FİZİKSEL TIP VE REHABİLİTASYON BİLİMLERİ DERGİSİ
Journal of Physical Medicine and Rehabilitation Sciences

ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.31609/jpmrs.2024-105182

New Inflammatory Indexes in Diabetic Neuropathy

Diyabetik Nöropatide Yeni İnflamatuar İndeksler

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ABSTRACT Objective: The aim of this study was to investigate systemic inflammatory indices in diabetic neuropathy (DN), which is one of the microvascular, common and preventable complications of diabetes that causes morbidity and mortality in Type 2 Diabetes Mellitus (DM) patients. **Material and Methods:** A total of 414 patients with DM were divided into 2 groups according to the presence of DN. Platelet, lymphocyte, monocyte counts, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratios (MLR), systemic inflammatory index (SII), systemic inflammatory response index (SIRI), and hemoglobin A1c (HbA1c) levels were analyzed in each group. **Results:** No difference was found in both groups in terms of age and gender. A total of 207 patients with DN and 207 patients with DM without DN symptoms and findings were included in the study. When the 2 groups were compared, a statistically significant increase in lSII, SIRI, HbA1c level and NLR rate was detected in the DN group ($p<0.001$). A positive correlation was found between SII and SIRI and the HbA1c level. The sensitivity and specificity were 71.69% and 83.33%, respectively, for SII in detecting DN. For SIRI, the sensitivity was 69.04% and the specificity was 62.22%. **Conclusion:** In the DN-positive group, this elevation in systemic inflammation parameters, which are inexpensive and can be easily calculated in routine blood tests, may be helpful in predicting the presence of chronic microvascular disease such as neuropathy.

Keywords: Inflammation; diabetic neuropathy; systemic immune-inflammation index; systemic inflammatory response index

ÖZET Amaç: Bu çalışmanın amacı, Tip 2 diyabet (DM) hastalarında morbidite ve mortaliteye neden olan, diyabetin mikrovasküler, yaygın ve önlenebilir komplikasyonlarından biri olan diyabetik nöropatide (DN) sistemik inflamatuar indekslerin araştırılmasıdır. **Gereç ve Yöntemler:** Tip 2 DM'li 414 hasta DN varlığına göre 2 gruba ayrıldı. Her 2 grupta hastaların serum trombosit, lenfosit, monosit sayıları, nötrofil/lenfosit oranı [neutrophil/lymphocyte ratio (NLR)], trombosit/lenfosit oranı [platelet/lymphocyte ratio (PLR)], monosit/lenfosit oranları [monocyte/lymphocyte ratios (MLR)], sistemik inflamatuar indeks [systemic inflammatory index (SII)], sistemik inflamatuar yanıt indeksi [systemic inflammatory response index (SIRI)], Hemoglobin A1c (HbA1c) seviyeleri değerlendirildi. **Bulgular:** Her 2 grupta yaş ve cinsiyet açısından farklılık saptanmadı. Çalışmaya DN semptom ve bulguları olan 207 DM'li hasta ile nöropati semptom ve bulguları olmayan 207 DM'li hasta dâhil edildi. Her 2 grup karşılaştırdığında DN grubunda SII, SIRI, HbA1c düzeyi ve NLR oranında istatistiksel anlamlı yükseklik saptandı ($p<0,001$). SII ile SIRI ve HbA1c düzeyi arasında pozitif korelasyon bulundu. DN varlığını tespit etmede SII'nin duyarlılığı ve özgüllüğü sırasıyla %71,69 ve %83,33 idi. SIRI için duyarlılık %69,04 ve özgüllük %62,22 idi. **Sonuç:** DN pozitif grupta ucuz olan ve rutin kan testlerinde kolaylıkla hesaplanabilen sistemik inflamasyon parametrelerindeki yükselme, nöropati gibi kronik mikrovasküler hastalık varlığının öngörülmesinde yardımcı olabilir.

Anahtar Kelimeler: İnflamasyon; diyabetik nöropati; sistemik immün inflamasyon indeksi; sistemik inflamasyon yanıt indeksi

Diabetic neuropathy (DN) is a microvascular, widespread complication of diabetes that causes morbidity and mortality in Type 2 Diabetes Mellitus (DM) patients and can be prevented with early diagnosis and treatment. Considering its complications, it is estimated that globally, Type 2 DM will be the 7th leading cause of death by 2030.[1,2]

The exact diagnostic criteria and pathophysiological mechanisms of DN remain unclear. It is thought that disruptions in glucose and lipid

TO CITE THIS ARTICLE:
Tuncer T, Sabaz Karakeçi E. New Inflammatory Indexes in Diabetic Neuropathy. Turkiye Klinikleri Journal of Physical Medicine and Rehabilitation Sciences. 2025;28(2):150-5.

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Peer review under responsibility of Journal of Physical Medicine and Rehabilitation Science.

Received: 18 Aug 2024 ***Received in revised form:*** 22 Jan 2025 ***Accepted:*** 28 Jan 2025 ***Available online:*** 17 Feb 2025

metabolism at the cellular and systemic level lead to the activation of various biochemical abnormal pathways and ultimately to the development of chronic inflammation.[3] Thus far, the most common investigation in the pathophysiology of DN has been on oxidative-nitrosative stress and inflammation. Low-grade inflammation and increased pro- and anti-inflammatory cytokine concentrations and other biomarkers that mobilize the immune system have been described in DN. Chronic low-grade inflammation increases the risk of Type 2 DM, atherosclerosis, neurodegeneration and tumor growth and is associated with decreased functional capacity and life span.[4] The fact that this inflammatory activation results in insulin resistance and metabolic disease can be explained by various reasons. Inflammatory signaling pathways may cause the inhibition of insulin signaling by directly inhibiting serine phosphorylation in the insulin receptor substrate protein.[5] Another factor is that leukocytes released into circulation by inflammatory mediators strengthen the inflammation signaling and tissue remodeling capacity of cells in tissues exposed to cellular stress.[6] Third, secreted inflammatory mediators provide systematic communication with insulin resistance.[6,7]

Important prospective clinical studies have shown a strong association between circulating inflammatory markers and proinflammatory cytokines and the risk of developing Type 2 DM.[8] Recently, complete blood count parameters such as the neutrophil/lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been thought to play an important role in inflammatory diseases.[9-12]

The systemic immune-inflammation index (SII), which is calculated by using platelet, neutrophil, and lymphocyte counts together, and the systemic inflammatory response index (SIRI) are recently defined parameters. In studies, it has been found to be a much more effective marker compared with PLR and NLR in predicting poor prognosis in esophageal and colon cancer and severe disease in cardiac ischaemia.[13-17] SII uses three blood cell subtypes (neutrophils, lymphocytes and platelets) and reflects the balance between inflammation and immunity responding to inflammation.[18,19] Although there are many studies with the SII, which has been shown to be important in malignancy, cardiac and systemic inflammatory rheumatic diseases and pulmonary diseases, there are limited number of studies in DN. In our study, we evaluated the SII-SIRI index in DN.

MATERIAL AND METHODS

In this study, 414 patients diagnosed with Type 2 DM in the Physical therapy and rehabilitation clinic of Elazığ Fethi Sekin City Hospital were analyzed. The study was conducted after obtaining approval from the non-interventional research ethics committee of Fırat University local ethic committee (date: May 25, 2023; no: 2023/09-40). All procedures performed involving human participants were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants included in the study. The number of patients was based on whether the SII parameter would have an effect on predicting the diagnosis of DN, and the number of people who should be included in the study was obtained by power analysis as 414, with 207 people in each group according to the 2-way hypothesis at 95% confidence level (1-α).

Patients were analyzed in two groups as patients with DN and diabetic patients without DN. The diagnosis of DN was confirmed by electromyography, and DN symptoms and signs were present in all patients with DN. Platelet, lymphocyte, monocyte counts, NLR, PLR, MLR and Hemoglobin (HbA1c) levels were analyzed. The SII value was evaluated by (platelet*neutrophil)/lymphocyte count and the SIRI value by (neutrophil*monocyte)/lymphocyte measurement.[20,21] Patients with symptoms and laboratory findings of active infection, concomitant inflammatory rheumatic disease, heart failure, renal and hepatic failure, immunosuppressive drug use, and recent surgery were not included in the study.

STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS version 21 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The conformity of the variables to the normal distribution was analyzed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests).

Descriptive analyses were performed using the mean and standard deviation (mean±standard deviation) for normally distributed variables and median and (minimum-maximum) values for non-normally distributed variables. Normally distributed numerical variables were compared by the Independent Samples t-test and non-normally distributed numerical variables were compared using Mann–Whitney U test. For correlation analyses, the Pearson test was used for normally distributed numerical variables and the Spearman correlation tests were used for non-normally distributed variables. $p<0.05$ results were considered statistically significant. Receiver Operating Characteristic (ROC) was used to determine the best cut-off value for SII, SIRI, NLR, MLR values in the prediction of diabetic polyneuropathy. $p<0.05$ was considered statistically significant.

RESULTS

Diabetic neuropathy was present in 207 of the 414 patients included in the study. In total, 60.1% of the patients were female (n=249) and 39.8% (n=165) were male. The mean age of the participants was 59.6±5.2 years. The mean disease duration was 8.23±4.25 years.

No significant difference was found between the two groups in terms of age and platelet count according to the presence of DN. Statistical difference was found in SII, SIRI, HbA1c level and NLR ($p<0.001$). The parameters compared between both groups are given in Table 1.

When the relationship between SII and SIRI and other parameters was analyzed, there was a positive correlation between the HbA1c level and both parameters. The correlation analysis results are shown in Table 2.

In the ROC analysis for the presence of DN, the area under the curve (AUC) value of the SII parameter was obtained as 0.686 and was statistically significant ($p<0.001$). The sensitivity and specificity were 71.69% and 83.33%, respectively. The AUC value of the SIRI parameter was obtained as 0.662 and was statistically significant ($p<0.001$). The sensitivity and specificity were 69.04% and 62.22%, respectively. The AUC value of the NLR parameter was 0.638 and was statistically significant ($p<0.001$). The sensitivity and specificity were 65.04% and 56.11%, respectively. The AUC value of the PLR parameter was 0.581 and was statistically significant. ($p=0.005$). The sensitivity and specificity were 54.42% and 60.56%, respectively. The AUC value of the MLR parameter was 0.589, which was statistically significant ($p=0.002$). The sensitivity was 42.48% and the specificity was 71.11%. The results of the ROC analysis are given in Table 3 and Figure 1.

TABLE 1: Comparison between groups according to the presence of diabetic neuropathy.

	Pozitive $\bar{X}$±SD	Negative $\bar{X}$±SD	p value
Age	59.8±5.3	59.5±5.2	0.590
Platelet	254.5±58.4	262.2±66.1	0.260
Neutrophil	4.25±1.1	4.8±1.3	**<0.001**
Lymphocyte	2.2±0.7	2.1±0.7	**0.036**
Monocyte	0.63±0.58	0.66±0.35	**0.045**
SII	478.2±215	681.4±362	**<0.001**
SIRI	1.7±7.7	1.67±1.18	**<0.001**
HbA1c	7.95±1.78	8.8±2	**<0.001**
NLR	2.02±0.86	2.61±1.52	**<0.001**
PLR	127.1±67.7	166.1±373	**0.005**
MLR	0.29±0.15	0.36±0.25	**0.002**

Mann-Whitney U testi, SD: Standard deviation; SII: Systemic inflammatory index; SIRI: Systemic inflammatory response index; HbA1c: Hemoglobin A1c; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MLR: Monocyte/lymphocyte ratios.

TABLE 2: Correlation analysis results.

	SII		SIRI	
	r value	p value	r value	p value
Age	-0.004	0.938	0.003	0.953
HbA1c	0.453	**<0.001**	0.490	**<0.001**
NLR	0.714	**<0.001**	0.690	**<0.001**
PLR	0.679	**<0.001**	0.391	**<0.001**
MLR	0.402	**<0.001**	0.678	**<0.001**

Spearman rank test. SII: systemic inflammatory index; SIRI: Systemic inflammatory response index; HbA1c: Hemoglobin; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MLR: Monocyte/lymphocyte ratios.

DISCUSSION

In this study, SII, SIRI, and other inflammation indices were found to be significantly higher in patients

TABLE 3: Receiver Operating Characteristic analysis result.

	AUC (%95 CI)	p value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SII	0.686 (0.635-0.737)	**<0.001**	71.69%	83.33%	77.10%	54.55%
SIRI	0.662 (0.609-0.715)	**<0.001**	69.04%	62.22%	68.37%	58.64%
NLR	0.638 (0.585-0.692)	**<0.001**	65.04%	56.11%	65.04%	56.11%
PLR	0.581 (0.525-0.637)	**0.005**	54.42%	60.56%	63.40%	51.42%
MLR	0.589 (0.534-0.644)	**0.002**	42.48%	71.11%	64.86%	49.61%

AUC: The area under the curve; Confidence Interval; SII: Systemic inflammatory index; SIRI: Systemic inflammatory response index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MLR: Monocyte/lymphocyte ratios; PPV: Positive predictive value; NPC: Negative predictive value

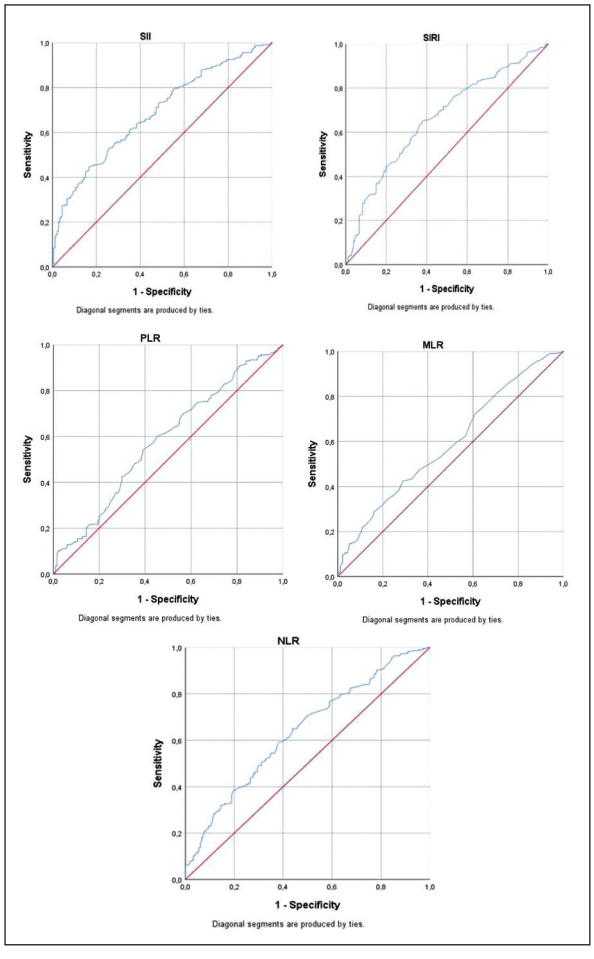

FIGURE 1: The ROC curve apelin for fibromyalgia syndrome.
ROC: Receiver operating characteristic.
SII: Systemic inflammatory index; SIRI: Systemic inflammatory response index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MLR: Monocyte/lymphocyte ratios.

with DN. A positive correlation was found between the SII and SIRI values and the HbA1c level. The specificity of SII and sensitivity of the SIRI parameter were found to be higher than other inflammatory markers (such as NLR, PLR, MLR).

SII is a novel inflammatory metric that is determined by the platelet count, neutrophils, and lymphocytes, all of which are crucial in the etiology of inflammation.[19] In the literature, SII has been studied in a wide variety of cancers as well as in conditions considered to be inflammatory diseases such as diabetes and microvascular complications of diabetes.[22-24] Microvascular damage is the main factor of both systemic and local inflammation with the participation of inflammatory cells such as neutrophils, monocytes, lymphocytes and platelets, which are associated with the development of diabetic nerve damage in patients with diabetes.[25] Peripheral blood neutrophils are specifically associated with the etiology of diabetic organ damage because hyperglycemia increases the quantity of neutrophils in the circulation. Neutrophils migrate to the site of damage via chemokines. Thus, the inflammatory cascade starts.[26] Leukocytes inflict oxidative and proteolytic damage on cells as well as inflammatory processes that are not dependent on infection.[27] Numerous cytokines and transcription factors, such as tumor necrosis factor-α, tumor necrosis factor-β, interleukin-1 (IL-1), and transforming growth factor, are secreted by activated leukocytes and play a crucial role in inflammation.[28-31] Because SII is influenced by both neutrophils and lymphocytes, increased SII levels in diabetic neuropathy were observed in our research. The results of this research may have significant therapeutic ramifications for the prompt detection and management of diabetic neuropathy in individuals with Type 2 DM.

Distal symmetric sensorimotor polyneuropathy is the most prevalent kind of neuropathy that affects both small and large fibers. It is often asymptomatic.

Numerous clinical conditions are also visible, such as autonomic dysfunction, mononeuropathic, and cranial nerve palsy. Current clinical research has demonstrated that persistent low-intensity inflammation is unquestionably important for DN. Studies on individuals with DN who do not experience pain have revealed that the latter group has increased levels of cytokines and inflammatory markers.[32] According to Magrinelli et al., DN patients exhibited elevated IL-6 and IL-10 levels, which were associated with certain abnormalities in large nerve fibers.[33] However, there appears to be a connection between the onset of nerve degeneration in DN and elevated levels of IL-6, IL-1, transforming growth factor-beta, and tumor necrosis factor.[4] Systemic inflammation has been found by Herder et al. to be predictive of the onset and course of DN over a period of 6.5 years.[34] They also found that Diabetic peripheral neuropathy (DPN) was associated with elevated levels of IL-6, soluble intracellular adhesion molecule-1 (ICAM-1), plasma high-sensitivity C-reactive protein, TNF-α and interleukin-1 receptor IL-1RA, and low levels of adiponectin. Herder et al. also recommended the use of IL-1RA and ICAM-1 as biomarkers to predict the course of DPN in diabetic patients, and they observed high levels of vascular cell adhesion molecule-1, chemokines, and E-selectin in DPN and its progression. In another study, the inflammatory marker was analyzed in subjects who had been diagnosed with DPN for more or less than 8 years, and it was discovered that there was an inverse relationship between the subjects' TNF-α level and the nerve conduction velocities of the n. suralis, n. medianus, and n. ulnaris.[34] Serum TNF-α concentrations in diabetic neuropathy participants were greater than those in control subjects, and the disease's duration tended to increase.[35]

A lot of attention has been placed on hematological indices in the scientific medical literature, including NLR, MLR, and PLR indices such as SII, SIRI, and all inflammatory indexes. NLR, MLR, PLR, and SII have emerged as useful vascular disease predictors among these inflammatory markers, according to analysis of recently published publications. In this regard, a number of studies have shown their prognostic value.[34-41] As a result of this study, inflammation markers especially such as SII, SIRI and NLR detected in the group with DN support the literature.

CONCLUSION

Diabetes-related inflammation and metabolic syndrome can accelerate the development of DN and discomfort. Only symptomatic pain relievers with varying degrees of effectiveness are now available, and there is still no authorized medication for the prevention or treatment of diabetic neuropathy. The primary pathogenic mechanism of diabetic neuropathy is inflammation. Inflammation and the onset of diabetic neuropathy are linked by intricate molecular networks and mechanisms. The investigation of the possibility of anti-inflammatory strategies for the suppression of neuropathy development will be made easier by developments in our knowledge of the functions of these important inflammatory molecules and pathways in diabetic neuropathy. The absence of a therapy questionnaire in the DN patient group is the primary research drawback.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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