



Transforming growth factor β 1, matrix metalloproteinase-2 and its tissue inhibitor in patients with pseudoexfoliation glaucoma/syndrome

Transformišući faktor rasta β 1, matriks metaloproteinaza-2 i njen tkivni inhibitor kod bolesnika sa pseudoeksfolijativnim sindromom/glaukomom

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Abstract

Background/Aim. Transforming growth factor- β 1 (TGF- β 1), oxidative stress and imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) may play an important role in pathogenesis of pseudoexfoliation syndrome/glaucoma (PEX Sy/Gl). The aim of the study was to measure concentrations of TGF- β 1, MMP-2, TIMP-2 in the aqueous humor in the examined group, as well as to compare the biochemical findings with the following clinical parameters: degree of chamber angle pigmentation, presence of pseudoexfoliation and the value of intraocular pressure (IOP). **Methods.** Aqueous samples from 30 patients with cataract, 30 patients with PEX Sy, 36 patients with PEX Gl, and 42 patients with primary open-angle glaucoma (POAG) were collected during phacoemulsification cataract surgery. TGF β 1, MMP-2, TIMP-2 Fluotokine Multi Analyze Profiling kits and Luminex technology were used to simultaneously measure TGF β 1, MMP-2 and TIMP-2. **Results.** TGF- β 1, MMP-2, TIMP-2 were detected in human aqueous from all the groups with the highest level in the group

with PEX Gl. Statistically, a significant correlation between the levels of TGF β 1, MMP-2, TIMP-2 in the aqueous humor of the patients with PEX Gl and the IOP value was confirmed ($p < 0.05$). In this group, the positive correlations between the TGF β 1 concentration in the aqueous humor and the presence of pseudoexfoliation ($p < 0.01$), on the one hand, and between the TIMP-2 level and the presence of pseudoexfoliation ($p < 0.05$), on the other, were reported. A statistically significant positive correlation of TGF- β 1 and MMP-2, and the degree of chamber angle pigmentation in the PEX Gl group was confirmed ($p < 0.05$). In the POAG group, TIMP-2 values were in a negative correlation with the degree of pigmentation ($p < 0.05$), and the IOP value ($p < 0.05$). **Conclusion.** TGF β 1 and MMP-2 affect the degree of chamber angle pigmentation and the degree of pseudoexfoliation in patients with pseudoexfoliative glaucoma.

Key words:

transforming growth factor beta 1; matrix metalloproteinase 2; tissue inhibitor of metalloproteinase-2; exfoliation syndrome.

Apstrakt

Uvod/Cilj. Transformišući faktor rasta β 1 (TGF- β 1), oksidativni stres i disbalans između matriks metaloproteinaza (MMPs) i njihovih tkivnih inhibitora (TIMPs) igraju važnu ulogu u patogenezi pseudoeksfolijativnog sindroma/glaukoma PEX Sy/Gl. Cilj ove studije bio je da se utvrdi koncentracija TGF- β 1, MMP-2, TIMPs-2 u očnoj vodici izabranih grupa bolesnika, kao i da se uporede biohemijski nalazi sa odgovarajućim kliničkim parametrima: stepen pigmentacije komornog ugla, prisustvo pseudoeksfolijacija i vrednost intraokularnog pritiska (IOP). **Metode.** Tokom operacije fakoemulzifikacije katarakte prikupljena je očna

vodica od 30 bolesnika sa kataraktom, 30 bolesnika sa PEX Sy, 36 bolesnika sa PEX Gl i 42 bolesnika sa primarnim glaukomom otvorenog ugla (POAG). Za određivanje nivoa TGF- β 1, MMP-2 i TIMP-2 korišćen je komplet Quantikine (R&D System, UK), a vrednosti su iščitavane pomoću Luminex analizatora. **Rezultati.** Vrednosti TGF- β 1, MMP-2 i TIMP-2 u očnoj vodici bile su povišene u grupi bolesnika sa PEX Gl. Postojala je statistički značajna korelacija između nivoa TGF- β 1, MMP-2 i TIMP-2 u očnoj vodici i visine IOP kod bolesnika sa PEX Gl ($p < 0,05$). U ovim grupama je nađena statistički značajna korelacija između koncentracije TGF- β 1 u očnoj vodici i prisustva pseudoeksfolijacija ($p < 0,01$), sa jedne strane i nivoa TIMP-2 i prisu-

stva pseudoeksfolijacija sa druge strane ($p < 0,05$). Potvrđena je i statistički značajna pozitivna korelacija nivoa TGF- β 1, MMP-2 i stepena pigmentacije komornog ugla ($p < 0,05$) u grupi bolesnika sa PEX Gl. U grupi bolesnika sa POAG vrednost TIMP-2 je u negativnoj korelaciji sa stepenom pigmentacije komornog ugla i vrednostima IOP ($p < 0,05$). **Zaključak.** TGF- β 1 i MMP-2 utiču na stepen pigmentacije

komornog ugla i prisustva pseudoeksfolijacija kod bolesnika sa PEX glaukomom.

Ključne reči:

faktor rasta, transformišući, beta 1; matriks metaloproteinaza 2; tkivni inhibitor matriks metaloproteinaze-2; eksfolijativni sindrom.

Introduction

Pseudoexfoliation syndrome (PEX Sy) is an elastosis-like systemic disease characterized by the production and progressive accumulation of extracellular fibrillar material, known as pseudoexfoliative material, on the tissues of the anterior segment of the eye and different visceral organs¹⁻³. In many countries PEX Sy is common in population over the age of 60, and in many cases it leads to the appearance of pseudoexfoliation glaucoma (PEX Gl), one of the most frequent causes of poor visual acuity and blindness^{4,5}. The real pathogenesis of PEX Sy is still not known enough. Recent studies have shown that PEX Sy is a microfibrilopathy and that transforming growth factor β 1 (TGF- β 1), oxidative stress and an imbalance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play a role in its appearance. The aim of the study was to determine concentrations of TGF- β 1, MMP-2, TIMP-2 in the aqueous humor in patients with PEX Gl, PEX Sy, primary open-angle glaucoma (POAG) and cataract (Cat), and also, to compare the biochemical findings with the following clinical parameters: degree of angle pigmentation, presence of pseudoexfoliation and the value of intraocular pressure (IOP).

Methods

Four groups of patients were included in this prospective study: the group I – 42 patients with PEX Gl, group II – 30 patients with PEX Sy, group III – 36 patients with POAG, and the group IV – 30 patients with Cat.

The ophthalmological examination was conducted at the Clinic of Ophthalmology, Clinical Center Niš (Niš, Serbia).

Biochemical analyses were done in the Center of Medical Biochemistry of Clinical Center Niš, and the Ophthalmology, Department of the University of Erlangen-Nürnberg (Germany).

Transforming growth factor β 1 was determined by the ELISA method using a commercially available kit (Quantikine; R&D System, UK).

The MMP-2 values in the aqueous humor of patients were determined with the multiplex method for quantitative measurement using a commercially available test (Quantikine; R&D System, UK). The values were read by the Luminox analyser.

For this study the aqueous humor of the patients was used. Aqueous humor was extracted by paracentesis through the limbus of the cornea during the trabeculectomy or routine phacoemulsification paying special attention not to touch the endothelium, iris or lens as well as extracting the aqueous

humor without any traces of blood. After its aspiration and securing in sterile test tubes, aqueous humor samples (80–100 μ l) were immediately frozen in liquid nitrogen and then stored and kept at the temperature of -80°C .

All the patients gave their written informed consent. All the patients underwent pupillary dilation a day before the surgery so that the presence of pseudoexfoliation could be confirmed. The classification of the presence of pseudoexfoliation was done from I⁰ to III⁰. Thus, I⁰ marked that PEX material was visible only on the anterior side of the lens after the pupillary dilation; II⁰ – PEX material was occasionally visible on the pupillary edge, and III⁰ – pseudoexfoliation was constantly visible along the whole circumference of the pupillary edge and on the anterior side of the lens, with or without iridodonesis and phacodonesis. The width and pigmentation of the chamber angle were classified according to the Scheie classification.

A one-way analysis of variance (One –Way ANOVA) and a Post Hoc (Tukey HSD) analysis were used to check the difference in the average age between the examined groups. To check the hypotheses that there are differences in the presence of certain attributes between the groups, Fisher's Exact Probability Test was used. To evaluate the differences in IOP values between the patients with different kinds of glaucoma, the Mann-Whitney *U*-Wilcoxon Rank Sum *W*-test was used. This test was also used to compare the values of the concentration of certain enzymes in the aqueous humor of the patients. The level of significance was adapted by the Bonferoni inequality and for the time being it is 0.01. The correlation between enzymes and clinical parameters was conducted with the help of Pearson's linear correlation coefficient. For the statistical analysis of the data, SPSS Windows (Ver. 8.0) was used.

Results

The average age of the patients with PEX Gl was 68.9 ± 7.6 years; of the patients with PEX Sy 66.8 ± 4.6 years; of the patients with POAG 62.8 ± 8.8 years; and, finally, of the patients with cataract 64.8 ± 3.7 years. Statistically, the patients with PEX Gl were significantly older in relation to the patients with POAG ($p < 0.001$). The average value of IOP was 43.1 ± 13 mm Hg in the group with PEX Gl, while in the group with POAG the average value of IOP was 34.8 ± 11.4 mm Hg and this difference proves to be statistically significant ($p < 0.001$).

The presence of pseudoexfoliation is shown in Figure 1. The patients with PEX Gl had significantly higher grade of pseudoexfoliation compared to the patients with PEX Sy ($p < 0.001$).

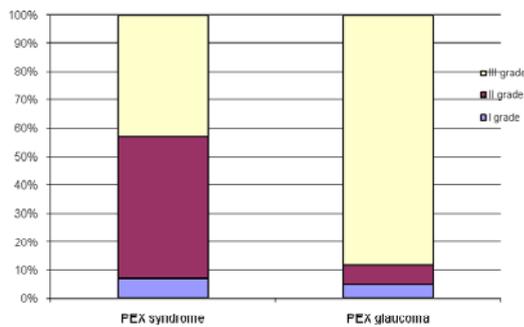


Fig. 1 – The presence of pseudoexfoliation (PEX) in the patients with PEX glaucoma and PEX syndrome

Figure 2 shows a degree of chamber angle pigmentation (according to Scheie) in the patients with POAG and those with pseudoexfoliation syndrome.

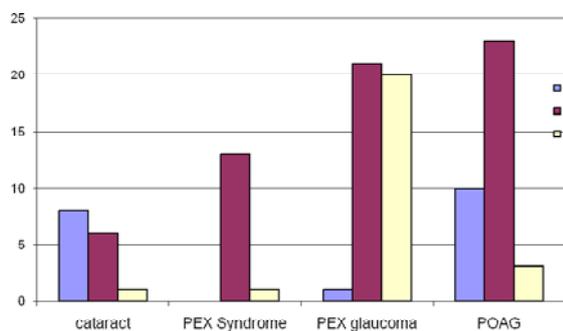


Fig. 2 – Degree of chamber angle pigmentation (according to Scheie) in the patients with primary open-angle glaucoma (POAG) and pseudoexfoliation (PEX) syndrome

The greatest number of POAG patients had I° chamber angle pigmentation according to Scheie (96.7%). In the PEX Gl group, the gonioscopic findings mostly showed II° ili III° chamber angle pigmentation (86.7%). The observed difference in the chamber angle pigmentation degree between these two groups was statistically highly significant ($p < 0.0001$).

The values of TGF-β1, MMP-2 i TIMP-2 in the aqueous humor of the patients in all the groups is shown in Table 1. The average level of TGF-β1 in the aqueous humor of the patients with PEX Gl was 147.29 ± 76.54 pg/mL, while in the group with senile cataract it was 38.85 ± 28.47 pg/mL ($p < 0.0001$).

The mean values of this protease were 29031.5 ± 16725.8 pg/mL in the PEX Gl group, 24250.12 ± 42741.74 pg/mL in the PEX Sy group, 19346.07 ± 10871.13 pg/mL in the POAG group, and 15195.40 ± 11225.02 pg/mL in the Cataract group. Significant differences were found between MMP-2 in PEX Gl and both POAG and cataract groups ($p < 0.001$, and $p < 0.0001$, respectively). The difference in the values of MMP-2 in the aqueous humor of the patients with PEX Sy in comparison with the senile Cataract and POAG groups, respectively, was significant ($p < 0.05$).

The levels of TIMP-2 in aqueous humor ranged from 19.947 pg/mL in the patients with cataract to 43.521 pg/mL in the patients with PEX Gl. A significant increase in aqueous humor TIMP-2 levels was measured in both PEX Gl and POAG groups compared with PEX Sy and Cataract groups ($p < 0.001$ and $p < 0.01$, respectively).

Table 2 shows a correlation of the levels of TGF-β1, MMP-2, TIMP-2 in the aqueous humor of patients with the degree of pigmentation, the presence of pseudoexfoliation and IOP value. Statistically, a significant correlation between

Table 1
Concentration of transforming growth factor β1 (TGF-β1), matrix metalloproteinase-2 (MMP-2) and its tissue inhibitor (TIMP-2) in aqueous humor of the patients

Group	TGF- β1 (pg/mL)	MMP-2 (pg/mL)	TIMP-2 (pg/mL)
PEX Gl	147.29 ± 76.54 **· ***	29031.5 ± 16725.8 *· **· ***	43521 ± 19737 **· ***
POAG	73.96 ± 48.50 ##	19346.07 ± 10871.13	26103 ± 14989
PEX Sy	108.26 ± 30.85 ***, #	24250.12 ± 42741.74 #	39103 ± 4961
Senile cataract	38.85 ± 28.47	15195.40 ± 11225.02	19947.7 ± 5181

PEX Gl – pseudoexfoliation glaucoma; PEX Sy – pseudoexfoliation syndrome;

POAG – primary open-angle glaucoma.

* $p < 0.05$ in relation to PEX syndrome

** $p < 0.001$ in relation to POAG

*** $p < 0.0001$ in relation to senile cataract

$p < 0.05$ in relation to POAG

$p < 0.01$ in relation to senile cataract

Table 2
Correlation of transforming growth factor β1 (TGF-β1), matrix metalloproteinase-2 (MMP-2) and its tissue inhibitor (TIMP-2) in aqueous humor of the patients with the degree of pigmentation, presence of pseudoexfoliation (PEX) and intraocular pressure (IOP) values

Biochemical parameters	PEXGI			POAG	
	Degree of PEX	IOP	Pigmentation of the chamber angle	Pigmentation of the chamber angle	IOP
MMP-2		$c = 0.33$ $p < 0.05$	$c = 0.36$ $p < 0.05$		
TIMP-2	$c = 0.46$ $p < 0.05$	$c = 0.43$ $p < 0.05$		$c = -0.48$ $p < 0.01$	$c = -0.36$ $p < 0.05$
TGF-β1	$c = 0.47$ $p < 0.01$	$c = 0.48$ $p < 0.01$	$c = 0.312$ $p < 0.05$		

POAG – primary open-angle glaucoma

PEXGI – pseudoexfoliation glaucoma

the levels of TGF- β 1, MMP-2, TIMP-2 in the aqueous humor of the patients with PEX Gl and the IOP value was confirmed ($p < 0.05$). In this group, positive correlations were established between the level of TGF β 1 and TIMP-2 in aqueous humor and the presence of pseudoexfoliation ($c = 0.47$; $p < 0.01$ and $c = 0.46$, $p < 0.05$, respectively). In the PEX Gy group a statistically significant positive correlation of TGF- β 1 and MMP-2, and the degree of angle pigmentation was confirmed ($c = 0.312$; $p < 0.05$). In the POAG group, the TIMP-2 values were in a negative correlation with the degree of angle pigmentation ($c = -0.48$, $p < 0.05$), and the IOP value ($c = 0.36$; $p < 0.05$).

Discussion

The pathological accumulation of abnormal fibrillar extracellular material, which is a characteristic of PEX Sy in numerous extra- and intraocular tissues, can result in a great number of clinical complications and the development of PEX Gl¹⁻⁴. PEX syndrome is one of the main causes of PEX Gl. Clinical changes in the eye are often asymmetrical and can be manifested as trabeculopathy, iridopathy, zonulopathy, endotheliopathy, pigment dispersion and increased trabecular pigmentation, high values of IOP, as well as great daily fluctuations of IOP accompanied by the rapid deterioration of the optic nerve head and a progressive visual field loss^{3, 6-10}.

However, a precise etiology of this systemic disease of extracellular matrix still remains unknown, though it is considered TGF β 1 causes an imbalance between MMPs and their TIMPs, leading to a progressive accumulation of exfoliation material in the trabecular tissue, which further results in elevated IOP¹¹⁻¹³. The normal balance requires a balanced interaction of MMPs and TIMPs, and the normal relation of enzymes to the inhibitor is 1 : 1. Any changes in the balance can result in the excessive accumulation or degradation of extracellular matrix (ECM)^{6, 7, 14, 15}.

In this study the values of total TGF- β 1 in aqueous humor of the patients with PEX Gl and PEX Sy, respectively, were significantly higher in relation to the values of this enzyme in aqueous humor of the patients with POAG and cataract, respectively ($p < 0.0001$), while the activity of total TGF- β 1 in the aqueous humor of the patients with PEX Gl was different from and higher than the activity of this enzyme in the aqueous humor of patients with PEX Sy, but the difference was not statistically significant – it can be said that it was at the verge of statistical significance ($p < 0.01$).

Statistically, the values of total TGF- β 1 in aqueous humor of the patients with POAG were considerably higher in relation to the values of aqueous humor in patients with senile cataract ($p < 0.0001$). The values of TGF- β 1 in the aqueous humor of the patients with POAG statistically were considerably lower than the values in the aqueous humor of the patients with PEX Sy ($p < 0.05$).

The patients of different groups with different ophthalmological diseases had different – statistically significant – values of MMP-2 in aqueous humor ($p < 0.0001$).

MMP-2 was detectable in aqueous humor of all the patients. The values of MMP-2 in the aqueous humor of the patients with PEX Gl were statistically significantly higher in comparison with the values in the patients of senile cataract ($p < 0.0001$), while that difference in comparison with the values of this proenzyme in aqueous humor of the patients with POAG was also significant ($p < 0.001$).

The MMP-2 values in aqueous humor of the patients with PEX Gl were not significantly higher in comparison with the values of this proenzyme in aqueous humor of the patients with PEX Sy ($p > 0.05$), while the difference in the values of this proenzyme in the aqueous humor of the patients with PEX Sy in comparison with the senile cataract and POAG groups, respectively, was ($p < 0.05$). The TIMP-2 values ranged from 19,947 pg/mL to 43,521 pg/mL. A significant increase in TIMP-2 in aqueous humor of the patients both with PEX Gl and PEX Sy was noticed in comparison with the values measured in the patients both with POAG and cataract ($p < 0.001$).

In their study, Schlotzer-Schrehard et al.¹⁶ examined whether they could detect latent and active TGF- β 1 i TGF- β 2 in aqueous humor using the ELISA method. Both latent and active ones could be detected in aqueous humor and serum of the patients with the PEX eye. The level of total and active TGF- β 1 respectively was statistically significantly higher in patients both with PEX Sy and PEX Gl in comparison with the group with cataract and open-angle glaucoma respectively, while the difference was not noticed between the groups with PEX changes. These authors also found that the TGF- β 1 values in serum statistically were not significantly different among the examined groups.

Koliakos et al.¹³ also found increased levels of TGF- β 1 in the patients with PEX Sy ranging from 6.1 to 54.6 (median value 17.06 ± 11.02) pg/mL, which statistically was a significant rise in comparison with the group with cataract.

Slotzer-Schrehard et al.¹⁴ measured a total and active quantity of MMPs and TIMPs in patients with PEX Gl, PEX Sy and POAG, using the Western Blot, elektroforesis and the ELISA method. MMP-2 (both as proenzyme and in its complex form) was found in considerable quantity ranging from 18.6 to 232.4 ng/mL. Despite this high variability, the total quantity of MMP-2 statistically was considerably elevated in aqueous humor of the patients with PEX Sy with or without glaucoma, respectively, in comparison with aqueous humor of the patients with POAG and cataract, respectively. Free, unbound MMP-2 made 22–24% of the total quantity in aqueous humor and was significantly increased in the patients with PEX Sy. The concentrations of TIMPs in aqueous humor were six to seven times as high as the concentrations of MMPs, and they had the predominant role in the activation of MMPs. MMP-2 and TIMP-2 should be balanced and any imbalance can affect the biological activity of the cell. It was noticed that the concentrations of MMPs and TIMPs in aqueous humor were considerably higher in patients with pseudoexfoliation with or without glaucoma, respectively, in comparison with the patients with primary open-angle glaucoma, especially MMP-2, -3, TIMP-1, -2¹⁷⁻²⁵.

Konstas et al.²⁶ in their study found a statistically considerable decrease in the quantity of total TGF- β 1 in samples

from patients who had PEX Gl and used the prostaglandin, latanoprost (0.005% eye drops) monotherapy in comparison with the patients who had PEX Gl and used beta blockers in the form of timolol maleate, (0.5% eye drops). These authors believed that TGF- β 1 increased the TIMP-2 and MMP-2 expressions in the eyes with pseudoexfoliation, and that latanoprost interrupted the positive feedback mechanism of TGF- β 1 accumulation. However, the reduction mechanism of TGF- β 1, MMP-2 i TIMP-2 by latanoprost required further clarification.

Patients with PEX Gl had a statistically significantly higher degree of pseudoexfoliative changes in comparison with patients with PEX Sy ($p < 0.0001$). The greatest number of POAG patients had I^o chamber angle pigmentation according to Scheie (96.7%). In the PEX Gl group, the gonioscopic findings mostly showed II^o or III^o chamber angle pigmentation (86.7%). The observed difference in chamber angle pigmentation degree between these two groups was statistically highly significant ($p < 0.0001$).

In the PEX Gl group, it was confirmed that TGF β 1 was positively correlated with MMP-2 ($c = 0.51$; $p < 0.01$), and a positive correlation between MMP-2 and its tissue inhibitor TIMP-2 was also noticed ($c = 0.54$; $p < 0.01$).

Statistically, a significant correlation between the levels of TGF β 1, MMP-2, TIMP-2 in aqueous humor of the patients with PEX Gl and the IOP value was confirmed ($p < 0.05$). In this group, positive correlations between TGF

β 1 concentration in aqueous humor and the presence of pseudoexfoliation ($c = 0.47$; $p < 0.01$), on the one hand, and between TIMP-2 level and the presence of pseudoexfoliation ($c = 0.46$, $p < 0.05$), on the other, were reported.

In this study the relation of TGF β 1 and MMP-2 levels, and the degree of chamber angle pigmentation was established, but that connection was not statistically significant in the PEX Sy group ($p > 0.05$), while a statistically significant positive correlation of TGF β 1 and MMP-2, and the degree of chamber angle pigmentation in the PEX Gl group was confirmed ($c = 0.312$; $p < 0.05$). In the POAG group, the TIMP-2 values were in a negative correlation with the degree of pigmentation ($c = -0.48$, $p < 0.05$), and the IOP value ($c = 0.36$; $p < 0.05$).

At the same time, the MMP-2 values, on one hand, and the presence of exfoliation PEX, on the other, did not show a statistically significant connection in the PEX Gl patients and PEX Sy patients.

Conclusion

Concentrations of TGF β 1 and MMP-2 in the aqueous humor of patients with pseudoexfoliative changes are considerably elevated, and TGF β 1 and MMP-2 affect the degree of chamber angle pigmentation and the degree of pseudoexfoliation presence in patients with pseudoexfoliative glaucoma.

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