Contact Lens-Associated Dry Eye Disease: Recent Advances Worldwide and in Japan

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Contact lens wearers complain of various types of contact lens discomfort (CLD), which may result in the discontinuation of contact lenses. CLD is often associated with dry eye disease. A contact lens divides the tear film into two layers: the pre- and post-lens tear film. This change leads to instability of the pre-lens tear film, thinning of pre- and post-lens tear film thickness, and increased friction between the contact lens and the ocular surface. The Japanese Dry Eye Society recommends the diagnosis of tear film abnormality first (tear film-oriented diagnosis [TFOD]) and the treatment of dry eye disease based on TFOD (tear film-oriented therapy [TFOT]). These concepts can be applied for contact lens-associated dry eye disease (CLADE). Noninvasive tear film breakup time, tear volume evaluation, vital staining, and assessment of Meibomian glands are performed to evaluate the tear film. On vital staining analysis of CLADE, lid wiper epitheliopathy and conjunctival edge staining are major findings. In TFOT of CLADE, secretagogues of water or mucins, such as diquafosol and rebamipide, have been first used in Japan. Material, design, wettability, and friction coefficient of the contact lens could affect CLADE. Changes of contact lens may be an option in TFOD. However, the effects of contact lens properties on the tear film and ocular surface are still unclear. Further controlled studies are needed in the future.

Keywords: contact lens-associated dry eye, contact lens discomfort, CLD, CLADE, dry eye, tear film, tear film-oriented therapy, tear film-oriented diagnosis, contact lens material genesis, diagnosis, and treatment is crucial in the field of ophthalmology.

MECHANISM OF CONTACT LENS-ASSOCIATED DRY EYE DISEASE

When a contact lens is inserted on the ocular surface, the tear film becomes separated into pre- and post-lens tear film. Because the tear film becomes separated, the volume of aqueous layer at the pre-lens tear film is decreased. The wettability of the contact lens surface is not as high as that of the corneal surface due to the lack of a hydrophilic mucin layer. Therefore, the pre-lens tear film becomes unstable and easily breakable within a short period after blinking. Because the tear film functions as a lubricant, the friction between the eyelid and the ocular surface increases at the site of tear film breakup. If the tear volume is not sufficient, the post-lens tear film also becomes thin, and the friction between the contact lens and the corneal/conjunctival surface increases. This friction between the contact lens and the ocular surface may cause foreign body, dryness, and discomfort sensations. This mechanism is shown in Figure 2.

Meibomian glands play a key role in maintaining a healthy tear film by providing the constituents of the lipid layer on tear fluid. The lipid layer stabilizes the tear film by preventing the evaporation of the aqueous component and lowering the surface tension of the tear film. Arita et al. showed increased meibomian gland dropout in contact lens wearers. The detailed mechanism is unclear, but two possibilities exist. One is an indirect mechanism, explained by the decrease of

FIGURE 2. Mechanism, ocular manifestations, and treatment of CLADE. A healthy tear film comprises an outermost lipid layer and an aqueous layer atop the epithelium (A). When a contact lens is inserted, the tear film is separated into pre- and post-lens tear film. This causes the thinning of the tear film and an increase in friction between the contact lens and the ocular surface (B). When CLADE occurs, short BUT in the pre-lens tear film, lid wiper staining, and keratoconjunctival vital staining are observed as a consequence of tear film deterioration and increased friction (C). Treatment of CLADE is done according to the TFOT concept (D). CL, contact lens; FL, fluorescein; RG, Rose Bengal; LG, lissamine green.
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Incomplete blink in soft contact lens wearers. Moreover, blinking. However, several reports showed the association with CLADE symptoms. Other properties, including water content, surface properties, tensile modulus of the contact lens, and edge design, may be associated with the pathogenesis of CLADE.

Blinking is also essential to maintaining a healthy ocular surface. Even in normal subjects, incomplete blinking is observed in 20% of subjects. Especially among rigid gas permeable (RGP) wearers, the rate of subjects with incomplete blinking in which the eyelid does not close completely is higher than that among non–contact lens wearers. In soft contact lens wearers, there are no data regarding incomplete blinking. However, several reports showed the association between corneal fluorescein staining score and rate of incomplete blink in soft contact lens wearers. Moreover, soft contact lens wearers with incomplete blinking tend to show CLADE symptoms.

Friction between the contact lens and keratoconjunctival surface will cause inflammation on the ocular surface. These changes may lead to the infiltration of inflammatory cells, which may result in the secretion of inflammatory cytokine and matrix metalloproteases (MMPs). The inflammatory cytokines and MMPs may cause damage in the ocular surface epithelium and subsequent instability of the tear film.

**Signs and Symptoms of CLADE**

Patients with CLADE show various symptoms, including foreign body sensation, dryness, eye strain, and blurred vision. End-of-day discomfort is also typical in CLADE, and the symptoms are worse in the evening/night than during the day. These symptoms are caused by the deterioration of the ocular surface due to prolonged dryness or visual display terminal (VDT) work. In patients with dry eye disease, impaired visual acuity has been reported using functional visual acuity, which can measure dynamic changes of visual acuity. Previous reports showed that early tear film breakup due to dry eye causes irregular astigmatism or increased higher-order aberration. These changes of optical quality will result in the decreased visual function in CLADE.

**Tear Film–Oriented Diagnosis of CLADE**

To treat dry eye disease, proper diagnosis is essential. In Japan, the tear film-oriented diagnosis (TFOD) concept has been proposed by the Japanese Dry Eye Society. Under this concept, each layer of tear film is assessed first. Subsequently, treatment is initiated according to the abnormality of each tear film layer (tear film-oriented therapy [TFOT]). Based on this concept, two secretagogue eye drops were often used for treatment of dry eye in Japan: diquafosol (an aequous and mucin secretagogue) and rebamipide (a mucin secretagogue). To evaluate the aqueous layer, the Shirmer I test is useful to evaluate tear secretion on a certain stimulus. Tear meniscus analysis using anterior segment optical coherence tomography (OCT) emerged as a noninvasive method to assess tear volume. Another new methodology is strip meniscometry, which can measure retained tear volume at the tear meniscus in only 5 seconds.

To evaluate the lipid layer, lipid interferometry is a useful tool. DR-1 (Kowa, Nagoya, Japan) provides information regarding kinetic movement of the tear film lipid layer, including the central cornea. An important parameter derived from lipid interferometry is noninvasive tear-film breakup time (NIBUT), which measures pre-lens tear film stability. Many studies showed that NIBUT of pre-lens tear film was associated with discomfort during contact lens wear. However, one study has shown that the ocular surface disease index (OSDI) score does not correlate with pre-lens NIBUT in contact lens wearers. A previous report showed that high-water content contact lenses were associated with shorter thinner lipid layer thickness and shorter NIBUT than low-water content contact lenses. LipiView (Johnson & Johnson, Jacksonville, FL, USA) can assess lipid layer thickness at the inferior part of cornea.

**To assess the tear film mucin layer, a new diagnostic method based on the fluorescein breakup pattern can be used for subjects without contact lenses. However, this method cannot be used for subjects wearing contact lenses. Further studies should be done in this field.**

To evaluate the corneal or conjunctival epithelium, vital staining including fluorescein staining or Rose Bengal (lissamine green) staining can detect abnormal epithelium. Ocular surface findings in CLADE patients are different from dry eye patients without wearing contact lens. In RGP contact lens wearers, 3 and 9 o’clock staining is often observed. This finding is explained by the tear film thinning caused by the adjacent tear meniscus under the RGP. In soft contact lens wearers, characteristic inferior fluorescein staining (smile mark staining) is reported. However, in soft contact lens wearers, corneal staining is not a common finding in dry eye because corneal epithelial abnormalities are masked by the contact lens. In contrast, the bulbar conjunctiva, where the edge of the contact lens is attached, often shows positive fluorescein staining (so-called edge staining). Characteristic fluorescein or Rose Bengal staining at the edge of the eyelid was first reported by Korb et al. in 2002 as an LWE. They reported that LWE was found in 80% of CLADE subjects but in only 13% of asymptomatic contact lens wearers and established an association between CLADE and LWE. Similarly, in Japan, Shiraishi et al. reported high frequency of LWE among contact lens wearers. These ocular findings in CLADE are summarized in Figure 3.

It is well known that dry eye affects visual function. Several reports in contact lens wearers showed the deterioration of visual function is caused by the instability of the pre-lens tear film. When the interblink interval is longer than the pre-lens tear-film breakup time, the irregular surface of the contact lens could be exposed and cause higher-order aberration or irregular astigmatism, ultimately resulting in decreased visual function.

Many authors have reported increased tear evaporation in contact lens wearers, but some controversy exists. We conducted adverse chamber experiments and showed increased tear evaporation after wearing hydrogel contact lenses, but not silicon hydrogel lenses. Many factors, including material, water content, and surface properties of the contact lens, could be associated with evaporation.

Increased tear osmolality was reported as a core mechanism of dry eye disease in the TFOS Dry Eye Workshop II. Although there are issues in terms of repeatability and inter-eye
VDT work affects the tear film by increasing tear fluid evaporation. Recent research showed that VDT work changed lacrimal gland function, ultimately resulting in decreased tear secretion. 40

MGD

Meibomian glands supply the lipid layer on the pre-lens tear film, thus stabilizing it. Contact lens wearers have more meibomian gland dropout compared with non-contact lens wearers. 6

TFOT OF CLADE

As mentioned above, TFOT has been proposed by the Japanese Dry Eye Society.

Treatment for CLADE targets either the tear film or the contact lens. Because the tear film has three layers, namely the lipid, aqueous, and mucin-coated epithelium layers, treatment aims to target each layer of the tear film. Moreover, anti-inflammatory treatment is conducted to suppress the ocular surface inflammation caused by the friction between the contact lens and keratoconjunctival epithelium.

TREATMENT TARGETING THE TEAR FILM

Artificial tear eye drops have long been the first treatment choice for aqueous-deficient CLADE. However, the development of an aqueous secretagogue has changed the treatment strategy in Japan. Diquafosol is an agonist of the P2Y2 receptor that promotes aqueous and mucin secretion from the conjunctiva. Using an animal model of contact lens wearing, both pre- and post-lens tear film thickness were reported to increase after 3% diquafosol eye drop (Diquas ophthalmic solution 5%; Santen Pharmaceutical, Osaka, Japan) instillation. 41 A human study also showed the increased tear meniscus height after topical application of 3% diquafosol eye drops, proving its efficacy for contact lens wearers. 42 Diquafosol improves tear stability, vital staining score, and symptoms. 43 If diquafosol is not sufficient, a punctal plug could be an option. Rebamipide promotes secretion and production of mucin in the conjunctival epithelium. Two studies reported its efficacy in soft contact lens wearers with discomfort. 44, 45

For lipid layer treatment, if MGD has been diagnosed, lid hygiene, warm compress, and topical or systemic antibiotics are the primary options. In addition, diquafosol improves MGD. 46 Although there is still no consensus whether the effect of diquafosol is direct (the P2Y2 receptor is expressed in the meibomian gland epithelial cells) or indirect for MGD, it may be one option for contact lens wearers with MGD. In Japan, lipid emulsion eye drops are not commercially available, but are widely used in other countries. The LipiFlow Thermal Pulsation System (Johnson & Johnson) is a treatment device for MGD that works by heating and compressing meibomian gland. The LipiFlow Thermal Pulsation System is currently not available in Japan, but several reports from other countries showed the efficacy of the treatment in dry eye disease with MGD. 47, 48 Although there is no established evidence in the treatment of CLADE, it may be effective for CLADE with obstructive MGD. Intense pulsed light (IPL) is a new treatment for MGD, but the mechanism of IPL treatment is not well understood. However, Craig et al. performed a double-masked, placebo-controlled, paired-eye study and found that IPL suppressed tear evaporation and improved symptoms and lipid layer thickness. 49

To improve epithelial abnormalities such as LWE and conjunctival edge staining, a mucin secretagogue (diquafosol or
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**TREATMENT TARGETING THE CONTACT LENS**

A unique point of TFOT for CLADE is that it recommends the change of the contact lens. High water content may absorb tear fluid into the contact lens, subsequently decreasing pre- and post-lens tear film thickness. Several studies on in hydrogel contact lenses supported this hypothesis.\(^{35,50}\) However, there is no such evidence for silicon hydrogel contact lenses. Because there are many confounding factors, including tensile modulus, it is hard to evaluate the sole effect of water content on comfort. Contact lens surface properties affect wettability. High wettability contact lens can maintain a stable tear film, which may result in the improvement of CLD. Contact lens fitting can also affect CLADE. Some contact lens movement is necessary for the exchange of post-lens tear fluid. However, loose fitting has been reported to be associated with limbal hyperemia and CLD.\(^{51,52}\) Other parameters, including base curve, lens thickness, and edge design, may also affect CLADE. Contact lens wetting agents are often added in the packaging solution. Viscous materials such as polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG) are added to improve CLADE symptoms. Previous reports showed that wetting agents added in the contact lens stock solution are more effective and work for a longer time than when used as eye drops.\(^{53,54}\) However, it is unknown which wetting agent is the best to prevent CLADE. Generally, silicon hydrogel lenses can achieve lower water content than hydrogel contact lenses. However, silicon hydrogel contact lenses are firmer than hydrogel contact lenses. This firmness of lens material can lead to increased conjunctival staining and discomfort. The balance between water content and firmness is important to maintain comfortable wear of contact lens. New-generation silicon hydrogel contact lenses are designed to keep this good balance and high wettability of the contact lens surface. There is no evidence that silicon hydrogel contact lenses are better than hydrogel contact lenses in terms of improvement of CLADE. However, previous controlled adverse chamber experiments showed that a silicon hydrogel contact lens (narafilcon A) showed less changes in functional visual acuity, tear film breakup time, and tear osmolality than a hydrogel contact lens (etafilcon A). \(^{55}\)

The Dk/t value of the contact lens represents oxygen distribution to the cornea. It is possible that the Dk/t value is associated with comfort during contact lens wear by affecting the ocular surface epithelium. However, there are no peer-reviewed articles on this matter.

**TREATMENT FOR TARGETING SUPPRESSION OF OCULAR SURFACE INFLAMMATION**

Ocular surface epithelial damage in dry eye disease induces inflammation in the cornea and conjunctiva. In Japan, treatment primarily aims to improve the tear volume and friction between the contact lens and ocular surface. In other countries, treatment is often primarily targeted at suppressing ocular surface inflammation in the treatment of dry eye disease.

The treatment effect of topical cyclosporine is still controversial in the treatment of CLADE. Willen et al. randomly assigned CLADE patients into two groups: rewetting eye drops or a 0.05% cyclosporine ophthalmic emulsion.\(^{55}\) They could not find any difference in symptoms, tear function, or ocular surface abnormalities.

In contrast, Hom\(^{56}\) conducted a similar study using rewetting eye drops and a 0.05% cyclosporine ophthalmic emulsion and found that the cyclosporine group showed better improvement of dry eye symptoms and conjunctival staining than the rewetting eye drop group. Because CLADE is multifactorial condition, these discrepancies might be expected. For future studies, if we can select patients with a specific cause of CLADE, such as low tear secretion, we may be able to evaluate which type of CLADE benefits more with anti-inflammatory treatments such as cyclosporine.

**RECENT ADVANCES IN JAPAN**

Uchino et al. reported the results of the Koumi epidemiologic study, a population-based cross-sectional study conducted at the rural mountain area in Japan.\(^{58}\) The study included 3294 subjects aged 40 years old or older living in Koumi town. They defined dry eye as previously diagnosed or having severe symptoms of dry eye disease according to a questionnaire. The results showed that men wearing contact lenses showed 4.38 times higher the risk of previously diagnosed dry eye or 4.48 times higher the risk of having severe dry eye symptoms than non-contact lens wearers. Similarly, women wearing contact lenses showed 4.56 times higher the risk of previously diagnosed dry eye or 2.37 times higher the risk of having severe dry eye symptoms than non-contact lens wearers. Wearing soft contact lenses is a risk factor for dry eye not only among the elderly but also among the youth. Another study including high school students also showed that soft contact lens wear was a risk for clinically diagnosed dry eye.\(^6\)

We conducted a fieldwork study and evaluated tear film function and ocular surface abnormality in office workers.\(^{59}\) Interestingly, even if subjects did not wear contact lenses on the examination day, tear meniscus was lower in contact lens wearers than in non-contact lens wearers. Moreover, subjects with prolonged VDT work showed lower tear meniscus height than subjects without it. They also reported that that the combination of contact lens wear and long-time VDT work deteriorated dry eye symptoms according to the Ocular Surface Disease Index (OSDI) questionnaire.

A recent advance in dry eye examination in Japan is the classification of dry eye disease based on the fluorescein breakup pattern.\(^{53}\) Tear film fluorescein breakup pattern is classified into five groups. Generally, there are several types of dry eye, including the aqueous-deficient type, increased evaporation type, and decreased wettability type. Based on Yokoi's breakup-pattern classification, we can diagnose the type of dry eye and start the appropriate treatment for each patient in Japan. Although fluorescein cannot be used in eyes wearing contact lenses, noninvasive tear film analysis using other devices such as a lipid interferometer may be used. If the cause of CLADE can be detected from the breakup pattern, treatment will definitely be more effective.

In Japan, aqueous or mucin secretagogues are mainly used for dry eye treatment. Nagahara et al. conducted an animal study comparing the pre- and post-lens tear film after applying artificial tears, hyaluronic acid, or 3% diquafosol eye drops in rabbits. Only topical 3% diquafosol was found to increase pre-lens tear film.\(^{55}\) They also conducted a clinical study and found that increased tear meniscus in contact lens wearers was maintained 60 minutes after topical application of 3% diquafosol eye drops.\(^{57}\) Further studies are needed to evaluate the efficacy of topical 3% diquafosol eye drops to treat CLADE.
Rebamipide ophthalmic suspension (Mucosta ophthalmic suspension UD2%; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) is another secretagogue that stimulates the production and secretion of mucin in the conjunctival epithelium. Shigeyasu et al. showed that 2% rebamipide eye drops increased an intensity of wheat germ agglutinin conjugate of fluorescein, which is a marker of membrane-associated mucins in soft contact lens wearers with discomfort. 45 They also reported that 2% rebamipide eye drops improved kerato-conjunctival fluorescein staining. Igarashi et al. 44 investigated the effect of rebamipide ophthalmic suspension for contact lens discomfort with dry eye. They found that rebamipide improved both vital staining and tear film breakup time, and moreover improved symptoms measured by the OSDI questionnaire.

In relation to the contact lens material, there is no evidence whether hydrogel or silicon hydrogel is better for patients with CLADE. We compared tear and visual functions between the two materials in an adverse chamber and found that a silicon hydrogel contact lens (narafilcon A) showed less changes in tear osmolarity and visual function than a hydrogel contact lens (etafilcon A). 31 Although this experimental environment is extremely severe in terms of humidity and temperature, it showed the possible advantages of silicon hydrogel contact lenses compared with hydrogel contact lenses.

**Future Directions**

The goal of CLADE research is to understand its pathogenesis with the hope of reducing the number of people who will terminate wearing contact lenses due to CLADE. CLADE can be caused by multiple factors, including tear film and ocular surface conditions, as well as various contact lens features such as material, design, wettability, and coefficient of friction. These make CLADE research more complex. In addition, there is paucity of information regarding how silicon hydrogel contact lenses affect tear film and ocular surface. To understand how each contact lens parameter affects CLADE, further studies including both basic and clinical research are needed in the future.

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