The Comparison of Serum Uric Acid Level in Patients with Diabetic Neuropathy with Diabetics without Neuropathy
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ABSTRACT

Introduction: Diabetes type 2 and its complication, diabetic neuropathy, is increasingly a health threatening problem in the world. The increase in blood uric acid levels has accompanied endothelial malfunction, ischemic heart disease, brain stroke, peripheral artery disease and mortality caused by coronary vessels disease. We studied the effects of uric acid on diabetic neuropathy in type 2 diabetics.

Material and Methods: 135 diabetics type II referring to Golestan Hospital divided in two groups: "neuropathics" (65 patients) and "without neuropathy" (70 patients). Serum uric acid, ESR and qualified CRP was measured and compared between two groups.

Results: The comparison of mean ESR in both groups showed a meaningful higher level of ESR in case group rather than control group (p-value: 0.003) But there wasn’t any meaningful difference in qualitative CRP evaluation between two groups, The uric acid serum levels of case group patients were meaningfully higher than control group patients (p-value > 0.0001). A meaningful correlation of ESR and serum uric acid level was seen also in this research, but there wasn’t any meaningful correlation between ESR and serum uric acid level in control group patients.

Conclusion: It seems that serum level of uric acid can be as a predicting factor for diabetic neuropathy.

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Introduction
Diabetes type 2 is increasingly a health threatening problem in the world. Diabetic neuropathy is one of the complications of diabetes which cause degradation of peripheral neurons in hands and feet.

The main types of diabetic neuropathy are:
1- Sensory-motor spreading neuropathy
2- Local neuropathy
3- Autonomic neuropathy

Diabetics may develop neuropathy at any time but overt symptoms come up in about 10 years after the diagnosis of diabetes. Most of the diabetics have neuropathy but don’t show symptoms. And the symptoms appear in about one third of patients. Neuropathy usually happens to smokers over 40 years old and people having difficulty controlling their blood sugar level. There are several factors causing diabetic neuropathy which the most important among them are hyperglycemia and hyper pressure in diabetics.

The diagnosis of neuropathy is done based on symptoms and clinical examination by physician. There are other diagnostic ways such as Nerve Conduction Study.

Peripheral neuropathy is damage in small vessels of type II diabetes which causes increase in risk of foot lesions and other complications. Chronic hyperglycemia is the most important etiologic factor.
but there is increasing evidence that factors inducing vascular risks (such as obesity, hyperlipidemia, hypertension and smoking), overt clinical atherosclerosis (such as coronary vessels disease and peripheral artery disease) and also genetic polymorphism are involved in pathogenesis of peripheral neuropathy. Uric acid is probably a basic heart threatening factor. The increase in blood uric acid levels has accompanied endothelial malfunction, ischemic heart disease, brain stroke, peripheral artery disease and mortality cause by coronary vessels disease. In type II diabetes, the elevated levels of uric acid have been relative to macro vascular disease and more to brain stroke and peripheral artery disease.

In a research which has been done on 66 type II diabetic patients having peripheral neuropathy and 66 patients without peripheral neuropathy (which were matched with diabetic patients having neuropathy on age, renal function analyzed by serum creatinine and also duration of diabetes), serum uric acid levels were meaningfully higher in diabetic patients having neuropathy than diabetic patients without neuropathy. Also, a meaningful statistical relation between serum uric acid level and severity of neuropathy measured by Neuropathy Disability Score (NDS) was observed.

CRP was significantly higher in diabetic patients having neuropathy. And a meaningful correlation between serum uric acid and CRP was observed in both groups. Diabetic patients having neuropathy showed noticeable higher levels of triglycerides than diabetic patients without neuropathy. The higher LDL level in diabetic patients having neuropathy, than diabetic patients without neuropathy, was not statistically meaningful.

There was meaningful correlation between serum uric acid level and concentration of triglycerides in diabetic group having neuropathy, but this fact wasn’t confirmed in diabetic patients without neuropathy. Similarly, a meaningful correlation between serum uric acid and LDL cholesterol levels was observed in diabetic patients having neuropathy but it wasn’t seen in patients without neuropathy. On the other hand, serum uric acid and HDL cholesterol levels of diabetic patients having neuropathy (not diabetic patients without neuropathy) showed meaningful inverse relation.

It was concluded in this research that the level of serum uric acid was increased in type II diabetic patients having neuropathy in comparison to patients without neuropathy. There was meaningful relation between serum uric acid level and NDS in patients having neuropathy. According to the fact that NDS is a proved criterion for clinical severity of neuropathy, it seems that uric acid is not only related to the existence of neuropathy but also to the severity of this complication. Type2 diabetics having neuropathy had higher C-reaction protein (CRP) levels in this research than patients without neuropathy.

Another study showed that, diabetic foot lesions and their severity is related to the increase of acute phase proteins (such as CRP), cytokines and chemokines, regardless of accompanying infections.

Accompaniment of subclinical inflammation with diabetic polyneuropathy and neuropathic disorders were shown as increase in CRP and IL6 levels.

Evidence shows that, high levels of triglycerides and oxidized LDL can cause neuronal damage due to oxidative stress and because of that, hyperlipidemia can be another target in treatment of diabetic neuropathy.

In the study of Pananas et al, a meaningful relation between serum uric acid and CPR was observed but the relation between serum uric acid and lipid components (triglycerides, total cholesterol, LDL, HDL) was only seen in diabetics having neuropathy. These findings suggest that, high uric acid levels in patients having neuropathy and dyslipidemia, like patients having metabolic syndrome, is accompanied by inflammation. According to the mentioned findings, uric acid may be a proper risk marker (in addition to other markers for peripheral neuropathy).

It was shown in another research that, the level of serum uric acid in diabetics is more than the population having glucose intolerance and this level is higher in latter group than normal population. There are limited numbers of researches on the effect of gender on the relation between diabetic neuropathy and level of serum uric acid.

It is shown in a research that, the level of uric acid has been higher in diabetic women than non-diabetic women, while the level of uric acid in men having or not having diabetes didn’t have any meaningful difference.

Material and Method
After gathering the data, T-test and paired T-test will be used to compare the mean of measured levels and p<0.05 is assumed meaningful.

First all of the diabetic patients referring to diabetic clinic of Golestan hospital of Ahwaz were examined by general physicians, then were evaluated based on Michigan’s classification standards and after that were referred to EMG/NCV center of the hospital for confirming the diagnosis. All of the mentioned
patient’s electro diagnostically evaluated for observation of diabetic neuropathy. And were divided into two groups according to having or not having neuropathy (based on EMG/NCV standards). The level of serum uric acid, ESR and CRP were measured for both groups and got compared.

All of the patients were evaluated by one person and EMG/NVC machines of the EMG/NVC center at Golestan hospital. Also the level of serum uric acid of all patients was measured at central laboratory of Golestan hospital and by one person. All patients or their legal representatives completed and endorsed the written consent of participation in this research.

Referred people were gotten under electro diagnostic evaluation after being analyzed by inclusion and exclusion criteria.

Inclusion criteria:
1- People having type II diabetes aged 45-80

Exclusion criteria:
1- History of having any other neuropathies (uremic CIDP, toxic, congenital…)
2- History of stroke (ischemic or hemorrhagic)
3- History of spinal disorders
4- History of severe trauma in limbs
5- People having chronic renal failure

Results

According to the sample size being 62 persons in each group. Sampling continued after reaching the quorum of 65 persons in the group having neuropathy (the abundance of diabetics having neuropathic criterions was more than patients not having neuropathy in electro diagnostic evaluation) and stopped by reaching 70 persons for the group without neuropathy. Demographic specifications and the results came out of planned tests are in tables below. Patients whose neuropathy was classified other than diabetic neuropathy were eliminated from the study during electro diagnostic evaluations.

Table 1: Abundance of participants in research by gender

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Percent</th>
<th>Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics having diabetic neuropathy</td>
<td>Male</td>
<td>63.1</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>37.1</td>
<td>26</td>
</tr>
<tr>
<td>Diabetics without diabetic neuropathy</td>
<td>Male</td>
<td>62.9</td>
<td>44</td>
</tr>
<tr>
<td>Group</td>
<td>Female</td>
<td>100</td>
<td>70</td>
</tr>
</tbody>
</table>

Comparing the age of participants in two groups of having diabetic neuropathy and without diabetic neuropathy demonstrated, p-value in Levene test is 0.66 meaning that the variance of age between two groups didn’t have meaningful difference. According to the p-value of 0.8 in independent t-test, the mean age of two groups don’t have meaningful difference.

Comparing two groups of diabetic patients having diabetic neuropathy and diabetic patients without diabetic neuropathy by duration of having diabetes, serum level of HbA1C and blood hyper pressure. The patients of 2 groups didn’t have a meaningful difference for duration of having diabetes, mean of blood sugar during past 3 months (HbA1C) and having hyper pressure.

Comparing the uric acid serum level of participants in two groups of diabetics having diabetic neuropathy and without neuropathy. The p-value for Levene test is 0.95 meaning that the variance of uric acid serum level of two groups didn’t have meaningful difference. According to the p-value of 0.0001 for independent t-test, the mean of uric acid serum level of the two groups have meaningful difference.

Comparing ESR in participants of the two groups of diabetics having diabetic neuropathy and without diabetic neuropathy, the p-value of Levene test is 0.95 meaning that the variance of ESR didn’t have meaningful difference for two groups. According to the p-value of 0.53 for independent t-test, the mean ESR of two groups doesn’t have meaningful differences. Comparison of CRP in participants of
two groups of diabetics having diabetic neuropathy and without neuropathy with Chi 2 test didn’t show any meaningful difference in these two groups. (p=0.31)

Discussion

Two groups of diabetics having neuropathy (case group) and diabetics without neuropathy (control group) didn’t have meaningful differences in age, gender, duration of the disease, HbA1C, cigarette usage, blood hyper pressure and micro albuminuria. Mean age of group having neuropathy was 57.80 years and for the group without neuropathy was 58.07 years (p=0.08).

Previous research showed meaningful difference of CRP, ESR in case and control group1. The relation between the increase of CRP level and autonomic neuropathy was shown in a research for type 1 diabetic patients4. Also there was evidence showing the existence of subclinical inflammation in autonomic neuropathy of type I diabetes as an increase in IL6 levels5.

The relation between diabetic neuropathy and hyperlipidemia is a known matter7,8,9.

In our research the comparison of mean ESR in both groups also showed a meaningful higher level of ESR in case group rather than control group (p-value: 0.003) But in our observation of qualitative CRP evaluation of the two groups, there wasn’t any meaningful difference.

Also the uric acid serum levels of case group patients were meaningfully higher than control group patients (p value < 0.0001).

A meaningful correlation of ESR and serum uric acid level was seen also in this research (p-value< 0.05 ), but there wasn’t any meaningful correlation between ESR and serum uric acid level in control group patients.

According to previous studies, there is a relation between diabetic neuropathy and risk factors like obesity, hyperlipidemia, blood hyper pressure and clinical atherosclerosis (such as coronary or peripheral vessels disease)1.

According the result of this research, it seems that serum level of uric acid can be as a predicting factor for diabetic neuropathy.

We suggest at the end:

1- Using quantitative CRP instead of qualitative in laboratory evaluations.

2- Evaluating the correlation between severity of diabetic neuropathy and serum level of uric acid

3- Evaluating the role of treatments reducing uric acid decreasing the incidence of diabetic neuropathy.

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