The Clinical Effect of Triglyceride Glucose index, an insulin Resistance Marker, on Predicting Paclitaxel-induced Neuropathy

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Abstract

**Objectives:** Neuropathy is one of the most common side effects in the treatment of paclitaxel. Neuropathy, which develops with the treatment of paclitaxel, cisplatin, and oxaliplatin, is a limiting factor in the treatment and may lead to the termination of the patient’s treatment. The metabolic consequences of chemotherapy have not been extensively studied. It is known that insulin resistance and hyperglycemia develop in a subgroup of patients. Triglyceride Glucose index (TyG) index is used as an insulin resistance marker. In our study, we aimed to examine the relationship between insulin resistance and neuropathic pain due to paclitaxel chemotherapy.

**Methods:** The blood lipid profile, hemogram profile and biochemical parameters routinely checked from the histopathologically diagnosed cases over 18 years of age were scanned and recorded between 06.01.2017 - 09.01.2021. Before the first chemotherapy, before the third month of chemotherapy, serum glucose, high-density lipoprotein, low-density lipoprotein in patients who developed neuropathy within 3 months and did not develop neuropathic pain in patients who underwent paclitaxel (paclitaxel 80 mg / m2 12 weeks 1 per week) chemotherapy protocol due to cancer diagnosis, triglyceride, total cholesterol and hemogram parameters were recorded by retrospective file scanning method. Triglyceride glucose index (TyG index (mg/dl)) = \( \ln \left( \frac{\text{fasting triglyceride (mg/dl) x fasting blood glucose (mg/dl)}}{2} \right) \) Calculated TyG index 4.49 and higher was evaluated as insulin resistance Neuropathy pain score was calculated with the DN4 neuropathic pain questionnaire, which is a validated test.

**Results:** In our study, we found that the TyG index was higher in patients who developed neuropathic pain before paclitaxel treatment was started, compared to those who did not develop neuropathic pain.

**Conclusion:** We believe that more comprehensive studies are needed by increasing the number of patients on the etiopathogenesis of the neuropathy development mechanism.

**Keywords:** Cancer, neuropathy, paclitaxel, triglyceride glucose index

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In recent years, paclitaxel has been among the most important chemotherapeutics. Paclitaxel provides microtubule stabilization. It is used in many tumor types as well as in the treatment of breast cancer and in the next steps. The efficacy of paclitaxel in both adjuvant and neoadjuvant therapy has been proven in many Phase 3 randomized studies. Neupathy is one of the most common side effects in paclitaxel treatment. Neuropathy, which develops with treatment with paclitaxel, cisplatin, and oxaliplatin, is a limiting factor in the treatment and may lead to the termination of the patient’s treatment. The metabolic consequences of chemotherapy have not been extensively studied. It is known that insulin resistance and hyperglycemia develop in a subgroup of patients. Triglyceride Glucose index (TyG) index is used as an insulin resistance marker. In our study, we aimed to examine the relationship between insulin resistance and neuropathic pain due to paclitaxel chemotherapy.
factor in the treatment and may cause the patient to terminate the treatment. Neuropathy has a negative effect on quality of life.[2] Painful neuropathy may occur in 25-56% of taxan treatment.[3]

Epiodemiological studies have found a relationship between chronic pain and glucose metabolism. It has been shown that hyperglycemia can trigger hyperalgesia. It has been determined that post-diabetic hyperalgesia induced by stz in rats can occur not only with hyperglycemia, but also with the effect of insulin on neurons, as well as pain hyperalgesia.[4]

Glucocorticoids are drugs commonly used in cancer patients. It is used in the treatment of nausea and in premedication before treatment chemotherapy. Glucocorticoids cause changes in several steps in the insulin signaling pathway. As a result of the use of glucocorticoids, hyperglycemia and insulin resistance are very common as side effects. Insulin resistance develops in approximately 30% of patients as a result of glucocorticoids.[5,6]

A significant increase in total and central adiposity and insulin resistance was found in a study conducted on 99 women who received chemotherapy for breast cancer treatment.[7] In a retrospective study, 23% of colon cancer patients treated with 5FU had hyperglycemia (11% impaired fasting glucose, 12% diabetes). The development of diabetes was found to occur in 75% of the patients, while chemotherapy treatment was continued, while 25% of them occurred one year later.[8] The metabolic consequences of chemotherapy have not been extensively studied. It is known that insulin resistance and hyperglycemia develop in a subgroup of patients. The Tyg index is used as an insulin resistance marker.[9] In our study, we aimed to examine the relationship between insulin resistance and neuropathy due to paclitaxel chemotherapy. This is the first study in literature.

**Methods**

The blood lipid profile, hemagram profile and biochemical parameters routinely checked from the histopathologically diagnosed cases over 18 years of age were scanned and recorded between 06.01.2017-09.01.2021. Before the first chemotherapy, before the third month of chemotherapy, serum glucose, high-density lipoprotein, low-density lipoprotein in patients who developed neuropathic pain within 3 months and did not develop neuropathic pain in patients who underwent paclitaxel (paclitaxel 80 mg/m² 12 weeks 1 per week) chemotherapy protocol due to cancer diagnosis, triglyceride, total cholesterol and hemogram parameters were recorded by retrospective file scanning method. Triglyceride glucose index (TyG index (mg/dl)) = ln [fasting triglyceride (mg/dl) x fasting blood glucose (mg/dl) /2] Calculated TyG index 4.49 and higher was evaluated as insulin resistance

Neuropathy pain score was calculated with the DN4 neuropathic pain questionnaire, which is a validated test. It was evaluated as neuropathic pain over 4 points in the pain questionnaire. Validity and reliability in Turkish was done by Ünal et al.[10] Neuropathic pain score of insulin resistance was calculated by DN4 The effect on pain will be investigated. The ethics committee of the study was confirmed by Afyon Health Sciences University, Clinical Research Ethics Committee with the number 505-2011-KAEK-2.

**Statistical Analysis**

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum) as well as the distribution of the data were evaluated with the Shapiro-Wilk Test. The Mann-Whitney U Test was used for two-group comparisons of quantitative data. Wilcoxon test was used for two-period comparisons. Significance was evaluated at p<0.01 and p<0.05 levels.

**Results**

The age value ranged from 36 to 82, with an average of 59.83±12.48 years. The TyG-Index value before paclitaxel ranged from 4.34 to 5.83, with a mean of 4.91±0.34. The value after the TyG-Index ranged between 4.33 and 5.54, with a mean of 5±0.32 (Table 1).

The age value does not show a statistically significant difference according to the neuropathy status (p>0.05). The body surface area value does not show a statistically sig-

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**Table 1. Measurement averages**

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Min-max (Median)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>59.83±12.48</td>
<td>36-82 (61)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.71±0.22</td>
<td>1.09-2.23</td>
</tr>
<tr>
<td>TyG-Index paclitaxel pre-treatment</td>
<td>4.91±0.34</td>
<td>4.34-5.83 (4.9)</td>
</tr>
<tr>
<td>TyG-Index paclitaxel post-treatment</td>
<td>5±0.32</td>
<td>4.33-5.54 (4.99)</td>
</tr>
</tbody>
</table>

SD: Standart deviation; Min: Minimum; Max: Maximum; BMI: Body mass index; TyG-Index: Triglyceride glucose index

**Table 2. Neuropathy status**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Neuropathic pain</td>
<td>No</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>62.1</td>
</tr>
</tbody>
</table>

37.9% (n=11) of the participants did not have neuropathy and 62.1% (n=18) did
significant difference according to the neuropathy status (p>0.05) (Table 2). The pre-chemotherapy TyG-index value of the group without neuropathy was found to be lower than the group with neuropathy, which was statistically significant (p=0.001; p<0.05). The value of TyG-index after chemotherapy does not show a statistically significant difference according to neuropathy status (p>0.05) (Table 3).

### Discussion

In our study, we found that the TyG index was higher in patients who developed neuropathic pain before paclitaxel treatment was started, compared to those who did not develop neuropathic pain. Insulin resistance is thought to play an important role in the development of peripheral neuropathy in metabolic syndrome. It is known that high glucose levels in the blood cause nerve damage.\[^{11,12}\]

Diabetic patients undergoing chemotherapy treatment may have a higher risk of neuropathy. Diabetic patients were excluded from most studies of chemotherapy-induced neuropathy. Schneider et al.\[^{13}\] They found glycemic instability and an increased risk of obesity and neuropathy in patients who received taxane group chemotherapy for breast cancer treatment. In the study conducted by Barrio et al.,\[^{14}\] the incidence of neuropathy was found to be higher in patients who received taxane chemotherapy compared to those who did not have diabetes. Our study is compatible with the literature. Neuropathy of diabetic patients should be followed more closely under taxane treatment.\[^{14}\] Mitochondrial dysfunction and oxidative stress are involved in the pathophysiology of insulin resistance in metabolic tissues.\[^{16}\] Insulin plays a role in regulating mitochondrial metabolism and oxidative capacity with PI3K/Akt signal.\[^{15,16}\] It has been thought that disruption of insulin signaling due to insulin resistance makes peripheral nerve neurons more vulnerable to metabolic conditions such as hyperglycemia and contributes to the development of neuropathy.\[^{17,18}\]

Metabolic syndrome dyslipidemia is involved in the pathogenesis of diabetes cancer formation. Neurons are sensitive to insulin.\[^{19}\] Neuropathy insulin resistance is involved in the pathogenesis of neurological diseases. The study of chemotherapy-induced neuropathy in cancer patients with diabetes comorbidity is limited. We think that it would be appropriate to evaluate insulin resistance while applying a chemotherapy regimen that develops neurotoxicity, such as the taxane group, and to follow up the patients with insulin resistance more closely in terms of neuropathy risk. It may be the subject of research that it may provide a protective effect on the development of paclitaxel-induced neuropathy in the treatment of insulin resistance. We believe that more comprehensive studies are needed by increasing the number of patients.

### Disclosures

**Acknowledgements:** The authors are thankful to the Afyon Private Parkhayat Hospital Department of Medical Oncology in study was performed.

**Ethics Committee Approval:** The study was approved by The Afyon Health Sciences University Clinical Research Ethics Committee (Date: 05/11/2021, No: 505-2011-KAEK-2).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.


### References


2. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: prevention and treat-