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The significance of neutrophil/lympocyte ratio and platelet/lymphocyte ratio in predicting diabetic polyneuropathy and neuropathic pain severity as inflammatory factors

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Background and purpose – Neuropathic pain may appear as one of the first symptoms that take the patient to the physician in type 2 diabetes, which can be asymptomatic for years. Although it is accepted that diabetes is a trigger for vascular inflammation, it has been suggested that inflammation itself may trigger diabetes. In our study, we aimed to investigate the relationship between diabetic polyneuropathy and neuropathic pain and inflammatory markers.
Methods – The study included 44 healthy controls, 46 diabetic patients with normal electroneuromyography (ENMG) and 44 diabetic patients with polyneuropathy detected in ENMG. Sedimentation, C-reactive protein (CRP), Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLO) and mean platelet volume (MPV) values were recorded in the sera of the patients. The Douleur Neuropathic 4 (DNP4) Questions was used to evaluate the presence of neuropathic pain in the patients, and the Visual Analogue Scale (VAS) was used to evaluate the severity of pain.
Results – NLR, CRP, sedimentation levels were statistically significantly higher in the DMP+ and DMP– patient groups compared to the control group. PLO and MPV levels were significantly higher in the DMP+ patient

A neutrophil-lymphocyta arány és a thrombocyta-lymphocyta arány mint gyulladásos faktorok jelentősége a diabeteses polyneuropathia és a neuropathiás fájdalom súlyosságának előrejelzésében

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Háttér és cél – A neuropathiás fájdalom az egyik első tünet lehet, ami orvoshoz viszi a beteget 2-es típusú cukorbetegségben, ami évekig tünetmentes lehet. Bár elfogadott, hogy a cukorbetegség érrendszeri gyulladást kiváltó tényező, felmerült, hogy maga a gyulladás is kiválthatja a cukorbetegséget. Tanulmányunkban a diabeteses polyneuropathia és a neuropathiás fájdalom, valamint a gyulladásos markerek közötti kapcsolat vizsgálatát tűztük ki célul.
Módszerek – A vizsgálatba 44 egészséges kontroll, 46 diabeteses beteg normális elektroneuromiográfiás (ENMG) lelettel és 44, ENMG-vel kimutatott polyneuropathiás diabeteses beteg került bevonásra. A betegek szérumából a szedimentáció, a C-reaktív fehérje (CRP), a neutrophil-lymphocyta arány (NLR), a thrombocyta-lymphocyta arány (PLO) és az átlagos thrombocyta-térfogat (MPV) értékeit rögzítettük. A betegeknél a neuropathiás fájdalom jelenlétének értékelésére a Douleur Neuropathic 4 (DNP4) Kérdőívet használtuk, míg a fájdalom súlyosságának értékelésére a vizuális analóg skálát (VAS).
Eredmények – Az NLR, a CRP és a süllyedés szintje statisztikailag szignifikánsan magasabb volt a DMP+ és a DMP– betegcsoportban, mint a kontrollcsoportban. A PLO- és MPV-szintek szignifikánsan magasabbak

group compared to both the DMP– patient group and the control group.

The means of VAS and DN4 scores were statistically significantly higher in the DMP+ patient group than in the DMP– patient group. In the DMP– patient group, the NLR levels of those with neuropathic pain according to the DN4 scale were statistically significantly higher than those without neuropathic pain.

Conclusion – Diabetic neuropathy is one of the common complications of diabetes, affecting about half of patients. Our study shows that NLR, PLO, MPV values can be used as parameters to help us make an easy and fast diagnosis in diabetic polyneuropathy. However, their reliability in the diagnosis of diabetic polyneuropathy should be evaluated with studies to be conducted with larger patient and control groups.

Keywords: diabetic peripheral neuropathy, neuropathic pain, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLO)

voltak a DMP+ betegcsoportban mind a DMP– betegcsoporthoz, mind a kontrollcsoporthoz képest.

A VAS- és a DN4-pontszámok középértékei statisztikailag szignifikánsan magasabbak voltak a DMP+ betegcsoportban, mint a DMP– betegcsoportban. A DMP– betegcsoportban a DN4-skála szerint neuropathiás fájdalomban szenvedők NLR-szintje statisztikailag szignifikánsan magasabb volt, mint a neuropathiás fájdalomban nem szenvedőké.

Következtetés – A diabeteses neuropathia a cukorbetegség egyik gyakori szövődménye, a betegek mintegy felét érinti. Vizsgálatunk azt mutatja, hogy az NLR-, PLO- és MPV-értékek segítségével könnyen és gyorsan felállítható a diabeteses polyneuropathia diagnózisa. Mindazonáltal, ezen értékek megbízhatóságát a diabeteses polyneuropathia diagnózisában nagyobb beteg- és kontrollcsoportokon elvégzendő vizsgálatokkal kell értékelni.

Kulcsszavak: diabeteses perifériás neuropathia, neuropathiás fájdalom, neutrophil-lymphocyta arány (NLR), thrombocyta-lymphocyta arány (PLO)

Type 2 diabetes mellitus (DM) is a worldwide health problem and it is expected that 783.2 million people will be affected with type 2 diabetes mellitus (DM) by 2045[1]. Diabetic polyneuropathy (DPN) and neuropathic pain (NP) due to DPN is one of the most common complications of diabetic neuropathy. Its lifetime incidence in type 2 DM patients is approximately 45%[2]. Neuropathic pain can be asymptomatic for years and it can be one of the first symptoms that can cause the patient with type 2 diabetes to see a physician[3].

Although it is accepted that diabetes is a trigger for vascular inflammation, it has been suggested that inflammation itself may trigger diabetes. It has been proven that increased C-reactive protein (CRP), body mass index (BMI), triglyceride, and glucose levels increase the risk of developing type 2 diabetes[4]. There is some evidence that low-level systemic inflammation is an important determinant in the development and follow-up complications of type 2 DM[5, 6].

Recently, multiple markers and hematological indices, including neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), have been used as markers of the systemic inflammatory response[7, 8]. An increase in NLR levels has been reported as an important marker for the diagnosis of diabetic retinopathy and a risk factor for major cardiovascular cases[9, 10]. In a recent study, NLR has been associated with non-arteritic anterior ischemic optic neuropathy[11]. In our literature review, it is seen that there are studies reporting a significant relationship between NLR and peripheral polyneuropathy in Type 2 DM patients[1, 12]. However, no study was found that evaluated the relationships between NLR and PLR ratio with NP and DPN.

In our study, it is aimed to investigate the relationships between diabetic polyneuropathy and neuropathic pain and NLR and PLR, which are new markers of inflammation.

Methods

Study participants

The study was conducted with 90 patients who visited the neurology clinic of Medical Faculty Hospital at Harran University between January 2017 and May 2017 and were diagnosed with type-2 diabetes by the Polyclinic of endocrinology and metabolism diseases in our hospital. As control groups the study also involved 44 healthy people who were at the same age.

The patients and the control group were informed about the procedure to be performed before the study and they were asked to sign consent forms. The patient and control groups were examined for polyneuropathy by using electroneuromyography (ENMG). Forty six patients with diabetes with normal ENMG and 44 patients with diabetes who were diagnosed with polyneuropathy as a result of ENMG were determined as the patient group. Nerve conduction studies were performed with ENMG to exclude the presence of any polyneuropathy in the healthy control group.

The patients with chronic or acute infection, chronic renal failure, extremity amputation, previous or existing malignancy, entrapment neuropathy detected by ENMG, plexopathy, radiculopathy or having undergone surgery due to it, and other risk factors for peripheral neuropathy (B12 deficiency, hypothyroidism, amyotrophic lateral sclerosis, amyloidosis, connective tissue diseases, vasculitis, chronic alcohol use, drug use, etc.) were excluded from the study. The control group included healthy volunteers who did not have any systemic diseases including diabetes, acute or chronic infection, any long-term drug use (immunosuppressive, antibiotics, antiepileptic drugs etc.), and polyneuropathy, which was excluded by ENMG.

Measurements

The neutrophil/lymphocyte ratio was calculated by dividing the number of neutrophils obtained in the complete blood count of the patient group and the control group by the number of lymphocytes. Similarly, platelet/lymphocyte ratio was calculated by dividing the platelet count by the lymphocyte count. Mean serum glycosylated hemoglobin (HbA_{1c}), sedimentation, CRP, MPV, NLR and PLR values of the patient and control groups were recorded.

Douleur Neuropathique 4 Questions (SN-4) was used to evaluate neuropathic pain and Visual Analogue Scale (VAS) was used to evaluate pain management in patients with diabetes. VAS is a scale used in understanding the severity of pain and in its clinical follow-up. VAS is used to digitize values that cannot be measured numerically. To do so, a line of 10 cm was drawn. The initial endpoint of this line, namely the zero point, was defined as "no pain" and the last endpoint as "severe pain". The patients were asked to indicate where his or her condition fits along this line[13].

The DN4 questionnaire consists of 10 questions, 7 of which are related to symptoms and 3 of which reflect clinical examination findings. In this questionnaire, each yes answer is evaluated as 1 point. Neuropathic pain is acknowledged in patients with a total score of 4 and above[14].

Keypoint electromyography device (Version 2.38, Medtronic Dantec, Skovlunde, Denmark) was used for recording, data saving and analysis. In line with the protocol, more than one motor and sensory nerve conduction studies were performed in both lower extremities and at least one upper extremity. In this context, motor nerve conduction of both peroneal and tibial nerves, and sensory conduction of both medial plantar and peroneal superficial nerves were examined. Likewise, motor and sensory conductions of the median and ulnar nerves in at least one upper extremity were examined.

Statistical analysis

Statistical analyses were performed using the SPSS computer program for Windows Version 11.5 (Statistical Package for the Social Sciences). The metadata were represented with averages ± standard deviations, numbers and percentages. Categorical variables were compared using chi-square test. In the normally distributed constant data comparison, the Student's t-test was used. The patient group was compared with control group via One-Way Anova. In the non-normally distributed group, the Mann-Whitney U test was used. The Kruskal-Wallis test was used to compare more than two independent groups. The correlation among variables was found through Pearson Correlation Test. The results were evaluated at 95% confidence interval and significance was thought at $p<0,05$ level.

Results

The mean age of DM patients with polyneuropathy (DMP+) was 54.59±10.26, the mean age of DM patients without polyneuropathy (DMP–) was 54.69±10.05, and the mean age of the control group was 51.95±9.14. The clinical and demographic characteristics of the patients are given in **Table 1**.

NLR level in DMP+ and DMP– patient group was significantly higher when compared to control group (p=0.020, p1=0.036). NLR level in DMP+ patient group was higher than that of DMP– patient group, but it was not statistically significant. PLR level in DMP+ patient group was significantly higher when compared to both DMP– patient group and control group (p=0.000, p=0.002). Mean serum HbA_{1c} level was significantly higher in DMP+ patient group than in DMP– patient group (p=0.000). Serum CRP level was found significantly higher in both DMP+ patient group and DMP– patient group when compared to control group (p=0.000, p=0.002). However, no statistical significance was seen between DMP+ and DMP– patient groups. DMP+ and DMP– patient groups had significantly higher sedimentation levels than control group. The sedimentation level in DMP+ patient group was higher than in the DMP– patient group, but it was not statistically significant. The MPV level was significantly higher in DMP+ patient

Table 1. *Demographic and clinical characteristics of the groups*

		DMP+ n=44	DMP– n=46	Control n=38	P
Age		54.59 ± 10.26	54.69 ± 10.05	52.60 ± 6.17	0.637
Gender	Male	23 (18.0%)	14 (10.9%)	22 (17.2%)	0.236
	Female	21 (16.4%)	32 (25.0%)	16 (12.5%)	
BMI		26.60 ± 3.66	30.97 ± 5.10	29.21 ± 3.31	0.134
Duration of DM (years)		12.22 ± 6.34	8.54 ± 4.12		0.026
	Drugs used				
	Insulin	7 (15.9%)	2 (4.3%)		
	OAD	18 (0.9)	30 (65.2%)		
	Insulin+OAD	16 (6.4%)	9 (19.6%)		
	Diet	3 (6.8%)	5 (0.9%)		

DMP+: diabetic patients with polyneuropathy, DMP–: diabetic patients without polyneuropathy, BMI: body mass index, OAD: oral antidiabetic drugs

group when compared to DMP– patient group and control group (p=0.018, p=0.001). Mean VAS score was significantly higher in DMP+ patient group than in DMP– patient group (p=0.000, p=0.000). Likewise, mean DN4 score was significantly higher in DMP+ patient group than in DMP– patient group **(Table 2)**.

In DMP– patient group, the NLR levels of those with neuropathic pain (2.52±1.25) according to the DN4 scale were statistically significantly higher than those without neuropathic pain (1.84±0.70) (p=0.023).

There was a significant positive correlation between the VAS scale and DN4 scale results applied to the patients. No significant correlation was observed between other biochemistry markers and VAS **(Table 3)**.

In DMP+ patient group, 7 patients (%15,9) had normal DN4 scale score while 37 patients (%84,1) were found to have NP. In DMP– patient group, 30 patients (65.2%) had normal DN4 scale score whereas 16 patients (34.8%) were found to have NP. Regarding NLR levels, a statistical significance was found between patients with normal DN4 scale score and patients with pathologies (p=0,045). No statistically significant difference was found between other biochemistry markers **(Table 4)**. A significant positive correlation was found between DN4 scores and HbA1c levels (p=0.042) **(Table 5)**.

Discussion

In the development of diabetic polyneuropathy, hyperglycemia, duration of diabetes, old age, hypertension, hypoinsulinemia, hyperinsulinemia, smoking and alcohol use, albuminuria, body mass index, hypercholesterolemia and genetic factors are regarded as major risk factors. Diabetic polyneuropathy is more common in men

Table 2. *Biochemical parameter of the groups*

Parameter	DMP+	DMP–	Control	*P*-value	*P1*-value	*P2*-value
HbA_{1c} (%)	11.24 ± 2.40	8.07 ± 2.18	5.47 ± 0.34	*0.000*	*0.000*	*0.000*
ESR (mm/h)	26.56 ± 16.13	21.97 ± 10.41	13.93 ± 7.93	*0.000*	*0.005*	0.168
CRP (mg/dl)	0.69 ± 0.32	0.60 ± 0.41	0.41 ± 0.20	*0.000*	*0.002*	0.392
MPV	8.58 ± 2.24	7.42 ± 1.07	7.96 ± 1.59	*0.018*	0.798	*0.001*
NLR	2.12 ± 0.97	2.08 ± 0.97	1.62 ± 0.35	*0.020*	*0.036*	*0.965*
PLR	128.58 ± 33.08	109.90 ± 20.19	97.19 ± 20.56	*0.000*	0.063	*0.002*
VAS	5.54 ± 2.06	3.54 ± 2.50				*0.000*
DN4	5.95 ± 2.11	3.26 ± 2.05				*0.000*

HbA_1: glycosylated hemoglobin, ESR: erytrocyhte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, VAS: Visual Analogue Scale, DN-4: Douleur Neuropathic 4 Question , P: comparison between those with polyneuropathy and the control group, P1: comparison between those without polyneuropathy and the control group, P2: comparison between the patient groups with and without polyneuropathy

Table 3. *Correlation between VAS and other variables*

		Variables							
		NLR	HbA1c	CRP	ESR	MPV	DN4	PLR	WBC
VAS	R	0,127	0,037	–0,009	0,049	0,152	*0,750*	–0,066	0,121
	P	0,235	0,732	0,936	0,648	0,152	*0,000*	0,535	0,257

than in women[4, 15]. Similarly, in our study, duration of the disease and male gender were found to be statistically significantly correlated with the development of diabetic polyneuropathy.

Hemoglobin A_{1c} is a marker that shows glucose tolerance and glucose regulation in diabetes, formed by slow and non-enzymatic glycosylation of hemoglobin[16]. In a study involving 1077 diabetic patients, *Abougalambou* et al. found the prevalence of diabetic neuropathy as 54.7%. The average HbA_{1c} levels of the patients in the study were high, and the HbA_{1c} value was a modifiable risk factor for the development of diabetic polyneuropathy[17]. Similarly, in our study, the differences of mean HbA_{1c} value in DMP+ patients was found to be statistically significant when compared to the DMP– patient group and to the control group. In addition, a significant positive correlation was found between DN4 scores and HbA_{1c} levels. These findings show that increased Hba_{1c} levels may pose a risk for the development of polyneuropathy in diabetic patients and that increases in HbA_{1c} levels are associated with the emergence of neuropathic pain symptoms.

Table 4. *Biochemical markers according to DN4 scale results*

Biochemical Markers	DN4 Scale Results	Mean ± SD	*P*-value
HbA1c (%)	Normal	9.09 ± 2.75	0.131
	Neuropathic pain	9.99 ± 2.76	
CRP (mg/dl)	Normal	0.61 ± 0.43	0.548
	Neuropathic pain	0.66 ± 0.31	
ESR (mm/h)	Normal	21.18 ± 15.22	0.091
	Neuropathic pain	26.33 ± 12.11	
MPV	Normal	7.54 ± 1.76	0.053
	Neuropathic pain	8.30 ± 1.83	
NLR	Normal	1.87 ± 0.67	*0.045*
	Neuropathic pain	2.26 ± 1.10	
PLR	Normal Neuropathic pain	119.33 ± 28.79 118.82 ± 28.89	0.934

HbA_1:glycosylated hemoglobin, ESR: erytrocyhte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, P: comparison between the biochemical markers and DN4 Scale results

There are many theories on the pathogenesis of diabetic neuropathy. One of them is oxidative stress and inflammation stemming from it. In many studies, diabetic patients are reported to have high levels of CRP, interleukin (IL) -1, IL-6 and inflammatory cytokine such as tumour necrosis factor (TNF) -α[18–20]. It is a well-known fact that low-level systemic inflammation plays an important role in the development of type 2 DM and microvascular and macrovascular complications of diabetes, including diabetic polyneuropathy[6, 7]. In our study, serum CRP and sedimentation rates were found to be higher in the DMP+ patient group than in the DMP– and control groups.

In a study by *Zaccardi* et al., patients with and without diabetes were compared in terms of MPV levels and it was found that patients with diabetes have significantly higher levels of MPV[21]. In another study by Özşenel et al., patients with diabetes-induced retinopathy and nephropathy and patients without any diabetes-induced complications were compared in terms of MPV rates, but no statistically significant difference was found[22]. Recently, NLR has widely been accepted as biomarker as it shows both high neutrophil levels demonstrating acute inflammation and negative effects of low lymphocyte levels illustrat-

Table 5. *Correlation between DN4 and other variables*

		Variables							
		NLR	HbA_{1c}	CRP	ESR	MPV	DN4	PLR	WBC
DN4	R	0.127	0.037	–0.009	0.049	0.152	*0.750*	–0.066	0.121
	P	0.235	0.732	0.936	0.648	0.152	*0.000*	0.535	0.257

ing physiological stress. The combination of NLR and PLR levels with other inflammatory markers has been reported as a good marker of inflammatory status. In a study by Ünal et al., a close relationship between NLR, PLR, anemia and albuminuria was reported in diabetic patients[23]. In another study by *Peng Luo* et al., NLR rates were examined in Type 2 DM patients as it was thought that chronic systemic inflammation contributes to the development of cardiovascular cases, and DM is a systemic inflammation. It has been suggested that NLR may be an independent risk factor for cerebrovascular diseases[24]. It has also been reported that PLR has a predictive effect for diabetes mellitus and its complications[25, 26].

In our study, NLR, PLR, and MPV levels were found to be statistically significantly higher in the DMP+ patient group compared to the control group. Likewise, PLR and MPV levels were found to be statistically significantly higher in the DMP+ group compared to the DMP– group. However, the NLR value was found to be higher in the DMP+ group than in the DMP– group, but not statistically significantly. These findings demonstrate that NLR, PLR and MPV levels, which are easily and cheaply obtained parameters, can be used as markers to predict the development of diabetic polyneuropathy. We think that the insignificant NLR difference may be due to the small size of our patient group and thus we recommend that it should be investigated in larger patient groups.

Diabetic peripheral neuropathy usually develops gradually and insidiously. It can manifest as pain, numbness, tingling, weakness and balance disorders, which can even lead to amputation[27]. Some patients are asymptomatic at the early stage and EMG examination may be normal even if they have clinical findings, which can lead to neglecting the disease. Neuropathic pain seen in patients with DPN negatively affects their quality of life. Involvement of unmyelinated C, thin myelinated Aδ, thick myelinated Aα, and Aβ-type neuronal fibres are typical. Although the exact order in which these fibres are affected is not known, there is evidence that thin fibres are involved earlier and that neuropathic pain precedes sensory losses and decreased nerve conduction velocity[28]. It has much negative effect on working life, sleeping pattern and life pleasure. Patients with diabetic neuropathy develop anxiety disorders (35%) and depression (28%)[29]. In our study, the VAS pain score was found to be statistically significantly higher in DMP+ patients compared to DMP– patients. The DN4 score was found to be higher in the DMP+ group. When the whole patient population was examined in terms of NLR and DN4 questionnaire, it was found that the NLR levels of the patients with a pathological DN4 score and neuropathic pain were statistically significantly higher than that of the patients with a normal DN4 score. In the DMP– patient group, NLR levels of those with neuropathic pain according to the DN4 scale were found to be significantly higher than of those without neuropathic pain. In line with these findings, we think that in this patient group determined as DMP– as a result of EMG examination, thin fibre neuropathy and related neuropathic pain may be present, and that NLR value can be used as a marker in the diagnosis of early diabetic polyneuropathy in DM patients.

When the VAS score and DN4 score of DMP+ patients in the patient group were examined, it was seen that they had significantly higher scores when compared to DMP– patients. In addition, the VAS and DN4 scores of both patient groups were statistically correlated, supporting each other.

Conclusion

In our study, statistically significant findings were obtained which support many other studies suggesting the factors of HbA_{1c}, CRP, sedimentation increases, and length of disease duration as risk factors for the development of diabetic polyneuropathy. In addition, statistically significant findings were found showing that new inflammatory markers, NLR, PLR and MPV levels, which were the focus of our study, could be markers for the development of DPN. In terms of neuropathic pain, a significant correlation was found between NLR level and DN4 score. This leads us to think that the combination of NLR level and DN4 score may be a good marker for the development of diabetic polyneuropathy.

The systemic complications of diabetes are still major public health problems. Diabetic neuropathy is one of the important complications that negatively affect the quality of life of people with diabetes. Therefore, there is a need for inexpensive and easy-to-access markers that we can use to diagnose neuropathy at an early stage.

There is no study in the literature that reveals the relationship between diabetic neuropathy, neuropathic pain and NLR, PLR and MPV. In this respect, our study is unique. However, the small number of patients in our study is a disadvantageous aspect. Therefore, its reliability in diagnosing patients with diabetic polyneuropathy should be further examined with studies with larger patient and control groups.

DATA AVAILABILITY – Data supporting the findings of this study are available from the corresponding author on request.

DECLARATIONS – The ethics committee of Harran University approved the study.

CONFLICT OF INTEREST – The authors declare no competing interests.

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