Estimation of Serum Homocysteine Level in Patients with Type 2 Diabetic Neuropathy

Ebtesam Fahmy¹, Hanan Amer¹, Amany M. Rabah¹, Nervana El-Fayoumy¹, Hala Mokhtar²
Departments of Neurology, Cairo University¹; Nutrition of the National Research Centre²; Egypt

ABSTRACT

Background: Hyperhomocysteinemia and non-insulin-dependent diabetes mellitus (NIDDM) are both associated with premature vascular disease. Data indicate that homocysteine is independently associated with the prevalence of peripheral sensorimotor and autonomic neuropathy in type 2 diabetic patients. Objective: To investigate the association between homocysteine level and the prevalence of neuropathy in type 2 diabetes mellitus. Methods: Twenty six type 2 diabetic patients and 16 healthy control subjects were enrolled. Neuropathy was diagnosed according to clinical symptoms, clinical examination and electrophysiological sensory and motor testing. Homocysteine-related parameters (plasma homocysteine, folate and vitamin B12) were determined. Results: Diabetic patients had a significantly higher plasma levels of homocysteine compared to controls, (p=0.001). Significantly lower serum levels of vitamin B12 and folic acid were detected in diabetic patients compared to controls, (p=0.000; 0.011 respectively). Females had significantly lower mean levels of folic acid and Vitamin B12 than males (p= 0.045, 0.037 respectively). A significant positive correlation was found between duration of diabetes; PPBS; HbA1c and homocysteine levels, (P= 0.019, 0.005, 0.000 respectively). A significant positive correlation was found between homocysteine level with PPBS and HbA1c, (P=0.019, 0.001 respectively). Levels of folic acid and Vit B12 were positively correlated (p= 0.000). No correlation was also found between homocysteine level with PPBS and HbA1c, (P=0.019, 0.001 respectively). Significantly lower serum levels of vitamin B12 and folic acid levels. Conclusion: Elevated serum homocysteine is associated with the presence of diabetic neuropathy in type 2 diabetic patients. Future studies are needed to establish hyperhomocysteinaemia as a clinically significant modifiable risk factor in the pathogenesis of diabetic neuropathy. (Egypt J Neurol Psychiat Neurosurg. 2010; 47(1): 59-66)

Key Words: Homocysteine, NIDDM, Neuropathy.

INTRODUCTION

Over the last years, there has been a great interest in homocysteine, primarily because of the realization that elevated levels of plasma homocysteine is an important risk factor for vascular occlusive diseases such as coronary artery disease, cerebral vascular accidents, and deep-vein thrombosis. Homocysteine (Hcy) is a non-essential sulfur-containing amino acid whose metabolism stands at the intersection of two pathways: remethylation to methionine, which requires folate, vitamin B12 and vitamin B6; and transsulfuration to cystathionine, which requires pyridoxal-5-phosphate. Genetically inherited defects of the enzymes involved in the remethylation or transsulfuration process of methionine or methylenetetrahydrofolate reductase thermolability are the most important determinants of marked Homocysteinemia. Mild hyperhomocysteinemia seen in fasting conditions is due to mild impairment in the remethylation pathway due to nutrient deficiency as folate or vitamin B12 deficiencies.

High levels of plasma homocysteine are toxic to the vascular endothelium via the formation of free radicals. These free radicals cause direct injury to the endothelium by disrupting its integrity, exposing the underlying vascular matrix and smooth muscle, enhancing low density lipoprotein peroxidation and promoting a hypercoagulable state platelets activation and thrombus formation.

Elevated homocysteine levels, whether due to nutrient deficiencies or defective genes, can easily be normalized in virtually all cases, simply and inexpensively, using a combination of nutritional supplements. The most effective defense against homocysteine buildup is a combination of vitamins B-6, B-12 and folic acid, which convert homocysteine into nontoxic substances.

Hyperhomocysteinemia and non-insulin-dependent diabetes mellitus (NIDDM) are both associated with premature vascular disease. Accordingly, the association between homocysteine and the prevalence of neuropathy in type 2 diabetes mellitus was investigated. Data indicate that homocysteine is independently associated with the prevalence of sensorimotor peripheral neuropathy (DSPN) and autonomic neuropathy (DAN) in type 2 diabetic patients.
The aim of this study is to: (1) evaluate the mean serum levels of Homocysteine, vitamin B12 and folic acid levels in patients with peripheral neuropathy associated with type 2 DM compared to age and sex matched control healthy subjects and (2) to assess the follow up serum levels of Homocysteine and clinical response of diabetic patients after intake of folic acid and vitamin B12 supplements for 3 months.

**SUBJECTS AND METHODS**

The present study is carried out on 26 type 2 diabetic patients according to criteria suggested by the American Diabetes Association for diagnosis and classification of diabetes mellitus, (fasting blood sugar ≥ 126 mg/dL). Patients were 10 males (36.5%) and 16 females (61.5%). Their age ranged from 37 to 58 years (mean 45.46±5.65). All patients were on treatment for diabetes. 16 patients (61.5%) were on oral hypoglycemic drugs while 10 patients (38.5%) were on insulin injections. None of these conventionally used hypoglycemic drugs are known to influence plasma levels of homocysteine. Sixteen healthy subjects 5 males (31.3%) and 11 females (68.8%), their age ranged from 35-60 years (mean 44.81±5.45), sex and age matched for patients (P= 0.64 and P= 0.726) respectively. The duration of diabetes ranged from 3-18 years with a mean of 8.46±3.73 years.

Excluded from the study were patients with other causes of peripheral polyneuropathy as: Heridofamilial, infective, toxic, mechanical causes, connective tissue diseases and other metabolic diseases. Patients with renal dysfunction known to be associated with high homocysteine levels and patients treated with drugs like fibrates or vitamin supplements (including ascorbic acid) in the previous 6 months were also excluded.

Subjects were submitted to the following procedures:

1) **Thorough Clinical assessment including:**
   - A detailed medical history about the duration of diabetes, the presence of renal disease, hypertension, current medications and symptoms suggestive of peripheral neuropathy.
   - Complete general and neurological examination.

2) **Clinical evaluation of diabetic neuropathy using the Neuropathy Impairment Score (NIS):**
   The Neuropathy Impairment Score was developed and modified by Dyck et al.\(^{15}\). It is a global score of muscle weakness and reflex and sensory abnormalities indicative of neuropathy based on a neurological examination. The components were scored for the right and left sides of the body, and combined into a score for each person. The higher the score the worse the neuropathy.

3) **Electrophysiological Studies:**
   All patients had characterizing nerve conduction and needle electromyography examinations. Nerves and muscles were selected for study according to clinical symptoms and findings. Nerves examined for motor conductions were (median, ulnar, posterior tibial and peroneal nerves) and for sensory conductions were (median, ulnar, sural and superficial peroneal nerves).

4) **Routine laboratory workup including:**
   Complete blood picture. Erythrocyte sedimentation rate (ESR), Liver function and kidney function tests, Fasting and postprandial blood sugar and Glycated hemoglobin (HbA1c).

5) **Assessment of homocysteine-related parameters:**
   - Plasma homocysteine level was measured for diabetic patients and controls. A 2-ml fasting blood sample was obtained from each participant. The blood was centrifuged within 30 min after collection at 3000 g for 6 min. The plasma was removed and analysed for homocysteine by enzymatic immunnoassay method (EIA).\(^{16}\) Hyperhomocysteinaemia was defined when homocysteine levels were higher than 15 µmol/l.
   - Folic acid and vitamin B12 levels were measured for diabetic patients and controls according to the classic method of radioimmunoassay.\(^{17}\) Another follow up measurement of plasma homocysteine, folic acid, and vitamin B12 levels were done for 15 diabetic patients after oral supplements of folic acid (500 microgm/ day) and vitamin B12 in the form of intramuscular injection (1000 µg twice/week) for 3 successive months.

**RESULTS**

**Clinical Characteristics of Neuropathy:**

The main symptom encountered in all patients (100%) was troubling pain (burning, stabbing or shock-like) and paraesthesia especially in the lower
limbs. Distal numbness especially of the feet was reported by 21 patients (80.7%). Mild weakness in the limbs was reported by 5 patients (19.23%). Facial nerve weakness was reported by 6 patients (23.08%), 4 on the right side and 2 on the left side.

Neurological examination revealed distal sensory polyneuropathy in 15 patients (57.69%), distal sensory polyneuropathy and lower motor facial palsy in 6 patients (23.08%) and distal sensory-motor polyneuropathy in 5 patients (19.23%). Ankle reflex was lost in 18 patients (69.23%) and diminished in 8 patients (30.77%). Impairment of deep sensation was detected in 12 patients (46.15%).

The Neuropathy Impairment Score ranged from 4 – 14 with a mean of 8.38. The NI score was 10 in 10 patients (38.46%), 6 in 8 patients (30.76%) and 8 in 5 patients (19.23%), 14 in 1 patient (3.85%), 4 in 1 patient (3.85%) and 12 in 1 patient (3.85%).

Electrophysiological studies results:

Needle electromyography showed frequent fibrillations, polyphasic motor unit potentials, prolonged duration and reduction of the compound motor and sensory action potentials and decrease in recruitment of motor unit potentials. Nerve conduction study showed increase in distal latency and delay in conduction velocities. Out of 26 diabetic patients, 11 patients (42.3%) had demyelinating neuropathy, 5 (19.2%) had axonal neuropathy, 6 (23.1%) had mixed neuropathy while 4 patients (15.4%) had normal nerve conduction studies.

Laboratory Results:

1. Blood sugar and Hb A1c levels:

   Fasting blood glucose in patients ranged from 110-260 mg/dL (mean=157.15±35.12 mg/dL) and in controls it ranged from 70-102 mg/dL (mean = 87.25±9.23 mg/dL). Post-prandial blood glucose in patients ranged from 157-360 mg/dL (mean= 214.04±51.33 mg/dL) and in controls it ranged from 90-118 mg/dL (mean = 101.25±9.31 mg/dL).

   Glysosylated hemoglobin (Hb A1c) in patients ranged from 6-11% with a mean of 8.25±1.19 %, while in controls it ranged from 4-6 % (mean= 5.1±0.622). The difference between patients and controls as regards mean fasting and post-prandial blood glucose and HbA1c was statistically significant, (p= 0.000, 0.000, 0.001, respectively).

2. Homocysteine, Vit B12 and folic acid levels:

   The range, mean and SD of the serum levels of homocysteine, folic acid and Vitamin B12 in patient and control groups are shown in Table (1). A statistically highly significant difference was detected between diabetic patients and controls regarding the mean homocysteine level, being significantly higher in diabetic patients. A highly significant difference was also detected between diabetic patients and controls regarding the mean vitamin B12 level, being significantly lower in patients. Mean folic acid level was significantly lower in diabetic patients compared to controls.

   A statistically significant difference was observed between male and female patients regarding mean levels of Folic acid and vitamin B12 being significantly lower in females (p= 0.045, 0.037 respectively). However, no significant difference was detected between male and female patients regarding mean levels of homocysteine, (P= 0.548).

   The mean levels of Homocysteine, folic acid and Vitamin B12 in 15 patients before and after treatment for with folic acid and Vit. B12 supplements for 3 months are shown in Table (2). All patients (n=15) showed improvement of symptoms of pain, paraesthesia and the facial and limb weakness after folic acid and vitamin B12 supplements. Hypoesthesia was also improved in 3 patients (20%).

   The mean serum homocysteine level was lower after treatment compared to the pre-treatment values however, the difference was not statistically significant. The mean serum folic acid level was increased after treatment, though the difference was not statistically significant. Only the mean serum level of vitamin B12 showed significant increase after treatment.

   No statistically significant difference was found between patients on oral hypoglycemics and patients on insulin regarding homocysteine, Vit B12 and folic acid levels (p= 0.831, 0.695, 0.536 respectively).

Correlations:

   Although the age of the patients did not significantly correlate with FBS, PPBS, HbA1c, homocysteine, folic acid or vitamin B12 levels, the duration of diabetes had a significant positive correlation with PPBS, HbA1c and homocysteine levels, (P= 0.019, 0.005 and 0.000 respectively) (Table 3).

   A significant positive correlation was also found between homocysteine level and PPBS and HbA1c, (P= 0.019 and 0.001 respectively). Vitamin B12 and Folic acid levels were significantly positively correlated (p= 0.000) (Table 4).

   No correlation was found between the type of neuropathy (revealed by nerve conduction studies) and fasting and postprandial blood sugar levels or the HBA1c (p = 0.439, 0.321, 0.188 respectively). Also it did not correlate with homocysteine, vitamin B12 and folic acid levels (p = 0.808, 0.126, 0.464 respectively).

   A significant positive correlation was detected between the neuropathy impairment score (NIS) and the post prandial sugar and HA1c (p = 0.009, 0.04 respectively; however, the correlation between NIS and homocysteine, folic acid and vitamin B12 was non significant (p = 0.124, 0.366, 0.632 respectively).
Table 1. Range, mean and SD of Homocysteine, folic acid and Vitamin B12 in patient and control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (No.= 26)</th>
<th>Controls (No.= 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine level (µmol/L)</td>
<td>2.5 – 27</td>
<td>11.13 ± 6.98</td>
<td>2.4 – 6.2</td>
</tr>
<tr>
<td>Folic acid level (nmol/L)</td>
<td>3 -12.5</td>
<td>7.10 ± 2.71</td>
<td>3 -14.5</td>
</tr>
<tr>
<td>Vitamin B12 level (pmol/L)</td>
<td>75 – 750</td>
<td>393.73 ± 181.61</td>
<td>300 – 1500</td>
</tr>
</tbody>
</table>

** Highly significant *statistically significant

Table 2. Mean and SD of Homocysteine, folic acid and Vitamin B12 in 15 diabetic patients before and after treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine level (µmol/L)</td>
<td>7.460 ± 4.18</td>
<td>6.550 ± 3.51</td>
<td>0.604</td>
</tr>
<tr>
<td>Folic acid level (ng/L)</td>
<td>6.170 ± 2.41</td>
<td>7.720 ± 2.74</td>
<td>0.196</td>
</tr>
<tr>
<td>Vitamin B12 level (pg/L)</td>
<td>278.70 ± 130.14</td>
<td>682.00 ± 583.74</td>
<td>0.047*</td>
</tr>
</tbody>
</table>

*statistically significant

Table 3. Correlation between laboratory data and age and duration of illness.

<table>
<thead>
<tr>
<th>AGE OF PATIENT</th>
<th>DURATION OF ILLNESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>FBS</td>
<td>-0.089</td>
</tr>
<tr>
<td>PPBS</td>
<td>-0.067</td>
</tr>
<tr>
<td>HbA1c</td>
<td>-0.006</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>0.047</td>
</tr>
<tr>
<td>Folic acid</td>
<td>-0.145</td>
</tr>
<tr>
<td>Vit. B12</td>
<td>-0.017</td>
</tr>
</tbody>
</table>

| R              | P                   |
| FBS            | 0.247               | 0.224            |
| PPBS           | 0.456               | 0.019*           |
| HbA1c          | 0.592               | 0.001**          |
| Homocysteine   | -0.029              | 0.887            |
| Folic acid     | 0.736               | 0.000**          |
| Vit. B12       | 0.704               | 0.074            |

** Highly significant *Statistically significant

Table 4. Correlation between laboratory data in diabetic patients.

<table>
<thead>
<tr>
<th></th>
<th>Homocysteine</th>
<th>Folic acid</th>
<th>Vit. B12</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>FBS</td>
<td>0.247</td>
<td>0.022</td>
<td>0.051</td>
</tr>
<tr>
<td>PPBS</td>
<td>0.456</td>
<td>0.019*</td>
<td>0.061</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.592</td>
<td>0.001**</td>
<td>0.055</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>-0.029</td>
<td>0.887</td>
<td>-0.078</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0.736</td>
<td>0.000**</td>
<td></td>
</tr>
<tr>
<td>Vit. B12</td>
<td>0.704</td>
<td>0.074</td>
<td></td>
</tr>
</tbody>
</table>

** Highly significant *statistically significant

DISCUSSION

Elevated plasma levels of homocysteine is accused for increasing the risk for atherosclerosis, stroke, peripheral neuropathy, cognitive impairment in elderly, possibly Alzheimer's disease, and neural tube defects in pregnant women. Distal polyneuropathy is a major complication of diabetes mellitus, and may lead to lower limb amputations. Both metabolic and vascular abnormalities may contribute to the development of impaired nerve function in diabetic patients. Since, Hyperhomocysteinemia and type 2 diabetes mellitus (NIDDM) are both associated with premature vascular disease, we tried to investigate the association between homocysteine and the presence of neuropathy in type 2 diabetic patients. In our study, plasma homocysteine level was found to be significantly higher in diabetic patients with neuropathy compared to healthy controls. Our findings agreed with Ambrosch and colleagues, who...
estimated homocysteine level in 65 patients with type 2 diabetes; 43 of them had diabetic neuropathy, they found that the frequency of hyperhomocysteinemia was significantly increased in neuropathic patients rather than patients without neuropathy which concluded that homocysteine is independently associated with the prevalence of diabetic neuropathy in a collective of Type 2 diabetic patients.

In another large prospective study working on a group of patients with diabetic complications; Cohen and associates24, found that total homocysteine (tHcy) was independently associated with diabetic autonomic neuropathy (DAN), but not associated with diabetic sensorimotor peripheral neuropathy (DSPN) They conclude that hyperhomocysteinemia may be a risk factor for DAN but not for DSPN. This relationship may be related to differential small fiber injury.

On the contrary, a recent study20 conducted on 155 diabetic patients with type 2 diabetes mellitus concluded that homocysteinemia is probably not related to the prevalence of peripheral neuropathy in diabetics. This study divided the patients into two groups (Group I: tHcy ≥ 15 micromol/l and Group II: tHcy <15 micromol/l) and found that the prevalence of peripheral neuropathy was similar in both groups. A similar conclusion was also reported by Hoogeveen and colleagues21, who found that hyperhomocysteinaemia is not related to risk of distal somatic polyneuropathy in NIDDM.

Plasma folate and vitamin B12 influence homocysteine metabolism as co-substrate and cofactor, respectively. Homocysteine level is inversely related to plasma levels of these substances. Inadequate levels of these vitamins have important health consequences which could be independent of their role in homocysteine metabolism.19,22

The benefit of vitamin B complex supplements in certain neurological disorders is a point of controversy. In our study, plasma serum folic acid and vitamin B12 levels were significantly lower in diabetic patients compared to controls. And in the group of patients who received vitamin B12 and folic acid supplements; only the mean serum level of vitamin B12 showed significant increase after treatment which was associated with clinical improvement, while the lowering of homocysteine levels and the increase in the mean serum folic acid levels after treatment were insignificant Our results agreed with Flynn and colleagues22, who demonstrated in their Longitudinal Aging Study that B12 supplementation (100 microgram by mouth daily) was effective in alleviating hyperhomocysteinaemia in those patients with a baseline B12 level < 350 (pg/L).

In The Homocysteine Lowering Trialists’ Collaboration, meta-analysis of 12 clinical trials,24,25 it was shown that folic acid by mouth (0.5−5 mg daily) resulted in a reduction of Hcy by 25%, the addition of 0.5 mg vitamin B12 by mouth daily reduced the Hcy levels by another 3% to 10% over the reduction with folic acid alone.

On the other hand, supplements combining folic acid and vitamins B9 and B12 did not reduce the risk of major cardiovascular events in patients with coronary artery disease7 (CAD). Nusier and El-Dawairi26 also approved that hyperhomocysteinemia is considered a risk for CAD development, however, vitamin B12 and folic acid supplements did not reduce the risk of myocardial infarction in such patients.

An interesting point was revealed by the study done by Morris et al.27, who found that intake of vitamin B12 improves cognitive decline while folic acid supplement is associated with more cognitive decline in the elderly. They concluded that folic acid may mask unrecognized B12 deficiency in old age, and the supply of folic acid in elderly may exaggerate cognitive decline by masking thus increasing B12 deficiency.

In our study, no significant correlation was found between serum homocysteine level and the serum levels of folic acid and vitamin B12, also there was clinical improvement of the patients who received supplement of B12 vitamin despite insignificant reduction of homocysteine level after treatment. These observations may lead to an important question whether the effect of vitamin B deficiency on the nervous system is only mediated through elevation of homocysteine or may be related to other independent mechanisms. Evidence has been provided by clinical studies that vitamins B complex decrease oxidative stress by increasing the level of S-adenosyl methionine (SAM). SAM increases the production of glutathione, decrease lipid peroxidation and prevent neuronal death in an experimental model of ischemia. Vitamins B deficiency produce a low ratio of SAM and SA homocysteine which causes DNA damage and thereby apoptosis which is an important explanation for homocysteine neurotoxicity.28

In the present study, no significant correlation was detected between age of patients and homocysteine level. However, most previous studies showed that the mean homocysteine concentrations were higher at older ages. For every 20 years of age, Hcy increases on average by 1.3 μmol/L.29,30 Failure of our study to detect correlation between age and homocysteine level is attributed to the small sample size, narrow age range of our sample (37-58 years) and no old aged subjects were included.

No significant difference was detected between male and female patients regarding mean levels of homocysteine, however, observations from published studies showed that plasma homocysteine concentrations are increased in men more than women.29,31 Men have average 1 μmol/L higher Hcy values than women. Higher homocysteine
concentrations in males could be attributed to the large muscle mass and greater creatine phosphate synthesis in men rather than women, also to the lowering effect of estrogens in women and differences in vitamin status and homocysteine formation between sexes. We did not find significant correlation between sex and homocysteine level possibly because of the small sample size included in this study.

In our patients, Homocysteine level was positively correlated to the duration of DM, post prandial blood glucose and HbA1c, which indicate that proper control of diabetes may play a role in lowering homocysteine level, and subsequently decrease risk of diabetic complications including peripheral neuropathy.

In conclusion, homocysteine is associated with the presence of diabetic neuropathy in Type 2 diabetic patients. However, our study is a small scale study, and larger community-based studies are probably needed to further clarify the role of hyperhomocysteinemia as a clinically significant modifiable risk factor for the development of neuropathy in patients with type 2 DM and to examine the value of vitamin B complex supplements especially B12, B6 and folic acid in the management of diabetic neuropathy.

REFERENCES


المختصر العربي

استهدف هذا البحث دراسة العلاقة بين نسبة مستويات الحمض الأميني الديوكسي بروتين وحمض الفوليك وفيتامين B12 في الدم عند مرضى التهاب الأعصاب الطرفية الناتج عن اصابات مرضي السكر، ودراسة ارتباط هذه العلاقة بين المرض وعمر المرضى ومستوي السكر في الدم. وقد أجري البحث على 26 مريضاً بالسكري من النوع غير المعتمد على الأنسولين - نوع 2 - و16 فرداً صحياً كمجموعة مقارنة.

وقد خضع مرضى السكر إلى:

1. الكشف الإكلينيكي الفائق، مع استخدام مقياس شدة التهاب الأعصاب الطرفية المعدل.
2. التحاليل المعملية التي اشتملت على: تحليل روتيني، وتحليل سكر الدم، وتحليل هيموجلوبين السكري.
3. نسبة الديوكسي بروتين وحمض الفوليك وفيتامين B12 في مصل الدم.
4. تخطيط الأعصاب الطرفية للفخذ، والقدم، والصدى لفحص الأصابات.

وقد تخلصت أبحاث البحث في النتائج الآتية:

- وجود فارق ذو دلالة إحصائية بين مرضى السكر، والمجموعة المثالية من حيث ارتفاع نسبة قياس مستويات الحمض الأميني الديوكسي بروتين والديوكسي بروتين وفيتامين B12 في المرضى.
- انخفاض نسبة حمض الفوليك وفيتامين B12 عند النساء مقارنة بذكورهما عند الرجال.
- وجود علاقة ذات دلالة إحصائية موجبة بين قياسات دم الديوكسي بروتين في الدم، ومدة المرض، ومستويات السكري بالدم، فيما لم توجد علاقة ذات دلالة إحصائية بين مستوي الديوكسي بروتين وفيتامين B12 في مصل الدم، أو نوع التغذية والأعصاب الطرفية عند المرضى.