

GENDER RELATED DIFFERENCES IN HUMOR MATRIX METALLOPROTEINASES MMP-2 ACTIVITY AND TISSUE INHIBITOR OF MATRIX METALLOPROTEINASES IN PATIENTS WITH PSEUDOEXFOLIATION SYNDROME/GLAUCOMA

Jasmina Djordjević-Jocić, Gordana Zlatanović, Dragan Veselinović, Gordana Stankovic-Babić, Sonja Cekić¹

Pseudoexfoliation syndrome (PEX Sy) is a common age-related disorder of the extracellular matrix that is frequently associated with severe secondary chronic open-angle glaucoma and cataract. Pseudoexfoliation glaucoma (PEX gl) is one of the most common causes of optic disc damage, low visual accuracy, damage of visual field and blindness. Deposits of white material on the anterior lens surface are the most consistent and important diagnostic feature of PEX syndrome/glaucoma. It is thought that PEX represents aberrant extracellular matrix synthesis.

The aim of this paper was to evaluate gender related difference in level of matrix metalloproteinases MMP-2 and tissue inhibitor of matrix metalloproteinases (TIMP-1, TIMP-2, TIMP-3, TIMP-4) in aqueous humor in patients with pseudoexfoliation syndrome/glaucoma.

Aqueous humor was aspirated during surgery from 15 patients with PEX syndrome without glaucoma, 42 patients with PEX glaucoma, 36 patients with POAG and 14 age-matched control patients with cataract during cataract surgery or trabeculectomy. Data about medical history, medications, and demographic information were obtained from case notes. In all patients we determined Intra Ocular Pressure (IOP) by (measurement by Goldman applanation tonometry), PEX appearance (determined with slit lamp examination). Fluorokine MultiAnalite Profiling kits (R&D Systems, Minneapolis, MN) and Luminex technology (Luminex Corporation, Austin, TX) were used to simultaneously measure MMP-2, and TIMP-1, TIMP-2, TIMP-3 and TIMP-4 in aqueous humor samples.

Patients with PEX glaucoma are older and of male sex than patients with POAG. Male patients with PEX glaucoma and POAG were significantly older than female patients. Patients with PEX Sy have bilateral ocular changes more often compared to other groups. There were no significant gender differences in aqueous humor MMP-2, TIMP-2, TIMP-3, TIMP-4 levels among examined groups. In the group with PEX syndrome significantly higher level of TIMP-1 was registered in male patients.

Despite significant variation in humor protease and protease inhibitors level among patients with different clinical forms of glaucoma and cataract there are not important gender related difference. Only level of TIMP-1 is significantly higher in male patients with PEX Syndrome. The level of TIMP-4 is significantly higher in male older patients with PEX glaucoma. *Acta Medica Medianae 2010;49(1):5-12.*

Key words: gender, matrix metalloproteinases, MMP-2, inhibitor, pseudoexfoliation, syndrome, glaucoma, TIMP

Ophthalmology Clinic, Clinical Center Niš

Contact: Jasmina Đorđević- Jocić

Klinika za oftalmologiju

Bul. dr Zorana Đinđića 48, 18000 Niš

e-mail: jdjordjevic.jocic@gmail.com

Introduction

Pseudoexfoliation syndrome (PEX Sy) is a common age-related disorder of the extracellular matrix that is frequently associated with severe chronic secondary open-angle glaucoma and cataract. PEX syndrome may affect up to 30% of people older than 60 in a worldwide distribution. Pseudoexfoliation glaucoma (PEX gl) is one of the most common cause of optic disc damage, low

visual acuity, damage of visual field and blindness (1-4). In Framingham Eye Study,(5) the age prevalence of PEX Sy in patients without glaucoma raises up to 0.6% in age of 52-64 years, and up to 5% in patients with 75-85 years of age. Aasveld (6) showed similar findings: 0,4% in patients 50-59 years of age and 7,9% for 80-89 years of age. The common clinical findings in PEX syndrome are: white deposits in pupillary region and anterior lens surface, iridopathy, zonulopathy, endothelopathy, iris pigment dispersion and amplified trabecular pigmentation in chamber angle, increased Intra Ocular Pressure (IOP) with high daily variation followed by fast impairment of optic nerve head and progressive lost of visual field (7).

Deposits of the white material on the anterior lens surface are the most consistent and important diagnostic features of PEX syndrome/glaucoma. The classic pattern of three distinct zones becomes visible when the pupil is fully dilated. Whereas the classic picture of manifest PEX has been often described, the early stages of exfoliation formation have not been well defined. Next to the lens, exfoliation material is most prominent at the papillary border. Pigment loss from the iris sphincter region and its deposition on anterior chamber structures is a hallmark of PEX syndrome/glaucoma (8-9).

Similarly, it is considered that an excessive accumulation of extracellular material in the juxtacanalicular tissue of the meshwork has been postulated to cause an increased outflow resistance in eyes with pseudoexfoliation glaucoma (PEX gl). Similarly an impaired trabecular meshwork matrix turnover, which is critical to the regulation and maintenance of aqueous humor outflow, has been included in the development of primary open angle glaucoma (POAG) (10).

Although the precise pathogenesis and its mode of evolution remain unclear, it is thought that PEX represents aberrant extracellular matrix synthesis. Extracellular matrix turnover is mediated by matrix metalloproteinases (MMPs), a large family of endopeptidases with variable substrate spectra, whose presence has been described in the human aqueous humor. The activity of these enzymes is regulated in part by specific endogenous inhibitors and tissue inhibitors of metalloproteinases (TIMPs) (11-16).

Aim

The aim of this paper was to evaluate gender related differences in the level of matrix metalloproteinases MMP-2 and tissue inhibitor of matrix metalloproteinases (TIMP-1,-2,-3,4) in aqueous humor in patients with glaucoma.

Materials and methods

Aqueous humour was obtained from patients who underwent a routine cataract surgery. All patients had slit lamp examination the day before or the morning before surgery by the same investigator (SLH) and they were categorised into four main groups:

I group: Pseudoexfoliation syndrome (PEX Sy) 15 patients

II group Pseudoexfoliation glaucoma (PEX Glaucoma) 42 patients

III group Primary Open Angle Glaucoma (POAG) 36 patients

IV group Control (patients with cataract). 14 patients

Data on medical history, medications, and demographic information were obtained from the case notes. Intra Ocular Pressure (IOP) was determined in all patients by Goldman applanation tonometry and PEX appearance (determined with slit lamp examination)

Aqueous humour sampling

Aqueous humor was aspirated during surgery from 15 patients with PEX syndrome without glaucoma, 42 patients with PEX glaucoma, 36 patients with POAG and 14 age-matched control patients with cataract during cataract surgery or trabeculectomy.

Aqueous humor (80–100 μ L) was withdrawn through an ab externo limbal paracentesis site with a 27-gauge needle on a tuberculin syringe. Meticulous care was taken to avoid touching intraocular tissues and to prevent contamination of aqueous samples with blood. The samples were immediately frozen in liquid nitrogen and stored at -80°C . Samples of serum were also collected from patients of each group and equally stored. Some of the patients with PEX glaucoma or POAG had undergone previous argon laser trabeculoplasty and received various antiglaucoma medications.

Patients with other ocular or systemic disease, such as inflammatory diseases or diabetes mellitus, were excluded from the study. Patients had given a written consent prior to the operative treatment whereas aqueous humour was obtained prior to the procedure. Research protocol was approved by the clinical research ethics committee of the Clinical Center in Nis.

A total of 107 aqueous humour samples were collected; 60 samples were from female subjects and 47 were from male.

Enzyme immunoassays

Enzyme Immunoassays of MMPs and TIMPs

Fluorokine MultiAnalite Profiling kits (R&D Systems, Minneapolis, MN) and Luminex technology (Luminex Corporation, Austin, TX) were used to simultaneously measure MMP-2, and TIMP-1, TIMP-2, TIMP-3 and TIMP-4 in aqueous humor samples.

Statistical analysis:

Fisher's accurate probability test was used for nonparametric variable analysis. Results of the immuno-enzyme examination were expressed as mean \pm SD. Kolmogorov-Smirnov test was used to determine normal distribution of the data and Levene's tests for homogeneity of variance was performed. Group symbols were compared and analysed using One-Way ANOVA procedure. The robustness of ANOVA test was determined with the Welch test. Tamhane's T2 test was used if equality of variances did not occur while Tukey HSD test was used if the tested variances were equal.

The results are presented with Simple Bar Summaries for Groups of Cases.

Results

Baseline characteristics of the examined patients are shown in Table 1. There were significant differences in gender distribution among examined groups of patients. The patients with PEX

glaucoma were older and of male gender than those with POAG (Table 1).

Patients with PEX Sy had bilateral ocular changes more often compared to other groups (Table 1).

There were no significant gender differences in aqueous humour MMP-2 levels among the examined groups (Figure 1).

There were no significant gender differences in aqueous humour TIMP-1 levels among the examined groups except in the group with PEX syndrome. In this group significantly higher level of TIMP-1 was registered in male patients ($p < 0.05$) (Figure 2).

There were no significant gender differences in aqueous humour TIMP-2 levels among the examined groups (Figure 3).

There were no significant gender differences in aqueous humour TIMP-3 levels among the examined groups (Figure 4).

There was significant gender difference in aqueous humour TIMP-4 levels among examined groups (Figure 5).

There were no significant gender differences in the average age among patients with cataract and PEX syndrome. Male patients with PEX glaucoma and POAG were significantly older than female patients ($p < 0.05$) (Figure 6).

Table 1. Baseline characteristics of patients

	cataract n=15	PEX Sy n=14	PEX glaucoma n=42	POAG n=36
Male/female N (%)	6/9 (40/60)	5/9 (36/64)	26/16 (62/38) a***	10/26 (28/72)
age (years)	64.8±3.7	66.8±4.6	68.9±7.6 b*	62.8±8.8
IOP (mmHg)	11.07±5.4	18.14±1.8	43.1±13 c***	34.8±11.4
PEX apperence N (%)	-	14 (100)	42 (100)	-
unilateral/bilateral N (%)	8/6 (57/43)	3/11 (21/79) d*	22/20 (52/48)	17/19 (47/53)

Differences were significant on the level * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$

Fisher's test: d* $p < 0.05$ vs other groups

ANOVA: age ($F=4.6$, $p < 0.05$); IOP ($F=32.2$, $p < 0.001$);

Post Hoc; Tukey HSD or Tamhane's T2: a*** $p < 0.001$ vs POAG; b* $p < 0.05$, c*** $p < 0.001$ vs. POAG;

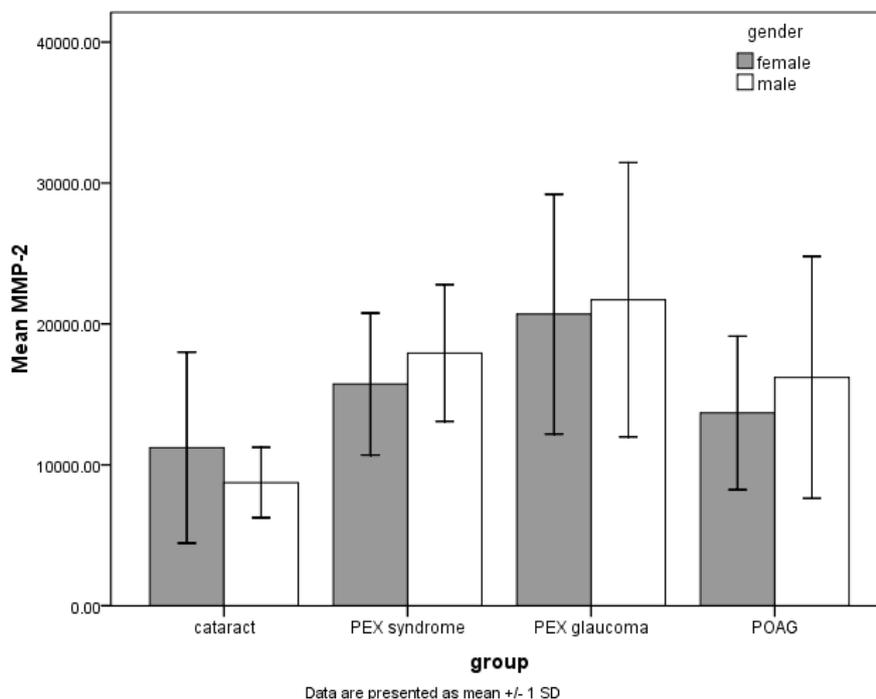


Figure 1 Comparison of gender differences of aqueous humor MMP-2 (matrix metal proteinase) levels among PEX Sy (pseudoexfoliation syndrome), PEX glaucoma (pseudoexfoliation glaucoma), POAG (primaru open angle glaucoma) and cataract (control) groups.

Data were represented as mean±(SEM) as depicted on the bar chart summaries for groups of cases. The group means were compared and analyzed using Student t test assuming unequal variances. A p value < 0.05 was considered to be statistically significant. NS for all parameters

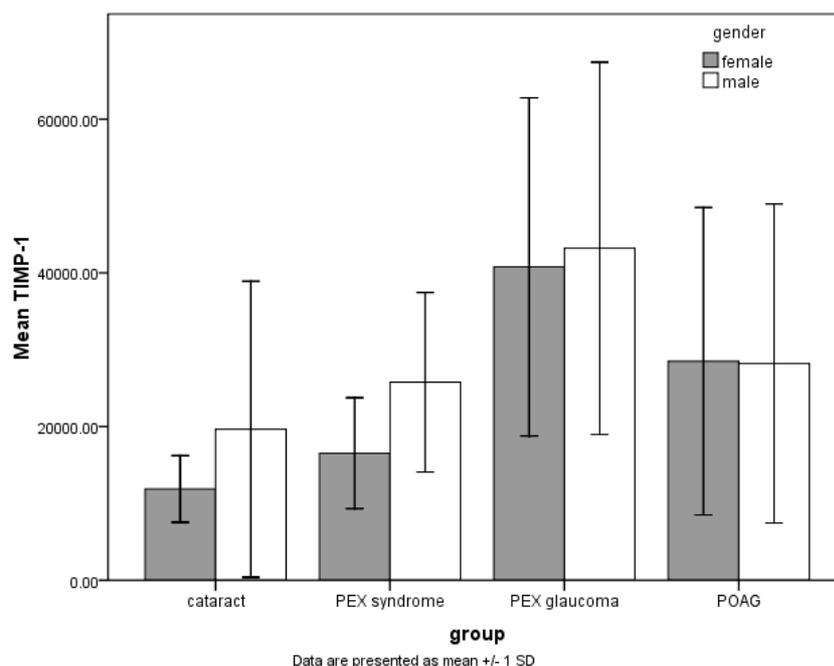


Figure 2 Comparison of gender difference of aqueous humour TIMP-1 (tissue inhibitors of matrix metalloproteinases-1) levels among PEX Sy (pseudoexfoliation syndrome), PEX glaucoma (pseudoexfoliation glaucoma, POAG (primary open angle glaucoma) and cataract (control) groups.

Data were represented as mean \pm (SEM) as depicted on the bar chart summaries for groups of cases. The group means were compared and analyzed using Student t test assuming unequal variances. A p value <0.05 was considered to be statistically significant. *p<0.05 vs. female

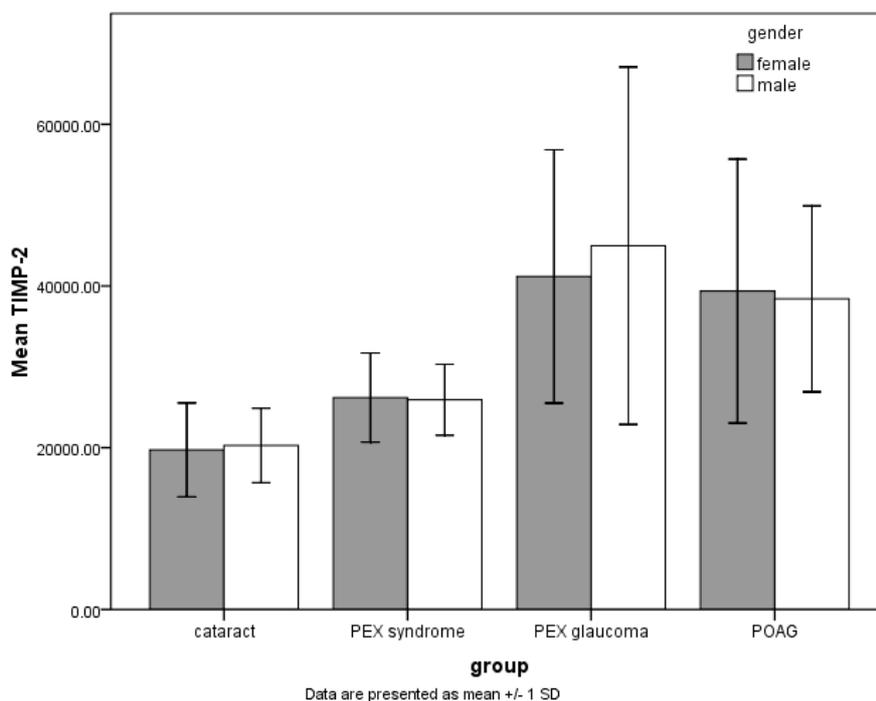


Figure 3 Comparison of gender differences of aqueous humor TIMP-2 (tissue inhibitors of matrix metalloproteinases-2) levels among PEX Sy (pseudoexfoliation syndrome), PEX glaucoma (pseudoexfoliation glaucoma, POAG (primaru open angle glaucoma) and cataract (control) groups

Data were represented as mean \pm (SEM) as depicted on the bar chart summaries for groups of cases. The group means were compared and analyzed using Student t test assuming unequal variances. A p value <0.05 was considered to be statistically significant. NS for all parameters

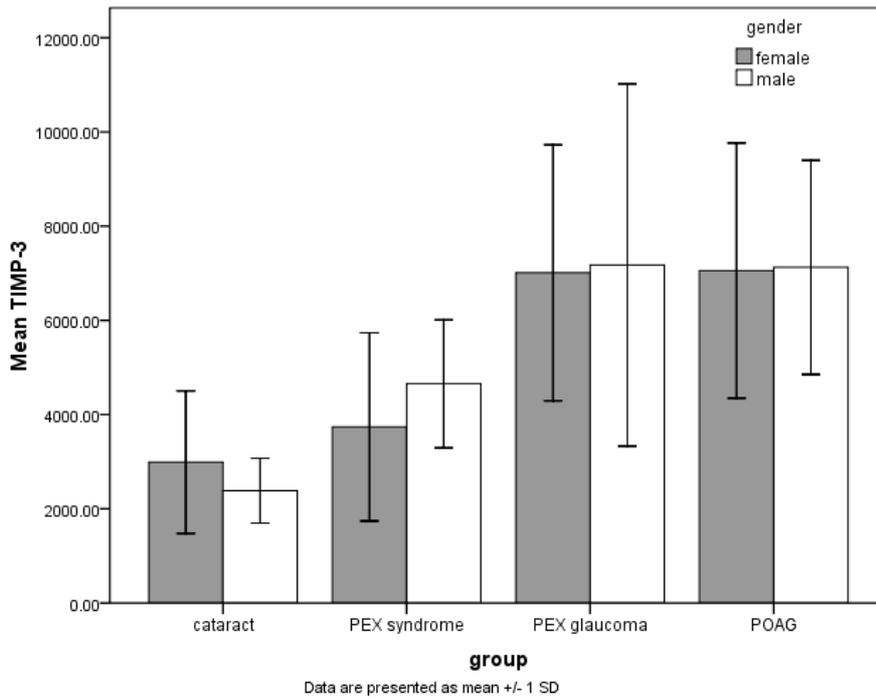


Figure 4 Comparison of gender differences of aqueous humor TIMP-3 (tissue inhibitors of matrix metalloproteinases-2) levels among PEX Sy (pseudoexfoliation syndrome), PEX glaucoma (pseudoexfoliation glaucoma, POAG (primary open angle glaucoma) and cataract (control) groups.

Data were represented as mean±(SEM) as depicted on the bar chart summaries for groups of cases. The group means were compared and analyzed using Student t test assuming unequal variances. A p value <0.05 was considered to be statistically significant. NS for all parameters

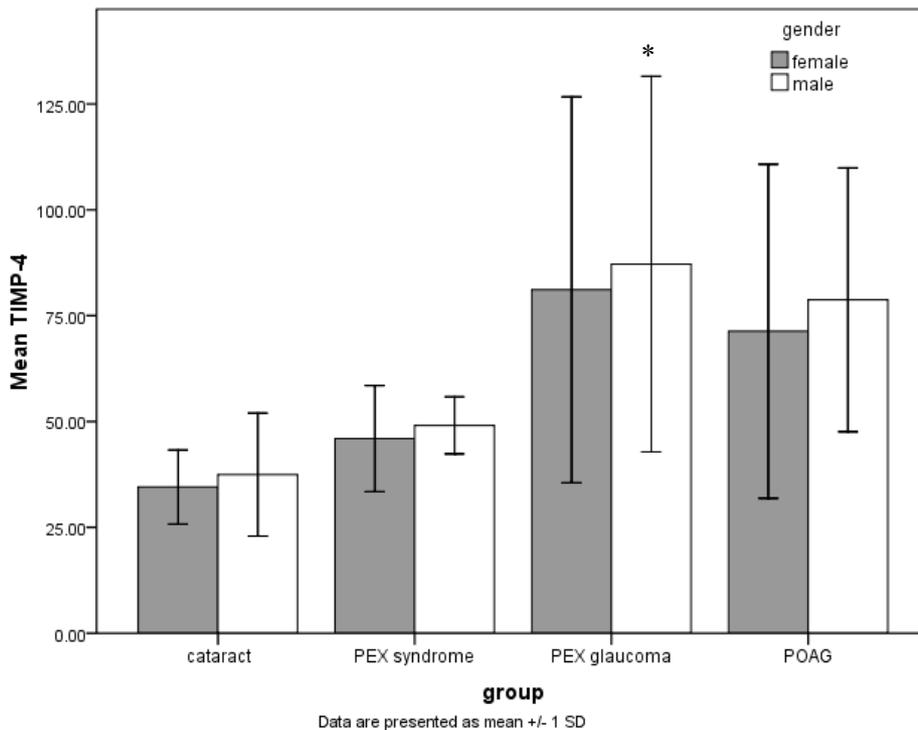


Figure 5 Comparison of gender differences of aqueous humor TIMP-4 (tissue inhibitors of matrix metalloproteinases-2) levels among PEX Sy (pseudoexfoliation syndrome), PEX glaucoma (pseudoexfoliation glaucoma, POAG (primaru open angle glaucoma) and cataract (control) groups.

Data were represented as mean±(SEM) as depicted on the bar chart summaries for groups of cases. The group means were compared and analyzed using Student t test assuming unequal variances. A p value <0.05 was considered to be statistically significant. *p<0.05

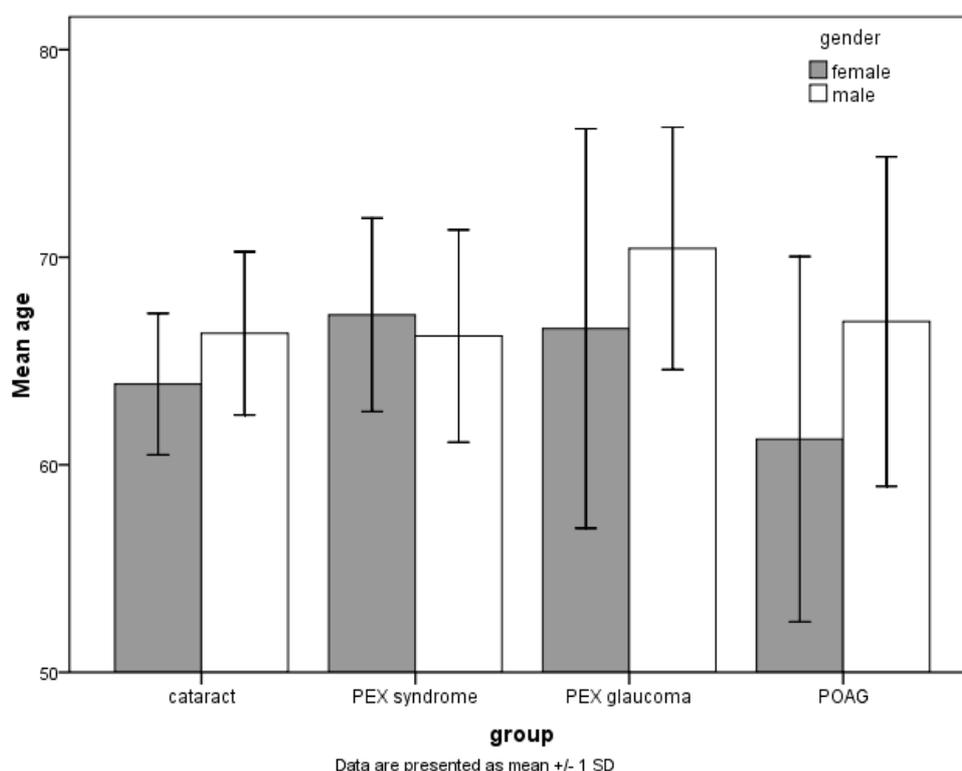


Figure 6. Comparison of gender differences when average age is concerned among PEX Sy (pseudoexfoliation syndrome), PEX glaucoma (pseudoexfoliation glaucoma), POAG (primaru open angle glaucoma) and cataract (control) groups.

Data were represented as mean±(SEM) as depicted on the bar chart summaries for groups of cases. The group means were compared and analyzed using Student t test assuming unequal variances. A p value <0.05 was considered to be statistically significant. *p<0.05 vs male

Discussion

Pseudoexfoliative Syndrome is extracellular matrix disease characterised by excessive production and progressive accumulation of fibrillar material in anterior ocular segment, which is barely visible on pupular edge and anterior lens surface. In the conducted study, patients with PEX glaucoma were older than other examined patients especially compared to POAG. The male patients were significantly older in the group with PEX glaucoma and POAG (Table 1, Figure 6). The male patients suffered from PEX glaucoma (Table 1) more commonly. This is in line with literature data, that PEX glaucoma incidence raises with age. Arnarsson, (5) in Reykjavik Eye Study - Iceland showed prevalence of PEX in 10,7% of patients. Astrom (6) et al. showed PEX Sy prevalence of 23% in patients <66 years of age. The incidence raises up to 61% in population older than 87 years. Interestingly, both studies showed a slightly higher prevalence of PEX in female patients. Also, Tarkkanen et al. showed (17) that incidence of PEX increases between 80-90 years of age.

In the conducted study, patients with PEX Sy had more common bilateral ocular changes, while patients with PEX glaucoma had more common unilateral ocular changes (Table 1). Most patients with pseudoexfoliation (PEX) syndrome showed only unilateral ocular involvement. However, the general nature of the

disorder suggests that PEX syndrome is clinically asymmetric rather than strictly unilateral (18). Patients with PEX glaucoma had a higher value of IOP and accelerated course of disease compared to POAG patients (Table 1). Topouzis (2, 19) et al. in the Thessaloniki Eye study, which included 2261 patients, showed unilateral ocular changes in 11,9% of patients, with a higher incidence among older than 80 years.

Matrix metalloproteinases are a large family of calcium- and zinc-dependent extracellular endoproteinases that degrade extracellular matrix (ECM) proteins. MMPs have been divided into six classes based on substrate specificity and sequence similarities: collagenases, gelatinases, stromeolysin, matrilysins, membrane- tip MMPs and other MMPs. The enzymes are synthesized and secreted as inactive proenzymes and activated by proteolytic cleavage of a polypeptide from the molecule. MMPs are activated by anspecific plasma and specific tissue-derived inhibitors, such as alfa macroglobulins and TIMPs. Four TIMPs have been described to date that actually have the capacity to inhibit all active MMPs. (12-15)

In PEX glaucoma eyes pseudoexfoliation material accumulates in ocular tissues, including TM. The origin of this material is not fully understood. There has been a great deal of debate whether this pseudoexfoliation material or pigment particles or both can block aqueous outflow and be responsible for the elevated IOP.

The MMPs and TIMPs present in aqueous humor may participate in the remodeling of ECM in the tissue encircling frontal ocular chambers. It is considered that disequilibrium between MMPs and TIMPs levels may be an important factor in the maintenance and regulation of ECM in the TM (16,20-22). The studies investigating gender related differences in MMP and TIMP activity are very rare.

We found significantly higher activity of aqueous humor TIMP-1 in male patients with PEX syndrome, and also we found significantly higher activity of aqueous humor TIMP-4 in older male patients in group with PEX glaucoma. Other investigated TIMPs and MMP-2 did not show any significant gender differences (Figure 1-5). Many literature data indicate interrelation of TIMP-1

and MMP-2. Their disbalance, however, can have a great impact on extracellular matrix disorders in patients with PEX Sy. Also we must bear in the mind that the impaired balance of MMP could lead to a complicated bacterial or viral infection of the eye, especially after cataract surgery (23).

Conclusion

Despite significant variation in the humour protease and the protease inhibitors level in patients with different clinical types of glaucoma and cataract there are no significant gender related differences but the very level of TIMP-1 which is significantly higher in male patients with PEX Syndrome. The level of TIMP-4 is significantly higher in male older patients with PEX glaucoma.

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POLNO USLOVLJENE RAZLIKE U AKTIVNOSTI MATRIKS METALOPROTEINAZE MMP-2 I TKIVNIH INHIBITORA MATRIKS METALOPROTEINAZA OČNE VODICE BOLESNIKA SA PSEUDOEKSFOLIJATIVNIM SINDROMOM/ GLAUKOMOM

Jasmina Djordjević-Jocić, Gordana Zlatanović, Dragan Veselinović, Gordana Stankovic-Babić, Sonja Cekić¹

Pseudoeksfolijativni sindrom (PEX sy) je bolest ekstracelularnog matriksa, češća kod starijih osoba i često udružena sa uznapredovalim hroničnim sekundarnim glaukomom otvorenog ugla (PEX glaukom) i kataraktom. PEX glaukom je jedan od najčešćih uzroka propadanja optičkog diska, slabe vidne oštine, propadanja širine vidnog polja i slepila. Smatra se da prisustvo PEX materijala predstavlja posledicu aberantne sinteze ekstracelularnog matriksa koja je u bliskoj vezi sa cirkulacijom očne vodice.

Cilj ove studije bio je da ispita polno uslovljene razlike u nivoima matriks metaloproteinaze MMP-2 i tkivnih inhibitora matriksnih metaloproteinaza (TIMP-1, TIMP-2, TIMP-3 i TIMP-4) u očnoj vodici bolesnika sa PEX sindromom, PEX glaukomom i primarnim glaukomom otvorenog ugla (POAG).

Uzorci očne vodice su aspirirani za vreme rutinske hirurgije katarakte i trabekulektomije od 15 bolesnika sa PEX sindromom, od 42 bolesnika sa PEX glaukomom, 36 bolesnika sa primarnim glaukomom otvorenog ugla i od 14 bolesnika sa kataraktom. Podaci o početku bolesti, terapiji i demografskim karakteristikama dobijeni su direktno od bolesnika. Svim bolesnicima je izmeren intraokularni pritisak (IOP) Goldmanovim aplanacionim tonometrom, i definisano prisustvo PEX materijala pomoću biomiskoskopa. Vrednosti MMP-2, TIMP-1, TIMP-2, TIMP-3, TIMP-4 u očnoj vodici bolesnika određivane su multipleks metodom za kvantitativno merenje, testovima firme koji su bili komercijalno dostupni (R&D Systems, Minneapolis, MN). Vrednosti su iščitavane pomoću Luminex analizatora. Bolesnici sa PEX glaukomom bili su češće osobe muškog pola i značajno starije životne dobi od bolesnika sa POAG. U grupi sa PEX glaukomom i POAG, muškarci su bili nešto stariji u odnosu na žene. Bolesnici sa PEX sindromom češće su imali promene na oba oka u poređenju sa ostalim grupama. Nije registrovana značajnija razlika u vrednostima MMP-2, TIMP-2, TIMP-3, TIMP-4 u očnoj vodici između polova. Jedino je u grupi sa PEX sindromom registrovan značajno viši nivo TIMP-1 kod muškaraca u odnosu na žene.

Uprkos značajnoj razlici u nivoima MMP-2 i TIMPs u očnoj vodici pacijenata sa različitim kliničkim oblicima glaucoma i kataraktom, nema značajne razlike povezne sa polom bolesnika. Jedino je nivo TIMP-1 značajno povišen u bolesnika muškog pola sa PEX sindromom. Vrednosti TIMP-4 u očnoj vodici pacijenata sa PEX glaukomom su bile značajno više kod osoba muškog pola starije životne dobi. *Acta Medica Medianae* 2010;49(1):5-12.

Ključne reči: pol, matriks metaloproteinaze, MMP-2, inhibitor, pseudoeksfolijacija, sindrom, glaukom, TIMP