

Original Research Article

The Clinical Effect of Triglyceride Glucose Index, an Insulin Resistance Marker, in Predicting Neuropathy Induced by the FOLFOX Chemotherapy Protocol

ABSTRACT

Objective: FOLFOX chemotherapy protocol is a chemotherapeutic agent used in both adjuvant and **palliative**(nothing called palliative chemotherapy , may use term of neoadjuvant and adjuvant chemotherapy instead) chemotherapy of many malignancies such as colon, rectum, stomach, gallbladder, and pancreatic cancer. Despite its therapeutic efficacy, neuropathy is the most dose-limiting factor. The treatment of neuropathy has not been determined yet. Many clinical studies are ongoing for the treatment and prevention of neuropathy. In our study, we aimed to examine the relationship between insulin resistance and neuropathic pain due to FOLFOX chemotherapy protocol.

Material and Method: The triglyceride glucose index (TyG-I) before the first chemotherapy, at the 3rd and 6th months of the patients who developed neuropathic pain within 6 months and did not develop neuropathic pain in the patients who underwent FOLFOX chemotherapy protocol due to the diagnosis of cancer, was calculated. Neuropathy pain score was calculated using a validated test, the DN4 neuropathic pain questionnaire. In the pain questionnaire, it was evaluated as neuropathic pain over 4 points. The difference between the patients who developed neuropathic pain and those who did not develop neuropathic pain was evaluated. The effect of TyG-I, an insulin resistance marker, on neuropathic pain was examined.

Conclusion and Discussion: In our study, no difference was found between chemotherapy-induced neuropathic pain and TyG index in patients who underwent FOLFOX chemotherapy protocol. Additional risk factors in the pathophysiology of oxaliplatin-induced neuropathy are limited in the literature. Studies in the literature have not found a relationship between oxaliplatin-induced neuropathy and diabetes. Additional risk factors affecting the development of chemotherapy-induced neuropathy still continue to be the subject of research.

Keywords: FOLFOX, cancer, Neuropathy, TyG index

INTRODUCTION

FOLFOX chemotherapy protocol is a chemotherapeutic agent used in both adjuvant and palliative chemotherapy of many malignancies such as colon, rectum, stomach, gallbladder, pancreatic cancer. Despite its therapeutic efficacy, neuropathy is the most dose-limiting factor. The treatment of neuropathy has not been determined yet. Many clinical studies are ongoing for the treatment and prevention of neuropathy.

Epidemiological 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 streptozotocin in rats can occur not only with hyperglycemia, but also with the effect of insulin on neurons, as well as pain hyperalgesia [1]. Glucocorticoids are drugs commonly used in cancer patients. It is used in the treatment of nausea and in premedication before chemotherapy treatment. 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 glucocorticoid use [2,3].

In a study conducted on 99 women who received chemotherapy for breast cancer treatment, a significant increase in total and central adiposity and insulin resistance was found [4]. In a retrospective study, it was found that 23% of colon cancer patients treated with 5FU had hyperglycemia (11% impaired fasting glucose, 12% diabetes) [5].

The metabolic consequences of chemotherapy have not been extensively studied. It is known that insulin resistance and hyperglycemia developed in a subgroup of patients. In our study, we aimed to examine the relationship between insulin resistance and neuropathic pain developing due to FOLFOX chemotherapy protocol. It will be studied for the first time in the literature.

MATERIAL METHOD

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 until 01.06.2017 - 01.09.2021. Due to cancer diagnosis, FOLFOX (oxaliplatin (85 mg/m²) iv 2-

hour infusion 1st day, leucovorin (400 mg/m²) iv 2-hour infusion 1st day, 5-FU (400 mg/m²) iv 15-minute infusion 1. day 5-FU (2400 mg/m²) with 48-hour infusion, whose cycles were performed in 2 weeks 1) in patients who underwent chemotherapy protocol, and in patients who developed neuropathic pain within 6 months and did not develop neuropathic pain, serum glucose before the first chemotherapy, at the 3rd and 6th months before chemotherapy, High-density lipoprotein, low-density lipoprotein, 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]. TyG index of 4.49 and above 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 Ünal et al. made by [6]. Ethics committee approval of the study was accepted by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee with the approval of the ethics committee on 11.05.2021, meeting number 2021/12 and number 505-2011-KAEK-2.

STATISTICS

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 the comparison of the quantitative data between two groups. The Wilcoxon test was used for the comparisons of the two periods. Significance was evaluated at $p < 0.01$ and $p < 0.05$ levels.

RESULTS

The age value ranged between 30 and 80, with an average of 61.66 ± 11.46 years. Body surface area value ranged between 1.45 and 187, with an average of 8.49 ± 32.2 . Its pre-TyG-I value ranged between 4.47 and 5.54, with a mean of 4.97 ± 0.3 . The value after TyG-I varied between 4.45 and 5.68, with a mean of 4.99 ± 0.3 . (table 1). Of the participants, 31.4% (n=11) did not have neuropathy and 68.6% (n=24) did.(table 2).

Age value does not show a statistically significant difference according to neuropathic pain status ($p > 0.05$). Body surface area value does not show a statistically significant difference

according to neuropathic pain status ($p>0.05$). The pre-TyG-I value does not show a statistically significant difference according to neuropathic pain status ($p>0.05$). According to the neuropathic pain status, the value after tyg-i does not show a statistically significant difference ($p>0.05$) (table3).

Discussion

Chemotherapy treatment is still one of the most important treatment modalities. Oxaliplatin in colorectal cancer and taxan group agents in breast cancer treatment are the main treatments in adjuvant treatment. In both, one of the main limiting and side effects is neuropathy. And it has a negative effect on the quality of life of patients. There is no preventive and curative treatment modality yet. In our study, no difference was found between chemotherapy-induced neuropathic pain and TyG index in patients who underwent FOLFOX chemotherapy protocol. Uwah et al. no relationship was found between oxaliplatin-induced neuropathy and diabetes [7]. In their study, Zribi et al. found that diabetes had no effect on oxaliplatin-induced neuropathy, which was consistent with our study [8]. 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 [9,10] and the risk of neuropathy may be higher in diabetic patients receiving chemotherapy. Diabetic patients were excluded in most studies of chemotherapy-induced neuropathy Schneider et al. They found glycemic instability and an increased risk of obesity and neuropathy in patients who received taxane group chemotherapy for breast cancer treatment [11]. In the study conducted by Barrio et al., the incidence of neuropathy was found to be higher in patients receiving taxan chemotherapy compared to non-diabetic patients [12].

In a meta-analysis by Gu et al, a significant relationship was found between chemotherapy-induced neuropathy and diabetes, except for the oxaliplatin treatment subgroup [13]. Different chemotherapeutic agents can cause damage to neurons by different mechanisms. Additional risk factors affecting the development of chemotherapy-induced neuropathy still remain the subject of research.

REFERENCES

1. Romanovsky D, Hastings SL, Stimers JR, Dobretsov M. Relevance of hyperglycemia to early mechanical hyperalgesia in streptozotocin-induced diabetes. *J Peripher Nerv Syst.* 2004 Jun;9(2):62-9. doi: 10.1111/j.1085 9489.2004.009204.x.
2. Pilkey J, Streeter L, Beel A, Hiebert T, Jou XL. Corticosteroid-Induced Diabetes in Palliative Care. *J Palliat Med.* 2012 Jun;15(6):681-9. doi: 10.1089/jpm.2011.0513.
3. Ariaans G, S. de Jong, Gietema JA, Lefrandt JD, E.G.E. de Vries, Jalving M. Cancer-drug induced insulin resistance: Innocent bystander or unusual suspect. *Complications of Treatment.* 2015; Volume 41, Issue 4, P376-384.
4. Carolina J, MotaaJoao MG, Felipe ML, et al. Chemotherapy negatively impacts body composition, physical function and metabolic profile in patients with breast cancer Author links open overlay panel *Clin Nutr.* 2021 May;40(5):3421-3428. doi: 10.1016/j.clnu.2020.11.020.
5. Feng JP, Yuan XL, Li M, et al. Secondary diabetes associated with 5-fluorouracil-based chemotherapy regimens in non-diabetic patients with colorectal cancer: results from a single-centre cohort study. *Colorectal Dis.* 2013 Jan;15(1):27-33. doi: 10.1111/j.1463-1318.2012.03097.x.
6. Unal-Cevik I, Sarioglu-Ay S, Evcik DA. Comparison of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: validity and reliability of the Turkish version of DNA. *J Pain.* 2010;11(11):1129-35.
7. Augusta NU, Joan A, John CL, Sherry P, William T. The effect of diabetes on oxaliplatin-induced peripheral neuropathy. *Clin Colorectal Cancer.* 2012 Dec;11(4):275-9
8. Aref Z, Sonia BN, Syrine H, Jihen A, Sana F, Mehdi Balti, and Abderrazek Haddaoui. Oxaliplatin-induced peripheral neuropathy risk factors and management in Tunisian population. *Pan Afr Med J.* 2020; 35: 83.
9. Soroku Y, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? *J. Diabetes Investig.* 2011;2,18–32.

10. Dewanjee S, Das, S.; Das, A.K.; Bhattacharjee, N.; Dihingia, A.; Dua, T.K.; Kalita, J.; Manna, P. Molecular mechanism of diabetic neuropathy and its pharmacotherapeutic targets. *Eur. J. Pharmacol.* 2018; 833, 472–523.
11. Schneider BP, Zhao F, Wang M, et al. Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. *J. Clin. Oncol.* 2012; 30.
12. De La Morena Barrio P, Vicente C, González-Billalabeitia MA, et al. Delayed recovery and increased severity of paclitaxel-induced peripheral neuropathy in patients with diabetes. *J. Natl. Compr. Cancer Netw.* 2015;13, 417–423.
13. Jialin G, Hong L, Chen C, et al. Diabetes mellitus as a risk factor for chemotherapy-induced peripheral neuropathy: a meta-analysis. *Supportive Care in Cancer.* 2021;29,7461–7469.

Table 1. Measuring Averages

	<i>Ort±Ss</i>	<i>Min-Max (Median)</i>
<i>Age</i>	61,66±11,46	30-80 (62)
<i>Body Surface Area</i>	8,49±32,2	1,45-187 (1,74)
<i>Before TYG-I</i>	4,97±0,3	4,47-5,54 (4,99)
<i>After TYG-I</i>	4,99±0,3	4,45-5,68 (4,95)

Table 2: Distribution by Neuropathic Pain Status

		N	%
Neuropathic Pain Condition	No	11	31,4
	Yes	24	68,6

Table 3: Comparison of Measurements According to Neuropathic Pain Status

	<i>Neuropathic Pain Condition</i>	<i>n</i>	<i>Ort±Ss</i>	<i>Min-Max (Median)</i>	<i>p</i>
Age	No	11	57,73±12,31	30-70 (60)	0,213
	Yes	24	63,46±10,84	45-80 (65,5)	
Body surface area	No	11	1,68±0,17	1,45-1,92 (1,73)	0,145
	Yes	24	11,6±38,74	1,48-187 (1,75)	
TyG index before treatment	No	11	4,87±0,27	4,47-5,23 (4,91)	0,207
	Yes	24	5,01±0,3	4,47-5,54 (5,05)	
TyG index post treatment	No	11	4,98±0,28	4,45-5,33 (4,97)	0,840
	Yes	24	4,99±0,31	4,53-5,68 (4,93)	

*Mann Whitney U Testi *p<0,05 **p<0,01*

UNDER PEER REVIEW