Evaluation of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and mean platelet volume levels in pediatric keratoconus patients

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Abstract:

PURPOSE: To examine the level of neutrophil–lymphocyte ratio and platelet-lymphocyte ratio in the pediatric patient group with keratoconus.

METHODS: Patients aged 5–18 years with a diagnosis of keratoconus followed by the corneal department and children in the similar age group who were determined as controls were included in the study. Their topographies were evaluated. In both groups, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and mean platelet volume (MPV) were measured.

RESULTS: The study group consisted of children aged 15 ± 1.4 years and the control group 13 ± 1.3 years of age. The mean central corneal thickness of the patients in the patient group was 445.64 μm, and in the control group was 532.25 μm. The NLR was 3.37 ± 1.04 in the patient group and 2.31 ± 0.82 in the control group. The PLR was significantly increased in the KC group (147.54 ± 41.36) than in the control group (118.71 ± 27.11) ($P = 0.042$). MPV in the patient group was 12.18 ± 2.76 and 7.00 ± 1.37 in the control group. This value was found to be statistically significant ($P = 0.047$) when the control group and the patient group were compared.

CONCLUSION: Platelet/lymphocyte ratio and mean platelet volume, which are thought to be new markers of systemic inflammation, may be new indices in keratoconus in pediatric patients.

Keywords:

Keratoconus, mean platelet volume, neutrophil–leukocyte ratio, platelet–lymphocyte ratio

Introduction

Keratoconus is a progressive corneal disease that is associated with stromal thinning and protrusion in the central and paracentral cornea that develops progressive irregular astigmatism and myopia.[1] Genetic, environmental, hormonal, and biochemical factors may play a role in pathogenesis. The reported incidence of keratoconus is 1.3–22.3 cases per 100,000 and the prevalence is 0.4–86 cases per 100,000. It is one of the most common indications of corneal transplantation.[2]

The initial disease occurs during puberty with asymmetric astigmatism in both eyes. The rapid progression in young patients may result in a faster visual impairment that has a negative effect on their social and educational development.[3]

Keratoconus was first defined as a noninflammatory disease; the idea that it has an inflammatory component has gained weight in recent years. However, its pathogenesis is still not fully understood, it was demonstrated that increased inflammatory mediator levels are present in the tears and serum of patients with keratoconus. Higher serum levels of interleukin (IL)-1B, IL-6, tumor necrosis factor (TNF)-α, matrix metalloproteinase 9 (MMP-9) and NF-κB were found in KC patients.[4]

Neutrophil/lymphocyte ratio (NLR), an inflammatory marker, has been related to the status and prognosis of many systemic

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diseases in recent years.[5] Furthermore, it is thought that the platelet-lymphocyte ratio (PLR) can be used to evaluate the severity of the inflammatory reaction in various diseases.[6,7] Mean platelet volume (MPV) has been shown to be associated with inflammation severity.[8] Although NLR and PLR have been investigated in the adult keratoconus patient group, there is no known study in the pediatric patient group yet.[9-11] The aim of this study is to investigate the relationship between inflammatory parameters NLR, PLR, and MPV with keratoconus in pediatric keratoconus patients.

Methods

This study was performed under the guidelines stated by the Institutional Ethics Committee of Kocaeli City Hospital and in compliance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

Twenty patients aged 5–18 years who were diagnosed with keratoconus and followed up with serial topography in Kocaeli City Hospital, Department of Ophthalmology, and 20 healthy pediatric participants in a similar age group as controls were included in this study.

Exclusion criteria were as follows: (1) history of ocular surgery and ocular diseases, such as keratitis, diabetic retinopathy, dry eye, uveitis, and atopy, (2) systemic, ocular, or inflammatory diseases and (3) current anti-inflammatory therapies for any reason.

All patients underwent a complete ophthalmic examination, including best-corrected visual acuity (logarithm of the minimum angle of resolution) measurement, slit-lamp examination, dilated fundus examination, and corneal topography. Sirius topography system (Costruzioni Strumenti Ophthalmics, Florence, Italy) was used for corneal topography in all participants. Maximum keratometry value (Kmax) of the corneal anterior surface and the thinnest pachymetry were measured. The diagnosis of KC was confirmed with the modified Rabinowitz–McDonnel test.

Drawned venous blood samples (5 ml) were analyzed by an automated blood cell counter within an hour of sampling. Levels of platelets, neutrophils, and lymphocytes were obtained from the automated complete blood count measures. The NLR and PLR were calculated as the neutrophil count and platelet count divided by the lymphocyte count, respectively.

Statistical analysis: All statistical analyses were performed using IBM SPSS 20.0 (SPSS, Chicago, IL, USA) and MedCalc 14.0. Shapiro–Wilk's test was used to assess the assumption of normality. Numeric variables were presented with mean ± standard deviation. Categorical variables were summarized as counts (percentages). Comparisons of numeric variables between the keratoconus and control groups were carried out using independent samples *t*-test. The association between two categorical variables was examined using Chi-square test. A $P < 0.05$ was considered statistically significant.

Results

The demographic and clinical characteristics of all participants are shown in Table 1. Twenty patients (9 females, 11 males) and 20 healthy individuals (10 females, 10 males) of similar age were included in the study. The mean age in the KC group was 15 ± 1.4 years and 13 ± 1.3 years in the control group. There was no significant difference between the study and control groups based on gender and age ($P = 0.946$ and $P = 0.165$, respectively). The mean central corneal thickness was 445.64 μm in the KC group and 532.25 μm in the control group. In the KC group, Kmax: 51.94 Kflat: 44.21 for the right eye, Kmax: 56.32 Kflat: 48.63 for the left eye; in the control group, Kmax: 44.44 Kflat: 43.67 for the right eye, Kmax: 44.62 Kflat: 43.53 for the left eye.

KC group had similar NLR values compared with those of the controls (3.37 ± 1.04 vs. 2.31 ± 0.82) ($P = 0.697$). The PLR was significantly increased in the KC group (147.54 ± 41.36) than in the control group (118.71 ± 27.11) ($P = 0.042$). The mean MPV in the KC group was 12.18 ± 2.76 and 7.00 ± 1.37 in the control group. When the control group and KC group were compared, it was found to be statistically significant ($P = 0.047$).

Discussion

This is the first study to evaluate NLR and PLR levels in pediatric patients with KC disease. This study showed that NLR was not different in the pediatric KC group, but PLR and MPV were significantly different in the pediatric KC group when compared with healthy controls.

While keratoconus is considered to be a noninflammatory disease, studies conducted in recent years have changed the idea to inflammatory processes are the basis of the disease.[4] Inflammatory markers such as IL-1 α/β, TNF-α, and IL-6, IL-8, and TGF-β have been shown to be high in serum, tear and corneas of KC patients.[4,12,13] When the epithelium at the cone apex of KC patients was examined, it was shown that inflammatory factors TNF-α, IL-6, and MMP-9 were elevated compared to the peripheral cornea, and were also associated with corneal curvature and deformity parameters.[14] It is thought that the balance between pro-oxidant and antioxidant enzymes and cofactors, which are important for the protection of cellular homeostasis, is impaired in the KC, and there is an increase in the by-products such as reactive oxygen (ROS) in the

Table 1: The demographic and clinical characteristics of keratoconus patients and controls

Variables	KC ($n=20$)	Control ($n=20$)	*P*
Sex, *n* (%)			
Male	11 (55)	10 (50)	0.946[a]
Female	9 (45)	10 (50)	
Age (years)	15±1.4	13±1.3	0.165[b]
NLR	2.31±0.82	3.37±1.04	0.697[b]
PLR	147.54±41.36	118.7±27.11	0.042[b]
MPV (fL)	12.18±2.16	7.00±1.37	0.047[b]

[a]Chi-square test, [b]Independent samples *t*-test. KC: Keratoconus, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume

pro-oxidant pathway, which causes oxidative stress that leads to chronic inflammation, in the cells in the etiopathogenesis of the KC.[4] Another imbalance in the pathogenesis of KC is between proteolytic and antiproteolytic enzymes in the cornea. MMPs are one of the most important proteolytic enzymes involved in KC pathogenesis.[15]

Recently, NLR and PLR were reported as new indexes related to systemic diseases driven by inflammation.[16-18] In addition to systemic diseases, the relationship of NLR and PLR with ocular diseases has been investigated in recent years. An increase in NLR was also found in age-related macular degeneration,[19] PEX,[20] and dry eye syndrome[21] in which inflammation plays an important role.[19-21] There are also studies evaluating NLR on keratoconus. In the study of Karaca *et al*., in which they compared NLR in progressive KC, nonprogressive KC and control groups, they did not detect a significant change in NLR in the nonprogressive group when compared to the control group, however, they found an increase in NLR in the progressive group.[9] Elbeyli *et al*. found significantly higher NLR values in KC group compared to the healthy controls.[11] In another study in which monocyte/HDL cholesterol ratio (MHR) and NLR were studied as indicators of inflammation and oxidative stress in patients with KC, MHR and NLR values were found to be significantly higher in patients with KC disease compared to the control group.[22] Similar to our study, in the studyin which NLR and PLR were evaluated in advanced KC patients conducted by Reyhan *et al*., NLR values were not statistically different in the KC group compared to the control group.[23] Bozkurt *et al*. found no significant difference between the control group and KC group in terms of NLR levels in their study to evaluate the parameters sensitive to inflammation in patients with KC as in our study.[10]

NLR has been extensively studied as a new inflammatory marker in both systemic and ocular diseases, and it is seen that PLR, which is obtained in a similar way to NLR, is less studied in the literature compared to NLR. Bozkurt *et al*. showed that PLR was significantly higher in the KC group.[10] In another study examining the relationship between PLR and KC by, the level of PLR was found to be significantly higher.[11] However, Reyhan *et al*. found no difference in PLR index in progressive and nonprogressive KC compared to the control group.[23] Similar to these studies, we demonstrated significantly higher PLR values in pediatric KC patients. Since all of the studies conducted on keratoconus cases are in adult patients, we are not able to compare them exactly. Future studies are needed to prove our results demonstrating increased PLR values in pediatric KC patients.

MPV is a parameter that indicates the average size of platelets. MPV is the most commonly used marker of platelet production and activation, and its increased levels expressing larger platelets are thought to be associated with inflammation.[24] However, the role of platelets in keratoconus has not been fully studied and the possible importance of platelets in keratoconus may be due to their pro-inflammatory properties. In a study, IL-1 β, IL-6 and IL-8 were added to whole blood analyzed, and as a result, it was shown that platelets have receptors for all three interleukins, were hyperactivated and had a pronounced dissemination and aggregation tendency.[25]

Platelets are accepted as inflammatory cells and can produce ROS.[26] There is increasing evidence to suggest that KC is mediated by ROS production and oxidative stress caused by the impaired balance between protective enzymes and antioxidants.[4] However, the mechanisms involved in ROS production in keratoconus have not yet been understood. Our study supports the idea that inflammatory processes are involved in the pathogenesis of keratoconus that we found increase MPV levels in pediatric KC group.

One of the limitations of our study is the small number of patients. Another limitation is that we did not form a progressive and nonprogressive study group. However, it should be kept in mind that the majority of our patients are in the adolescent period and in the age group where the main disease progression is seen.

Conclusion

Unlike adults, PLR and MPV may be more valuable indicators than NLR in pediatric KC and can be used as new biomarkers. To get better evidence, additional prospective, randomized controlled studies with larger case series in pediatric age group are required.

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Conflicts of interest

There are no conflicts of interest.

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