Analysis of tear cytokines and clinical correlations in Sjögren syndrome dry eye patients and non–Sjögren syndrome dry eye patients

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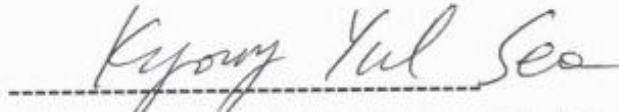
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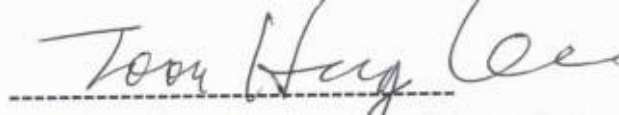
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ABSTRACT

Analysis of Tear Cytokines and Clinical Correlations in Sjögren's Syndrome Dry Eye Patients and Non-Sjögren's Syndrome Dry Eye Patients

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Purpose: To compare concentrations of tear cytokines in three groups comprised of Sjögren syndrome (SS) dry eye, non-Sjögren syndrome (non-SS) dry eye and normal subjects. Correlations between ocular surface parameters and tear cytokines were also investigated.

Methods: SS dry eye patients (n=24; 40 eyes) were diagnosed with primary SS according to the criteria set by the American-European Consensus Group. Non-SS dry eye patients (n=25; 40 eyes) and normal subjects (n=21; 35 eyes) were also enrolled. Tear concentrations of interleukin (IL)-17, IL-6, IL-10, IL-4, IL-2, interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α) were measured by a multiplex immunobead assay. Ocular Surface Disease Index (OSDI), tear film breakup time (TBUT), Schirmer I test, and fluorescein staining scores were obtained from dry eye patients.

Results: All cytokine levels except for IL-2 were highest in SS group, followed by Non-SS dry eye group and control subjects. Concentrations of IL-17, TNF-α, and IL-6 were significantly different among the three

groups (IL-17: SS>control P<0.001, non-SS>control P=0.042, SS>non-SS P<0.001; TNF-α: SS>control P=0.006, non-SS>control P=0.034, SS>non-SS P=0.029; IL-6: SS>control P=0.002, non-SS>control P=0.032, SS>non-SS P=0.002). IL-17 was significantly correlated with TBUT (R=-0.22, P=0.012) and Schirmer I test (R=-0.36, P=0.027) scores in the SS group. IL-6 was significantly correlated only with TBUT (R=-0.38, P=0.02) in the non-SS group.

Conclusions: Differences in tear cytokine levels and correlation patterns between SS dry eye and non-SS dry eye patients suggest the involvement of different inflammatory processes as causes of dry eye syndrome

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I. INTRODUCTION

Dry eye syndrome is a common disease. It is associated with discomfort, visual disturbance, and visual loss.[1-4] Despite the frequency of this disorder, it has been difficult to develop an effective treatment due to its resemblance with other ocular surface diseases and anatomical problems, as well as discrepancies between symptoms reported by patients and their doctors' observations. The general treatment for dry eyes is application of artificial tears. Recently, inflammation has been shown to be an important factor in the pathogenesis of dry eye syndrome.[5-10] On the basis of many studies about inflammation associated with dry eye, dry eye was defined as disease which is accompanied by increased tear osmolarity and inflammation on the ocular surface in Dry eye Workshop (DEWS) 2007[2]. Because inflammation is thought to be responsible for many symptoms, anti-inflammatory therapies including topical corticosteroids, tetracyclines, and topical cyclosporine A are prescribed.[4,11-13]

Many previous studies showed correlation of inflammation with dry eye. Intercellular adhesion molecule-1 (ICAM-1) antigen and Human leukocyte antigen (HLA) class II were known to be increased in conjunctival epithelium in Sjögren's syndrome (SS) dry eye patients. Okada and associates[15] showed that tumor necrosis factor α (TNF-α) interrupted corneal epithelial cell migration in healing process from damage induced by dry eye in animal model. Kimura[16] and

associates found that TNF-α and interleukin (IL)-1β destroyed corneal barrier function. Such studies in regards to inflammatory cytokines and chemokines have evaluated the pathogenesis of dry eyes, as well as possible treatments for the inflammation induced in dry eye syndrome. Taken together many previous results of studies[2,5,6] about inflammation in dry eye, inflammatory reaction is assumed that it consists of afferent arm and efferent arm. The afferent arm of dry eye inflammation is a phase of CD4+ T cell activation. Desiccation stress on the ocular surface activates dendritic cells and activated dendritic cells migrate to the regional lymph node. In regional lymph node, dendritic cells activate CD4+ T cells. Primed and targeted CD4+ T cells start homing to the ocular surface and release many inflammatory cytokines. This is called an efferent arm. Released cytokines destroy cornea surface and this process induce the vicious cycle of inflammation. It has been generally known that mainly associated immunocyte is CD4+ T cell. Previously, it was thought that CD4+ T cell was divided to T helper type 1 lymphocyte (Th1), T helper type 2 lymphocyte (Th2), and regulatory T cell (Treg).[17] Treg regulates CD4+ T cell. Th1 cells releasing several cytokines and chemokines such as interferon γ (IFN-γ) and IL-2 lead an immune reaction induced by intracellular bacteria and virus.[18] Th2 cell is known to affect eosinophils or basophils and participate in immune reaction induced by parasites through releasing cytokines and chemokines such as IL-4, IL-5, and IL-13.[18] New type of T helper lymphocyte having IL-23 receptor and releasing IL-17, IL-21, and IL-22 was discovered in the mid-1990s. It is named the T helper type 17 lymphocytes (Th17) and related with immune process of neutrophil. IL-17, which is produced by a Th17 cells, was identified as a potent cytokine inducing secretion of various proinflammatory cytokines and chemokines such as macrophage inflammatory protein 2, granulocyte colony stimulating factor, matrix metalloproteinase and IL-6.[18,19] Recently, it has been studied the role of IL-17 in inflammation and disruption of the corneal barrier after desiccating stress.[5,20,21] Through those studies, it is postulated that activated

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Th17 cells by dendritic cells impede Treg and maintain inflammatory reaction on the ocular surface.

Correlation of inflammation and immune reaction in dry eye supports validity of using anti- inflammatory or immunosuppressive drugs for dry eye treatment. Regulation or block of certain step in those reactions can be the starting point of developing new drug.

Ocular surface inflammatory reaction can be estimated by a tear cytokine analysis. So, many studies of tear cytokine analysis have been done by collecting tear of the subjects. In the study of dry eye, classifying dry eye subtypes is important because dry eye can be induced by various systemic diseases or local factors. Dry eye is classified as aqueous deficient type or evaporate type according to major etiologic cause by the DEWS 2007.[2] Aqueous deficient type dry eye includes SS dry eye which includes dry eye caused by lacrimal gland problems, reflex block, or age-related dry eye. Evaporate type dry eye is divided into two subgroups as intrinsic or extrinsic. Meibomian gland disease or lid aperture disorder induces intrinsic type dry eye. Other ocular surface diseases and vitamin A deficiency cause extrinsic-type dry eye. Although these classifications were not mutually exclusive, we pursued this study on the assumption that there would be a difference of inflammatory cytokine concentration in tear depending on the dry eye type. Among dry eye subtypes, SS dry eye patients are associated with systemic autoimmune disease. Accordingly, tear cytokine levels may vary between SS dry eye and other dry eye subtypes. So, in this study, we compared the levels of IL-17 in tears of dry eye syndrome patients and normal subjects. Dry eye syndrome patients were divided into two groups: SS dry eye and non-Sjögren syndrome (non-SS) dry eye without meibomian gland morphologic change. In addition to IL-17, IFN-γ, TNF-α, IL-10, IL-6, IL-4, and IL-2 were analyzed. Correlations between tear levels of cytokines and severity of clinical signs and symptoms were also analyzed.

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II. MATERIALS AND METHODS

1. SUBJECTS

We prospectively analyzed the levels of inflammatory cytokines in tears. Forty eyes of 24 SS dry eye patients and 40 eyes of 25 non-SS dry eye patients were enrolled in the study. Thirty-five eyes of 21 normal subjects were used as controls. This prospective cross sectional study was approved by the Institutional Review Board (4-2009-0694) of Yonsei University College of Medicine, and informed consent was obtained from all subjects. All SS dry eye patients were diagnosed with primary SS according to the criteria set by the American-European Consensus Group for Sjögren syndrome.[22] Most importantly, the serum antibodies of all SS patients were positive. Because of the unique female to male prevalence ratio observed in SS (F:M=9:1),[23] we included only female patients to prevent misinterpretation of data.

All dry eye patients had experienced symptoms of dry eyes for more than 6 months and used only artificial tears that did not contain preservatives (topical anti-inflammatory drugs such as 0.05% cyclosporine A or steroids were not used). For inclusion in the dry eyes group, patients had to have either undergone corneal and conjunctival staining or an Ocular Surface Disease Index (OSDI) over 20,[24,25] in addition to a tear film break up time (TBUT) of < 5 seconds or a Schirmer I test score of < 10 mm. Exclusion criteria included a history of previous ocular surgery, contact lens use, and any ocular surface inflammation or infection not directly related to dry eyes. Patients who demonstrated 2 or more morphologic changes in meibomian glands, including vascular dilation, acinar atrophy, or orifice metaplasia, on the posterior lid margin were also excluded. Normal subjects comprised subjects that were not pregnant, not on medication (systemic or topical), did not have a history of contact lens use, as well as exhibited no ocular symptoms or signs such as corneal erosion or corneal staining.

2. OCULAR SURFACE EVALUATION

To evaluate ocular surfaces and symptoms, we examined TBUT, Schirmer I test, corneal and conjunctival staining grade, and OSDI in all patients and normal subjects. The Oxford scheme (score 0-5) was used to grade corneal and conjunctival staining.[26]

3. TEAR CYTOKINES

As IL-17 level has been shown to be associated with autoimmune reaction of SS[27-32], we measured IL-17 level in 3 study groups. We also measured IFN-γ and IL-2 levels, which are known to be related with Th1 activation and response.[29-31] IL-6 and TNF-α, which were shown to be increased in previous studies about cytokine levels of dry eye patients[7-10,32,33] were also measured. Recently, some studies showed that not only Th1 cytokines, but also Th2 cytokines were correlated with SS.[29,34] Therefore, we assessed and compared IL-4 and IL-10 cytokine levels in tears among study groups.

All examinations were performed on each eye separately and performed at sufficient time intervals (more than 10 minutes) to minimize the impact of having the same researcher conduct the experiments.

4. TEAR SAMPLE COLLECTION AND ANALYSIS

To collect tear samples, 30 μL of phosphate-buffered saline was instilled into the inferior fornix (without topical anesthetics). A total of 20 μL of tear fluid and buffer were collected with a micropipette at the medial and lateral canthus. To minimize ocular surface irritation, we collected the mixture of tear fluid and buffer solution as soon as possible. The fluid was placed into a 1.5-mL Eppendorf tube and stored at -70℃ until further examination.

Cytokine concentrations were measured using a multiplex immunobead assay (BDTM Cytometric Bead Array Human Soluble Protein Flex Set, BD Biosciences, San Jose, CA, USA) and flow cytometry (BDTM FACS LSR II,

BD Biosciences).

5. STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS for Windows version 15.0.
Cytokine concentrations among the 3 study groups were compared by analysis of
variance with Tukey post hoc testing. Correlations between cytokine
concentration and clinical parameters (OSDI, TBUT, Schirmer I test, stainig
grade) were analyzed by Pearson correlation coefficient.

III. RESULTS

The demographics and clinical features of the SS dry eye group, non-SS dry eye
group, and control group are shown in Table 1. There were no significant
differences in mean age among the 3 groups. Between the 2 dry eye groups, there
were also no significant differences in mean OSDI, staining grade scale, TBUT,
and Schirmer I test.

Table 1. Demographics and clinical characteristics of Sjögren syndrome dry eye patients, non-Sjögren syndrome dry eye patients, and normal subjects.

Characteristics	Sjögren Syndrome Dry Eye	Non-Sjögren Syndrome Dry Eye	Control	*P*-value[a] *(SS vs Non-SS)*
Number of eyes (OD/OS)	40 (18/22)	40 (18/22)	35 (18/17)	
Mean Age (range)	55.9±9.96 (37 to 74)	55.4±12.44 (32 to 79)	52.8±13.19 (37 to 76)	0.984
OSDI (0-100)	41.56±23.22	33.05±13.67	10.48±10.98	0.135
Grade (0-5)	1.86±1.4	0.8±1.2	0	0.198
TBUT(s)	3.88±1.98	4.56±2.54	8.91±3.89	0.52
Schirmer I (mm)	4.98±3.12	7.12±4.53	11.88±6.48	0.291

OSDI= Ocular Surface Disease Index; Grade estimated by The Oxford scheme; TBUT=tear break up time.

[a]The mean value was compared by ANOVA and multiple comparison. *P*-values were calculated by Tukey post hoc testing between the two dry eye groups. We presented *P* -values between SS dry eye and non-SS dry eye in this table (by Tukey post hoc test).

1. TEAR CYTOKINE LEVELS

   The mean values of cytokine levels in tears are shown in Table 2. Figure 1 shows the differences in cytokine concentrations among the 3 groups. All of the mean concentrations of tear cytokines in the SS dry eye group were higher than those of the other 2 groups. The mean concentrations of IL-17, TNF-α, IL-10, IL-6, and IL-4 in the SS dry eye group were significantly greater than those in the control group (Figure 1A, IL-17: P<0.001, TNF-α: P=0.006, IL-10: P=0.049, IL-6: P=0.002, IL-4: P=0.019). There were also significant differences in IL-17, TNF-α, and IL-6 between the non-SS dry eye group and the control group (Figure 1B, IL-17: P=0.042, TNF-α: P=0.034, IL-6: P=0.032). Between the two

dry eye groups, the mean concentrations of IL-17, TNF-α, IL-6, IL-4, and IL-2 were significantly different   (Figure 1C, P-value was presented in Table 2.)

Table 2. Levels of cytokines in Sjögren syndrome dry eye patients, non-Sjögren syndrome dry eye patients, and normal subjects.

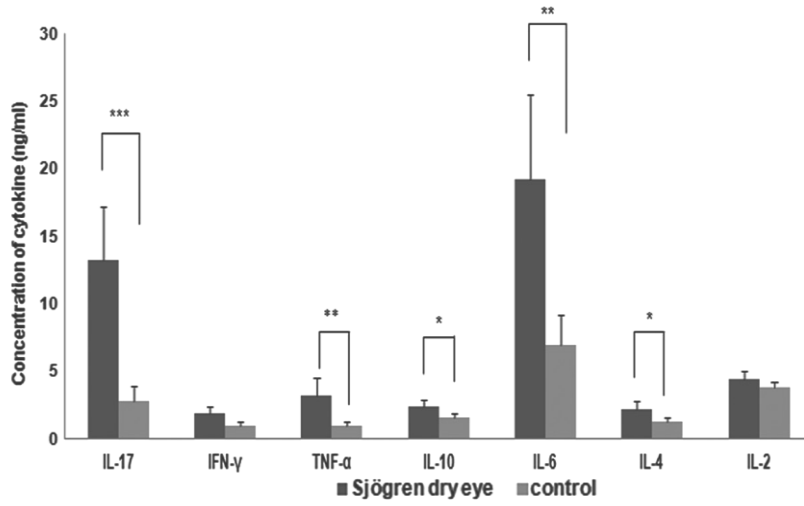| Cytokine (ng/ml)	Sjögren Syndrome Dry Eye	Non-Sjögren Syndrome Dry Eye	Control	P-value[a] (SS vs. Non-SS)
IL-17	13.22±12.7	3.99±5.18	2.78±3.51	**<0.001**
IFN-γ	1.89±1.65	1.24±1.30	1.00±0.83	0.09
TNF-α	3.24±4.26	1.67±1.46	0.95±0.91	**0.029**
IL-10	2.36±1.67	1.70±1.23	1.63±0.91	0.074
IL-6	19.22±20.11	12.12±13.54	6.97±6.73	**0.002**
IL-4	2.23±1.81	1.21±1.30	1.30±0.98	**0.015**
IL-2	4.38±2.14	3.24±1.58	3.76±1.30	**0.025**

IL= interleukin; IFN=interferon; TNF=tumor necrosis factor

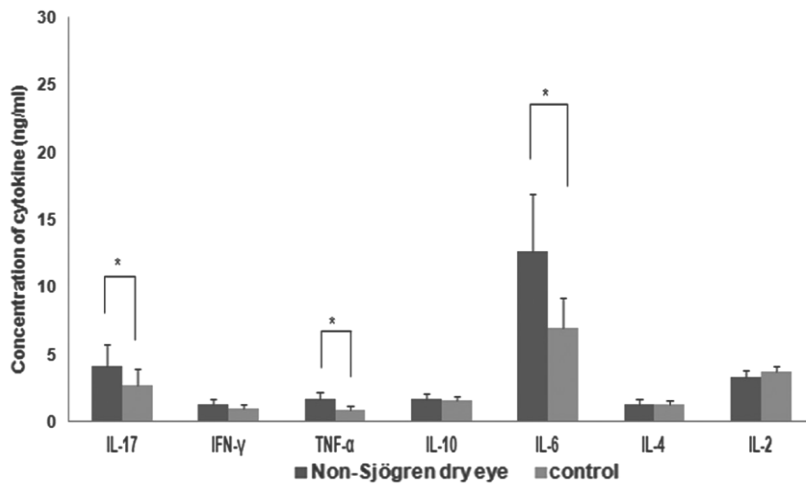[a]The mean value was compared by analysis of variance (ANOVA) with Tukey post hoc test.

We presented P-values only between SS dry eye and non-SS dry eye in this table (by Tukey post hoc test).

Significant differences are designated in bold.
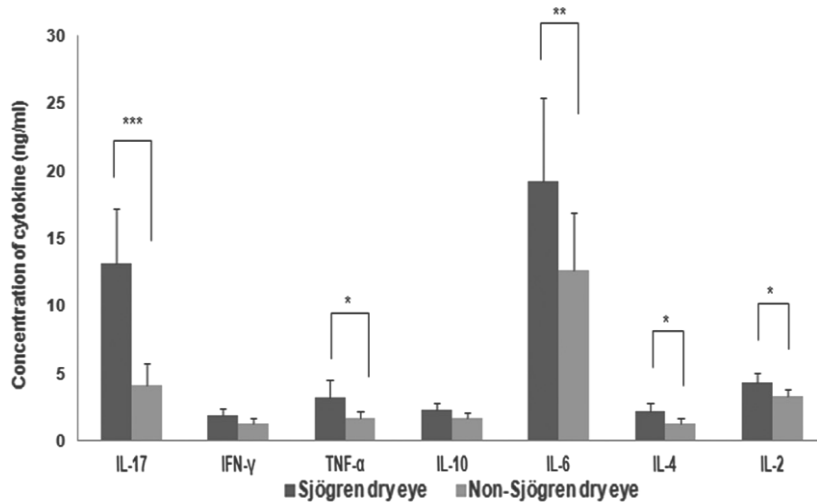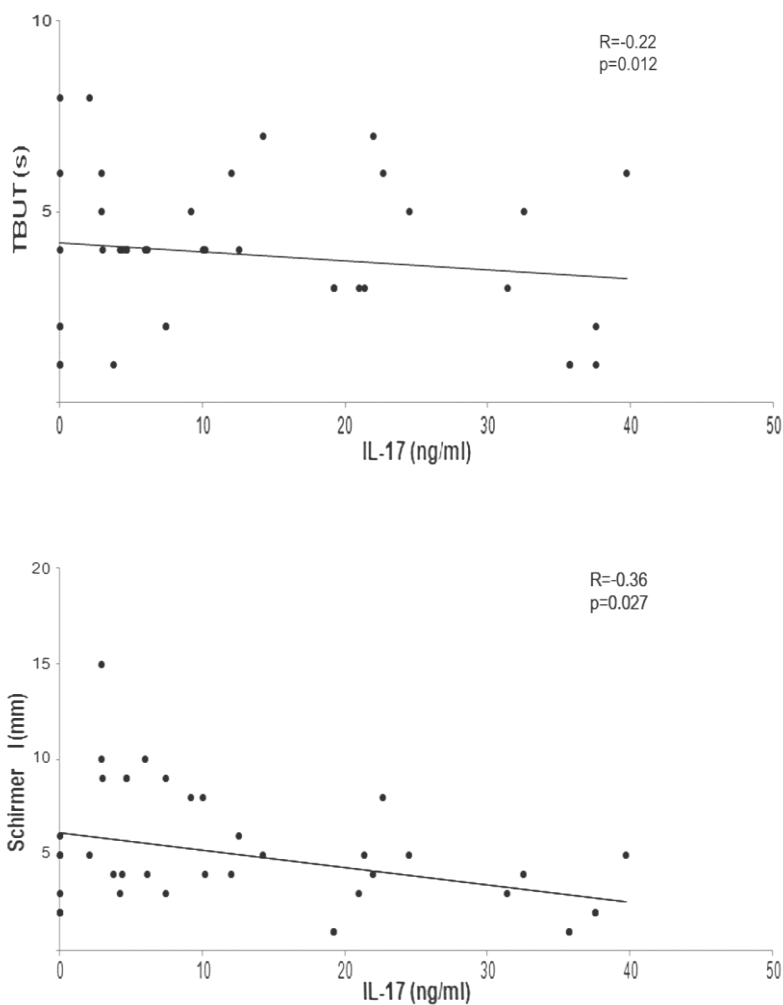
A.

B.

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C.

Figure 1. Tear cytokine levels in Sjögren syndrome (SS) dry eye patients,
non-Sjögren syndrome (non-SS) dry eye patients, and normal subjects.
Comparison of tear cytokine mean values between the SS dry eye group and
control group (A), between the non-SS dry eye group and control group (B),
between the SS dry eye group and non-SS dry eye group. (C)   Bars designate
the means with 95% confidence intervals. P-values were calculated by one-way
analysis of variance and multiple comparisons. (*P<0.05; **P<0.01;
***P<0.001)

2. CORRELATIONS BETWEEN TEAR CYTOKINES AND OCULAR SURFACE PARAMETERS

  We next investigated correlations between tear cytokines and parameters of
ocular surfaces including OSDI, corneal and conjunctival grade, TBUT, and
Schirmer I test for the 2 dry eye groups. In the SS dry eye group, only IL-17 and
TNF-α level were significantly correlated with ocular surface parameters.
Whereas IL-17 level was shown to be significantly correlated with TBUT and
Schirmer I test, TNF-α was only significantly correlated with Schirmer I test

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(Figure 2A, IL-17 with TBUT: R=-0.22, P=0.012; IL-17 with Schirmer I: R=-0.36, P=0.027; TNF-α with Schirmer I: R=-0.17, P=0.014). In the non-SS dry eye group, only TBUT and IL-6 level were significantly correlated with ocular surface parameters (Figure 2B, R=-0.38, P=0.017). The other cytokines were not significantly correlated with ocular surface parameters.

A. Sjögren syndrome dry eye

B. Non-Sjögren syndrome dry eye
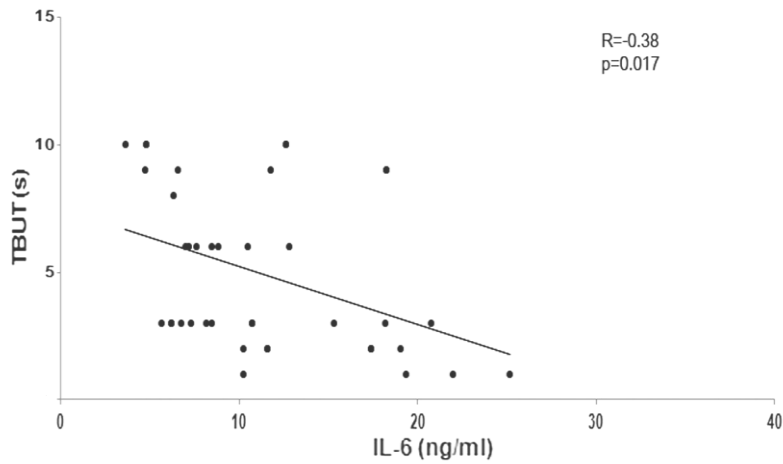

Figure 2. Correlation between cytokine levels in tears and clinical parameters. Only the 4 graphs that indicated significant correlation are presented. In the Sjögren syndrome (SS) dry eye group, tear IL-17 level was significantly correlated with Schirmer I test and Tear break up time (TBUT). There was also significant correlation between tear TNF-α with Schirmer I in the SS dry eye

group. In the non-Sjögren syndrome (non-SS) dry eye group, only IL-6 was significantly correlated with TBUT. Pearson correlation coefficients were calculated to analyze correlations.

IV. DISCUSSION

Recently, Kang and associates[35] reported that tear IL-17 concentrations were significantly greater in various ocular surface inflammatory diseases, including SS dry eyes and simple dry eyes, without meibomian gland disease than in normal subjects. As mentioned in the introduction, previous studies showed a correlation for IL -17 in the immunopathogenesis of dry eye disease.[5,6,35] According to our results, increases in IL-17 concentration were observed in both dry eye patient groups, supporting the possibility of an important role for IL-17 in dry eye inflammation processes. Moreover, the differences in IL-17 level between the SS dry eye group and non-SS dry eye group demonstrate a stronger participation of IL-17 in SS dry eye.

In the SS dry eye group, IL-10 and IL-4 were significantly increased in comparison to the control group. However, there were no significant differences between the non-SS dry eye group and the control group. IL-4 was also significantly different between two dry eye groups. SS was thought to be a Th1 dominant disease in the past.[27,29] However, cytokines involved in Th2 immune response, such as IL-10, were shown to be elevated in salivary glands and serum in SS patients.[29,34] In addition, Th17, characterized by the secretion of inflammatory cytokines IL-17 and IL-23, was also shown to be involved in autoimmunity and inflammation in SS.[27-29] Our findings support the relationship of a Th2 response in SS, and suggest that IL-4 and IL-10 influence SS dry eye inflammatory processes.

Yoon and associates[8] showed that IL-6 levels in tears of dry eye patients were correlated with TBUT, Schirmer I test, keratoepithelial score, and goblet cell

density. The study by Lam and associates[7] also suggested a correlation between IL-6 levels in tears of dry eye patients and ocular surface parameters, such as systemic symptom score, Schirmer I test, and corneal and conjunctival staining scores. Other study that quantitated tear cytokine levels and their clinical correlations in patients with moderate evaporative type dry eye disease attributable to meibomian gland disease showed correlations between TBUT and IL-1Ra; between Schirmer I test and IL-1Ra, IL-6, IL-8/CXCL8, fracktalkine/CX3CL1, IP-10/CXCL10, and VEGF; and pain and IL-6 and IL-8/CXCL8.[9] In comparison to IL-6 and TNF-α, correlation between IL-17 level in tears and clinical parameters is not well known. Previous studies showed IL-17 serum level concentrations to be significantly correlated with fluorescein staining score [27,36]. In addition, Kang and associates[31] reported that IL-17 concentrations in tears were correlated with corneal and conjunctival fluorescein staining in dry eye patients with systemic inflammatory disease. However, their study included not only SS dry eye patients, but also other dry eye patients with systemic inflammatory disease, such as graft-versus-host disease, Stevens-Johnson syndrome, SS, rheumatoid arthritis, and systemic lupus erythematous. In contrast, our study investigated cytokine concentrations only in SS dry eye patients without evidence of other systemic inflammatory disease. In addition, all patients of the SS dry eye comprised serum antibody positive primary SS patients. Furthermore, we additionally included non-SS dry eye patients without abnormal meibomian gland shape and function for comparison with SS dry eye. These factors along with similar preoperative conditions, which were not significantly different between the 2 dry eye groups, should instill confidence in the findings of this study.

  Comparing previous studies and our study, it is thought that IL-6 exhibits reliable correlation with TBUT in non-SS dry eye. However, the fact that IL-6 did not significantly correlate with clinical parameters in SS dry eye patients indicates that inflammatory cytokines exert different influences in SS dry eye and

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non-SS dry eye. Although we can confirm some correlations mentioned above, and correlation analysis demonstrate different inflammation reactions between the 2 dry eye groups, additional studies are necessary to assess correlation among cytokine concentration, clinical parameters, and dry eye severity, because the clinical utility of commonly used tests such as conjunctival and corneal staining, meibomian score, TBUT, Schirmer test did not correlate well with dry eye severity in previous studies.[37,38] In addition, tear film osmolarity which was found to be the single best marker of dry eye disease severity and associated with apoptosis in human corneal epithelial cells in previous studies[37,39] must be considered in further studies.

IL-17, which is mainly produced by Th-17 cells, mediates production of inflammatory cytokines and plays an important role in adaptive and innate immunity.[40,41] The ocular surface contains significant amounts of cytokines including IL-6, IL-1, TGF-β1, and IL-23, which can induce Th-17 cell differentiation.[20,21,42] This cytokine rich environment suggests an important role for cytokines in dry eye disease. Fujita and associates suggested the possibility of different cause of dry eye between SS dry eye patients and non-SS dry eye patients in the study about dry eye in rheumatoid arthritis patients.[43] The study of Fujita and associates[43] and Lemp's editorial[44] about that study suggested the possibility of different dry eye pathways that consist of SS dry eye affected by systemic inflammation preferentially and non-SS dry eye affected by local factors (elevated osmolarity, the behavior of mucins, alteration in lipid layer, altered apoptosis of lacrimal and ocular surface cells) preferentially.

V. CONCLUSION

The differences in tear cytokine levels and correlation patterns in each dry eye group of our study support the possibility of different inflammatory processes according to dry eye type including dry eye without systemic inflammatory

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disease. It can be presumed that SS dry eye may be affected by systemic or local immunologic reaction related to IL-17, while non-SS dry eye may be related to stressful situations such as desiccation, which can induce increases in cytokines like IL-6. Many studies on cytokine levels in tears have been conducted with the objective of controlling ocular surface inflammation and improving treatments for dry eye patients. Thus, identifying specific cytokines involved in each dry eye type or correlation with clinical parameters is essential. In particular, our study, based on the results for IL-17, support the possibility of a T cell-specific therapy or immune modulating treatment for SS dry eye.

   Although this study comprised a relatively large sample size in comparison to previous studies, more large scale prospective studies including male patients are necessary to investigate distinct differences among dry eye groups. In SS dry eye patients, measuring of serum IL-17 may be helpful in analyzing IL-17 level in tears, because systemic inflammation can influence tear cytokine level. Further studies to identify inflammatory reactions in dry eyes may lead to greater control of inflammation in dry eye treatment, and improve treatment satisfaction in dry eye sufferers.

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ABSTRACT(IN KOREAN)

건성안 환자의 눈물 내 염증성 사이토카인의 농도 및 임상 양상과의 상관관계 분석

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목적: 쇼그렌 증후군 건성안 환자와 비 쇼그렌 증후군 건성안 환자의 눈물 내 사이토카인의 차이와 건성안의 임상 양상과 사이토카인과의 연관성의 차이를 살펴봄으로써 두 건성안에 관련된 염증반응의 차이를 확인하고자 함. 이를 통해 추후 염증 조절을 통한 건성안 치료에 있어 방향을 제시하고자 함

대상과 방법: 40안 24명의 쇼그렌 증후군 건성안 환자, 40안 25명의 비쇼그렌 증후군 건성안 환자, 그리고 35안 21명의 정상인을 대상으로 연구를 진행함. 눈물 내 interleukin (IL)-17, IL-6, IL-10, IL-4, IL-2, interferon γ (IFN- γ), tumor necrosis factor ɑ (TNF-α)의 농도를 multiple immunobead assay로 측정하여 각 군간에 비교하였고, 각 사이토카인의 농도와 임상 양상과의 연관성에 대해서도 분석하였음. 임상지표로는 Ocular Surface Disease Index (OSDI), tear film break up time (TBUT), Schirmer I test, fluorescein staining score가 사용 되었음.

결과: IL-2를 제외한 모든 염증성 사이토카인의 농도는 쇼그렌 증후군 건성안, 비쇼그렌 증후군 건성안, 정상인 순으로 나타났으며,

이중 IL-17, TNF-α, IL-6 가 유의한 차이를 보임. 임상 양상과의 연관성은, 쇼그렌 건성안 환자에서는 IL-17과 TBUT (R=-0.22, P=0.012), IL-17 과 Schirmer I (R=-0.36, P=0.027) 가 유의한 연관성을 가졌으며 비쇼그렌 건성안 환자에서는 IL-6와 TBUT 간의 연관성만 통계적으로 유의하였음.(R=-0.38, P=0.02).

결론: 쇼그렌 증후군 건성안 환자군과 비 쇼그렌 증후군 건성안 환자군의 눈물 내 사이토카인의 농도 차이는 건성안을 유발하는 염증 반응이 건성안 종류에 따라 차이가 있음을 보여줌. 이는 각 건성안 환자군에서 보이는 임상 양상과 사이토카인 간에 연관성 분석 결과의 차이로도 뒷받침 됨.

핵심되는 말: 눈물 내 사이토카인, 쇼그렌 증후군 건성안, 건성안, 인터류킨-17

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