Short Tear Film Breakup Time–Type Dry Eye

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Measurement of tear film breakup time (TBUT) has become a standard diagnostic procedure in the dry eye clinic. Short TBUT–type dry eye is characterized by TBUT of less than 5 seconds and dry eye symptoms such as ocular fatigue or dryness; the importance of this type has recently been gaining prominence. Patients with this condition show no reduction in tear production and no staining of the ocular surface. The severity of symptoms is almost the same as in dry eye in which the ocular surface is stained with rose bengal or fluorescein. In addition to discomfort, patients suffer from decreased vision due to the unstable tear film, which can be attributed to the relative abnormality of the lipid layer, aqueous layer, and/or mucin layer. The diagnosis should be performed carefully on the basis of the patient’s symptoms and the TBUT test, because the ocular surface appears normal and remains unstained.

Keywords: tear film, breakup time, subjective symptoms

The Asia Dry Eye Society (ADES) recently proposed a new definition of dry eye emphasizing the importance of an unstable tear film and subjective symptoms.1 The TFOS DEWS II report also considered tear film homeostasis, including tear film stability and neuropathic pain components.2 Overall, it seems that an unstable tear film and patient symptoms are the two most important factors for dry eye diagnosis and management. The ocular surface is covered by the tear film, which is protecting the cornea and conjunctiva. Because the tear film layer is important for the protection of the cornea, several techniques have been developed for testing the stability of the tear film layer, and one of them is tear film breakup measurement.3,4 Since then, tear film stability has been considered one of the most important parameters for the diagnosis of dry eye.5–8

According to the ADES definition, the two key components for the diagnosis of dry eye are a short tear film breakup time (TBUT) and subjective symptoms. The results of Schirmer test or vital staining of the ocular surface are not mandatory requirements for dry eye diagnosis. There are two main types of dry eye: one without any abnormalities in tear production or vital staining and the other with decreased tear secretion and/or positive ocular surface vital staining. The formation of dry eye, with only a short TBUT and severe subjective symptoms, was proposed as the decreased breakup time–type dry eye by Toda et al. in 1995.9 The important finding in this paper was that the symptoms of dry eye patients with the short TBUT type are the same as those in dry eye patients with rose bengal or fluorescein staining. Understanding this type of dry eye is especially important because the ocular surface in this condition appears completely normal with abundant tear volume and no ocular staining if the TBUT is not measured. Patients with this type of dry eye may or may not also be aqueous deficient. Also, this type of dry eye may or may not have vital staining. According to the definition of having short TBUT and subjective symptoms, the patient with sufficient tear volume, but without any vital staining, can be diagnosed with dry eye, and we refer to this subtype as short TBUT. Figure 1 shows the various types of dry eye. Note that short TBUT is an independent category (a subtype of dry eye). Although TBUT measurement is a simple procedure to perform in the clinic, not all eye doctors perform TBUT measurements for various reasons, such as difficulty controlling the volume of the fluorescein, taking extra time, or not realizing the value of the test itself. Following is the standard method for TBUT measurement. Place 1 to 2 μL (maintain consistency for each test) of preservative-free 1% fluorescein solution to the ocular surface using a micropipette or the preferred method. The patient should first blink several times. Then instruct the patient to keep their eyes open, without blinking. Measure the interval between the last complete blink and the first appearance of any disturbance, repeating the test three times, and take the average of the measurements. For the beginner, it is recommended to use a stopwatch or metronome for accuracy. The cutoff value for short TBUT is 5 seconds. Even during TBUT measurement, the ocular surface in these patients is clear and shows no abnormalities other than the short TBUT. This type of dry eye can be misdiagnosed as a neuronal disease or psychiatric disorder. Therefore, its recognition is extremely important and has been emphasized in this review. This review also highlights the concepts underlying short TBUT-type dry eye, with a special mention of its history, subjective symptoms, possible mechanism, treatment, and future research directions.

Recent Progress Around the World
The idea of short TBUT-type dry eye originated in Japan. Thus far, only a few studies, mostly in Japan and some in Korea, have been performed on this condition.9–27

History of the Short TBUT-Type Dry Eye
The first study emphasizing the similar severity of symptoms in patients without any other abnormalities was conducted by Toda et al. in 1995.9 It was considered strange that the symptoms of short TBUT-type dry eye were the same as those of severe vital staining–type dry eye with strong rose bengal or fluorescein staining as shown in Figure 2. Consequently, it was believed that a greater degree of rose bengal or fluorescein staining...
staining correlated with worsening symptoms. However, there was no correlation reported between the signs and symptoms, especially between vital staining and symptoms. This phenomenon is well known as “signs and symptoms discrepancy in dry eye.”

Later Yokoi et al. also reported similar results in 2015, showing that short TBUT-type dry eye has the same level of severe symptoms as dry eye with vital staining. Recently, the concept of neuropathic pain has emerged as an important factor for dry eye development, and hypersensitivity to the unstable tear film is considered the mechanism underlying dry eye. Kaido et al. reported in 2016 that hypersensitivity of the cornea exists in short TBUT-type dry eye, speculating that the severe symptoms of short TBUT-type dry eye may be due to the neuropathic pain components.

In addition to the neuropathic pain hypothesis, a new hypothesis explaining the severity of some types of short TBUT was proposed. Kaido et al. observed that microaccommodative microfluctuations are caused by the unstable tear film wherein the eye is trying to focus depending on the unstable tear film. In this scenario, the chronic unstable tear film adds a great burden to the ciliary muscle and produces fluctuations of the ciliary muscle (Fig. 3). When the tear film is stabilized, the fluctuation ceases and the symptoms resolve. Although this report covers a relatively small number of patients, it might suggest a new explanation for the background mechanism.

Since the first report in 1995, many more papers have been added to the literature describing short TBUT-type dry eye, and this number is expected to increase, especially in Asia. Although this type of dry eye has been considered relatively mild to moderate because of the limited abnormality of ocular surface, recently Kim et al. reported that the prevalence of depression among dry eye patients is higher in the mild type of dry eye, which overlaps with the short TBUT-type dry eye. The precise prevalence of short TBUT-type dry eye is unclear, but TBUT is expected to be high according to a study among office workers in Osaka. Kawashima et al. reported that the most unhappy patients in the dry eye group show severe symptoms with almost no alteration of the ocular surface and
tear stability. Taken together, the findings suggest that disease severity cannot be determined by damage of the ocular surface. Although the damage to the ocular surface is minimal in short TBUT-type dry eye, doctors need to consider this condition as a severe disease because it dramatically affects the quality of life of patients.

**VISUAL DISTURBANCES IN SHORT TBUT-TYPE DRY EYE**

It is becoming increasingly clear that a short TBUT causes deterioration of visual function. A stable tear film for a certain period of time is necessary for proper sight. Visual function is affected if the tear film layer is not able to provide a smooth layer. Patients with short TBUT-type dry eye may show completely normal visual acuity because the patient can read the Landolt ring just after the eye opening. Even though the tear film is unstable, it is smooth just after eye opening when the patient reads the Landolt ring. Patients are required to answer only once and do not need to answer continuously. In contrast, the newly developed instrument, the functional visual acuity meter, measures visual acuity over one minute continuously. Thus, a patient with an unstable tear film may give the wrong answer due to the irregularity of the tear film at a certain time period after eye opening (Fig. 4). Kaido et al. reported the prevalence of reduced functional visual acuity in short TBUT-type dry eye patients. Further details of functional visual acuity are discussed by Kaido in the special issue of *Investigative Ophthalmology & Visual Science (IOVS).*

Koh et al. also reported the existence of higher-order aberrations in short TBUT-type dry eye using continuous topography. The higher order aberrations of the cornea of dry eye patients, including short TBUT-type dry eye, are discussed in detail in the special issue of *IOVS* by Koh.
MECHANISM OF SHORT TBUT

According to the tear film-oriented diagnosis and therapy concepts, any of the three layers (i.e., the aqueous, lipid, and/or mucin) can affect the stability of the tear film.\(^1\)\(^4\)\(^5\) Stability of the tear film is compromised when the aqueous components are reduced in volume.\(^46\) The tear film layer becomes unstable when the lipid is deficient, leading to accelerated evaporation. The first consensus report of dry eye classification by Lemp\(^47\) in 1995 described this type as ‘evaporative dry eye,’ and it is believed that this evaporative type includes some cases of the short TBUT type. Dysfunction of the mucin layer can downregulate the wettability of the ocular surface and reduce the thickness of the tear film layer. The original article by Toda et al. reported a frequent association of reduced goblet cell density in the short TBUT type, which is possibly due to chronic inflammations such as allergy and speculated the involvement of mucin abnormalities.\(^9\) Recently, Yokoi et al.\(^46\) proposed five patterns of tear film breakup, suggesting that the spot and dimple types are the typical short TBUT types of dry eye. Please refer to the review by Yokoi and Georgiev in the special issue of *IOVS*.\(^50\) Furthermore Den et al. and Uchino et al. reported the association of mucin components with TBUT and subjective complaints (Fig. 5), suggesting the involvement of mucin as a major player in short TBUT-type dry eye development.\(^49\)\(^50\)

TREATMENT OF SHORT TBUT-TYPE DRY EYE

According to the theory underlying tear film oriented therapy (TFOT), tear stability can be improved by improvements in either of the following factors: aqueous, lipid, and mucin. Artificial eyedrops or hyaluronic acid eyedrops can aid in increasing the aqueous components, resulting in a more stable tear film, but the time of the efficacy is limited due to the quick disappearance of the aqueous components. Punctal occlusion has been one of the effective ways to increase the tear volume, especially the aqueous component dramatically, resulting in the tear film stability. Punctal occlusion is very effective in stabilizing the tear film layer by increasing the tear volume, but it is often accompanied by unwanted epiphora.\(^13\) There is no randomized clinical trial showing patients having mucin or lipid deficiencies could be treated by punctal occlusion. However, it is expected that tear film stability can be increased by punctal occlusion. With the introduction of diquafosol sodium in Japan and other Asian countries, the situation has changed. Preliminary studies have shown diquafosol sodium increases tear volume, stabilizing the tear film layer and extending TBUT.\(^12\)\(^18\)\(^51\) Studies have shown that the effect of short-term use of diquafosol sodium is limited, but with long-term use, a preliminary study on Sjögren syndrome patients has shown it increases the tear volume and treats the dry eye condition with short TBUT more efficiently.\(^52\) Additionally, the paper by Kaido et al.\(^36\) on corneal sensitivity also showed that diquafosol sodium normalized corneal sensitivity and dry eye symptoms in patients with short TBUT. Lipid layer improvement by lid hygiene, etc., may be another therapeutic option,\(^53\)\(^54\) but there is limited evidence for its use in the treatment of short TBUT-type dry eye. Although it is not a direct treatment for the lipid layer, the strategy to increase the ambient humidity and prevent excessive evaporation is a practical and safe method using moisture eyeglasses. This method maintains a higher moisture level and improves the TBUT by using moisture eyeglasses.\(^55\)\(^56\)

As discussed previously in the mechanism section, the mucin layer is the most important layer for disease pathogenesis. Until the introduction of diquafosol sodium and rebamipide, there was no mucin secretagogue. These drugs are now available in Japan and other Asian countries, and the short TBUT-type dry eye could be a treatable disease.\(^12\)\(^18\)\(^51\) Rebamipide was shown to be effective in improving objective and subjective signs of dry eye,\(^57\) and a preliminary study showed its effectiveness for short TBUT.\(^19\) The only drawback is the time lag until the optimum efficacy is obtained. The solution to this limitation is combination therapy with punctal occlusion, which expedites the effectiveness, and is sometimes selected.
The neuropathic pain components can also function as important therapeutic targets, but there is no drug in the market targeting this approach. Appropriate exercise, diet, sleep, and mental happiness may improve the neuropathic components.58 Galor et al. and other groups are exploring multiple treatment approaches in this field, and new developments are expected in the near future.31–35

FUTURE DIRECTIONS

In this article, the emerging short TBUT subtype of dry eye disease has been reviewed. As described previously, this type of dry eye is very important because the ocular surface appears almost normal without any rose bengal or fluorescein staining. This subtype is often easy to overlook in the absence of detailed tear breakup measurements and careful attention to the patient’s subjective complaints. However, the symptoms are nearly as severe as those in dry eye patients with severe vital staining,9,20 and the visual function is also affected due to the unstable tear film.31 The burden on the eye is ever-increasing owing to the enhanced use of visual display terminals. Furthermore, in an ever-aging society, the incidence of dry eye has been observed to be increasing.59 More research studies are necessary to understand the underlying mechanisms of short TBUT and the hypersensitivity of the cornea. Meanwhile, ophthalmologists, both dry eye specialists and general eye specialists, must also recognize short TBUT-type dry eye for proper diagnosis and treatment.

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