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ORIGINAL ARTICLE

Serum thrombospondin-1, growth differentiation factor-15, and resolvin D1 and E1 levels in the pathogenesis of keratoconus

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ABSTRACT

Purpose: This study aimed to evaluate the serum levels of thrombospondin-1, growth differentiation factor-15, resolvin D1, and resolvin E1 in patients with keratoconus. **Methods:** Thirty-five patients with keratoconus and 35 control subjects of similar age and sex were evaluated. The keratoconus group was divided into four stages according to the modified Krumeich classification. Commercial kits were used to determine thrombospondin-1, growth differentiation factor-15, resolvin D1, and resolvin E1 levels in serum samples using enzyme-linked immunosorbent assay (ELISA). Serum thrombospondin-1, growth differentiation factor-15, resolvin D1, and resolvin E1 levels were compared between the patient and control groups. **Results:** The keratoconus group consisted of 14 females and 21 males, and the control group consisted of 14 females and 21 males, with mean ages of 29.4±8.8 and 30.0±7.8 yr, respectively. There were significant differences in serum thrombospondin-1, growth differentiation factor-15, resolvin D1, and resolvin E1 levels between the serum of the keratoconus and control groups (p=0.006, p<0.001, p<0.001, and p=0.001, respectively). No significant correlations were found between keratoconus stage and serum thrombospondin-1, growth differentiation factor-15, resolvin D1 and resolvin E1 levels (r=−0.025, p=0.892; r=−0.019, p=0.913; r=−0.036, p=0.838; and r=−0.108, p=0.538, respectively). **Conclusion:** Serum levels of thrombospondin-1, growth differentiation factor-15, resolvin D1, and resolvin E1 were significantly lower in patients with keratoconus. These results suggest that these parameters may be associated with the pathogenesis of keratoconus.

KEYWORDS: Keratoconus/pathology; Thrombospondin 1/blood; Growth differentiation factor 15/blood; Docosahexaenoic acids/blood; Eicosapentaenoic acid/blood; Inflammation mediators

INTRODUCTION

Keratoconus (KC) is a progressive ectatic disorder characterized by corneal thinning and protrusion, leading to irregular astigmatism and visual impairment. It primarily affects young individuals, and its pathogenesis involves a complex interplay of genetic and environmental factors[1,2]. Although traditionally described as a non-inflammatory disease, KC is increasingly associated with various inflammatory mediators that alter the corneal microenvironment[3].

Factors such as eye rubbing, contact lens wear, atopy, and UV irradiation contribute to a persistent, low-grade inflammatory state[3,4]. In the pathogenesis of KC, elevated levels of cytokines (e.g., IL-6 and TNF-α) and matrix metalloproteinases (MMPs)

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disrupt the homeostatic balance of the extracellular matrix (ECM). This process, often regulated by transforming growth factor-beta (TGF-β), leads to impaired wound healing and abnormal tissue remodeling, further accelerating disease progression[5,6].

The thrombospondin family comprises five ECM proteins, thrombospondin-1 (TSP-1) to thrombospondin-5 (TSP-5), which influence *in vivo* processes such as angiogenesis, wound healing, and inflammation through interactions with various cell-surface receptors, cytokines, proteases, and growth factors. Among these proteins, TSP-1 is the primary activator of TGF-β[7]. Growth differentiation factor-15 (GDF-15), a member of the TGF-β superfamily, plays an important role in cell proliferation, inflammation, and cellular stress responses[8]. TGF-β is known to be one of the key cytokines involved in the pathogenesis of KC[9]. Therefore, TSP-1 and GDF-15 may play a role in KC pathogenesis.

Resolvins are derived from the omega-3 essential fatty acids eicosapentaenoic acid and docosahexaenoic acid. Two main pathways are involved in the production of E-series resolvins from eicosapentaenoic acid and D-series resolvins from docosahexaenoic acid. Resolvins are active during the resolution phase of acute inflammatory disorders and participate in biological processes that promote the resolution of inflammation[10]. Therefore, resolvins may also be involved in the pathogenesis of KC because of their role in inflammatory regulation.

To the best of our knowledge, no previous study has investigated the relationship between KC and TSP-1, GDF-15, RvD1, and RvE1. Therefore, this study aimed to evaluate the serum levels of these molecules and investigate their potential contributions to the molecular mechanisms underlying KC.

METHODS

The study included 70 participants enrolled in the Faculty of Medicine, Department of Ophthalmology, Tokat Gaziosmanpaşa University. The study population comprised 35 patients with KC and 35 control subjects. The control group consisted of age-matched healthy volunteers without ocular disease who were selected randomly. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

All participants underwent a comprehensive ophthalmological examination, including visual acuity assessment using the Snellen chart, slit-lamp biomicroscopy, dilated fundus examination, intraocular pressure measurement using Goldmann applanation tonometry, and corneal topography. Keratoconus was diagnosed according to the criteria of the Collaborative Longitudinal Evaluation of Keratoconus study[11]. Patients were subsequently classified into four stages using the modified Krumeich classification[6]. In cases of bilateral disease, the eye with the more advanced stage was included in the analysis.

The exclusion criteria included ocular diseases such as uveitis, glaucoma, scleritis, and a history of corneal trauma. Individuals with systemic inflammation, a history of cancer, autoimmune disorders, or chronic conditions such as hypertension were also excluded. In addition, participants receiving anti-inflammatory or antioxidant treatment (including vitamin supplements) and pregnant women were excluded. Individuals with a documented history of, or clinical signs suggestive of, systemic or ocular allergic disease were excluded based on a detailed medical history and clinical assessment. No laboratory-based tests for allergy or systemic inflammation were performed.

Blood sample collection and measurements

Venous blood samples for the measurement of TSP-1, GDF-15, RvD1, and RvE1 were collected from all participants between 8:00 and 10:00 AM after at least 8 h of fasting. Serum was immediately separated by centrifugation at 3,000× g for 10 min. The separated serum samples were then stored at −80°C until analysis.

Serum TSP-1 concentrations were measured using a commercially available Human TSP-1 Enzyme-Linked Immunosorbent Assay Kit (Bioassay Technology Laboratory, Cat. No. E1110Hu). Enzymatic reactions were quantified using an automatic microplate photometer. TSP-1 concentrations were determined by comparing the optical density values of the samples with the standard curve. The assay sensitivity for TSP-1 was 2.39ng/mL, with a linear range of 5-700ng/mL. The interassay coefficient of variation was 10%. Samples with concentrations above the assay range were diluted and measured in duplicate.

Serum GDF-15 concentrations were measured using a commercially available Human GDF-15 ELISA Kit (Bioassay Technology Laboratory, Cat. No. E0037Hu). Enzymatic reactions were quantified using an automatic microplate photometer. GDF-15 concentrations were determined by comparing the optical density values of the samples with the standard curve. The assay sensitivity for GDF-15 was 557 ng/mL, with a linear range of 10-3,000 ng/mL. The interassay coefficient of variation was 10%. Samples with concentrations above the assay range were diluted and measured in duplicate.

Serum RvD1 concentrations were measured using a commercially available Human RvD1 ELISA Kit (Bioassay Technology Laboratory, Cat. No. E7450Hu). Enzymatic reactions were quantified using an automatic microplate photometer. RvD1 concentrations were determined by comparing the optical density values of the samples with the standard curve. The assay sensitivity for RvD1 was 19.01ng/mL, with a linear range of 37.5-2,400ng/mL. The interassay coefficient of variation was 10%. Samples with concentrations above the assay range were diluted and measured in duplicate.

Serum RvE1 concentrations were measured using a commercially available Human RvE1 ELISA Kit (Bioassay Technology Laboratory, Cat. No. E7078Hu). Enzymatic reactions were quantified using an automatic microplate photometer. RvE1 concentrations were determined by comparing the optical density values of the samples with the standard curve. The assay sensitivity for RvE1 was 4.35 ng/mL, with a linear range of 10-640 ng/mL. The interassay coefficient of variation was 10%. Samples with concentrations above the assay range were diluted and measured in duplicate.

Statistical analysis

Data were analyzed using SPSS software version 22.0. Normality was assessed using the Shapiro-Wilk test. As the variables were not normally distributed, nonparametric tests were used. Serum TSP-1, GDF-15, RvD1, and RvE1 levels were compared between the KC and control groups using the Mann-Whitney *U* test. The Kruskal-Wallis test was used to compare biomarker levels among KC stages. Spearman's correlation analysis was performed to evaluate the relationships between biomarker levels and KC clinical parameters. A p-value <0.05 was considered statistically significant. Because of the exploratory nature of the study, a formal sample size calculation was not performed before recruitment. However, the sample size was determined based on similar pilot studies previously conducted in this field.

RESULTS

The KC group consisted of 35 patients (14 females and 21 males), and the control group consisted of 35 subjects (14 females and 21 males). The mean ages of the KC and control groups were 29.4±8.8 and 30.0±7.8 yr, respectively. There were no significant differences between the groups in terms of sex or age (p=1.0 and p=0.785, respectively). The number of patients with stage 1, 2, 3, and 4 KC was 9, 13, 7, and 6, respectively.

There were significant differences in serum TSP-1, GDF-15, RvD1, and RvE1 levels between the KC and control groups (p=0.006, p<0.001, p<0.001, and p=0.001, respectively; Table 1). When serum TSP-1, GDF-15, RvD1, and RvE1 levels were evaluated according to KC stage, no significant differences were observed among the stages (Table 2). Similarly, no significant correlations were found between KC stage and serum TSP-1, GDF-15, RvD1, or RvE1 levels (r=−0.025, p=0.892; r=−0.019, p=0.913; r=−0.036, p=0.838; and r=−0.108, p=0.538, respectively).

DISCUSSION

In the present study, serum levels of TSP-1, GDF-15, RvD1, and RvE1 were investigated in patients with KC. These

Table 1. Serum median levels of TSP-1, GDF-15, RvD1, and RvE1 in patients with KC and healthy controls.

	Keratoconus (n=35) Median (25th-75th percentiles) ng/L	Controls (n=35) Median (25th-75th percentiles) ng/L	p-value
TSP-1	83.5 (63.9-128.4)	164.3 (83.9-370.1)	0.006*
GDF-15	493.9 (405.3-607.8)	764.2 (503-1,192.7)	<0.001*
RvD1	612.2 (564.1-735.5)	950.1 (685.9-2,056.1)	<0.001*
RvE1	119.9 (107.1-139.3)	188.1 (121.2-471.8)	0.001*

*Statistically significant.

Table 2. TSP-1, GDF-15, RvD1, and RvE1 values according to keratoconus groups.

	Stage 1	Stage 2	Stage 3	Stage 4	p-value
GDF-15 ng/L	512.1±357.5	542±327.5	450.2±204.7	541.7±399.8	0.993
RvD1 ng/L	693.2±408.5	876.7±524.1	598.3±96.3	751.4±383.6	0.475
RvE1 ng/L	165.2±100.1	165.2±130.1	121.2±12.3	149.5±96.2	0.924
TSP-1 ng/L	141.8±122	135±117.9	74.4±25.5	125.1±108.6	0.874

molecules are involved in various biological processes, including inflammation, angiogenesis, and wound healing. We found significantly lower serum levels of these molecules in patients with KC than in the control subjects.

Keratoconus is a disorder of unknown etiology characterized by corneal thinning. Its pathophysiology is associated with stromal thinning and alterations in the ECM. TGF-β signaling is a key regulator of ECM secretion and organization in the anterior segment of the eye and has been implicated in KC pathogenesis[6].

TSP-1 is an ECM protein that regulates numerous physiological and pathological processes, including inflammation, wound healing, and angiogenesis, through interactions with various ligands such as cell receptors, cytokines, and growth factors[6,12]. It is an important activator of latent TGF-β and promotes its immunomodulatory and wound-healing functions.

Ocular surface inflammation regulates TSP-1 expression. TSP-1 plays a role in several ophthalmic conditions, including dry eye disease, ocular allergy, wound healing, angiogenesis, and corneal transplantation[12]. Tan et al.[13] investigated the immunoregulatory role of TSP-1 in dry eye disease. Application of recombinant TSP-1 eye drops to WT C57BL/6 mice reduced dendritic cell maturation, decreased local inflammatory cytokine expression (including IL-1β, IL-6, IL-23, and IL-17A), inhibited T-helper (Th)17 cell generation, and improved dry eye disease findings[13]. Matsuba et al.[14] reported that TSP-1 regulates the transformation of keratocytes into myofibroblasts through TGF-β during corneal wound healing. It has also been demonstrated that corneal restoration following a penetrating incision is markedly impaired in TSP-1-deficient mice[15]. Another study showed that TSP-1 is required for corneal sensory nerve development and repair, thereby reducing ocular surface dysfunction[16].

Unni et al.[17] reported elevated tear levels of TSP-1 in patients with KC, which contrasts with the findings of the present study. The discrepancy between our finding of lower serum TSP-1 levels and the elevated tear levels reported by Unni et al. may reflect compartment-specific differences in biomarker expression. Increased tear levels may represent a localized compensatory response to chronic ocular surface irritation in KC, whereas lower systemic levels may reflect a reduced overall regenerative and anti-inflammatory capacity. This difference suggests that the systemic environment in KC may differ from the local ocular microenvironment and warrants further investigation integrating both serum and tear analyses.

In the present study, serum TSP-1 levels were significantly lower in patients with KC. TSP-1 is a key regulator of TGF-β signaling and is involved in inflammation, angiogenesis, and wound healing. Negative regulation of TGF-β signaling in human KC cells may contribute to the altered ECM observed in KC. Therefore, reduced systemic TSP-1 levels may be associated with decreased anti-inflammatory capacity and impaired ECM remodeling and wound-healing processes in KC pathogenesis.

GDF-15 is a member of the TGF-β cytokine superfamily[16]. Although its exact mechanisms of action have not been fully elucidated, GDF-15 is known to act as an autocrine factor with anti-inflammatory and cellular repair properties[18]. Its expression increases in response to various stimuli, including oxidative stress, hypoxia, acute tissue injury, inflammation, interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and exposure to short-wavelength light[18].

Induction of ECM secretion by GDF-15 has been demonstrated in human trabecular meshwork cells[19]. Increased vitreous GDF-15 expression has been reported in inflammatory vitreoretinal disorders[8]. In addition, GDF-15 treatment has been shown to exert protective effects on retinal ganglion cells[20]. In the present study, serum GDF-15 concentrations were significantly lower in patients with KC. We believe that this finding may be associated with altered ECM remodeling, impaired wound-healing processes, and an inadequate anti-inflammatory response in these patients.

Resolvins reduce excessive infiltration of polymorphonuclear neutrophils into tissues and suppress the production of pro-inflammatory mediators, thereby exerting anti-inflammatory effects. They also promote macrophage phagocytosis of microbes and apoptotic cells and enhance phagocyte-mediated clearance, facilitating the return to tissue homeostasis[21].

RvD1 increases the number of regulatory T cells and anti-inflammatory macrophages and enhances the phagocytosis of apoptotic T cells, resulting in reduced numbers of apoptotic T cells. It also increases TGF-β expression[21]. These actions support its role in the resolution of inflammation. RvD1 is present in human tears, where it regulates goblet cell mucin secretion and protects the ocular surface under normal conditions[10]. Topical administration of RvD1 has been reported to promote corneal epithelial wound healing and restore mechanical sensation in a diabetic mouse model[22]. In addition, topical RvD1 analogs inhibit dendritic cell maturation and reduce alloimmune sensitization following corneal transplantation in mice[23]. RvD1 administration has also been shown to inhibit eosinophil accumulation and reduce B-cell IgE production[24]. Furthermore, topical RvD1 application reduced the ocular allergic response through local modulation of conjunctival immune responses in a mouse model[25].

RvE1 decreases neutrophil infiltration, blocks cytokine production, inhibits neutrophil transmigration, activates ADP-dependent platelets, and promotes polymorphonuclear cell apoptosis, thereby facilitating the resolution of inflammation[20,26]. In a mouse model, RvE1 reduced inflammation, increased tear volume, and preserved corneal epithelial integrity[27]. Both RvD1 and RvE1 inhibit goblet cell secretion and thereby reduce allergic inflammation in ocular allergy[28]. RvE1 treatment has also been shown to improve allogeneic corneal graft survival in a high-risk corneal transplantation model by inhibiting Th1/Th17-mediated inflammation[29].

Inflammation and allergic eye diseases are known to contribute to the pathogenesis of KC. RvD1 and RvE1 are involved in wound healing, inflammatory regulation, and allergic disorders. In the present study, serum concentrations of both RvD1 and RvE1 were significantly lower in patients with KC. These findings suggest a possible association between impaired control of inflammatory processes and reduced systemic levels of RvD1 and RvE1 in KC.

The absence of significant correlations between biomarker levels and KC stage may indicate that these systemic alterations reflect biological susceptibility rather than disease severity. A systemic reduction in TSP-1, GDF-15, and resolvins may create a predisposed environment that lowers the corneal threshold for damage. While disease progression is likely influenced primarily by local factors, these systemic findings may reflect deficiencies in baseline protective and reparative mechanisms. Therefore, these molecules may serve as indicators of disease predisposition rather than markers of clinical severity.

This study has several limitations. First, the relatively small sample size may limit the generalizability of the findings. Second, only serum biomarker levels were evaluated; tear fluid biomarkers and mRNA expression analyses were not assessed. Furthermore, objective laboratory markers such as serum IgE levels, eosinophil counts, and systemic inflammatory markers (e.g., C-reactive protein) were not evaluated. Because KC is associated with atopy, these factors may have influenced the studied biomarkers. Although our clinical exclusion criteria were designed to minimize these confounding effects, future studies incorporating comprehensive allergic and inflammatory profiling are needed to better define these systemic contributions. Finally, the lack of a formal a priori power analysis represents a limitation. Although the sample size was comparable to those of similar exploratory studies, this factor should be considered when interpreting the generalizability of the results.

In conclusion, the lower serum levels of TSP-1, GDF-15, RvD1, and RvE1 observed in this study may indicate a systemic imbalance in the anti-inflammatory and regenerative capacity of patients with KC. These findings may reflect a biological predisposition rather than a direct indicator of disease severity. Although significantly lower serum biomarker levels were identified, systemic measurements may not directly reflect local corneal processes. Therefore, these findings should be interpreted with caution and regarded as hypothesis-generating. Future longitudinal studies incorporating comprehensive allergic and inflammatory profiling are warranted to further evaluate the potential of these molecules as prognostic biomarkers and therapeutic targets for disease stabilization.

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REFERENCES

1. Vazirani J, Basu S. Keratoconus: current perspectives. Clin Ophthalmol. 2013;7:2019-30.
2. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42(4):297-319.
3. Wisse RP, Kuiper JJ, Gans R, Imhof S, Radstake TR, Van der Lelij A. Cytokine expression in keratoconus and its corneal microenvironment: a systematic review. Ocul Surf. 2015;13(4):272-83.
4. Kılıç R, Cumurcu T, Sancaktar E, Evliyaoğlu O, Sezer H. Systemic prolidase activity and oxidative stress in keratoconus. Curr Eye Res. 2016;41(1):28-33.
5. Vought R, Greenstein S, Gelles J, Hersh PS. The pathophysiology of keratoconus. Cornea. 2024;44(2):137-43.
6. Krumeich JH, Kezirian GM. Circular keratotomy to reduce astigmatism and improve vision in stage I and II keratoconus. J Refract Surg. 2009;25(4).:357-65.

7. Lopez-Dee Z, Pidcock K, Gutierrez LS. Thrombospondin-1: multiple paths to inflammation. Mediators Inflamm. 2011;2011:296069.
8. Ilhan HD, Bilgin AB, Toylu A, Dogan ME, Apaydin KC. The expression of GDF-15 in the human vitreous in the presence of retinal pathologies with ınflammatory component. Ocul Immunol Inflamm. 2016;24(2):178-83.
9. Priyadarsini S, McKay TB, Sarker-Nag A, Karamichos D. Keratoconus in vitro and the key players of the TGF-β pathway. Mol Vis. 2015;21:577-88.
10. Dartt DA, Hodges RR, Serhan CN. Immunoresolvent resolvin D1 maintains the health of the ocular surface. Adv Exp Med Biol. 2019;1161:13-25.
11. Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci. 1998;3(13):2537-46.
12. Adams JC, Lawler J. The thrombospondins. Cold Spring Harb Perspect Biol. 2011;3(10):a009712.
13. Tan X, Chen Y, Foulsham W, Amouzegar A, Inomata T, Liu Y, et al. The immunoregulatory role of corneal epithelium-derived thrombospondin-1 in dry eye disease. Ocul Surf. 2018;16(4):470-7.
14. Matsuba M, Hutcheon AE, Zieske JD. Localization of thrombospondin-1 and myofibroblasts during corneal wound repair. Exp Eye Res. 2011;93(4):534-40.
15. Blanco-Mezquita JT, Hutcheon AE, Zieske JD. Role of thrombospondin-1 in repair of penetrating corneal wounds. Invest Ophthalmol Vis Sci. 2013; 54(9):6262-8.
16. Tatematsu Y, Khan Q, Blanco T, Bair JA, Hodges RR, Masli S, et al. Thrombospondin-1 Is necessary for the development and repair of corneal nerves. Int J Mol Sci. 2018;19(10):3191.
17. Unni P, Phalahari S, Zhang R, Hsu E, Alluri S, Lee HJ. Elevated thrombospondin-1 in keratoconus patient tears. Invest Ophthalmol Vis Sci. 2024;65(7):3863.
18. Corre J, Hébraud B, Bourin P. Concise review: growth differentiation factor 15 in pathology: a clinical role? Stem Cells Transl Med. 2013;2(12):946-52.
19. Muralidharan AR, Maddala R, Skiba NP, Rao PV. Growth differentiation factor-15-ınduced contractile activity and extracellular matrix production in human trabecular meshwork cells. Invest Ophthalmol Vis Sci. 2016;57(15):6482-95.
20. Iwata Y, Inagaki S, Morozumi W, Nakamura S, Hara H, Shimazawa M. Treatment with GDF15, a TGFβ superfamily protein, induces protective effect on retinal ganglion cells. Exp Eye Res. 2021;202:108338.
21. Shofler D, Rai V, Mansager S, Cramer K, Agrawal DK. Impact of resolvin mediators in the immunopathology of diabetes and wound healing. Expert Rev Clin Immunol. 2021;17(6):681-90.
22. Zhang Z, Hu X, Qi X, Zhang Y, Wang Q, Zhou Q. Resolvin D1 promotes corneal epithelial wound healing and restoration of mechanical sensation in diabetic mice. Mol Vis. 2018;24:274-85.
23. Hua J, Jin Y, Chen Y, Inomata T, Lee H, Chauhan SK, et al. The resolvin D1 analogue controls maturation of dendritic cells and suppresses alloimmunity in corneal transplantation. Invest Ophthalmol Vis Sci. 2014;55(9):5944-51.
24. Kim N, Ramon S, Thatcher TH, Woeller CF, Sime PJ, Phipps RP. Specialized proresolving mediators (SPMs) inhibit human B-cell IgE production. Eur J Immunol. 2016;46(1):81-91.
25. Saban DR, Hodges RR, Mathew R, Reyes NJ, Yu C, Kaye R, et al. Resolvin D1 treatment on goblet cell mucin and immune responses in the chronic allergic eye disease (AED) model. Mucosal Immunol. 2019;12(1):145-53.
26. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest. 2018;128(7):2657-69.
27. Li N, He J, Schwartz CE, Gjorstrup P, Bazan HE. Resolvin E1 improves tear production and decreases inflammation in a dry eye mouse model. J Ocul Pharmacol Ther. 2010;26(5):431-9.
28. Dartt DA, Hodges RR, Li D, Shatos MA, Lashkari K, Serhan CN. Conjunctival goblet cell secretion stimulated by leukotrienes is reduced by resolvins D1 and E1 to promote resolution of inflammation. J Immunol. 2011;186(7):4455-66.
29. Wang H, Zhao Q, Luo D, Yin Y, Li T, Zhao M. resolvin e1 ınhibits corneal allograft rejection in high-risk corneal transplantation. Invest Ophthalmol Vis Sci. 2018;59(10):3911-9.