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# Explore the Best Solution for Dry Eye – Tear Film Stability

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## The Importance of Tear Film Stability

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The tear film (TF) covers the ocular surface and maintains proper vision and a defense against pathogens. It is important in the maintenance of normal health of the ocular surface. *Figure 1* shows the break-up of the TF. When the TF does not properly cover the ocular surface epithelium, the epithelium is damaged, resulting in dry eye. An unstable TF is therefore the major feature of dry eye.

### Figure 1. Unstable tear film is the central feature of dry eye



There are two definitions for dry eye: i) a disorder of an insufficient/abnormal TF or tear dynamics causing tear film instability, and ii) a multifactorial disease characterized by an unstable TF causing a variety of symptoms and/or visual impairments, sometimes accompanied by ocular surface damage (Asia Dry Eye Society). Both definitions state that TF stability is important for normal ocular surface function/maintenance. For dry eye patients, the core mechanism is TF instability.

Dry eye patients show two changes: primary changes in target tissues (lacrimal gland, ocular surface epithelium, meibomian glands, lacrimal duct system, and the immune system) that can be detected by slit-lamp microscopy; and secondary changes on the ocular surface of moderate/severe patients that can be detected by clinical/laboratory tests. The Asia Dry Eye Society definition suggests that inflammation induced by an unstable TF is a secondary change. Treatment should start as early as possible for dry eye patients. In China, dry eye patients are classified into five groups: aqueous deficiency dry eye, lipid deficiency dry eye, mucin deficiency dry eye, abnormal tear dynamics dry eye, and combined dry eye.

TF Oriented Therapy (TFOT), based on a new concept of TF stability, attempts to recover TF stability, and is more effective when based on the primary abnormal tear layer. Primary changes involve the cause of dry eye, and secondary changes involve inflammation and corneal/ocular surface epithelial defects. TFOT emphasizes the importance of TF as a main treatment target.

Chinese medicine has been used to treat dye eye. Treatment

options include accurate diagnosis followed by the required therapy, and personalized therapy based on the patient's overall physical condition that includes the ocular surface, systemic, and environmental parameters (*Figure 2*). The major principle of Chinese medicine is to supply precisely what is lacking, and interestingly this is a similar concept to TFOT. Sodium hyaluronate targets the aqueous/mucous layer to increase BUT and enhance TF stability (*Figure 3*).<sup>1</sup>

#### Figure 2. Opinions from Chinese medicine

- Supply exactly what is lacking.
- Treatment according to the symptoms. The patient is first diagnosed, then treated with the appropriate therapies.



• Personalized therapy involving a treatment plan according to the overall physical condition of the patient that includes the ocular condition, systemic condition, and environmental factors.

### Figure 3. TFOT (Tear Film Oriented Therapy)



Sodium hyaluronate also promotes wound healing in a rabbit model of corneal epithelial abrasion (*Figure 4*).<sup>2</sup> We used 0.3% hyaluronate eye drops to treat dry eye patients (40 patients/80 eyes) and showed that it improved symptoms as well as BUT and corneal staining scores.

## Figure 4. Hyalein shows a beneficial effect in promoting corneal wound healing



In summary, the concept of TF stability is important for treatment of dry eye patients, and TFOT can be useful in improving unstable TF.

http://www.dryeye.ne.jp/en/tfot/index.html
 Nakamura M, et al., Folia Ophthalmol Jpn. 1995;46:1256–1260.

# The Consequences of Tear Instability and Lipid Deficiency

## **Louis Tong**

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The reported frequency of adult meibomian gland dysfunction was  $\geq 50\%-60\%$  in Asian countries.<sup>1</sup> Normally, a disease becomes a priority for clinical research when it is present in 10%-30% of the general population. Because of the high prevalence of meibomian gland dysfunction, it is necessary to reconsider the conventional notion about this condition, and whether it is a 'disease' in the usual sense.

There is a relationship between reduced numbers of functional meibomian glands and a thinner lipid layer, and the lipid thickness is decreased in tears from patients with Sjögren syndrome, an autoimmune disease causing dry eye (*Figure 1*).<sup>2</sup> Post-LASIK dry eye is a common complication after surgery; however, lipid deficiency also occurs but is less well-known compared with aqueous deficient dry eye. LASIK damages corneal sensory nerves, reducing the lacrimal reflex, which is

involved in the efferent loop of the lacrimal arc that supplies the meibomian glands, causing a reduction in lipid production, lipid thickness, and tear stability. Two previous studies reported findings supporting this concept. One study found that at 3.5 months after LASIK, the lipid layer is significantly thinner compared with untreated control subjects. Another

found that at  $\geq 1$  year after LASIK, some patients show very thin lipid thicknesses, plus symptoms of dry eye related to tear instability and lipid deficiency (*Figure 2*).<sup>3,4</sup>





Figure 2. Lipid deficiency after LASIK



Although most patients' tear parameters return to normal after LASIK, some patients (~2.5%) still complain of dry eye symptoms that may actually be neuropathic pain. Although moisture is present around the eyes, and corneal nerves have recovered, the central excitotoxicity of the brain persists and the threshold for discomfort remains abnormally lowered.

Can these symptoms be prevented? Treatment commencing at this stage is not optimal, because tear functions have returned to normal; logically it is more effective to prevent the damage from occurring. Products such as Cationorm<sup>®</sup> can improve the lipid, aqueous, and mucin layers of the eye (*Figure 3*). It is important to optimize the timing, method, and duration of protective treatment for tear stability in LASIK patients, although studies are not able to provide precise guidance on the timing for this.

## Figure 3. Effect of Cationorm<sup>®</sup> eye drops on lipid, aqueous, and mucin layers



Visual blurring results from tear instability, because tears are the initial interface layer between the eye and the environment/atmosphere. Poor vision and optical aberrations are experienced when light passes through an irregular tear interface (*Figure 4*). Furthermore, if eye blinking is too infrequent, it exacerbates the effect of tear instability, and tear disruption occurs between blinks. This disruption can be monitored by fluorescein break-up patterns, break-up types, and noninvasive tear break-up patterns monitored by instruments like the OCULUS Keratograph<sup>®</sup> 5M or the Tomey RT-7000.

#### Figure 4. Tear instability explains optical aberrations



Blurred vision can also lead to psychological problems. Approximately 33% and 25% of 100 dry eye patients exceeded the screening threshold for depression and anxiety, respectively. The burden of disease in general is not always proportional to its effect, a disease that reduces mortality may have less burden than one that does not. The burden of eye disease is not trivial, and when associated with psychological problems and neurological dysfunctions, the overall suffering of the patient and increased healthcare burden can be tremendous. Therefore, health care policy makers need to revise their resource planning and approaches to overall management of these specific 'ophthalmic' disorders.

[1] Schaumberg DA, et al., Invest Ophthalmol Vis Sci. 2011;52:1994–2005.

<sup>[2]</sup> Menzies KL, et al., Invest Ophthalmol Vis Sci. 2015;56:836-41.

<sup>[3]</sup> Patel S, et al., J Refract Surg. 2001;17:17–24.

<sup>[4]</sup> Di Pascuale M, et al., J Cat Refract Surg. 2005;31:1741–9.

## Tear Film Stability in Dry Eye Management

## Kazuo Tsubota

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The current definition of dry eye includes visual disturbances and an unstable tear film (UTF),<sup>1</sup> but we propose a simpler definition of this disorder. Discussions at the Asia Dry Eye Society mentioned that only symptoms (break-up time [BUT] ≤5 seconds) and UTF were common criteria for Japanese, Chinese, and Korean dry eye patients. These symptoms were included in a new definition as follows: "Dry eye is a multifactorial disease characterized by UTF causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage."

The Osaka study reported that 94.6% of dry eye patients had a BUT <5 seconds, which was only 19.3% using the Schirmer test, or only 24.2% using ocular staining (*Figure 1*).<sup>2</sup> Therefore, measurement of the UTF is the most sensitive detection method.





It is important to emphasize that a UTF may induce depression or other psychological disorders. These patients have similar problems as those with the Sjögren-type of dry eye. The short BUT-type of dry eye is characterized by a BUT <5 seconds and corneal hypersensitivity that includes neuropathic pain. Our study reported that measurements of corneal sensitivity to touch was the same between short BUT patients and control subjects; however, sensitivity to blinking and pain was significantly increased in the short BUT group.<sup>3</sup> Therefore, the short BUT-type of dry eye has a short BUT, severe symptoms, corneal hypersensitivity, and minimal or no fluorescein staining (*Figure 2*).

#### Figure 2. Short break-up-type dry eye

- 1) Dry eye with short tear break-up time
- 2) Severe symptoms
- 3) Corneal hypersensitivity may contribute to dry eye symptoms
- 4) Minimal or no fluorescein staining of the ocular surface
- 5) Often accompanied by inflammation, allergy and/or VDT use

Shimazaki-Den et al. reported that MUC5AC and MUC16 mRNA expression levels were significantly lower in UTF and aqueous deficient patients compared with control subjects (*Figure 3*), indicating that mucin is important for TF

stability and that short BUT-type dry eye patients have decreased mucin levels.<sup>4</sup> Tear Film Oriented Therapy (TFOT) is based on tears having three layers (lipids, aqueous tears, and mucins), and on replacing missing component(s). The aqueous, mucin, and lipid layers are very important for the stability of the tear film. For the aqueous layer, DIQUAS<sup>®</sup> contains diquafosol sodium that increases the tear volume to provide aqueous tear components over a longer duration (>30 minutes) than artificial tears. DIQUAS<sup>®</sup> also has positive effects on the mucin layer by inducing mucin gene (*MUC1, MUC4, MUC16*) expression.

## Figure 3. Symptoms, visual function, and mucin expression of eyes with tear film instability

	Control	Unstable tear film	Aqueous deficient
MUC5AC (copies/ng)	20.9±24.2	0.20±0.41*	0.27±0.35*
MUC16 (copies/ng)	17.6±9.3	3.11±3.38*	0.82±1.14*

The mRNA expression levels of MUC5AC and MUC16 were significantly lower in the UTF and AD groups compared with the control group.

A 60-year-old female dry eye patient after LASIK showed corneal staining and UTF. Her vision was improved from 0.8 to 1.0 after 1 month of DIQUAS<sup>®</sup> treatment. The TF was stable (*Figure 4*) and the tear thickness and vision improved.

#### Figure 4. Changes of the ocular surface



In summary, a new definition of short BUT-type dry eye is important because the old concept originated from Sjögren syndrome (tear deficiency = dry eye). The new definition includes numerous causes of UTF. A Sjögren-type decreased tear production is still the major cause, but aqueous and mucin alterations are also important because patients with a Schirmer test of 33 mm still have UTF. Short BUT-type dry eye patients with no fluorescein or rose bengal staining suffer greatly from depression. It is therefore important to recognize short BUT-type dry eye patients. In summary, DIQUAS<sup>®</sup> is very useful for the treatment of short BUT-type dry eye.

Definition and Classification Subcommittee of the International Dry Eye Workshop. Ocul Surf. 2007;5:75–92

<sup>[2]</sup> Uchino M, et al., Am J Ophthalmol. 2013;156:759-66

<sup>[3]</sup> Kaido M, et al., Invest Ophthalmol Vis Sci. 2016;57:914-9

<sup>[4]</sup> Shimazaki-Den S, et al., Cornea 2013;32:1211-8

# **Q&A Summary**

**Q** Dr. Fung-Rong Hu: Patients with severe dry eye, especially aqueous tear deficiency, are treated with frequent instillation of preservative-free artificial tears. But now that DIQUAS<sup>®</sup> is available, what is the treatment frequency of DIQUAS<sup>®</sup> and should the dose be adjusted according to the BUT?

**A Dr. Kazuo Tsubota:** The most important point is that DIQUAS<sup>®</sup> should be administered six times a day for one month. Some patients with only minor irritation use it three times a day with no effect, so you must convince patients to use it six times a day for one month to stabilize the tear film.

Dr. Fung-Rong Hu: Should autologous serum be used for insufficiency of the mucin layer?
 Dr. Kazuo Tsubota: Autologous serum increases tear film stability, so it can be used for short BUT-type dry eye, but there are a variety of mechanisms involved so it may be different. It contains anti-inflammatory factors and induces epidermal and fibroblast growth factors to promote mucin production from the conjunctiva and goblet cells.

**Dr. Kazuo Tsubota:** Stabilizing the tear film currently appears to be a common treatment in China. **Dr. Zuguo Liu:** That is correct.

Dr. Kazuo Tsubota: Does Cationorm<sup>®</sup> provide a lipid layer, and is it commercially available in Singapore?
Dr. Louis Tong: It has recently become available, so we are using it more in our eye centers. Competitors'

products are also available, but they are not exactly the same because of the difference in lipid composition. Depending on which lipids are present in the product, more blurring can occur. Cationorm<sup>®</sup> has a better interaction with the ocular surface, so it helps to protect the epithelial cell layers as well as providing lipids.

**Dr. Kazuo Tsubota:** Our modern lifestyles, which involve the use of computers at night and a lack of exercise, have caused an increase in dry eye. Are you educating patients to change their lifestyle?

Dr. Louis Tong: Yes, very much so.

**Dr. Kazuo Tsubota:** Dry eye often causes reduced quality of life (unhappiness and less sleep).
 **Dr. Zuguo Liu:** We educate our patients regarding

A these complications. Sleep quality is very important. We investigated over 3000 patients divided into two groups—good vs. poor quality of sleep—and found less severe symptoms in the good-quality sleepers. In addition, smoking is another lifestyle factor that can worsen the quality of life of dry eye patients.

**Dr. Kazuo Tsubota:** That is important because dry eye is an unrecognized and underestimated disease that affects a patient's quality of life. We must increase research in this area to maximize their quality of life.

