Hematological and Atherogenic Indices in Patients with Exfoliation Syndrome and Exfoliation Glaucoma

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ABSTRACT

Purpose: To investigate the possible link between hematological and atherogenic indices reflecting inflammation and cardiovascular risk and exfoliation syndrome (XFS) and exfoliation glaucoma (XFG).

Materials and Methods: This study included a total of 83 participants (29 XFS, 25 XFG, and 29 healthy controls) who were scheduled for routine cataract surgery. Blood sampling was performed from the individuals and complete blood count (CBC), C-reactive protein (CRP), uric acid (UA), and serum lipids were measured. Neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), monocyte/high-density lipoprotein cholesterol (HDL-c) ratio (MHR), and platelet/lymphocyte ratio (PLR) were also calculated. Examined parameters were compared statistically.

Results: Statistically significant higher white blood cells, neutrophil count, UA and triglyceride (TG) levels were determined in the XFG group. NLR and MLR were significantly higher in the XFS and XFG groups compared to the control group. MHR was significantly higher in the XFG group than the control group. Lymphocyte count was significantly lower in the XFS and XFG groups compared to the control group. HDL-c was significantly lower in the XFG group compared to the other two groups. Furthermore, receiver operating curve analysis revealed that lymphocyte count, NLR, MLR, MHR, and HDL-c had significant predictive value for XFS, and NLR, MHR, and HDL-c for XFG.

Conclusion: In the light of current knowledge, XFS is a multisystem entity. This study results revealed that there was a link between XFS/XFG and hematological and atherogenic parameters reflecting inflammation and cardiovascular risk and these parameters may be important in the follow-up of XFS/XFG and related diseases.

Keywords: Exfoliation syndrome, Glaucoma, Inflammation, Hematological indices, Atherogenics indices

INTRODUCTION

Exfoliation syndrome (XFS) is an aging-related disorder of the extracellular matrix (ECM) that results in the accumulation and production of small, white fibrillar deposits in many intra- and extra-ocular tissues. Amyloid-like fibers have been found in the microscopic findings of this accumulation. Clinically, these aggregates are principally expressed in the anterior chamber of the eye and are evident in the juxtacanalicular tissue and the trabecular meshwork, causing blockage of aqueous humor outflow. XFS's etiology is still largely unknown, but there is some conjecture that it may have a genetic component. XFS is a relatively common cause of chronic open-angle glaucoma, and this secondary glaucoma is known as exfoliation glaucoma (XFG).[1,2]

The possible relationship between XFS and some several systemic diseases and low-grade chronic inflammation (LGCI)-related cerebrovascular and cardiovascular diseases (CVDs), have been demonstrated.[3-5] In particular, XFS is recognized as an independent risk factor for CVDs.[6,7] Additionally, XFS is associated with many cardiovascular risk factors such as dyslipidemia[8] and increased homocysteine.[9] On the other hand, it has been shown that endothelial dysfunction, oxidative stress, and LGCI play a role in the pathogenesis of XFS and XFG.[10,11]

Recently, the role of some atherogenic and hematological parameters and indices used as markers of chronic inflammation in the pathogenesis of many systemic diseases and also in XFS and XFG has been investigated.[8,12-14] However, these studies revealed conflicting results. The

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purpose of this research is to demonstrate the relationship between atherogenic and hematological indices and XFS/XFG with the collective perspective in a study.

MATERIALS AND METHODS

In this cross-sectional, controlled study, 29 XFS, 25 XFG, and 29 age and gender-matched healthy controls, who were scheduled for cataract surgery in the Ordu University Training and Research Hospital due to low-grade nuclear cataract between January 2019 and December 2020 were included. The study protocol was reviewed and approved by the Ordu University local ethics committee, considering the tenets of the Helsinki Declaration. The participants were informed about the surgical procedures, possible complications and the examinations to be applied. A written informed consent form was obtained from all individuals. The patients were inquired about the history of smoking and alcohol use and the history of chronic disease. Body mass index (BMI) calculation was made by recording the weight and heights.

All the participants underwent a comprehensive ophthalmologic examination, including best-corrected visual acuity (BCVA) test (Snellen Chart), Goldmann applanation tonometry (Haag Streit, Koeniz, Switzerland), biomicroscopy, gonioscopy, fundoscopy, optical coherence tomography (OCT), and perimetry before the surgery. Patients with exfoliation material detected at the angle, iris, or on the lens by Dr. B.E. in the biomicroscopic examination and with glaucomatous optic disc damage (confirmed with OCT and perimetry) and IOP >21 mmHg were included as XFG group, and those without retinal nerve fiber loss and IOP ≤21 mmHg as the XFS group. XFG patients had been diagnosed for at least 1 year. The control group consisted of patients (with low-grade cataract) who had no exfoliation and had an intraocular pressure below 21 mmHg. All examinations were performed under mydriasis after instillation of 0.1% tropicamide.

Patients with a history of ocular disease/surgery, previous eye trauma, systemic/ocular inflammatory disease, hematological disorder, severe hypertension, coronary artery disease, chronic obstructive pulmonary disease, diabetes, cancer, using anti-inflammatory, lipid-lowering drugs, and chronic alcoholics were excluded from the study.

Blood Sampling and Biochemical Analysis

Venous blood sampling was performed before cataract operation between 8 and 10 am after 8 hours of overnight fasting. Blood samples were analyzed freshly on the same day. Complete blood count (CBC, Sysmex XN-450 modular system, Sysmex, Kobe, Japan), High-density lipoprotein cholesterol (HDL-c), total cholesterol (TC), triglyceride (TG, ELISA, Bioassay Technology Laboratory, China), Low-density lipoprotein cholesterol (LDL-c, Calculated using the Friedewald equation), C-reactive protein (CRP, detected by nephelometric method, AU5800 System; Beckman Coulter Inc, Brea, CA, USA), uric acid (UA) (detected by the enzymatic colorimetric method with a commercial kit [Roche Diagnostics, Basel, Switzerland]) analysis were recorded. In addition, since it shows inflammation, the rates used frequently in the literature are Neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), monocyte(x1000/microliter)/HDL ratio (MHR), platelet/lymphocyte ratio (PLR), were calculated.

Statistical Analysis

All statistical analyses were performed with SPSS for Windows 22.0 package program (SPSS Inc., Chicago, IL, USA). Distribution normality of the continuous variables was performed using the Kolmogorov-Smirnov test. Continuous variables were compared using the Student t-test or Mann-Whitney U test, and categorical variables were compared using the Chi-square test. Comparison of multi groups was performed using one-way ANOVA test for parametric data and Kruskal-Wallis test for non-parametric data. Bonferroni correction was used as a post hoc test to determine which subgroups were different. $P < 0.05$ is the statistical significance value for reported results. Significance value was accepted as $p < 0.012$ in post hoc analysis. Multivariate logistic regression analysis was performed for possible confounding factors. The receiver operating characteristics (ROCs) analysis was performed to show the predictability of values found to be statistically significant. The sensitivity, specificity, and the best cut-off value of the predictable parameters were determined.

RESULTS

This work consisted a total of 83 individuals including 29 XFS (mean age: 61.7±6.5, 14M/15F) 25 XFG (mean age: 63.8±5.0, 13M/12F) patients, and 29 controls (mean age: 60.5±6.0, 15M/14F). There were no significant differences between the groups in terms of age and gender distribution. WBC, neutrophil count, lymphocyte count, NLR, MLR, MHR, and UA, HDL-c, TG levels showed statistically significant differences in multi-group comparison. WBC, neutrophil count, and UA, TG levels showed no significant difference in the comparison of control group and XFS group ($p=0.74$, $p=0.22$, $p=0.43$, and $p=0.96$ respectively),

whereas it was determined significant higher values in the XFG group (p=0.019, p=0.002, p=0.009, and p=0.042 respectively). Lymphocyte count was significantly higher in the control group compared to the other 2 groups. NLR and MLR were significantly higher in the XFS group (p=0.003, p=0.001, respectively) and XFG group (p=0.001, p=0.010, respectively) compared to the control group. There was no significant difference between the control group and XFS in terms of MHR (p=0.30), on the other hand, MHR was significantly higher in the XFG group compared to the control group (p=0.012). HDL-c was significantly lower in the XFG group compared to the other 2 groups. In Figure 1, box plot graphics show the comparison of the statistically significant values between the groups.

After multivariate logistic regression analysis, age, gender, BMI, and smoking did not demonstrate significant predictive value for the existence of exfoliation. Hypertension was found to be independent predictors of presence of exfoliation (Odds Ratio: 1.644 95% Cl: 1.120-1.998 p= 0.005) (Table 2).

Receiver Operating Curve (ROCs) analysis graphs presented the parameters with predictive value that can differentiate the presence of exfoliation (XFS + XFG) from the control group and XFG from the other two groups. (Figure 2) Accordingly, the parameters that could distinguish the presence of exfoliation (XFS + XFG) were lymphocyte count (Best cut off: 1.88, sensitivity: 65.5%, specificity: 81.3%), NLR (Best cut off: 1.80, sensitivity: 71.7%, specificity: 68.0%), MLR (Best cut off: 0.25, sensitivity: 73.9%, specificity: 72.0%), MHR (Best cut off:

Table 1: *Comparison of baseline characteristics and laboratory values between groups.*

Parameters	**Control N=29**	**XFS N=29**	**XFG N=25**	**P value**
Age (years)	60.5±6.0	61.7±6.5	63.8±5.0	0.310
Gender (male/female)	15/14	14/15	13/12	0.953
BMI (kg/m^2)	25.0±4.2	25.5±4.1	25.2±3.3	0.420
Smoking (yes/no)	14/15	16/13	14/11	0.079
Hypertension (yes/no)	–	20/9	20/5	0.482
Hematological Indices				
WBC (10^3/µL)	6.41±1.6^a	6.43±1.4^a	7.36±1.2^b	**0.029**
Neutrophil count (10^3/µL)	3.50±1.0^a	3.83±0.9^a	4.49±1.1^b	**0.004**
Lymphocyte count (10^3/µL)	2.06 (1.92 - 2.73)^a	1.73 (1.44 - 2.35)^a	1.74 (1.60 - 2.21)^a	**0.041**
Monocyte count (10^3/µL)	0.56±0.1	0.63±0.1	0.64±0.2	0.180
Platelet count (10^3/µL)	269 (221 - 298)	243 (197 - 279)	249 (217 - 289)	0.112
NLR	1.60±0.4^a	2.15±0.8^b	2.31±0.8^b	**0.002**
MLR	0.24 (0.21 - 0.29)^a	0.33 (0.27 - 0.40)^b	0.32 (0.25 - 0.36)^b	**0.001**
MHR	10.5±3.3	11.5±3.6	13.1±3.5	**0.044**$^¥$
PLR	122 (98 - 145)	119 (89 - 159)	120 (111 - 143)	0.741
Atherogenic Indices				
CRP (mg/dL)	1.6 (0.9 - 3.8)	1.8 (1.0 - 3.4)	1.7 (0.9 - 3.3)	0.551
UA (mg/dL)	4.40 (4.1 - 5.1)^a	5.05 (4.1 - 5.4)^a	5.50 (4.60 - 6.10)^b	**0.016**
TC (mg/dL)	194 (168 - 234)	197 (177 - 236)	193 (183 - 215)	0.768
LDL-c (mg/dL)	119.2±30.4	118.2±31.8	113.8±16.8	0.775
HDL-c (mg/dL)	53 (50 - 59)^a	52 (45 - 62)^a	45 (42 - 49)^b	**0.001**
TG (mg/dL)	122 (85 - 189)^a	123 (88 - 160)^a	145 (129 - 186)^b	**0.043**

Data are expressed as mean±SD, median (interquartile range). Statistically significant P values are in **bold** <0.05

XFS exfoliation syndrome; XFG exfoliation glaucoma; BMI body mass index; WBC white blood cells; NLR neutrophil-to-lymphocyte ratio; MLR monocyte-to-lymphocyte ratio; MHR monocyte-to-high-density lipoprotein cholesterol (HDL-c) ratio, PLR platelet-to-lymphocyte ratio; CRP C-reactive protein; UA uric acid; TC total cholesterol; LDL-c low-density lipoprotein cholesterol; TG triglycerid

p^{a,b}; Different letters denote the differences in significance p<0.012 with the Bonferroni correction analysis.

P$^¥$; Control vs XFS = 0.300, XFS vs XFG = 0.142, Control vs XFG = 0.012

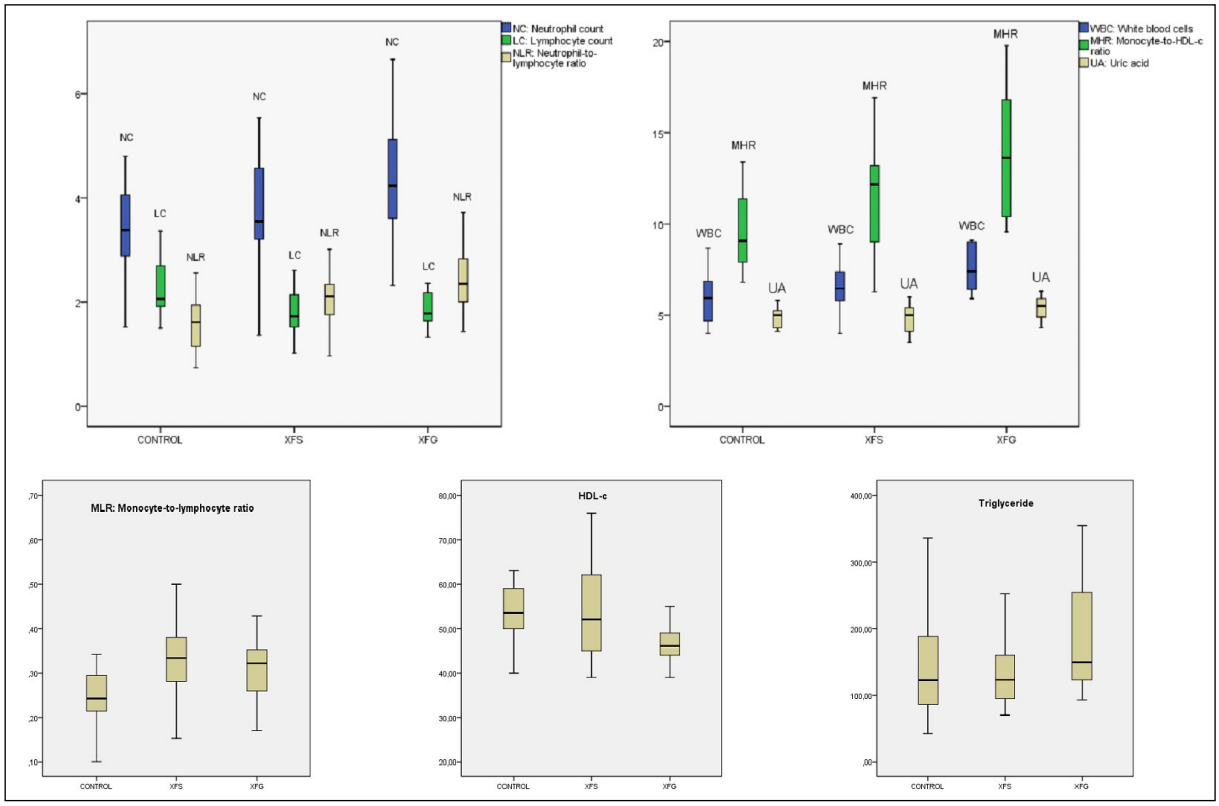

Figure 1: *Box plots show a comparison of statistically significant values between groups.*

Table 2: *Logistic regression analyzes to identify possible confounding factors of exfoliation syndrome and exfoliation glaucoma.*

	Odds Ratio	95% CI	p
Age (years)	0.914	0.815 – 1.012	0.569
Gender	0.902	0.812- 1.001	0.941
BMI (kg/m^2)	0.922	0.849 - 1.120	0.840
Smoking	0.950	0.912 - 1022	0.320
Hypertension	1.644	1.120 – 1.998	0.005
BMI; body mass index			

10.18, sensitivity: 76.1%, specificity: 56.0%), and HDL-c (Best cut off: 50.5, sensitivity: 62.8%, specificity: 66.7%). And also, the parameters that could predict XFG were NLR (Best cut off: 1.80, sensitivity: 81.8%, specificity: 52.0%), MHR (Best cut off: 11.63, sensitivity: 59.1%, specificity: 60.0%), and HDL-c (Best cut off: 50.5, sensitivity: 90.9%, specificity: 63.5%).

DISCUSSION

The current study results revealed that high WBC, neutrophil count, NLR, MLR, MHR, UA, TG levels, and low lymphocyte count and HDL-c levels may be associated with XFS and/or XFG. Besides, it was determined that lymphocyte count, NLR, MLR, MHR, and HDL-c could have predictive value for XFS and NLR, MHR, and HDL-c for XFG.

XFS is an extracellular matrix disorder that is often a common cause of secondary glaucoma and the exact responsible pathogenesis has not been fully elucidated.[15] Researchers have focused on the relationship between XFS / XFG and systemic circulatory parameters that indicate inflammation such as WBC, neutrophil count, cytokines, and new hematological indices.[12-17] Furthermore, since XFS is considered a risk factor for CVDs, the possible link between cardiovascular circulatory parameters (serum lipids, homocysteine, UA, alanine aminotransferase, apelin, and asymmetric dimethylarginine) and XFS has also been investigated.[8,9,18,19] So the current work has been planned to investigate hematological and atherogenic indices collectively which are inflammation and cardiovascular risk parameters in patients with XFS and XFG.

Ozgonul et al.[12] reported that XFS / XFG was not related to WBC and neutrophil count, and they also observed a relationship between low lymphocyte count and XFG. In the same study, it was found that NLR was high in both XFS and XFG, and PLR was high only in cases with XFG.[12] In another study, Kurtul et al.[13] did not detect any correlation between neutrophil count and XFS / XFG. In addition, they

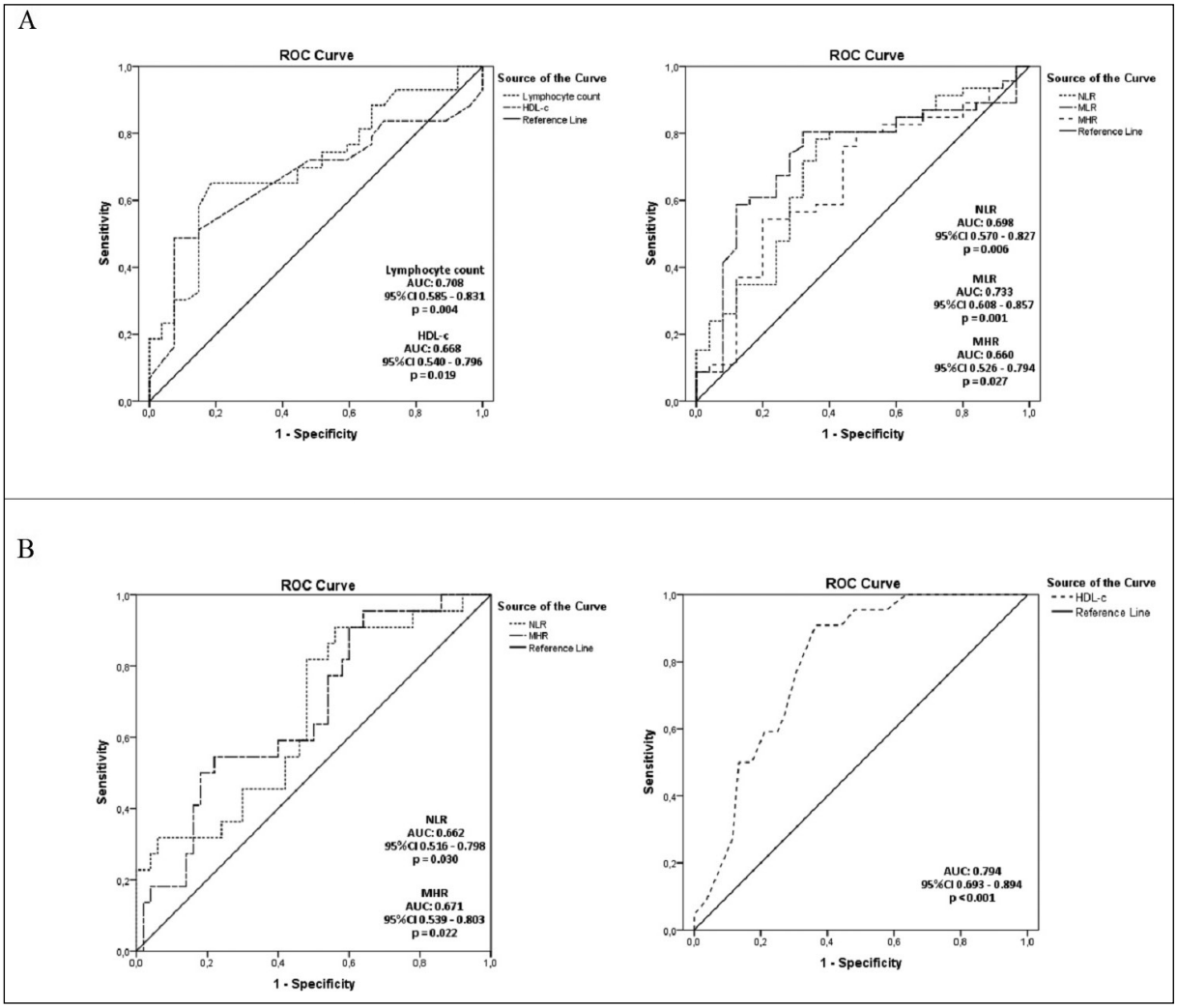

Figure 2: *Receiver operating curve analysis. A) Parameters that can distinguish the presence of exfoliation (exfoliation syndrome + exfoliation glaucoma) from the absence of exfoliation (control group). B) Parameters that can distinguish the presence of exfoliation glaucoma from its absence (control group + exfoliation syndrome).*

determined significant low lymphocyte count and high NLR in XFG patients.[13] Mirza et al.[14] detected significantly higher monocyte count and MHR in patients with XFS / XFG. Besides they showed that there was no significant change in lymphocyte count and lymphocyte/monocyte ratio (LMR).[14] So, the literature review showed that the findings of the hematological indices are contradictory. In our current study, we determined that high WBC and neutrophil count were associated with XFG, and low lymphocyte count was associated with both XFS and XFG. No significant difference was observed between the groups in terms of monocyte count. While NLR and MLR were found to be significantly higher in the XFS and XFG group, MHR was found to be significantly higher only in the XFG group when compared to the control group. Finally, there was no statistically significant difference for PLR among all the groups.

CRP is an evident marker of inflammation and also a recognized mediator of CVDs.[20] Yüksel et al.[16] showed that high sensitive CRP (hsCRP) is not related to XFS / XFG. Atalay et al.[21] found no significant difference for CRP in their study comparing XFG patients and the control group. In another work, Sorkhabi et al.[22] observed that serum CRP levels in XFS patients were statistically significantly higher compared to the control group. In a study investigating the relationship between the presence of exfoliation and YKL-40, Türkyılmaz et al.[23] reported that hsCRP levels were significantly higher in patients with exfoliation than in the control group. In our study, there was no significant difference between all the groups in terms of CRP. These different results may indicate the need for much more comprehensive exclusion criteria when studying the relationship between XFS and these parameters (hematological indices, CRP, etc.), which

are biomarkers of a wide range of inflammation-related diseases.

UA is the end product of purine metabolism. It has been suggested that increased adenosine levels due to hypoxia and ischemia in XFS may increase serum UA levels by catabolic reactions mediated by adenosine deaminase and xanthine oxidase.[24,25] Many experimental and clinical studies have shown that increased UA level is a poor prognostic factor for CVDs by triggering oxidative stress and inflammatory mechanisms.[26] Furthermore, there is a marked link between increased serum UA levels and endothelial dysfunction.[27] Simavlı et al.[18] detected any significant correlation between serum UA levels and XFS. Additionally, Yüksel et al.[16] reported that there is no relationship between XFS and XFG and serum UA levels. In our study, UA levels showed an insignificant slight increase in the XFS group and were found to be significantly higher in the XFG group compared to the control group.

Dyslipidemia causes endothelial dysfunction and prevents the removal of oxidative products, therefore it is closely related to atherogenesis.[28] In this context, the possible relationship between dyslipidemia and exfoliation has been investigated in different studies Mirza et al.[8] found that serum TC, LDL-c, and TG levels were significantly higher in XFS patients, while HDL-c levels were significantly lower. On the other hand, Ulus et al. found no significant difference in serum lipid profile between XFS and the control group in their investigation that searched cardiovascular involvement in XFS.[29] Kurtul et al.[30] determined high serum LDL-c levels and no significant difference in other serum lipids in patients with XFS and XFG. We have achieved lower HDL-c and higher TG levels in XFG patients compared to the other two groups. TC and LDL-c levels showed no significant change in the multigroup comparison. We also found that HDL-c has a predictive value for XFS and XFG. These different results may be due to many factors affecting the atherogenic indices in the blood. For example, in some studies, lipid-lowering treatment was accepted as an exclusion criterion, while in others this was not taken into account. In addition, serum lipids profile can be directly affected by many drugs such as metformin and pioglitazone.[31]

There are some limitations to our research. A small number of patients participated in this study. Anti-inflammatory and lipid-lowering drugs were excluded from consideration because they could have a direct impact on our measurements, but this did not apply to all drugs. Conditions such as acute infection or inflammation, which may go unnoticed, could have an impact on our measurements. This condition had to be ruled out with multiple blood tests. However, we had to make do with the lone blood sample that we had before the operation. We believe that the strict exclusion criteria in this study make up for this shortcoming. There is a statistically significant difference in the laboratory results, but they are still within normal limits. So it is impossible to say whether our results will be beneficial in clinical practice.

This study collectively examines the relationship of XFS / XFG with hematological indices showing inflammation and atherogenic indices reflecting cardiovascular risk, confirming the relationship of the underlying causes of XFS / XFG with LGCI and atherogenesis dependent mechanisms, although not with a direct link. Nevertheless, large scale studies with more stringent exclusion criteria are needed to understand the role of systemic factors in the pathogenesis of XFS / XFG.

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Declaration of Interest

No author has any possible conflict of interest. The authors alone are responsible for the content and preparation of the paper.

Data Avaibility

Not applicable

REFERENCES

1. Bell K, Ozaki M, Mori K, et al. Association of the CYP39A1 G204E Genetic Variant with Increased Risk of Glaucoma and Blindness in Patients with Exfoliation Syndrome. Ophthalmology 2022;129:406-13.
2. Cho HK, Seong H, Kee C, et al. MicroRNA profiles in aqueous humor between pseudoexfoliation glaucoma and normal tension glaucoma patients in a Korean population. Sci Rep 2022;13;12:6217.
3. Wirostko BM, Curtin K, Ritch R, et al. Risk for exfoliation syndrome in women with pelvic organ prolapse: A Utah Project on Exfoliation Syndrome (UPEXS) study. JAMA Ophthalmol 2016;134:1255-62.

4. Besch BM, Curtin K, Ritch R, Allingham RR, Wirostko BM. Association of Exfoliation Syndrome with Risk of Indirect Inguinal Hernia: The Utah Project on Exfoliation Syndrome. JAMA Ophthalmol. 2018;136:1368-74.
5. Shumway C, Curtin K, Taylor S, et al. Association between Obstructive Sleep Apnea and Exfoliation Syndrome: The Utah Project on Exfoliation Syndrome. Ophthalmol Glaucoma 2020;2589-4196.
6. Wang W, He M, Zhou M, Zhang X. Ocular pseudoexfoliation syndrome and vascular disease: a systematic review and metaanalysis. PLoS One 2014;9:e92767.
7. Katsi V, Pavlidis AN, Kallistratos MS, et al. Cardiovascular repercussions of the pseudoexfoliation syndrome. N Am J Med Sci. 2013;5(8):454–4599.
8. Mirza E. Atherogenic indices in pseudoexfoliation syndrome. Eye (Lond). 2019;33:1911-5.
9. Vessani RM, Ritch R, Liebmann JM, Jofe M. Plasma homocysteine is elevated in patients with exfoliation syndrome. Am J Ophthalmol. 2003;136:41-6.
10. Atalar PT, Atalar E, Kilic H, et al. Impaired systemic endothelial function in patients with pseudoexfoliation syndrome. Int Heart J. 2006;47:77-84.
11. Aydın YY, Yıldırım N, Yaz Y, et al. Role of Oxidative Stress in Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma. Turk J Ophthalmol. 2019;30:49:61-7.
12. Ozgonul C, Sertoglu E, Mumcuoglu T, Ozge G, Gokce G. Prediction of Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma by Using Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio. Ocul Immunol Inflamm. 2016;24:665-70.
13. Kurtul BE, Ozer PA, Kabatas EU. Elevated neutrophil-to-lymphocyte ratio in pseudoexfoliation syndrome. Eye (Lond). 2016;30:1045-8.
14. Mirza E, Oltulu R, Katipoğlu Z, Mirza GD, Özkağnıcı A. Monocyte/HDL Ratio and Lymphocyte/Monocyte Ratio in Patients with Pseudoexfoliation Syndrome. Ocul Immunol Inflamm. 2020;28:142-6.
15. Schlötzer-Schrehardt U, Zenkel M. The role of lysyl oxidase-like 1 (LOXL1) in exfoliation syndrome and glaucoma. Exp Eye Res. 2019;189:107818.
16. Yüksel N, Pirhan D, Altintaş O, Cağlar Y. Systemic high-sensitivity C-reactive protein level in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. J Glaucoma. 2010;19:373-6.
17. Gonen T, Guzel S, Keskinbora KH. YKL-40 is a local marker for inflammation in patients with pseudoexfoliation syndrome. Eye (Lond). 2019;33:772-6.
18. Simavlı H, Bucak YY, Tosun M, Erdurmuş M. Serum Uric Acid, Alanine Aminotransferase, Hemoglobin and Red Blood Cell Count Levels in Pseudoexfoliation Syndrome. J Ophthalmol. 2015;2015:914098.
19. Bezci Aygun F, Kocabeyoglu S, Irkec M, et al. Serum Apelin and Asymmetric Dimethylarginine Levels in Patients With Exfoliation Syndrome or Exfoliative Glaucoma. J Glaucoma. 2020;29:593-7.
20. Bisoendial RJ, Boekholdt SM, Menno Vergeer, Stroes ES, Kastelein JJ. C-reactive protein is a mediator of cardiovascular disease. Eur Heart J. 2010;31:2087-91.
21. Atalay K, Savur FG, Kirgiz A, Kaldırım HE, Zengi O. Serum levels of thyroid hormone, vitamin D, vitamin B12, folic acid, C-reactive protein, and hemoglobin in Pseudoexfoliation and primary open angle Glaucoma. J Fr Ophtalmol. 2019;42:730-8.
22. Sorkhabi R, Ghorbanihaghjo A, Ahoor M, Nahaei M, Rashtchizadeh N. High-sensitivity C-reactive Protein and Tumor Necrosis Factor Alpha in Pseudoexfoliation Syndrome. Oman Med J. 2013;28:16-9.
23. Türkyılmaz K, Öner V, Kırbas A, et al. Serum YKL-40 levels as a novel marker of inflammation and endothelial dysfunction in patients with pseudoexfoliation syndrome. Eye (Lond). 2013;27:854-9.
24. Yağci R, Gürel A, Ersöz I, et al. The activities of paraoxonase, xanthine oxidase, adenosine deaminase and the level of nitrite in pseudoexfoliation syndrome. Ophthalmic Res. 2009;42:155-9.
25. Schlötzer-Schrehardt U, Zenkel M, Decking U, et al. Selective upregulation of the A3 adenosine receptor in eyes with pseudoexfoliation syndrome and glaucoma. Invest Ophthalmol Vis Sci. 2005;46:2023-34.
26. Ndrepepa G. Uric Acid and Cardiovascular Disease. Clin Chim Acta. 2018;484:150-63
27. Kanellis J, Kang DH. Uric Acid as a Mediator of Endothelial Dysfunction, Inflammation, and Vascular Disease. Semin Nephrol. 2005;25:39-42.
28. Lu H, Daugherty A. Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35:485-91.
29. Ulus T, Nadir A, Yaz YA, et al. Cardiovascular involvement in patients with pseudoexfoliation syndrome. J Cardiovasc Med (Hagerstown). 2013;14:587-92.
30. Kurtul BE, Kurtul A, Altiaylik Ozer P, Kabatas EU, Ertugrul GT. Serum Lipid Levels in Pseudoexfoliation Syndrome. Semin Ophthalmol. 2017;32:281-4.
31. Bakhteyari A, Nikpour P, Mostafavi FS, et al. Impact of Metformin and Pioglitazone on Serum Level of Tumor Necrosis Factor-Alpha and Lipid Profiles during Implantation Window in Diabetic Rats. Int J Fertil Steril. 2019;13(2):148-53.