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The correlation between pseudoexfoliation syndrome and the Triglyceride-Glucose index

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Abstract

Purpose Pseudoexfoliation (PEX) syndrome is an age-related disease characterized by the accumulation of extracellular material in many ocular structures, skin and internal organs. Recent studies have shown that the Triglyceride-Glucose (TyG) index has clinical importance for the evaluation of vascular damage. The purpose of this study was to determine the relationship between PEX syndrome and TyG index, and to detect the risk in terms of vascular diseases.

Methods In the present study, 50 patients with PEX syndrome who were admitted to the ophthalmology outpatient clinic were evaluated along with 50 others who made up the control group. The Triglyceride-Glucose index was calculated with fasting plasma glucose and triglyceride values.

Results The mean age was 68.2 ± 1.2 years and 61.0% of the patients were male. There was no statistically significant difference between the two groups in terms of blood sugar and lipid profile (except triglyceride) ($p > 0.05$). The TyG index value was 8.9 ± 0.5 in the PEX group and 8.6 ± 0.6 in the control group. This difference was statistically significant ($p = 0.003$). In univariate regression analysis, TyG index (OR = 2.81; CI: 1.37–5.75; $p = 0.005$) was found to be correlated with PEX. In multivariate logistic regression analysis, this correlation remained statistically significant when adjusted for age and sex (OR = 2.89; CI: 1.35–6.18; $p = 0.006$).

Conclusion Results showed that the TyG index was high in patients diagnosed with PEX. The risk of vascular diseases can be determined by examining the TyG index in patients with PEX, and this predetermination would have significant consequences for public health.

Keywords Pseudoexfoliation · Triglyceride-Glucose index · Vascular disease · Atherogenic indicator

Key messages

- Pseudoexfoliation syndrome (PEX) can affect ocular structures as well as other tissues in the body, particularly connective tissue and visceral organs including the heart, lung, liver, skin, blood vessels, optic nerve, and meninges.
- Recent studies have shown that the Triglyceride-Glucose index (TyG) has clinical significance in the assessment of vascular damage.
- In our study, TyG index values, which are accepted as an atherogenic indicator, were found to be significantly higher in the PEX group when compared to the control group.

Introduction

Pseudoexfoliation (PEX) syndrome is an age-related disease characterized by the accumulation of extracellular material in many ocular structures, skin and internal organs [1]. PEX syndrome is reported to affect approximately 10 to 20% of the global population over 60 years of

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age [2]. The identifying feature of PEX syndrome consists of small, white deposits of material in the anterior segment, most commonly the pupillary margin, anterior lens capsule, zonules, and ciliary body, after pupil dilation. Electron microscopic examinations reveal the accumulation of exfoliation fibers in orbital tissues, skin samples, and internal organs. Therefore, PEX syndrome is thought to be a systemic disorder of the extracellular matrix [1].

Studies have predicted that PEX patients may experience endothelial dysfunction through the disruption of the basal membrane with the accumulation of fibrillar material on the arterial wall [3, 4]. Since PEX can be found in the whole body, especially in the vessel walls, it can be associated with different vascular diseases [5]. It is well known nowadays that PEX syndrome is associated with endothelial dysfunction and cardiovascular disease, as described in major reviews [6] (Table 1). Additionally, transient ischemic attack [7], angina pectoris, arterial hypertension, history of myocardial infarction and stroke [8], Alzheimer's disease [9], and sensorineural hearing loss [10] have also been found to be associated with PEX syndrome.

The Triglyceride-Glucose (TyG) index is used as a marker of insulin resistance in healthy individuals. Some studies showed that the TyG index is associated with new-onset diabetes, hypertension, and metabolic syndrome [11–13]. However, in recent studies, it is seen that this index is used as a marker of atherosclerosis in cardiovascular diseases [14, 15]. Zhao et al. found that a higher TyG index was associated with a higher risk of arterial stiffness and microvascular damage. In addition, this study showed that the TyG index has clinical importance for the evaluation of vascular damage [16]. No study investigating PEX syndrome with the TyG index was found in the literature. Because it has been thought that the TyG index may be a predictor of PEX disease, the purpose of the present study was to investigate the correlation between PEX syndrome and the TyG index.

Materials and methods

The study included 50 patients with PEX syndrome between the ages of 40 and 85 who came to the Kırşehir Training and Research Hospital Ophthalmology Clinic for eye examination between August 2021 and January 2022 along with 50 people without PEX material who came in for routine examinations who made up the control group. All patients underwent a detailed ophthalmologic examination including best corrected visual acuity (BCVA), measurement of intraocular pressure, and dilated anterior segment and fundus examination with slit lamp biomicroscopy. The diagnosis of PEX was made upon the observation of white material deposits in the anterior segment, papillary margin, or anterior lens capsule, after pupil dilation.

Demographic data, ocular examination findings, and clinical and laboratory parameters of all participants were obtained from Kırşehir Training and Research Hospital information system and laboratory archives and evaluated retrospectively. The study was approved by the Clinical Research Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine (No: 2021–13/147) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent before their participation.

Those with eye diseases other than PEX syndrome which were previously diagnosed by an ophthalmologist (previous chronic or recurrent inflammatory eye disease, ocular trauma, ocular infection, retinal disease; corneal abnormality; intraocular surgery within the previous three months), those under 18 years of age, those with advanced organ failure (liver, kidney), those with a history of active infection, those who use cigarettes and/or alcohol, and those who had impaired cognitive functions were excluded from the study.

Table 1 Literature review of articles showing positive cardiovascular risk factors in pseudoexfoliation (PEX)

First author (year of publication)	Country (race if available)	Sample size	Type of study	Risk factor	*p*-value or hazard ratio (95% CI)
Chung (2018)	Worldwide	1308 PEX in 11 studies	Meta-analysis before 2017	Cerebrovascular disease	1.76 (1.40–2.22)
Cung (2018)	Worldwide	9583 PEX in 20 studies	Meta-analysis before 2017	Cardiovascular disease	1.61 (1.37–1.90)
Wang (2014)	Meta-analysis	16 studies 8533 PEX and 135,720 controls	Meta-analysis before 2014	Vascular disease	1.72 (1.31–2.26) for any vascular disease, 1.61 (1.22–2.14) for coronary heart disease, 1.59 (1.12–2.23) for cerebrovascular disease, and 2.48 (1.30–4.72) for aortic aneurysm

Abbrevations *PEX*, pseudoexfoliation; *CI*, confidence interval; *OR*, odds ratio.

Routine blood samples were taken after a 12-h fasting period. Biochemical parameters were determined with the Automated Biochemical Analyzer Beckman Coulter AU5800. The Triglyceride-Glucose index was calculated with the formula Ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2] by the researchers in the Microsoft Excel® program.

Due to the retrospective design of the study, we conducted post hoc computational power analysis using G*Power 3.1.9.7 and calculated the power (1-b err probe) to be 0.91 with an effect size of 0.32 with the above-mentioned sample size ($n = 100$).

The Statistical Package for Social Sciences (SPSS) version 22 (IBM SPSS Inc., Chicago, USA) was used for statistical analysis. The normal distribution of data was evaluated through the Kolmogorov–Smirnov test. Normally distributed values were given as mean ± standard deviation, and non-normally distributed values were given as median (min–max). Student's *t*-test or the Mann–Whitney *U* test was used for continuous variables. The chi-square test was used to compare categorical data. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of PEX. The independent correlation between PEX and TyG index was examined in Model 1 that was adjusted for age and sex. With the TyG index score as the test variable and PEX as the status variable, the receiver-operating characteristic (ROC) curve was formulated and the diagnostic value of the TyG index score was determined according to the area under the curve (AUC). The optimal cut-off value was determined using the Youden index. $p < 0.05$ was considered significant for statistical analysis.

Results

A total of 100 participants were included in this study (mean age: 68.2 ± 1.2 years, male: 61.0%). The mean ages of the patients were 69.4 ± 7.8 years in the PEX group and 67.1 ± 15.1 years in the control group. PEX group consisted of 50 patients (30 women and 20 men) and control consisted of 50 patients (31 women and 19 men). The differences in age and gender between the two groups were not statistically significant ($p = 0.34$ and 0.83, respectively). Table 2 shows the demographic and laboratory parameters of the entire study population.

When the PEX group and the control group were compared, there was no statistically significant difference in terms of age ($p = 0.34$), sex ($p = 0.83$), diabetes mellitus ($p = 0.47$), hypertension ($p = 0.77$), and cardiovascular diseases ($p = 0.75$). When the laboratory parameters were examined, there was no statistically significant difference between the two groups in terms of blood sugar and lipid profile (except triglyceride) ($p > 0.05$). In addition to these findings, TyG index value was 8.9 ± 0.5 in the PEX group and 8.6 ± 0.6 in the control group. This difference was statistically significant ($p = 0.003$) (Fig. 1).

In univariate regression analysis, the TyG index (OR = 2.81; CI: 1.37–5.75; $p = 0.005$) was found to be correlated with PEX. When adjusted for age and sex in multivariate logistic regression analysis (Model 1), this correlation remained statistically significant (OR = 2.89; CI: 1.35–6.18; $p = 0.006$) (Table 3).

The ability of the TyG index to predict the presence of PEX was evaluated by ROC curve analysis. It was determined that the TyG index predicted the presence of PEX by a statistically significant margin. The cut-off value of the

Table 2 Characteristics of the sample

Variables	Total ($N = 100$)	PEX ($N = 50$)	Normal ($N = 50$)	*p*
Demographics				
Age (years), mean ± SD	68.2 ± 1.2	69.4 ± 7.8	67.1 ± 15.1	0.34
Gender (female), *n* (%)	61 (61.0)	30 (60.0)	31 (62.0)	0.83
Diabetes mellitus, *n* (%)	33 (33.0)	18 (36.0)	15 (30.0)	0.47
Hypertension, *n* (%)	47 (47.0)	27 (54.0)	20 (40.0)	0.77
Cardiovascular disease, *n* (%)	18 (18.0)	10 (20.0)	8 (16.0)	0.75
Laboratory parameters				
Glucose (mg/dL)	115.7 ± 3.7	121.6 ± 40.2	108.4 ± 28.9	0.06
Total cholesterol (mg/dL)	192.9 ± 4.7	201.1 ± 49.9	186.5 ± 45.6	0.13
Triglyceride (mg/dL)	134.1 ± 6.6	150.6 ± 67.1	117.7 ± 55.1	0.009*
HDL-C (mg/dL)	54.4 ± 4.9	58.4 ± 16.2	49.7 ± 11.0	0.36
LDL-C (mg/dL)	116.7 ± 3.7	121.7 ± 40.1	111.6 ± 30.7	0.17
TyG index	8.8 ± 0.1	8.97 ± 0.5	8.6 ± 0.6	0.003*

Abbrevations *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *PEX*, pseudoexfoliation syndrome; *TyG index*, Triglyceride-Glucose index

*$p < 0.05$

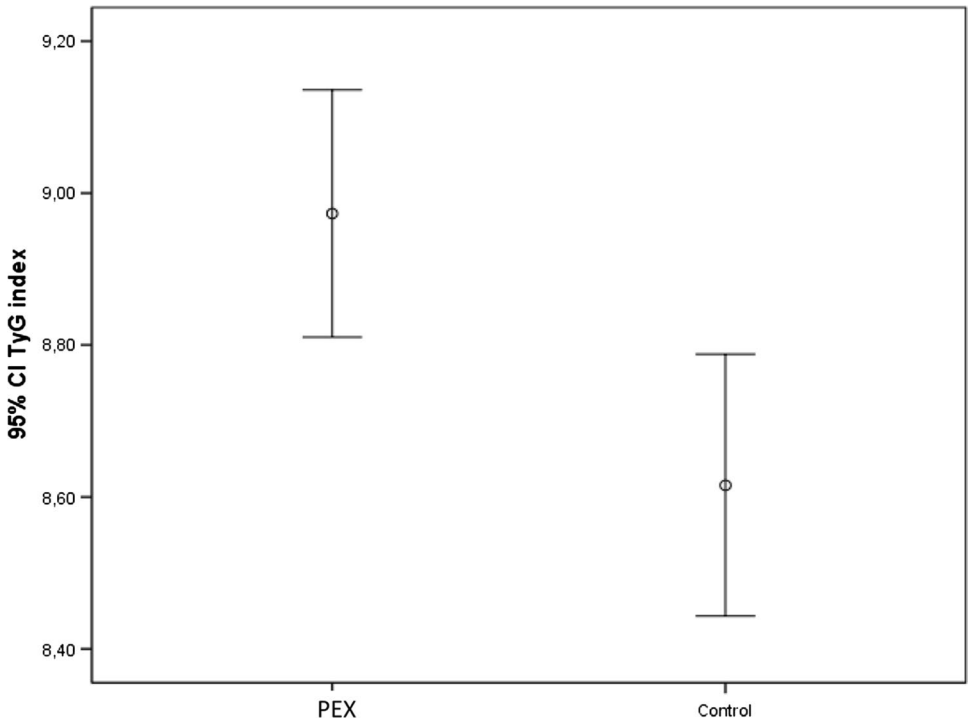

Fig. 1 Comparison of Triglyceride-Glucose (TyG) index between the pseudoexfoliation syndrome (PEX) and control groups

Table 3 Association of TyG index with PEX

	Unadjusted		Model 1	
	OR (95% CI)	*p*	OR (95% CI)	*p*
TyG index	2.81 (1.37–5.75)	0.005*	2.89 (1.35–6.18)	0.006*
Age	-		1.00 (0.96–1.04)	0.99
Gender (female)	-		0.78 (0.33–1.82)	0.56

Abbrevations *OR*, odds ratio; *CI*, confidence interval; *PEX*, pseudoexfoliation syndrome; *TyG index*, Triglyceride-Glucose index. Model 1: Adjusted for age and gender

*$p<0.05$

TyG index for PEX according to Youden's index was found to be 8.82 (AUC = 0.66, sensitivity 64%, specificity = 60%) ($p = 0.006$).

Discussion

In the present study, the TyG index value was found to be statistically higher in the PEX group than the control group and it was determined that this marker significantly predicted the presence of PEX. A high TyG index makes the probability of having PEX approximately 3 times greater. This correlation remained significant even after adjusting for possible confounding factors such as age, sex, and comorbidity. In the light of these findings, it is seen that the present study is the first in the literature when current studies are examined.

Atherosclerosis and vascular damage are considered to be important risk factors for cardiometabolic diseases. The TyG index has also emerged as a reliable marker of atherosclerosis [16]. Recent studies have shown the correlation of the TyG index with many vascular diseases. Luo et al. demonstrated in their study that a high TyG index level was correlated with the risk of major cardiac and cerebrovascular events [17]. Moreover, Alessandra et al. found that a high TyG index was also positively correlated with symptomatic coronary artery disease and that this marker could be used as a marker of atherosclerosis [18]. In the light of the results in the present study, it can be said that the TyG index is a statistically independent risk factor that also predicts the presence of PEX. However, more studies will be needed in order to elucidate the etiopathogenesis of PEX disease and better determine the role of the TyG index.

PEX syndrome is an age-related systemic disease affecting the anterior structures of the eye. Its worldwide distribution varies greatly across ethnicities and geographic regions. Exfoliative material consists of abnormal cross-linked fibrils deposited in certain organs such as the heart, blood vessels, lungs, or meninges, and often in the anterior structures of the eye. Although there are many studies on its pathophysiology, the process still remains unclear [19]. Possible mechanisms related to the effect of PEX on vascular structures were predicted. Pericellularly accumulating material may disrupt the basal membrane of cells and lead to degenerative fibrillopathy. These deposits may cause endothelial dysfunction [20]. Koliakos et al. demonstrated experimentally that the concentration of Endothelin-1, which is a potent vasoconstrictor in

plasma and aqueous humor, increased in PEX patients [21]. Many studies in the literature show that PEX is related to the increased risk of vascular diseases. In the meta-analysis by Wang et al., sixteen eligible studies that included 8533 PEX patients and 135,720 control patients were reviewed. This analysis revealed that having PEX increased the probability of vascular disease by 72% compared with the control group (coronary heart disease, cerebrovascular disease, aortic aneurysm) [22].

It is important to note that there is adequate evidence to justify the possible mediation of PEX and cardiovascular diseases by cardiovascular markers. For instance, recent studies have shown that Adropin, a peptide hormone that is expressed in the liver and the brain and has a protective role in endothelial cells, was associated with cardiovascular disease [23]. However, there are also studies reporting that PEX is not associated with cardiovascular diseases [24, 25]. In this regard, Yüksel et al. showed that high-sensitivity C-reactive protein known as a predictor of vascular atherosclerotic events such as coronary artery disease, atherothrombosis, and peripheral vascular disease was not elevated in patients with PEX [25]. In the current study, we demonstrated that TyG index values, which are considered a novel atherogenic indicator, were found to be significantly higher in the patient group diagnosed with PEX compared to the control group. However, it is difficult to determine whether the elevation of TyG causes PEX by inducing atherogenic events or whether increased vascular events due to the presence of PEX increase the TyG index. Prospective cohort studies are needed to evaluate the clinical implications of current findings.

Among the limitations of the study were the fact that it was cross-sectional, the sample size was small, and it was a single-center study.

Conclusions

Results of the study showed that the TyG index was found to be high in patients diagnosed with PEX. Therefore, detection of PEX during routine ophthalmological examination may be a warning sign of vascular diseases. Systemic evaluations will undoubtedly have important consequences for public health as a result.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the (Clinical Research Ethics Committee of Kırşehir AhiEvran University Faculty of Medicine (No: 2021–13/147) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

References

1. Ritch R, Schlötzer-Schrehardt U (2001) Exfoliation syndrome. Surv Ophthalmol 45(4):265–315. https://doi.org/10.1016/S0039-6257(00)00196-X
2. Ringvold A (1999) Epidemiology of the pseudo-exfoliation syndrome. Acta Ophthalmol Scand 77:371–375
3. Katsi V, Pavlidis AN, Kallistratos MS, Fitsios A, Bratsas A, Tousoulis D et al (2013) Cardiovascularrepercussions of the pseudoexfoliation syndrome. N Am J Med Sci 5(8):454–459. https://doi.org/10.4103/1947-2714.117294
4. Uri Aviv MD, Ner DB, Sharif N, Gur Z, Achiron A (2017) Pseudoexfoliation: an ocular finding with possiblesystemic implications. IMAJ 19(1):49–54
5. Yaz YA, Yıldırım N, Yaz Y, Tekin N, İnal M, Şahin FM (2019) Role of oxidative stress in pseudoexfoliationsyndrome and pseudoexfoliation glaucoma. Turk J Ophthalmol 49(2):61–67. https://doi.org/10.4274/tjo.galenos.2018.10734
6. Mansour AM, Konstas AG, Mansour HA, Charbaji AR, El Jawhari KM (2021) A case-cohort study of exfoliation risk factors and literature review. Middle East Afr J Ophthalmol 28(1):36–50
7. Repo LP, Teräsvirta ME, Koivisto KJ (1993) Generalized transluminanceof the iris and the frequency of the pseudoexfoliation syndrome in the eyes of transient ischemic attackpatients. Ophthalmol 100(3):352–355. https://doi.org/10.1016/S0161-6420(93)31642-8
8. Mitchell P, Wang JJ, Smith W (1997) Association of pseudoexfoliation syndrome with increased vascular risk. Am J Ophthalmol 124(5):685–687. https://doi.org/10.1016/S0002-9394(14)70908-0
9. Linner E, Popovic V, Gottfries C-G, Jonsson M, Sjögren M, Wallin A (2001) The exfoliation syndrome in cognitive impairmentof cerebrovascular or Alzheimer's type. Acta Ophthalmol Scandinavica 79(3):283–285. https://doi.org/10.1034/j.1600-0420.2001.790314.x
10. Cahill M, Early A, Stack S, Blayney AW, Eustace P (2002) Pseudoexfoliation and sensorineural hearing loss. Eye 16(3):261–266. https://doi.org/10.1038/sj/eye/6700011
11. Zhang M, Wang B, Liu Y, Sun X, Luo X, Wang C et al (2017) Cumulative increased risk of incident type 2 diabetes mellitus with increasing triglyceride glucose index in normal-weight people: the Rural Chinese Cohort Study. Cardiovasc Diabetol 16(1):30. https://doi.org/10.1186/s12933-017-0514-x
12. Zheng R, Mao Y (2017) Triglyceride and glucose (TyG) index as a predictor of incident hypertension: a 9 year longitudinal population-based study. Lipids Health Dis 16(1):1–7. https://doi.org/10.1186/s12944-017-0562-y
13. Moon S, Park JS, Ahn Y (2017) The cut-of values of triglycerides and glucose index for metabolic syndrome in american and korean adolescents. J Korean Med Sci 32(3):427–433. https://doi.org/10.3346/jkms.2017.32.3.427
14. Alizargar J, Bai CH, Hsieh NC, Wu SFV (2020) Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. Cardiovasc Diabetol 19(1):1–3
15. Won KB, Park GM, Lee SE, Cho IJ, Kim HC, Lee BK, Chang HJ (2018) Relationship of insulin resistance estimated by triglyceride glucose index to arterial stiffness. Lipids Health Dis 17(1):268. https://doi.org/10.1186/s12944-018-0914-2

16. Zhao S, Yu S, Chi C, Fan X, Tang J, Ji H, Teliewubai J, Zhang Y, Xu Y (2019) Association between macro- and microvascular damageand the triglyceride glucose index in community-dwelling elderly individuals:the Northern Shanghai Study. Cardiovasc Diabetol 18(1):95. https://doi.org/10.1186/s12933-019-0898-x
17. Luo E, Wang D, Yan G, Qiao Y, Liu B, Hou J, Tang C (2019) High triglyceride–glucose index is associated with poor prognosis in patients with acute ST-elevation myocardial infarction after percutaneous coronary intervention. Cardiovasc Diabetol 18(1):150. https://doi.org/10.1186/s12933-019-0957-3
18. da Silva A, Caldas AP, Hermsdorff HH, Bersch-Ferreira ÂC, Torreglosa CR, Weber B, Bressan J (2019) Triglyceride-glucose index is associated with symptomatic coronary artery disease in patients in secondary care. Cardiovasc Diabetol 18(1):1–8. https://doi.org/10.1186/s12933-019-0893-2
19. Schweitzer C (2018) Pseudoexfoliation syndrome and pseudoexfoliation glaucoma. J Fr Ophtalmol 41(1):78–90. https://doi.org/10.1016/j.jfo.2017.09.003
20. Katsi V, Pavlidis AN, Kallistratos MS, Fitsios A, Bratsas A et al (2013) Cardiovascular repercussions of the pseudoexfoliation syndrome. N Am J Med Sci 5:454–459. https://doi.org/10.4103/1947-2714.117294
21. Koliakos GG, Konstas AG, Schlotzer-Schrehardt U, Hollo G, Mitova D et al (2004) Endothelin-1 concentration is increased in the aqueous humour of patients with exfoliation syndrome. Br J Ophthalmol 88:523–527. https://doi.org/10.1136/bjo.2003.028290
22. Wang W, He M, Zhou M, Zhang X (2014) Ocular pseudoexfoliation syndrome and vascular disease: a systematic review and meta-analysis. PLoS ONE 25;9(3):e92767. https://doi.org/10.1371/journal.pone.0092767
23. Oğurel T, Oğurel R, Topuz M, Örnek N, Örnek K (2016) Plasma adropin level in patients with pseudoexfoliation. Int Ophthalmol 36(5):737–742. https://doi.org/10.1007/s10792-016-0185-8
24. Lesiewska H, Łukaszewska-Smyk A, Odrowąż-Sypniewska G, Krintus M, Mańkowska-Cyl A, Malukiewicz G (2017) Chosen vascular risk markers in pseudoexfoliation syndrome: an age-related disorder. J Ophthalmol 2017:5231095. https://doi.org/10.1155/2017/5231095)
25. Yüksel N, Pirhan D, Altintaş O, Cağlar Y (2010) Systemic high-sensitivity C-reactive protein level in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. J Glaucoma 19(6):373–376. https://doi.org/10.1097/IJG.0b013e3181bdb570