Case Report

A 75-year-old Japanese woman was referred to us for persistent irritation in September 2006. She reported a history of foreign body sensation in the left eye for 4 years. Slit lamp examination revealed hypertrophy, hyperemia, and pronounced fluorescein staining of the superior bulbar conjunctiva in the left eye (Figure 1-A, B). Schirmer's test results were 2 mm in the right eye and 1 mm in the left eye. The diagnosis of superior limbic keratoconjunctivitis (SLK) with aqueous deficiency dry eye was made based on these findings. Initially, treatment was attempted with 0.1% fluorometholone and 0.1% sodium hyaluronate eyedrops without success. Punctal plugs inserted to the upper and the lower puncta provided little symptomatic relief.

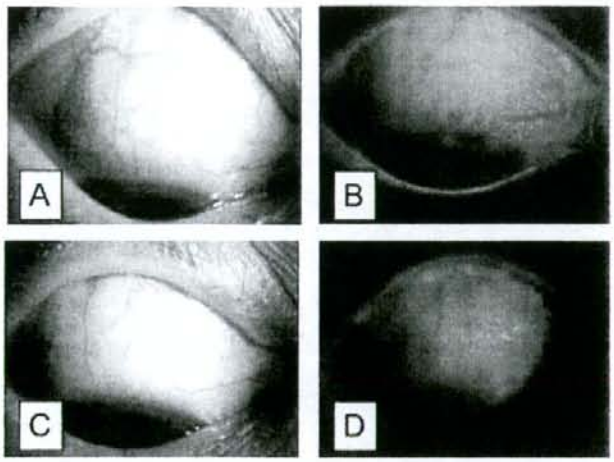
We applied fixation sutures to the superior bulbar conjunctiva in December 2006 to attempt to treat this refractory condition. First, the patient received a topical and subconjunctival injection of lidocaine 2%. A traction suture was made by placing a 6-0 silk suture at the limbus at the 12 o'clock position, so as to rotate the eye downward (Figure 2). Stretching the redundant superior bulbar conjunctiva with a spatula, anchoring sutures were then placed using 10-0 nylon sutures at a location 10-12 mm from the limbus to fixate the conjunctiva with the sclera. Two stitches were placed nasally from the superior rectus muscle, and three stitches were placed temporally. Postoperatively, the patient received 0.5% levofloxacin and 0.1% fluorometholone eyedrops four times daily for 2 weeks. Two weeks after the procedure, the patient reported complete resolution of symptoms. Slit-lamp examination revealed a marked reduction in conjunctival hyperemia and fluorescence staining of the affected area (Figure 1-C,D). The patient's findings remained stable through over one year of follow-up.

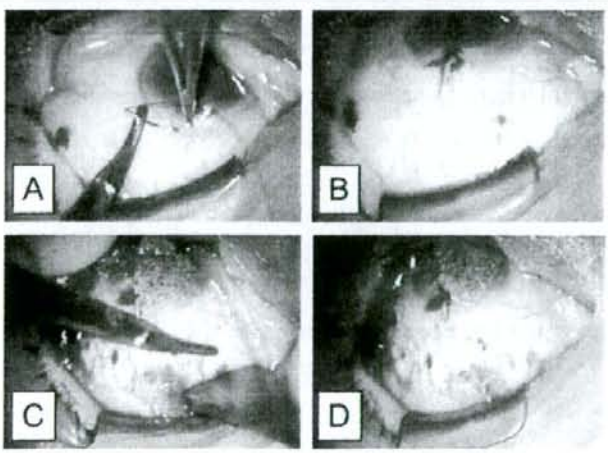
Questions:

1. What is the pathophysiology of SLK?

2. What medical treatment options exist for SLK?

3. What surgical options exist for SLK?





Answers

1 **What is the pathophysiology of SLK?**

Since Theodore published the first clinical description of SLK in 1963 [1], numerous etiologies have been proposed for this specific keratoconjunctivitis. [2] Although the etiology of SLK has not been definitively established, the authors hold the mechanical friction theory to be most plausible.

The mechanical friction theory originally advocated by Wright [3] is based on a characteristic feature of SLK, redundancy and loosening of the superior bulbar conjunctiva. The mechanical theory suggests that the superior bulbar conjunctiva is continually rubbed by the upper tarsus during blinking, resulting in chronic inflammation. This theory is supported by the clinical observations that SLK tends to be associated with thyroid dysfunction, and with the use of hydrophilic contact lenses. [4][5] SLK may also be present in eyes with essential blepharospasm, and eyes with previous upper lid blepharoplasty. [6] Thus, the pathophysiology of SLK appears to involve abnormal dynamics, or an abnormal interface load between the eyelid and the globe, resulting in friction on blinking that leads to chronic irritation and the development of keratoconjunctivitis. [7]

2. **What medical treatment options exist for SLK?**

A number of medical treatment modalities have been proposed for SLK. [2] The local application of silver nitrate, originally recommended by Theodore [1], appears to facilitate scarring and remodeling of the subconjunctival tissue, which in turn is proposed to decrease friction between the bulbar and palpebral conjunctiva. Bandage contact lenses, which are particularly effective in treating eyes with filamentary keratitis, are thought to exert a therapeutic effect by isolating the globe mechanically from the motion of the tarsus. [8]

Preexisting dry eye is linked to SLK [1][4], indicating that the loss of lubricity may contribute to the development of SLK. Lubricating eyedrops including artificial tears, sodium hyaluronate, and autologous serum, therefore, may of value to some degree. [9] Occlusion of the upper and/or lower puncta may be effective by increasing the amounts of tears that facilitate lubrication of the ocular surface. [10] Pharmacologic therapies intended to lesson ocular surface inflammation may also be considered. Corticosteroid, cyclosporine A, and cromolyn sodium have been used for this purpose. [6][11] In general, however, the effects of medical treatments are limited, and when they fail, surgical treatments become necessary.

3. **What surgical options exist for SLK?**

Thermocautery [10], simple resection [2][12], and recession of the abnormal conjunctiva [13] have been reported as effective surgical treatments for SLK. New surgical methods such as a crescent resection of the superior unaffected bulbar conjunctiva [14] and amniotic membrane transplantation [6] have recently been proposed. Additionally, in this case report, we describe the use of conjunctival fixation sutures, which, to our knowledge, is a novel approach for the treatment of SLK.

Surgical options for the treatment of SLK can be divided into two categories based on mechanism of action, procedures that seek to reinforce the adhesion of the conjunctiva to the sclera, and those that seek to correct the redundancy of the superior bulbar conjunctiva. Procedures in the first category include thermocautery, recession of the abnormal conjunctiva, and amniotic membrane transplantation. Procedures in the latter category include resection of the abnormal conjunctiva, or resection of the unaffected superior bulbar conjunctiva, as well as the conjunctival fixation suture method described in this case report.

Discussion

SLK, an inflammatory disease involving the region of the limbus and the superior bulbar conjunctiva, may result in conditions such as filamentary keratitis, superficial punctate keratopathy, and hyperemia of the limbus and superior bulbar conjunctiva. [2][4] There is prominent laxness of the superior bulbar conjunctiva when the upper lid was squeezed in patients with SLK. Recently, Yokoi et al. [14] and Kheirkhah et al. [6] independently reported that a redundant, loosened superior bulbar conjunctiva plays a significant role in the pathogenesis of SLK. These authors advocated categorizing SLK as a type of conjunctivochalasis, or recognizing SLK as superior conjunctivochalasis. [6][14]

Based in part on our successful experience using fixation sutures for the treatment of conjunctivochalasis, a method which was originally reported by Otaka and Kyu [15], we accordingly chose a similar technique for the treatment of refractory SLK. Though many surgical procedures to treat SLK have been investigated, fixation sutures offer the unique benefit of simple, quick, and minimally invasive application. Additionally, a large area of the superior bulbar conjunctiva remains unaffected by this procedure, which may be beneficial in the event of future ocular surgery, such as cataract or glaucoma surgery. We have now successfully treated a total of three patients with refractory SLK with the procedure described in this case report.

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Figure Legends

Figure 1. Before surgery, hyperemia and hypertrophic changes are seen in the superior bulbar conjunctiva (A). The affected area is intensively stained with fluorescein sodium (B). Two weeks after the operation, marked improvements in hyperemia and fluorescein staining are apparent (C, D).

Figure 2. . A traction suture is made by placing a 6-0 silk suture at the limbus at the 12 o'clock position in order to rotate the eye down ward (A, B). Stretching the redundant superior bulbar conjunctiva with a spatula, anchoring sutures were used by placing 10-0 nylon sutures at 10-12 mm from the limbus to fixate the conjunctiva to the sclera (C). Two stitches were placed nasally from the superior rectus muscle, and three stitches were placed temporally (D).

Eye & Contact Lens 34(1): 13–16, 2008

The Disease Burden of Keratoconus in Patients' Lives: Comparisons to a Japanese Normative Sample

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Purpose. Keratoconus is a chronic, noninflammatory, degenerative disease of the cornea that has an onset in young adulthood. The objective of this study was to evaluate vision-related quality of life (VR-QOL) in patients with keratoconus by using the Japanese version of the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25). **Methods.** Forty-five patients diagnosed with keratoconus at the Keio University School of Medicine were enrolled. Patients were divided into three subgroups according to corrected visual acuity. Group A included patients whose best-corrected visual acuity was at least 20/20 in both eyes. Group B included patients with a best-corrected visual acuity of at least 20/20 in only one eye. Group C included patients whose best-corrected visual acuity was worse than 20/20 in both eyes. Thirty-six age-matched subjects were recruited as control subjects. The Japanese version of the NEI-VFQ-25 was administered to each subject. **Results.** All NEI-VFQ-25 subscale scores were significantly lower ($P<0.05$) in patients with keratoconus than in the control subjects. Subscales evaluating general health, ocular pain, and vision-specific mental health showed particularly low values. Among patients with keratoconus, every subscale score other than color vision correlated with corrected visual acuity. **Conclusions.** The results support that and describe how multidimensional visual function and VR-QOL are impaired in patients with keratoconus, including those with normal visual acuity. Ophthalmologists and other clinicians should carefully evaluate and address the full range of quality of life issues that may affect patients with keratoconus.

Key Words: Contact lens—Keratoconus—Keratoplasty—Quality of life.

Keratoconus is a chronic, noninflammatory, degenerative disease of the cornea that has an onset in young adulthood and is characterized by a cone-shaped bulging of the corneal surface and stromal thinning.[1] Although some patients with keratoconus require keratoplasty to restore visual acuity, most patients are able to maintain normal visual acuity with the aid of contact lenses, although some patients experience contact lens intolerance.

The clinical status of patients with ocular disorders such as keratoconus is often evaluated through tests of objective function, such as visual acuity, refraction, and keratometric analysis. The past few decades have seen an increasing appreciation of the importance of assessing the illness experience in patients with ocular and other diseases in a comprehensive fashion that extends beyond measures of biologic status. Consequently, the concept of health-related quality of life (QOL) has been developed, which encompasses not only the biologic status of disease, but also the full range of complex effects that the illness and its various sequelae have on the life of the patient. Such sequelae may include the practical effects of the disease on the daily life of the patient, the side effects of treatment, issues of identity as the patient reconceives of himself or herself as an individual with a chronic illness, and social challenges involved in managing the disease and meeting the reactions of others to the illness. In this vein, in ophthalmology, concepts such as quality of vision and vision-related quality of life (VR-QOL) have been recently developed and are increasingly used. Several questionnaires have been developed to measure VR-QOL.[2–5]

Vision-related quality-of-life instruments can be divided into two broad categories: generic instruments, which are designed to be used in a broad spectrum of ocular disorders, and disease-specific instruments, which target patients with specific conditions. The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), a generic instrument, has been intensively investigated, and its validity has been established for various ocular disorders, including glaucoma, age-related macular degeneration, diabetic retinopathy, cytomegalovirus retinitis, and age-related cataracts.[6–13] The NEI-VFQ-25 evaluates not only visual function and limitations in daily activities related to impaired visual function, but also the impact of ocular disease on patients' lives from various standpoints.[6] The NEI-VFQ-25 has been translated into several languages, including Japanese. The reliability and the validity of the Japanese version of the NEI-VFQ-25 are considered comparable to those of the English version.[14,15]

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The authors have no proprietary interest in any materials in this article.

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Accepted February 23, 2007.

DOI: 10.1097/ICL.0b013e3180515282

Visual acuity is the most common measure of clinical status in patients with keratoconus. It is apparent, however, that normal visual acuity alone cannot ensure good QOV and VR-QOL in patients with keratoconus. In addition to possibly diminished visual acuity, patients with keratoconus also experience the anxiety of knowing that they may someday need to undergo surgery, such as keratoplasty, and of knowing that their condition may progress and possibly lead to low vision. They also endure the burden of frequent hospital visits. Additionally, most patients who depend on contact lenses experience anxiety because of decreased vision when they are not able to wear their lenses. Many patients with keratoconus have less than all-day wear with contact lenses because of irritation and have significantly reduced vision with glasses. Thus, it may be appropriate to use a more comprehensive QOL-related tool in the examination of these patients.[16]

This study sought to evaluate self-reported VR-QOL in patients with keratoconus by using the NEI-VFQ-25. The influence of disease severity on VR-QOL was also examined.

MATERIALS AND METHODS

Subjects

A total of 45 Japanese patients with bilateral keratoconus (12 women and 33 men) were enrolled. The average age was 36.3 ± 9.4 years (range, 20–63 years). All patients had been diagnosed with keratoconus at Keio University Hospital. Keratoconus diagnoses were made based on slitlamp examination findings and videokeratography. The patient sample included contact lens wearers, spectacle wearers, and patients with a history of keratoplasty in one eye. Patients with a history of other ocular diseases, such as retinal disease, cataracts, or glaucoma, were excluded from the study. Patients with a history of keratoplasty complications, such as allograft rejection, infection, and graft failure, were also excluded.

Patients were divided into three subgroups according to corrected visual acuity. Group A included patients whose best-corrected visual acuity in each eye was at least 20/20. Group B included patients with a best-corrected visual acuity of less than 20/20 in one eye. Group C included patients whose best-corrected visual acuity was less than 20/20 in both eyes. Thirty-six age-matched healthy Japanese subjects with no known ocular disorders other than refractive error were recruited as control subjects.

The principles of the Declaration of Helsinki were followed. Each subject received a thorough explanation of the purpose of the study and all procedures involved in the study and provided written informed consent before enrollment. Approval for this investigation was granted by the Committee for the Protection of Human Subjects at the Keio University School of Medicine.

The NEI-VFQ-25

The NEI-VFQ-25 consists of 25 core and 13 optional items. It is divided into the following 12 subscales: general health, general vision, ocular pain, near vision, distance vision, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, color vision, and peripheral vision. A self-administered Japanese version of the NEI-VFQ-25 was used in this study. The instrument generally took approximately 10 minutes for patients to complete and was administered to patients before the ophthalmologic examination.

TABLE 1. *Characteristics of Patients With Keratoconus and Control Subjects*

Characteristic	Patients with keratoconus (n = 45)	Control subjects (n = 36)
Mean age (years)	36.3 ± 9.4	36.3 ± 13.0
Gender		
Male	33 (73%)	23 (64%)
Female	12 (27%)	13 (36%)
Best-corrected visual acuity		
≥20/20 in both eyes	12 (27%)	36 (100%)
≥20/20 in one eye	26 (58%)	0
<20/20 in both eyes	7 (15%)	0
Means of refractive correction		
None	1 (2%)	10 (28%)
Spectacles	2 (4%)	10 (28%)
Soft contact lenses	1 (2%)	13 (36%)
Hard contact lenses	41 (92%)	3 (8%)
History of keratoplasty	12 (27%)	0

In the NEI-VFQ-25, each of its subscales is scored from 0 to 100, with higher scores representing better function. Clinical data, including patient age, sex, ocular and medical history, and history of ocular surgery, were obtained from medical records and patient interviews.

Statistical Analysis

Descriptive statistics were used and included measurement of means and dispersion. Descriptive data are presented as mean ± standard deviation and percentages. The Mann–Whitney test was used to compare the NEI-VFQ-25 scale scores between groups. To minimize bias, subscale scores were included in analyses only if all questions within the subscale were completed. All statistical analyses were performed with the SAS/STAT module of the SAS statistical software package (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline demographic characteristics of patients with keratoconus and control subjects, including any means of refractive correction used, are shown in Table 1. Most (91%) patients with keratoconus were hard contact lens wearers. There were 12 patients in group A, 26 patients in group B, and seven patients in group C.

The NEI-VFQ-25 subscale scores of patients with keratoconus and control subjects are shown in Table 2. All subscale scores of patients with keratoconus were significantly lower than those of control subjects ($P<0.01$, Mann–Whitney test). Particularly low subscale scores were seen for patients with keratoconus in the general health, general vision, ocular pain, and vision-specific mental health subscale categories.

The NEI-VFQ-25 subscale scores of groups A, B, and C and control subjects are shown in Figure 1. Increasing visual acuity, as assessed by group A through C category membership, correlated with increasing QOL or function scores in all subscales among patients with keratoconus. Even in group A, in which the best-corrected visual acuity was 20/20 or better in both eyes, all subscale scores other than general health and driving were significantly lower than those of age-matched control subjects ($P<0.05$, Mann–Whitney test).

TABLE 2. *VFQ-25 Subscale Scores of Patients With Keratoconus and Control Subjects*

Subscale	Patients with keratoconus (n = 45)	Control subjects (n = 36)
General health	56.3 ± 18.6[a]	71.2 ± 17.6
General vision	62.3 ± 16.9[a]	81.4 ± 11.7
Ocular pain	57.4 ± 23.8[a]	83.0 ± 13.6
Near vision	80.5 ± 15.8[a]	92.8 ± 9.7
Distance vision	73.7 ± 16.1[a]	89.0 ± 13.3
Vision-specific		
Social functioning	85.9 ± 13.7[a]	97.2 ± 7.04
Mental health	65.9 ± 23.8[a]	90.9 ± 13.8
Role difficulties	77.8 ± 19.6[a]	96.3 ± 9.3
Dependency	88.2 ± 11.9[a]	98.3 ± 5.3
Driving	72.3 ± 20.6[a]	79.1 ± 24.2
Color vision	92.4 ± 11.4[a]	98.6 ± 5.7
Peripheral vision	74.6 ± 23.3[a]	92.4 ± 13.1

[a]$P<0.01$ for keratoconus–control comparisons by the Mann–Whitney test.

DISCUSSION

All mean NEI-VFQ-25 subscale scores for patients with keratoconus were significantly lower than those of age-matched control subjects ($P<0.01$, Mann–Whitney test), which was in good accordance with the report of Kymes et al.[16] Additionally, subscale scores correlated with corrected visual acuity as assessed by group A through C category membership. The finding that visual function subscale scores, such as general vision, near vision, distance vision, and driving are decreased in patients with keratoconus is intuitive. Most patients in this study had a corrected visual acuity of less than 20/20 in at least one eye, and many patients additionally may have subtle visual disturbances not evident on standard acuity testing. The low QOL scores observed on the ocular pain subscale may be explained by the need for many patients with keratoconus to wear hard contact lenses. Finally, the notably low mental health subscale scores found among patients with keratoconus warrants attention, suggesting that the various burdens of living with keratoconus may pose a considerable challenge to patient mental health and that practitioners should be attuned to this possible issue when treating keratoconus. These factors may explain the personality trends in keratoconus.[17,18] Through attention to such larger implications of disease, the care of patients with keratoconus may be guided toward helping them gain control of and most productively adapt to the illness experience.

All visual function subscale scores in group A, other than general health and driving, were significantly decreased compared with control subjects ($P<0.05$, Mann–Whitney test). Such patients notably showed low QOL scores also in the general health and mental health subscales. This supports the hypothesis that apparently normal visual acuity does not necessarily reflect unimpaired VR-QOL in patients with keratoconus.

The results underscore the complex nature of vision- and ocular-related QOL in patients with keratoconus. Patients with keratoconus experience multidimensional visual function impairment and associated QOL issues, and parameters other than traditional measures of visual acuity appear necessary to evaluate VR-QOL in

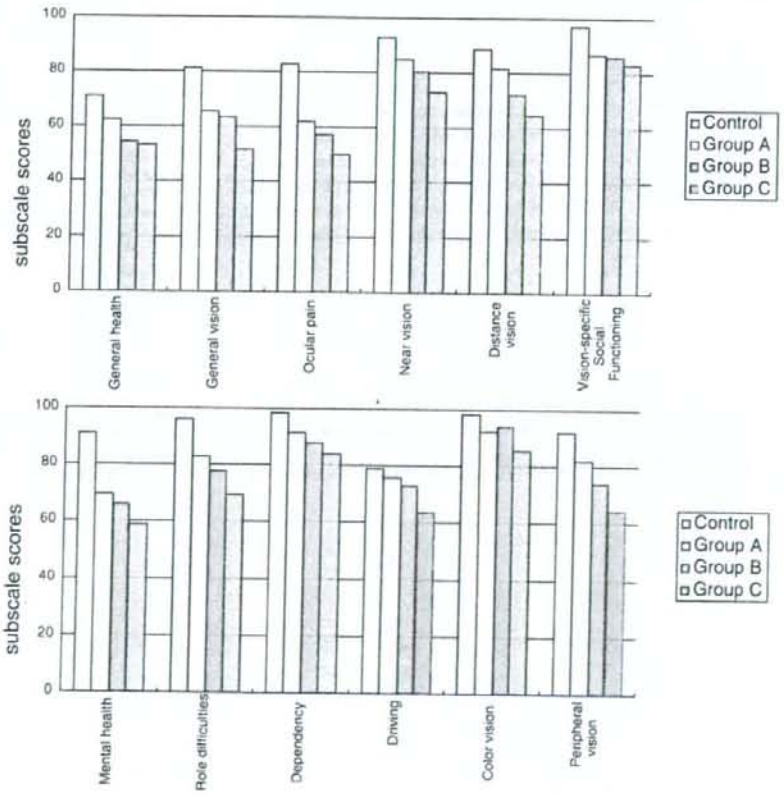

FIG. 1. Mean NEI-VFQ-25 subscale scores in groups A, B, and C and in control subjects. All group A, B, and C subscale scores (other than general health and driving in group A) were lower than those of age-matched control subjects ($P<0.05$, Mann–Whitney test).

patients with keratoconus. Possible explanations for the reduced VR-QOL observed in patients with keratoconus and normal measured visual acuity may include medical and biologic issues, such as changes in ocular surface characteristics resulting in tear film alterations,[19] which may render traditional measures of visual function incomplete in the examination of patients with keratoconus. Additionally, despite apparently normal visual function, patients with keratoconus may experience other disease-related burdens, such as contact lens intolerance, ocular pain caused by epithelial and stromal damage, the need to seek frequent ophthalmologic care, and anxiety related to disease progression and the possible need for surgery.

An important advantage of using generic instruments to measure VR-QOL, such as the NEI-VFQ-25 used in this study, is that such generic instruments facilitate the comparison of total and subscale scores among different groups of patients with various ocular disorders. When the results from the patients with keratoconus are compared with the findings from patients with other ocular disorders, such as uveitis, diabetic retinopathy, glaucoma, cataracts, and multiple sclerosis,[6–13,20,21] low scores in the ocular pain, general health, and mental health categories appear to be characteristic of patients with keratoconus.[16] The overall NEI-VFQ-25 profile of patients with keratoconus appears similar to that of patients with uveitis.[20] This may be partly related to the fact that both groups of patients experience ocular pain, frequently experience other chronic disorders beginning in young adulthood, require frequent ophthalmologic care, and fear progression to low vision.

The results of this study support the use of the NEI-VFQ-25 in patients with keratoconus and provide further evidence for the general applicability of this scale in various ocular disorders. The results underscore the importance of adopting a comprehensive approach to the examination and care of patients with keratoconus that incorporates but goes beyond measures of biologic disease status, such as visual acuity. Ophthalmologists and practitioners of other clinical specialties alike should be appraised of and bear in mind the full spectrum of QOL issues suffered by patients with keratoconus, such that the medical treatment that these patients receive may respond appropriately to the full range of issues these patients face.

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Eye & Contact Lens 34(1): 46–49, 2008

Deposition of Lipid, Protein, and Secretory Phospholipase A_2 on Hydrophilic Contact Lenses

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Purpose. Recent studies have shown that low tear phospholipid levels are associated with tear film instability in hydrophilic contact lens wearers. The concentration of secretory phospholipase A_2 ($sPLA_2$), the enzyme that hydrolyzes phospholipids, in tears is known to exceed the levels found in serum by four orders of magnitude. This study was performed to determine the levels of $sPLA_2$ from the deposition on two different frequent-replacement contact lens materials. **Methods.** Polymacon and etafilcon A contact lenses worn for 2 weeks by 16 experienced contact lens wearers were used for the analysis. Total lipids were determined by the sulfo-phospho-vanillin reaction. Phospholipids in lipid extracts were estimated by phosphorus determination with ammonium molybdate through enzymatic digestion. Total protein was measured by bicinchoninic acid analysis. Double-antibody sandwich enzyme-linked immunosorbent assay was used to determine $sPLA_2$ concentrations. **Results.** Total lipid deposition was found to be greater in the polymacon group (66.3 ± 16.3 μg/lens) than in the etafilcon A group, although phospholipids were not detected in either group. The etafilcon A group had greater deposition of protein (3.7 ± 0.7 mg/lens) than the polymacon group had. The etafilcon A group deposited statistically significantly more group IIa $sPLA_2$ (1.1 ± 0.3 μg /lens) than the polymacon group (0.07 ± 0.04 μg/lens) did ($P<0.001$). **Conclusions.** There was a significant difference in the lipid and protein deposition profiles in the two lenses tested. A significant amount of $sPLA_2$ in the deposition on contact lenses may play a role in tear film instability in hydrophilic contact lens wearers.

Key Words: Contact lens—Dry eye—Phospholipids—Secretory phospholipase A_2—Tears.

Contact lens–induced dry eye is one of the major causes of contact lens intolerance. Tear film stability, which is clinically estimated by tear film breakup time, is compromised in soft contact lens wearers,[1,2] especially in intolerant contact lens wearers.[3]

Recently, the structural and biologic roles of lipids in the tear film have been described in some detail.[4–6] The lipid layer is an essential component of the tear film by providing a smooth optical surface for the cornea and retarding evaporation from the ocular surface. In the current model of the tear film, the aqueous–mucin layer is covered by two thin layers consisting of lipids. Polar lipids, such as phospholipids, lie adjacent to the aqueous layer, and nonpolar lipids are present at the tear–air interface.[7] Recent studies have shown that the level of phospholipids in tears is the most influential factor for tear film stability, which is clinically estimated by tear film breakup time.[8] Thus, phospholipids, which link the nonpolar hydrophobic outer layer and the aqueous layer, are crucial for maintaining a stable tear film. A low level of phospholipids in the tears is associated with a short breakup time in hydrophilic contact lens wearers.[8–10]

Phospholipase A_2 (PLA_2) is a lipolytic enzyme that catalyzes the hydrolysis of phospholipids at the sn-2 position, yielding a free fatty acid and a lysophospholipid. PLA_2 has been categorized into at least 10 groups (I–X) based on amino acid sequence data.[11,12] Many of these enzymes are secreted extracellularly and are commonly referred to as secretory phospholipase A_2 ($sPLA_2$).[13] Of these, group IIa $sPLA_2$ (14 kilodaltons) is the most abundant form of $sPLA_2$ in tears.[14] It was found in concentrations in tears averaging 1.45 μg/mL[14] to 54.5 μg/mL,[15] which exceed the levels found in serum by four orders of magnitude. The presence of group IIa $sPLA_2$ in tears is supposed to be beneficial because of its bactericidal activity.[16,17] However, as suggested by Song et al.,[18] the excess of this enzyme may compromise the tear film stability, because it hydrolyzes phospholipids in tears.

As mentioned earlier, the level of phospholipids in tears of hydrophilic contact lens wearers is lower than that of healthy control subjects, which may be associated with instability of the tear film.[8–10] For the explanation of this phenomenon, two possibilities were hypothesized: Phospholipid deposition occurs on contact lenses, and phospholipids in tears are degraded by group IIa $sPLA_2$ deposited on contact lenses. To test these hypotheses, the levels of lipids, proteins, group IIa $sPLA_2$ content, and $sPLA_2$ activity were determined from the deposition on two different frequent-replacement hydrophilic contact lens materials.

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Supported in part by a grant from Ministry of Health, Labor, and Welfare, Japan.

The authors have no proprietary interest in any aspect of this article.

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Accepted April 2, 2007.

DOI: 10.1097/ICL.0b013e3180676d5d

MATERIALS AND METHODS

Subjects and Contact Lenses

Sixteen experienced, asymptomatic contact lens wearers (six men and 10 women) ranging in age from 21 to 44 years participated in the study. Eight subjects were polymacon lens (Medalist; Bausch & Lomb Japan, Tokyo, Japan; Food and Drug Administration group I, low water content and nonionic) wearers, and eight subjects were etafilcon A lens (2-Week ACUVUE; Johnson & Johnson Japan, Tokyo, Japan; Food and Drug Administration group IV, high water content and ionic) wearers. Lenses worn for 2 weeks were collected and stored at −80°C until analysis. Each lens was cut in half for lipid and protein deposits analysis. All subjects provided written informed consent for participation. The protocol was approved by the institutional review board.

Lipid Analysis

Lipids were extracted by a modification of the Bligh and Dyer procedure.[19] In brief, samples were placed in a test tube with 1.0 mL of an extraction solvent consisting of a 2:1 ratio of chloroform to methanol (Wako, Inc., Osaka, Japan) for 16 hours. After adding 0.2 mL of water, test tubes were vortexed for 30 seconds. The upper aqueous layer was discarded, and the lower organic solvent layer was used for the analysis.

Total lipids were measured by the sulfo-phospho-vanillin reaction. The lipid extracts were evaporated to dryness under nitrogen gas and reconstituted with 50 μL of distilled water. After adding 100 μL of 95% sulfuric acid (Wako, Inc.), the sample was boiled at 100°C for 10 minutes. Then, samples placed in a 96-well microplate were mixed with 150 μL of the working reagent, containing 1.2 mg/mL vanillin (Kokusai Shiyaku Co., Tokyo, Japan). The absorbance of the solution was measured at 655 nm with a spectrophotometer. A standard curve established with lipids solution (Kokusai Shiyaku Co.) was used to quantify the total lipids of the lens extract.

Phospholipids were estimated by phosphorus determination with ammonium molybdate through enzymatic digestion. After lipid extracts were evaporated to dryness under nitrogen gas, 50 μL of 10 mM TRIS hydrochloride (Sigma Chemical Co., St. Louis, MO) buffer (pH 7.8), containing 2.0 U/mL phospholipase C from *Bacillus cereus* (Sigma Chemical Co.), was added and incubated at 37°C for 20 minutes. The samples were incubated at 37°C for an additional 30 minutes after adding 50 μL of 175 mM diethanolamine hydrochloride (Sigma Chemical Co.) buffer (pH 9.6), containing 2.0 U/mL alkaline phosphatase from human placenta (Sigma Chemical Co.). Fifty microliters of samples were placed in a 96-well microplate and mixed with molybdate–malachite green reagent (BIOMOL, Inc., Plymouth Meeting, PA). The absorbance of the solution was measured at 620 nm with a spectrophotometer. A standard curve established with phospholipids mixture (Sigma Chemical Co.) was used to quantify the amounts of phospholipids.

Total Protein and $sPLA_2$ Analysis

A solvent consisting of a 1:1 mixture of 0.2% trifluoroacetic acid and acetonitrile (Wako, Inc.) was used to extract protein.[20] The lenses were placed in the extraction solution for 16 hours, and the extraction solution was subsequently analyzed. This method is a quick, efficient extraction technique for the removal of protein deposits from soft hydrophilic contact lenses. Determination of the total protein deposit from the lenses was carried out by a bicinchoninic acid analysis. The procedure consists of mixing 10 μL of sample solution with 300 μL of protein assay regent (Cytoskeleton, Inc., Denver, CO) comprising bicinchoninic acid and cupric sulfate in a 96-well microplate. Absorbance of the solution was measured at 595 nm with a spectrophotometer. A standard curve established with bovine serum (Sigma Chemical Co.) was used to quantify protein contents of the lens extract.

A double-antibody sandwich enzyme-linked immunosorbent assay was used to determine group IIa $sPLA_2$ concentrations in the protein samples. A commercial enzyme-linked immunosorbent assay kit (Cayman Chemicals, Ann Arbor, MI) was used according to the manufacturer's instructions. Samples were diluted to 1/500 or 1/5,000 concentrations. Absorbance was measured at 420 nm with a spectrophotometer.

Measurement of $sPLA_2$ activity was performed with a commercial $sPLA_2$ activity assay kit (Cayman Chemicals). The assay uses a 1,2-dithio analog of heptanoyl phosphatidylcholine, which serves as a substrate for most PLA_2, with the exception of cytosolic PLA_2. On hydrolysis of the thioester bond at the sn-2 position by PLA_2, free thiols were detected by using 5,5-dithio-bis(2-nitorobenzonic acid). Absorbance was measured at 420 nm with a spectrophotometer.

RESULTS

Total Lipids and Phospholipids

Total lipids and phospholipids deposition are shown in Figure 1. Total lipids were found to be greater in the polymacon group (66.3 ± 16.3 μg/lens) than in the etafilcon A group (44.1 ± 8.2 μg/lens). The difference between the two groups was statistically significant ($P<0.01$, Mann–Whitney test). Phospholipids were not detected in either group.

Total Protein

Results of total protein deposition analysis are shown in Figure 2. The etafilcon A group (3.7 ± 0.7 mg/lens) deposited substantially more protein than the polymacon group (0.03 ± 0.06 mg/lens) did. The difference was statistically significant ($P<0.001$, Mann–Whitney test).

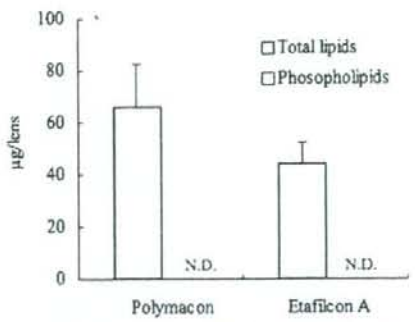

FIG. 1. Total lipids and phospholipids deposited on hydrophilic contact lenses. Total lipids were significantly greater in the polymacon group (66.3 ± 16.3 μg/lens) than in the etafilcon A group (44.1 ± 8.2 μg/lens). Phospholipids were not detected in either group.

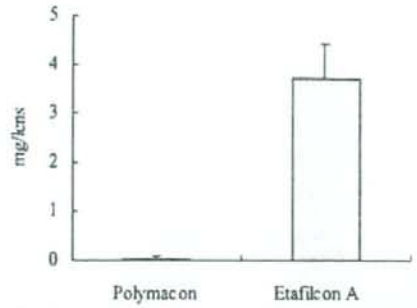

FIG. 2. Total proteins deposited on hydrophilic contact lenses. The etafilcon A group (3.7 ± 0.7 mg/lens) deposited significantly more protein than the polymacon group (0.03 ± 0.06 mg/lens) did.

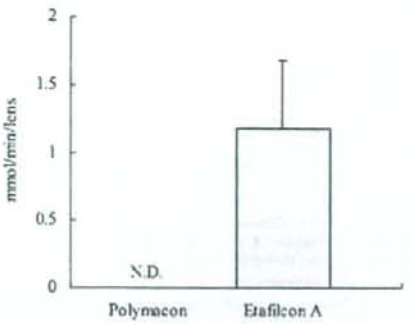

FIG. 4. $sPLA_2$ activity in the etafilcon A group was 1.18 ± 0.59 mmol/minute per lens, whereas $sPLA_2$ activity was not detected in the polymacon group.

Group IIa $sPLA_2$ and $sPLA_2$ Activity

The amount of group IIa $sPLA_2$ and its enzymatic activity deposited on contact lenses are shown in Figures 3 and 4. The etafilcon A group (1.1 ± 0.3 μg /lens) deposited more group IIa $sPLA_2$ than the polymacon group (0.07 ± 0.04 μg/lens) did. The difference was statistically significant ($P<0.001$, Mann–Whitney test). $sPLA_2$ deposited on the etafilcon A lenses retained its enzymatic activity. $sPLA_2$ activity in the etafilcon A group was 1.18 ± 0.59 mmol/minute per lens. In the polymacon group, $sPLA_2$ activity was not detected.

DISCUSSION

It is widely recognized that the adsorption of proteins and lipids on a contact lens is complex and depends on a number of factors. Notable among these are material water content and surface charge.[21–24] There was a significant difference in the lipid and protein deposition profiles between the two lenses tested in the current study. The lipid deposition profiles found in this study are consistent with previously published reports,[23,25] which concluded that hydrogel lenses with nonionic polymer matrices (i.e., groups I and II) deposit more lipids than materials that have ionic matrices (i.e., groups III and IV).[26] In the current study, however, phospholipid depositions were below the detection limit in either lens. Therefore, it is not likely that decreased phospholipid levels in tears of hydrophilic contact lens wearers is the result of the deposition of phospholipids on the lenses.

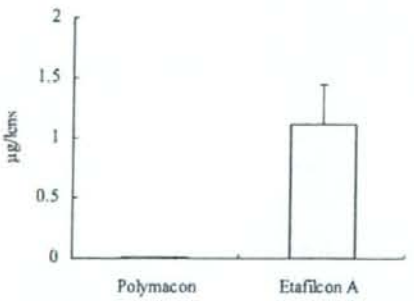

FIG. 3. Group IIa sPLA2 deposited on hydrophilic contact lenses. The etafilcon A group (1.1 ± 0.3 μg /lens) deposited significantly more group IIa $sPLA_2$ than the polymacon group (0.07 ± 0.04 μg/lens) did.

Etafilcon A (group IV material) attracted substantial quantities of protein, which was significantly greater than that measured for polymacon (group I material). Etafilcon A also had significantly more group IIa $sPLA_2$ than polymacon did. Protein deposition was predominantly controlled by the ionic charge of the lens material.[25] Methacrylic acid imparts a negative charge to the material and thus thermodynamically favors the deposition of positively charged species, such as lysozymes. Group IIa $sPLA_2$ is also highly cationic in tears[27] and allows productive electrostatic interactions with the negatively charged contact lens material.

It appears to be important that $sPLA_2$ deposited on etafilcon A lenses retained its enzymatic activity.[8,10] Hume et al.[17] reported that $sPLA_2$ deposited on contact lenses reduced the viable staphylococci adhering to the contact lens, which may be beneficial for the eye to prevent colonization by this pathogen. However, as suggested by Song et al.,[18] the excess of $sPLA_2$ may compromise tear film stability, which results in contact lens intolerance. Aho et al.[28] reported that contact lens wearers had statistically lower group IIa sPLA2 content in their tears at noon and at 4 P.M. than healthy control subjects did. They pointed out that the transient lowering effect on the group IIa sPLA2 content of tears may be the result of the absorption of group IIa sPLA2 onto the contact lenses. The current results appear to support these previous observations. Glasson et al.[29] reported that intolerant contact lens wearers had significantly greater concentration of group IIa $sPLA_2$ and peroxidized lipids in their tear fluids than tolerant subjects did. They suggested that decreased tear phospholipids and tear film instability may be the result of the action of group IIa $sPLA_2$ in the tear fluids. The current study found that a significant amount of group IIa $sPLA_2$ (1.1 ± 0.3 μg/lens) deposited on etafilcon A contact lenses. By assuming that the total tear volume of a healthy subject is 10 μL and that the concentration of group IIa $sPLA_2$ in normal tear fluids is 54.5 μg/mL,[15] 0.55 μg of group IIa $sPLA_2$ is present in the tears of healthy subjects. The amount of group IIa $sPLA_2$ deposited on etafilcon A contact lens is twice that in normal tear fluids. These results suggest an additional mechanism of contact lens–induced dry eye; group IIa $sPLA_2$ deposited on contact lenses may play a role in the development of tear film instability.

In summary, this study found that a significant amount of group IIa $sPLA_2$ deposited on contact lenses, at least on etafilcon A lenses. The enzyme deposited on contact lenses may promote

phospholipid hydrolysis in the tear fluids, which results in a decrease of phospholipids and an increase of free fatty acids in tears. These biochemical alterations in tears could cause tear film instability and may be associated with discomfort during contact lens wear.

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特　集
眼科領域におけるアンチエイジング医学

4. 加齢と眼表面疾患

— Aging and ocular surface disorders —

山田昌和*

はじめに

私たちは，目の前にいる人の顔を見ただけで大体の年齢が推定できる。皮膚のしわ，たるみ，色素沈着，頭髪の状態など顔面にはさまざまなところに年齢の影響が表れるのである。同じことが眼組織にもいえる。**図1**は20代の女性と70代の女性の前眼部写真である。眼表面にも加齢の影響が表れており，結膜の色素沈着，瞼裂斑，角膜周辺部の老人環などから，たとえ顔を見なくともどちらが高齢者のものか判定できる。

加齢に伴う眼表面の変化は，Ⅰ．腺組織の萎縮，機能低下，Ⅱ．老廃物，異常物質の眼表面への蓄積，Ⅲ．慢性の光(紫外線)障害，Ⅳ．上皮，上皮下組織の退行性変化，の4つに大きく分けることができそうである。**表1**に各々と関係する代表的な眼表面疾患を挙げる。この項では**表1**を基にして，眼表面の加齢に伴う変化，加齢に伴う眼表面疾患について考えてみることにしたい。

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Key words：加齢，眼表面，角膜，aging, ocular surface, cornea

Ⅰ. 腺組織の萎縮，機能低下

眼表面には，主涙腺，副涙腺，マイボーム腺，Zeis腺，Moll腺など多数の外分泌腺が存在し，正常な眼表面の維持に大きな役割を果たしている。外分泌腺の機能は加齢とともに低下しやすく，眼組織でも例外ではない。

図2はMathersら[1]の報告を基に，涙液量，涙液分泌量，涙液交換率の加齢性変化をグラフ化したものである。涙腺機能を示すこれらのパラメータはいずれも40歳代以降に大きく低下していく。40歳代以降にドライアイの有病率が高くなることと符合するデータと考えられる。極端なドライアイになりにくいのは，涙液分泌量の低下を涙液排出能の低下が補う形になるためと推察される。高齢者の涙液はlow input, low outputで維持されていることになる。

眼表面のもうひとつの主要な外分泌腺である

表1　加齢に伴う眼表面の変化

1) 腺組織の萎縮，機能低下
　涙液減少症，マイボーム腺機能不全
2) 老廃物，異常物質の眼表面への蓄積
　老人環，帯状角膜変性，メラノーシス
3) 慢性の光(紫外線)障害
　瞼裂斑，翼状片，扁平上皮癌
4) 上皮，上皮下組織の退行性変化
　結膜弛緩症，眼瞼皮膚弛緩症，眼瞼下垂

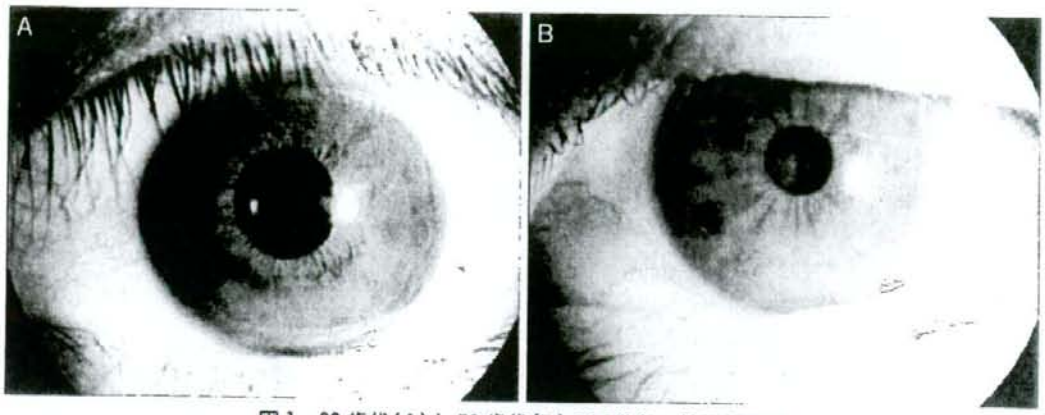

図1　20歳代(A)と70歳代(B)の正常者の前眼部写真
Bでは，結膜の色素沈着，瞼裂斑，角膜周辺部の老人環がみられ，前眼部だけで高齢者のものと判定できる。

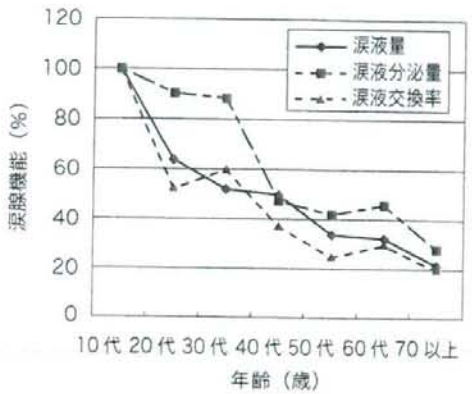

図2　加齢に伴う涙腺機能の変化
各種涙腺機能を10歳代を100%として年代別に示したもの(文献1を基に作図)。

マイボーム腺の機能も加齢とともに低下する。Hom ら[2]によるとマイボーム腺所見からマイボーム腺機能不全(MGD)を診断すると，その頻度は40歳代で34.9%，50歳代で51.4%となり，60歳以上では実に67.2%に達するという。MGDの頻度の増加に伴うように，加齢とともに涙液蒸発量も増加していくことも報告されており，量と質の両面で涙液機能が低下していくことは確かなようである[3]。ただし，マイボーム腺の所見があっても臨床的に症状のあるMGDになるとは限らず，何らかの代償性機転が働いていることが推測される。

以上のように，高齢者の涙液はlow input, low outputで維持されており，その質も低下している。眼表面を保護するという涙液本来の機能が低下しており，感染などさまざまなストレスに耐える力が低下している。高齢者では感染性結膜炎，角膜炎の発症頻度が高いのは，このことが関連しているものと考えられる。また，点眼薬による薬剤起因性角膜障害が生じやすいことにも留意したい。

II. 老廃物，異常物質の眼表面への蓄積

角結膜の加齢性変化と考えられているものには，老人環，瞼裂斑，Vogt's limbal girdle (type I，type II)，iron line，senile furrow，posterior crocodile shagreen，corneal farinata などがあり，加齢に伴う病的変化の代表例には翼状片，帯状角膜変性，滴状角膜，フックス角膜内皮ジストロフィなどがある[4]。

図3に70歳代男性の前眼部写真を示す。この症例では，下方の角膜実質が老人環よりも輪部側の部分で菲薄化しており，senile furrowと呼ばれる所見である。写真ではわかりにくいが鼻側の瞼裂斑の角膜よりの部分にはVogt's limbal girdle type Iがみられる。Vogt's limbal girdleは3時9時の角膜輪部付近にみられる灰白色の混濁であり，type Iはカルシウム塩の沈

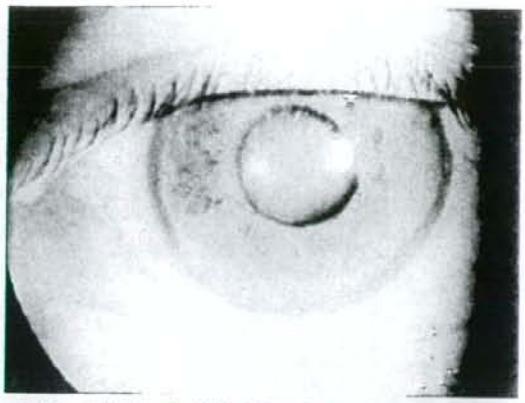

図3　角結膜の加齢性変化の典型例(70歳代男性)
老人環，senile furrow，瞼裂斑，Vogt's limbal girdle type Ⅰがみられる。

着がその本態であり，帯状角膜変性の初期段階とみなされている。一方，typeⅡは上皮下に類弾性線維の変性がみられ，瞼裂斑や翼状片と共通の病理学的変化を伴っている。1枚の前眼部写真からも眼表面の加齢性変化を挙げていくことは難しくないことがわかる。

筆者ら[5]が以前に50歳以上の眼科外来受診者303例を調査した結果では，老人環，瞼裂斑，Vogt's limbal girdle(type Ⅰ，typeⅡ)，iron lineの頻度が高く，その多くは加齢とともに頻度が上昇していた(**表2**)。老人環は角膜周辺部への脂質沈着，Vogt's limbal girdle type Ⅰはカルシウム塩の沈着であり，iron lineは上皮への鉄の沈着である。瞼裂斑とVogt's limbal girdle typeⅡも変性した異常物質の沈着と捉えることができるので，角膜の加齢性変化の多くは老廃物や異常物質の蓄積によるといえそうである。

表2　角結膜の加齢性変化の年代別頻度　(%)

年代(年齢)	50歳代	60歳代	70歳代	80歳以上
老人環	31.0	70.7	82.2	86.5
瞼裂斑	48.3	56.5	37.6	21.2
Vogt's limbal girdle type Ⅰ	5.2	6.6	9.9	13.5
Vogt's limbal girdle type Ⅱ	8.6	18.5	21.8	15.4
iron line	5.2	7.7	11.9	9.6

Ⅲ. 慢性の光(紫外線)障害

加齢による眼表面の変化として紫外線暴露の影響を見逃すことはできない。紫外線による眼表面の変化として代表的なのは翼状片，瞼裂斑，スフェロイド変性，扁平上皮癌である。

翼状片と紫外線暴露との関連はさまざまな疫学的なデータから証明されている[6]。翼状片の有病率は地域と人種でかなり異なっており，特に緯度との関連が大きい。緯度の高い北米都市部での翼状片の有病率は1.4%に過ぎないのに対し，オーストラリアでは9.6%，インドネシアでは10.0%とかなり高く，熱帯に属するバルバドス諸島の黒人では23.4%にのぼる。本邦でも本州と沖縄では翼状片の有病率がかなり異なることが報告されている。職業別では農業，漁業など屋外の職種や溶接工での有病率が高いことが知られており，この他の危険因子として，年齢，サングラス不使用などが挙げられている。扁平上皮癌も同様で，緯度の低い地域で育った場合の相対危険率は7倍，人種では白人の相対危険率は9倍と報告されている。

翼状片と紫外線暴露の関連は明らかとしても，その発症様式には不思議な面がある。翼状片はほとんどの症例で鼻側に生じ，**図4**のように両側に生じるのは2%，耳側に生じるのはわずかに1%と報告されている[7]。この理由として，鼻に反射した光が鼻側結膜に当たるから，睫毛は耳側が長いので耳側は光から保護されるから，などの説があったが，いずれも説得力に欠けていた。また，正面から紫外線暴露を受けやすいとすれば，外斜視の症例では非固視眼に翼状片の発症率が高そうであるが，実際には逆で固視眼のほうに翼状片が生じやすいことが報告されている[6]。

この点に関してはMaloof

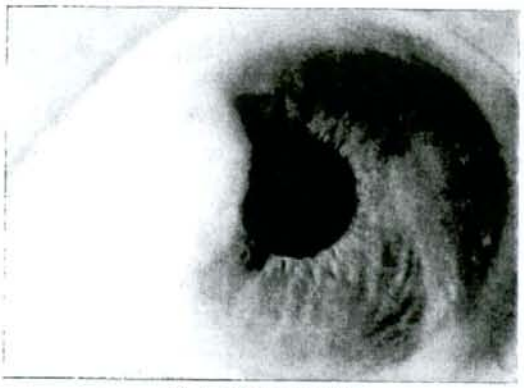

図4　両側の翼状片
翼状片が耳側に生じるのは稀で，ほとんどは鼻側に生じる。

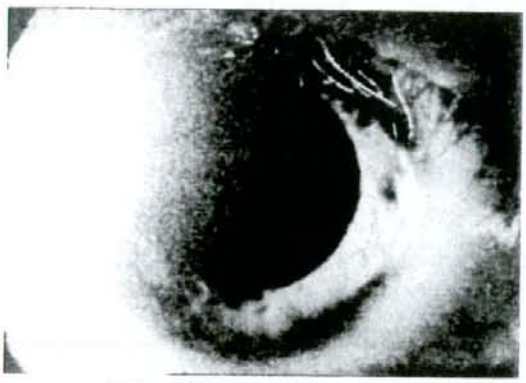

図5　側方から眼内に入った光
側方からペンライトで光を当てると，眼内に入った光は鼻側輪部に集光される。

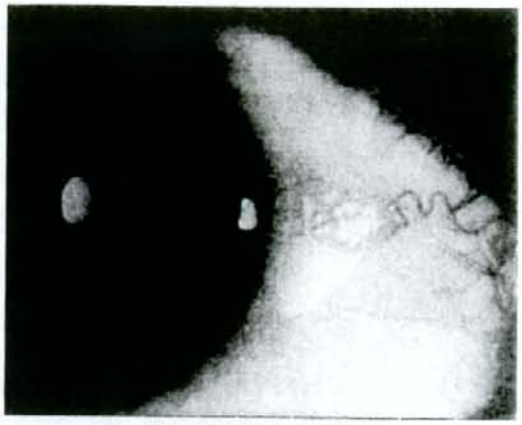

図6　瞼裂斑の自発蛍光
検出条件によっては瞼裂斑の早期発見に有用な可能性がある。

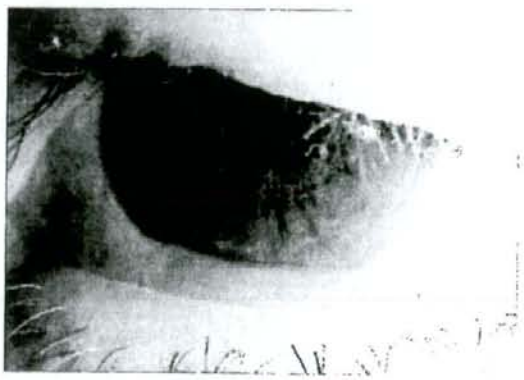

図7　結膜弛緩症
下方球結膜が弛緩した状態で，多彩な自覚症状を呈する。

ら[8]の魅力的な仮説が報告されている。翼状片は正面からの紫外線ではなく，側方からの紫外線暴露によって生じるという説である。側方から眼内に入った光は角膜で屈折して**図5**のように鼻側輪部で集光され，後方14度から入射した場合には最大20倍に集光するという。側方から入った紫外線による障害が鼻側輪部に慢性に持続的に生じた結果，翼状片の発症につながっていくという仮説であり，ほとんどの翼状片が鼻側に生じること，外斜視の症例で固視眼に翼状片が多いこと，など臨床疫学的事実を矛盾なく説明できる点に魅力がある。

翼状片の危険因子として，幼少時の生育環境（緯度の低い地域に在住する，屋外でよく遊ぶなど）の影響のほうが，成人となってからの環境より大きいという報告がある。Ooiら[9]は結膜の自発蛍光を撮影することで，瞼裂斑をより早期に発見できると報告している。筆者らも試しにブルーフリーフィルターを用いて前眼部を撮影してみたところ，瞼裂斑に一致して自発蛍光がみられることが確認できた(**図6**)。

驚くべきことに，Ooiら[9]の蛍光撮影装置を用いると12～15歳の小児の81％に既に瞼裂斑が存在しているというのである。瞼裂斑の自発蛍光による早期発見が可能であることを示すとともに，紫外線障害が小児期から生じているこ