Neutrophil Lymphocyte Ratio in Different Types of Glaucoma

Glokomun Farklı Tiplerinde Nötrofil Lenfosit Oranı

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ABSTRACT

Purpose: To evaluate the neutrophil-lymphocyte ratio (NLR) in patients with primary open angle glaucoma (POAG), and pseudoexfoliative glaucoma (PEG).

Material and Methods: A total 120 subjects consisted of 40 POAG patients (Group 1), 40 PEG patients (Group 2), and 40 age and sex matched non-glaucoma subjects (Group 3) were included in this retrospective study. The NLR calculation was made according to division of neutrophil numbers to lymphocyte numbers that were obtained from medical records of the subjects. The correlation between NLR and retinal nerve fiber layer (RNFL) thickness was also evaluated in all groups.

Results: The mean NLR values in Group 1, Group 2, and Group 3 was respectively as 2.3±0.2, 2.9±0.3, and 1.7±0. A significant difference was determined between Group 1 and Group 3 (p=0.012), also between Group 2 and Group 3 (p=0.001), with regard to mean NLR value. However, no significant difference was determined between Group 1 and Group 2 in mean NLR value (p=0.1). Additionally NLR was not found to be correlated with thinning in the RNFL.

Conclusions: The high NLR ratio may likely support the role of oxidative stress and inflammation in the development of glaucoma, especially in PEG patients.

Key Words: Glaucoma; neutrophil-lymphocyte ratio.

ÖZ

Amaç: Nötrofil-lenfosit oranı(NLO)'nın primer açık açılı glokomlu (PAAG) ve psödoeksfoliasyon glokomlu (PEG) hastalarda değerlendirmektir.

Gereç ve Yöntem: Kırk PAAG 'lu hasta (Grup 1), 40 PEG'li hasta (Grup 2) ve 40 glokomu olmayan yaş ve cinsiyet uyumlu bireyden (Grup 3) oluşan toplam 120 birey bu retrospektif çalışmaya dahil edildi. NLO hesaplaması bireylerin tıbbi kayıtlarından elde edilen nötrofil sayısının lenfosit sayısına bölünmesine göre yapıldı. NLO ve retina sinir lifi tabaka (RSLT) kalınlığı arasındaki korelasyon tüm gruplarda değerlendirildi.

Bulgular: Grup 1, Grup 2 ve Grup 3'deki ortalama NLO değeri sırasıyla 2.3±0.2, 2.9±0.3 ve 1.7±0 şeklindeydi. Grup 1 ve Grup 3 arasında (p=0.012) ve Grup 2 ve 3 arasında ortalama NLO değeri açısından istatistiksel olarak anlamlı fark vardı (p=0.001). Ancak Grup 1 ve Grup 2 arasında NLO açısından anlamlı fark yoktu (p=0.1). Ek olarak NLO'nun RSLT'deki incelme ile ilişkili olmadığı bulundu.

Sonuç: Yüksek NLO özellikle PEG'lu hastalarda glokom gelişimindeki oksidatif stres ve inflamasyonun rolünü destekleyebilir.

Anahtar Kelimeler: Nötrofil-lenfosit oranı, glokom.

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INTRODUCTION

Already commonly used as a marker of systemic inflammation during the course of chronic diseases,[1] the neutrophil-to-lymphocyte ratio (NLR) has also proven valuable in clarifying poor prognoses of myocardial infarction, hypertension, diabetes mellitus, psoriasis, and cancer, among other diseases.[2-6] In the pathogenesis of those conditions, as well as of inflammatory rheumatic ones such as rheumatoid arthritis, neutrophils may additionally increase oxidative stress (OS) by degranulating myeloperoxidase (MPO) at the site of inflammation.[7] Since both inflammation and OS play significant roles in the pathophysiological mechanisms of age-related macular degeneration,[8] keratoconus,[9] and retinal vein occlusion, the heightened severity of these and other progressive ocular disorders are particularly associated with high NLRs.[10]

Among such disorders, glaucoma consists of increased intraocular pressure (IOP) associated with optic neuropathy. Typically accompanied by progressive damage to the visual field,[11] glaucoma is a leading cause of irreversible blindness worldwide.[12] Although elevated IOP is arguably the chief risk factor for an individual's developing retinal cell damage in the pathogenesis of glaucoma, increased OS due to either vascular or metabolic deterioration might also cause retinal neuronal cell death in glaucoma.[13] In fact, not only was oxidative DNA damage demonstrated to compromise trabecular meshwork (TM) functioning,[14] but increased levels of OS in the serum of patients with primary open angle glaucoma (POAG) or pseudoexfoliative glaucoma (PEG)[15] support its contribution to the development of glaucoma as well.

In response to the above findings, in this retrospective study we sought to compare the NLR of patients with POAG or PEG, as well as that of individuals without glaucoma, in order to evaluate whether NLR may likely indicate changes in OS according to the presence and type of glaucoma.

MATERIAL AND METHODS

We conducted this retrospective case-control study within the Ophthalmology Department of the School of Medicine at Çanakkale Onsekiz Mart University (ÇOMU). After ÇOMU's ethics committee confirmed the study protocol's accordance with the Declaration of Helsinki for research involving humans, we retrospectively reviewed 279 medical records of patients either with or suspected of having glaucoma who were examined between January 2012 and March 2015. We ultimately formed a sample of 120 participants, 40 with POAG (Group 1), 40 with PEG (Group 2, n=40), and for a control group, 40 without glaucoma whatsoever (Group 3). From their medical records, we collected all of the participants' complete blood count (CBC) values recorded after they had fasted for 12 h and calculated the NLR of each by dividing the neutrophil count by the lymphocyte count.

We excluded from our sample all patients with systemic diseases that could affect NLR, including diabetes mellitus, hypertension, renal diseases, hepatic diseases, various malignancies, chronic obstructive lung diseases, hematological and autoimmune disorders, and chronic inflammatory diseases, as well as all patients with a history of smoking or taking aspirin or statins. We also excluded patients with leukocyte counts of fewer than 4,500 cells/µl or greater than 11,000 cells/μl, as well as those subjected to surgery within last 30 days, under treatment with antibiotics and immunosuppressants, or with active immunologic, inflammatory, or infectious diseases with fewer.

After forming our sample, along with NLR values, we compared the groups' average and sectorial (i.e., superior, inferior, temporal, and nasal) retinal nerve fiber layer (RNFL) thicknesses, both measured using optical coherence tomography (Spectral OCT/SLO system, OTI Ophthalmic Technologies, Inc., Toronto, Canada) and obtained within 6 months of the CBC measurement. We lastly performed correlation analysis of the values of NLR, RNFL thickness, and age.

Statistical Analysis: We conducted statistical analyses using the Statistical Package for the Social Sciences version 15 (SPSS Inc., Chicago, IL, USA). After investigating variables using visual (i.e., histograms and probability plots) and analytical methods (i.e., Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether the variables were normally distributed, we performed descriptive analyses and recorded the means (M) and standard deviations (SD) for all variables. Since NLR, age, and thicknesses of average and sectorial RNFL were not normally distributed, we also subjected values to Kruskal-Wallis tests to compare the parameters among all groups and performed Mann-Whitney U tests to gauge the significance of pairwise differences, namely by using the Bonferroni correction to adjust for multiple comparisons. We applied an overall 5% type-1 error level to infer statistical significance and used Spearman's rank-order correlation to evaluate correlations among NLR, average RNFL thickness, and sectorial RNFL thickness.

RESULTS

Demographic data and blood parameters of all groups appear in Table 1. The mean age of participants was 66.7±2.1 (21-87) years in Group 1, 68.5±1.1 (57-87) years in Group 2, and 65.6±1.5 (34-74) years in Group 3. We found no significant age- or sex-related differences among the three groups. In Groups 1, 2, and 3, the mean NLR was 2.3±0.2, 2.9±0.3, and 1.7±0.1, respectively, and a statistically significant difference emerged both between Groups 2 and 3 (p=.001) and between Groups 1 and 3 (p=.012), though not between Groups 1 and Group 2 (p=.1). Interestingly, in terms of the thickness of average and sectorial RNFLs, a statistically significant difference also emerged between Groups 2 and 3 and between Groups 1 and 3, though again not between Groups 1 and 2. NLR therefore did not correlate with average or sectorial RNFL thickness, the values of which appear in table 2.

Table 1: *Demographic data, and blood parameters of patients with primary open angle glaucoma (Group 1), patients with pseudoexfoliation glaucoma (Group 2), and subjects without glaucoma (Group 3, control group).*

	Group 1 (n=40)	p (1-2)	Group 2 (n=40)	p (2-3)	Group 3 (n=40)	p (1-3)
Age	66.7±2.1	0.3	68.5±1.1	0.3	65.6±1.5	0.2
Female/Male	24/16	0.3	22/18	0.4	23/17	0.4
# of neutrophils	4.4±0.2	0.6	4.4±0.2	0.03	3.8±0.1	0.04
# of lymphocytes	2.1±0.1	0.03	1.8±0.1	0.001	2.3±0.1	0.3
NLR	2.3±0.2	0.1	2.9±0.3	0.001	1.7±0.1	0.012

Table 2: *The thicknesses of average and sectorial (inferior, superior, nasal, temporal) RNFL in all groups.*

RNFL Thickness	Group 1 (n=40)	p (1-2)	Group 2 (n=40)	p (2-3)	Group 3 (n=40)	p (1-3)
Average	83.3±2.3	0.6	81.8±2.2	<0.001	96.5±1.9	<0.001
Inferior	101.5±3.9	0.7	103±3.7	<0.001	125.5±2.8	<0.001
Superior	102.1±2.8	0.4	98.7±3.4	<0.001	119.9±2.9	<0.001
Nasal	66.6±2.2	0.2	63.5±2.7	0.001	75.1±2.2	0.016
Temporal	64.3±2.2	0.2	59.9±1.9	0.001	69.6±2.2	0.03

DISCUSSION

Many studies of the pathophysiological mechanisms of glaucoma have demonstrated that the progressive loss of retinal ganglion cells (RGCs) and the excavation of the optic nerve head that occur during the course of the disease result from the involvement of multiple factors.[16-18] At the same time, given IOP's significant capacity to preserve the visual field, lowering the IOP has become a mainstay of managing glaucoma.[19] However, as in cases of normal-tension glaucoma, even if patients can reduce their IOPs to healthy levels, progressive RGC damage can nevertheless occur, particularly when coupled with the risk of hypoxia, glutamate-mediated toxicity, neurotrophin modulation, or OS.[20] In the presence of OS in particular, the substantial production of reactive OS (ROS) can relate to increased IOP levels due to endothelial cell damage in the TM, which regulates the permeability of endothelial cells in Schlemm's canal.[21] At least one study has also suggested that besides increasing IOP levels, oxidative DNA damage in the TM can independently give rise to optic nerve damage, namely by inducing the release of NO and endothelins from TM endothelium.[22]

In some clinical trials, an impaired balance between antioxidant and oxidant mechanisms indicating OS has emerged in bodily fluids of patients with either POAG or PEG. Moreno et al. have furthermore revealed increased free radical formation in patients with POAG, indicated either by increased malondialdehyde-thiobarbituric acid reactive substance (MDA-TBARS) or by decreased antioxidant activity in the aqueous humor.[23] A similar imbalance in terms of reduced total antioxidative capacity (TAC) and increased levels of oxidants has also appeared in the aqueous humor of patients with PEG.[24] At the same time, apart from aqueous humor samples, both increased levels of OS markers and decreased TAC levels have occurred in the serum samples of either POAG or PEG patients.[25] Therefore, evaluating the status of OS in the serum samples of patients with glaucoma seems to be a plausible method of predicting glaucoma's progression. To clarify this suggestion, we hypothesized that NLR may be useful as an indirect indicator of OS, since MPO is a neutrophil-welded enzyme involved in producing ROS- and NO-derived oxidants.[26] A positive association between MPO level in plasma and NLR has also occurred in patients with coronary artery diseases.[27]

In comparison to the control group, patients with POAG or PEG showed significantly high NLRs, a result which may be valuable in either reflecting or supporting the importance of inflammation and OS in the pathogenesis of two types of glaucoma. Moreover, since the significant increase in NLR was far greater in patients with PEG, high NLRs among these patients may offer insight into the relationship between OS and the formation of abnormal extracellular fibrillary material (i.e., pseudoexfoliation material) usually observed on the lens of patients with PEG. The deposit of such material has occurred in patients with various diseases associated with OS, including transient ischemic attack,[28] Alzheimer's disease,[29] asymptomatic myocardial dysfunction,30 stroke, myocardial infarction, systemic hypertension,[31] and aneurysm of the abdominal aorta.[32]

In this study, we found no correlation between NLR and decreased RNFL thickness. Since the development of glaucoma is multifactorial, RNFL thinning can occur depending on the involvement of other factors, not solely OS. However, compared with the control group, patients with PEG showed both a far more significantly severe decrease in RNFL thickness and a more significant NLR than patients with POAG. Despite this interesting association between glaucoma and NLR, prospective studies of these relationships need to strengthen the validity of NLR assessment in follow-up examinations of patients with glaucoma.

In that sense, involving the appraisal of OS markers in serum samples of these patients may be helpful in supporting the importance of NLR calculations in detecting patients prone to the development of glaucoma, particularly PEG. Therefore, our neglect to evaluate OS markers in the aqueous humor and serum of glaucoma patients, as well as our small sample size, were the major limitations of our retrospective study.

In sum, according to our investigation of the association between NLR and glaucoma, evaluations of NLR may likely provide information about increased OS, especially in patients with PEG. Moreover, NLR may be used for follow-up examinations regarding the progression of glaucoma. To verify and expand both findings, however, further studies are necessary.

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