPN.

KEYWORDS: Diabetes mellitus, neuropathy, uric acid.
INTRODUCTION
The main causes of mortality and morbidity are due to diabetic autoimmune neuropathy (DAN).\cite{1, 2} DAN is impaired secretion of sweat, which is also called sudomotor dysfunction (SD).\cite{3} The sudomotor dysfunction is happen due to severe injury of the postganglionic cholinergic sympathetic nerve fibers which are responsible for the innervations of sweat glands and causes dry skin.\cite{3}

Serum uric acid (SUA) is being known as a risk marker of cardiovascular morbidity.\cite{4} A high SUA level is closely associated with cardiovascular morbidity,\cite{5} coronary artery disease,\cite{6} and brain stroke.\cite{7} Moreover a relation between increased SUA levels and non-alcoholic fatty liver disease has been reported previously.\cite{8} Specifically type-1 diabetes patients with high SUA levels have been closely related with microvascular disease, i.e. stroke and peripheral arterial disease (PAD). While the relation between SUA and microvascular disease has received little attention. Indeed, type-2 diabetic patients and peripheral neuropathy patients have been reported that have higher SUA.\cite{9} There is a close relation has been focused between peripheral neuropathy and SUA levels, but till now no prominent linked has not been examined between SUA and DAN. The rational for this relation is that SUA reflects inflammatory activity,\cite{10} and the patients with DAN may exhibit increase inflammation.\cite{11} However the effect of SUA level and SD and type-2 diabetes mellitus relationship is unclear. From that background the study focuses to know about the association between SUA and SD in patients with type-2 diabetes mellitus.\cite{12}

METHODS
The study has been done for 6-months from February-2014 to July-2014 in Medinipur Medical College and Hospital, West Bengal, India. To conduct this study we selected about 600 patients, out of these 60 patients were diabetic neuropathy and 60 patients were selected without peripheral neuropathy were entered into the study. All patients had type-2 diabetes and were coordinated with consider to age, sex, duration of diabetes and body mass index (BMI). For screen of diabetic neuropathy from this population, we used the standard Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) criteria.\cite{8, 13} The average age of the subjects 35 to 70 years, other causes of neuropathy, the uses of other medication that alters serum uric acid level (like- thiazides, salicylate, allopurinol, pyrazinamide, niacia and glucocorticoids) any other history of hepatic or renal dysfunction, malnutrition or malabsorption and alcohol abuse were excluded from this study.
We collect the signed as an informed consent from each patient. Then from each patient we completed a questionnaire including general information, times or duration of diabetes, smoking history and also the foot ulcer history. We also measured height, weight and blood pressure according to standard procedure. For the diagnosis of peripheral diabetic neuropathy we performed a nerve conduction study. NSS and NDS criteria were used for the screen of peripheral diabetic neuropathy. NSS questionarie include question regarding the type of the sensation, area and time of the symptoms, time of waking up from the sleep at morning and the factors that relieve symptoms. NDS contains some neurologic parameters such as ankle reflex and perception of pinprick, vibration and cold. The criteria for the existence of DPN were a NDS score of 6, irrespective of NSS score or a NDS score of 3 to 5 in combination with a NSS score of 5.[8, 13, 14]

Nerve conduction studies were performed on tibial, peroneal and sural nerves in lower limbs, whereas amplitude conduction velocity and latency were measured. The calculated values were compared with references values.[15] DPN diagnosis was based on the recommended protocol. The case definition criteria for authentication of DPN were an abnormality (≥ 99th or ≤ 1st percentile) of nerve conduction in two separate nerves one of which must be the sural nerve.[9]

The severity of DPN was assessed by a combination of neuropathy signs, symptoms, nerve conduction studies abnormalities as mild, moderate and severe.[11] Assessment of serum uric acid, creatinine and HbA1C level were measured by using kit method (Coral Clinical Systems, Tulip group, Goa - 403 722, India) through semi automated analyzer.

Statistics
Origin 6.1 version was used to perform the statistical analysis. For determination of normal distribution of variables, kolmogorov Smirnov test was used. All data were expressed as mean±SD followed by multiple comparisons two tail ‘t’ test. Data with normal distribution were expressed as median and inter-quartile range P values less than 0.05 were considered to be significant.

RESULTS
The basis characteristics and biochemical parameters of case study of experimental and control group are representing in table-1. The data shows the mean age of the subjects in control group was 56.8±6.1 years and in experimental group it was 55.6±5.3 years. Thirty
two patients in each group were females. In case of experimental group the history of diabetic foot ulcer was significantly higher in comparison to control group. But other variables did not have significant differences between two groups. The results showed that the serum uric acid level was significantly higher in experimental group in comparison to the control group. But in case of serum creatinine and HbA1C level, there was no significant difference was noted between these two groups.

Table 1: Basic characteristics and biochemical parameters of the experimental and control group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experimental group (n=60)</th>
<th>Control group (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n, %)</td>
<td>32 (53.3%)</td>
<td>32 (53.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>55.6±5.3</td>
<td>56.8±6.1</td>
<td>0.401</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>30.3±3.9</td>
<td>28.6±3.8</td>
<td>0.073</td>
</tr>
<tr>
<td>Duration of diabetes (years) (mean±SD)</td>
<td>9.5±3.1</td>
<td>8.9±2.8</td>
<td>0.478</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>20 (33.3%)</td>
<td>28 (46.62%)</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>26 (43.3%)</td>
<td>20 (33.3%)</td>
<td>0.486</td>
</tr>
<tr>
<td>Both</td>
<td>14 (23.3%)</td>
<td>12 (19.98%)</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>12 (19.98%)</td>
<td>6 (9.99%)</td>
<td>0.291</td>
</tr>
<tr>
<td>History of diabetic foot ulcer (%)</td>
<td>14 (23.3%)</td>
<td>0 (0%)</td>
<td>0.007</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>46 (76.6%)</td>
<td>36 (59.94%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Systolic blood pressure (mm/Hg) (mean±SD)</td>
<td>134.3±16.6</td>
<td>131.1±17.2</td>
<td>0.412</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm/Hg) (mean±SD)</td>
<td>83 (80-90)*</td>
<td>82 (80-90)*</td>
<td>0.563</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl) (mean±SD)</td>
<td>7.6±0.76</td>
<td>4.8±0.82</td>
<td>0.048</td>
</tr>
<tr>
<td>Serum creaintine (mg/dl) (mean±SD)</td>
<td>0.9±0.03</td>
<td>0.8±0.02</td>
<td>0.345</td>
</tr>
<tr>
<td>HbA1C (%) (mean±SD)</td>
<td>7.7±0.3</td>
<td>7.6±0.3</td>
<td>0.712</td>
</tr>
</tbody>
</table>

*Median and inter-quartile range. Others as mean±SD.

DISCUSSION

Experimental results showed the high uric acid level in diabetic patient with peripheral diabetic neuropathy. Several studies showed that high serum uric acid levels are main causes of different diabetic complications. Few studies suggest that uric acid is a mediator in the prediction of the development of albuminuria in type-1 diabetic patients.[16] A study suggest that there was insignificance difference in uric acid levels between those with and without diabetic retinopathy, but other report proved that two different groups of diabetic foot patients with and without retinopathy showed higher concentration of serum uric acid in diabetic foot patients with retinal disease.[7,12]
Two separate studies showed that high serum uric acid in diabetic patients with and without peripheral neuropathy and with and without sudomotor dysfunction.\textsuperscript{[17, 18]} First study suggest that serum uric acid was increased who suffering from neuropathy.\textsuperscript{[18]}

We studied electro diagnostic tests to NSS-NDS criteria for better credentials of peripheral neuropathy. From the clinical view point, when the main etiologic feature in the pathogenesis of diabetic neuropathy is hyperglycemia, it seems that the new factors may decrease the residual risk. Some unknown reason and uric acid may play important roles in this context. So, the role of uric acid in other long duration complications of diabetes was suggested in some experiments, its contribution for the improvement or development of diabetic neuropathy is probable. In this study, we tried to search out those factors that influence serum uric acid levels, such as BMI and renal function in experimental and control groups. This study is proving the authentication of the peripheral neuropathy by the electrodiagnostic technique as the nominal criteria for the diagnosis of DPN.\textsuperscript{[11]} Though more studies are required to explain the specific role for uric acid in the pathogenesis of diabetic neuropathy, the results of the current study raised the probable function of uric acid in this process. Proving this hypothesis will increase our considerate about the pathogenesis of diabetic neuropathy. The changes in uric acid level may cause changes in development of diabetic neuropathy needs more studies. In conclusion, the result of our study shows the probable role of serum uric acid levels in the improvement of peripheral diabetic neuropathy.

**ABBREVIATIONS**
DPN, diabetic peripheral neuropathy; BMI, body mass index; HbA1C, glycated hemoglobin; DAN, diabetic autoimmune neuropathy; SUA, serum uric acid; PAD, peripheral arterial disease; SD, sudomotor dysfunction; NSS, neuropathy symptom score; NDS, neuropathy disability score.

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**REFERENCES**
