Tear Film–Oriented Diagnosis and Tear Film–Oriented Therapy for Dry Eye Based on Tear Film Dynamics

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In December 2010 and January 2012, 3% diquafosol sodium ophthalmic solution and 2% rebamipide ophthalmic suspension, respectively, appeared first in Japan as prescription drugs for the treatment of dry eye (DE). Since then, not only the diagnosis and treatment but also the understanding of the pathophysiology of DE have greatly advanced, and a new concept of layer-by-layer diagnosis and treatment for DE, respectively termed “tear-film–oriented diagnosis” (TFOD) and “tear-film–oriented therapy” (TFOT) was born. This new concept is currently in the process of expanding from Japan to other Asian countries. TFOD is the method used for the differential diagnosis of DE, which includes aqueous-deficiency DE (ADDE), decreased wettability DE (DWDE), and increased evaporation DE (IEDE), through the dynamics of tear film (TF) and breakup patterns (BUPs) after the eye is opened. BUPs and/or each diagnosed DE subtype are/is able to distinguish the insufficient components of the ocular surface that are responsible for each BUP in a layer-by-layer fashion. Aqueous fluid, membrane-associated mucins (especially MUC16), and the lipid layer and/or secretory mucins must be insufficient in ADDE, DWDE, and IEDE, respectively, and this allows for a layer-by-layer treatment to be proposed for each BUP via the supplementation of the insufficient components, using the topical therapy currently available. In Japan, TF breakup is regarded as a visible core mechanism for DE, and an abnormal breakup time (i.e., ≤5 seconds) and symptoms are currently used for the diagnosis of DE. Therefore, TF breakup is regarded as an ideal and practical pathway for clinicians to manage DE.

Keywords: dry eye, tear film oriented diagnosis, tear film oriented therapy, tear film breakup, breakup pattern

When healthy eyes are compared with eyes with dry eye (DE) disease through the staining of tears with fluorescein, tear-film breakup (TFBU) may not be observed in a healthy eye until around 10 seconds, even when the eye is kept open. In contrast, in DE eyes, when the eye is kept open, fluorescein breakup (BU) can generally be observed within 5 seconds as dark spots, often together with epithelial damage. This faster fluorescein BU of the precorneal tear film (TF), as well as the associated epithelial damages, has long been regarded in Japan as a sign of visible abnormalities in DE to differentiate DEs from normal eyes. In addition, TFBU has been regarded in Japan as a visible core mechanism of DE, and great emphasis has been placed on abnormal fluorescein BU time (BUT) (i.e., ≤5 seconds) and epithelial damage of the ocular surface. Moreover, further understanding of short-BUT-type DE (SBUTDE)¹,² has pushed our emphasis in DE more toward the abnormal BUT, because in this type of DE, in spite of minimal association with epithelial damage,¹,² symptoms are equivalent to DE with epithelial damage.³ The common understanding of SBUTDE in Asian countries has become the common definition of DE adopted by the Asia Dry Eye Society,⁴ and has also produced great impact on the definition and diagnostic criteria for DE in Japan.⁵ On the other hand, according to the Dry Eye Workshop (DEWS)⁶ or DEWSII reports, based on the fact that TFBU causes hyperosmolarity of tears—which also causes ocular surface inflammation that ultimately leads to TFBU, thus constituting a vicious cycle in these abnormalities—hyperosmolarity and inflammation, respectively, are now regarded as the key points for the diagnosis and the treatment for DE in other countries.⁷,⁸

In regard to the differences between countries as to the “points of emphasis” for the diagnosis and treatment for DE, differences in the available prescription drugs are also presumably related. In Japan, eye drops that can enhance TF stability are available, while in Western countries, eye drops having an anti-inflammatory effect other than that produced by steroids are available. However, in Japan, although the importance of inflammation in DE is acknowledged, the inflammation is regarded as a result of the vicious cycle between TFBU and damaged corneal surface epithelium, not the cause of the vicious cycle in DE (Fig. 1).

Recent advancements in eye drop treatments for DE have resulted in a strengthening of our concept and approach to DE via the greater emphasis on TFBU as a core mechanism of DE, thus revising the current definition and diagnostic criteria for DE.⁹ According to our 2006 definition,⁹ DE is defined as a chronic disease of tears and ocular surface epithelium. In contrast, according to our 2016 criteria,⁵ DE is a disease characterized by unstable TF. It should be noted that in the 2016 criteria,⁵ the Schirmer 1 test and evaluation of ocular-surface epithelial damage are excluded. Moreover, a probable diagnosis for DE is not included. Hence, the examination solely involves the detection of abnormalities in fluorescein BUT (i.e., ≤5 seconds) and positive eye symptoms related to discomfort.
and visual disturbance. Through this revision, SBUTDE\textsuperscript{1,2} was formerly diagnosed as a probable DE owing to negative ocular-surface epithelial damage and Schirmer 1 test scores, but the compatible extent of symptoms with definite DE\textsuperscript{3} is diagnosed as definite DE requiring a treatment via the improvement of TF stability. Thus, the recent advancements of eye drop treatments in Japan that enhance TF stability have not only made the diagnosis of SBUTDE definitive, but also helped promote the Japanese concept that the instability of TF or TFBU is a visible core mechanism of DE.

**TF-ORIENTED DIAGNOSIS AND TF-ORIENTED THERAPY FOR DE**

The corneal surface is composed of epithelium and TF, and TF is composed of the lipid layer and aqueous layer. In this structure, lipid layer, aqueous fluid, secretory mucins (especially MUC5AC\textsuperscript{10}), and membrane-associated mucins (especially MUC16, the longest\textsuperscript{11}) are the essential components for maintaining TF stability. Therefore, an insufficiency in any one of these components (i.e., the lipid layer, aqueous fluid, MUC5AC, or MUC16) is thought to result in TF instability, thus leading to TFBU.\textsuperscript{12–15} As stated above, TFBU must be one of the most important and visible core mechanisms in DE. Therefore, through the evaluation of TF dynamics when taking BUPs into consideration, the insufficient TF components that are responsible for each BUP can be found. Furthermore, it was also found that through the classification of BUPs, DE can be classified into three independent subtypes, that is, aqueous-deficient DE (ADDE), decreased wettability DE (DWDE), and increased evaporation DE (IEDE), and that aqueous fluid, membrane associated- mucins (especially MUC16\textsuperscript{11}), and lipid layer and/or secretory mucins (especially MUC5AC\textsuperscript{10}) must be insufficient in ADDE, DWDE, and IEDE, respectively. Based on the BUPs and/or the DE subtypes, it will be possible to propose which TF components should be replenished/supplemented by the currently available topical formulations. This novel concept of a layer-by-layer diagnosis and therapy for DE is coined ‘‘TF-oriented diagnosis’’ (TFOD) and ‘‘TF-oriented therapy’’ (TFOT), respectively.\textsuperscript{4,16,17}

**PROCESS FOR THE ESTABLISHMENT OF PRECORNEAL TF IN NORMAL EYES**

To properly understand the TF behavior (TF dynamics) and TFBU after the eye is opened, it is essential to understand the process for the establishment of precorneal TF in normal eyes. When the eye is opened, the upper tear meniscus (TM) pulls up the aqueous tears retained at the lower TM\textsuperscript{18} and deposits them at the corneal surface.\textsuperscript{16,17} The deposition process is assisted via the hydrophilic nature of the membrane associated mucins (especially MUC 16, the longest among them).\textsuperscript{16,17} As a second step after the eye is opened, the TF lipid layer (TFLL) spreads upwards, driven by the surface tension gradient between the lipid-covered surface near the lower TM and the TFLL-deficient upper tear surface.\textsuperscript{19–22} However, this upward
spread of the TFLL simultaneously drags the underlying aqueous tears upward.\textsuperscript{19,20} Combined with the suction pressure from the lower TM (meniscus-induced TF thinning\textsuperscript{26}), this results in temporarily thinner aqueous TF at the inferior part of the cornea. Within this thinner TF area at the inferior part of the cornea, when TFBU is not triggered, precorneal TF is subsequently completely established. In normal eyes, the complete establishment of precorneal TF takes approximately 2 seconds.\textsuperscript{25} During the upward spread of the TFLL, due to the upward drag of the underlying aqueous tears, just behind the leading edge of the spreading TFLL, a dimple (i.e., a type of transient thinning) is expected to be formed\textsuperscript{24–27} that gradually disappears until the establishment of the TF. It agrees well with the experimentally measured \textsim 1-\mu m decrease of aqueous tear thickness over the central cornea induced by the upward drag of aqueous tears by the spreading TFLL.\textsuperscript{20,25} After the complete establishment of TF, a black line\textsuperscript{26} (meniscus-induced TF thinning\textsuperscript{26}) perches the tears at the menisci, and stable, gel-like\textsuperscript{25} precorneal TF is formed.\textsuperscript{20}

### TF BUPS in DE

Even in normal eyes, TFBU occurs after the complete establishment of TF when the eye is kept open. However, it should be noted that in DE cases, there are four other fundamental types of TF BUPS\textsuperscript{17} that occur, based on the pathophysiologically different mechanisms, and they characterize the difference of DE subtype (Fig. 2). As was previously reported,\textsuperscript{17} to effectively diagnose the BUPS, before the observation of fluorescein BUPS, the following steps should be performed: (1) Not to increase tear volume, it is essential to perform a less invasive method for staining tears, that is, a fluorescein strip being vigorously shaken and just touching the central top of the strip to the lower lid margin. (2) After several blinks, verbally instruct the patient to briskly open the eye after gently closing the eye as a kind of provocative test to discover the hidden BU; it should be observed whether or not rapid expansion of BU can be seen when the eye is kept open. In the classification of BUPS, reproducible BUPS must be regarded as more important, which is more related to their pathophysiology.

The presented classification of BUPS in DE is based on the detailed biophysical and surface chemistry concepts developed over decades of basic science research and on the statistical analysis of extensive clinical data, as discussed in detail in our previous study.\textsuperscript{17} The clinical study involved 106 DE patients for which the following assessments were performed: DE-related symptoms when using the visual analog scale (100 mm = maximum), tear meniscus radius (mm), TF lipid layer thickness\textsuperscript{18} perches the tears at the menisci, and stable, gel-like\textsuperscript{25} precorneal TF is formed.\textsuperscript{20}

TF BUPS in ADDE

In the most severe ADDE cases, owing to the deficiency of the aqueous component, tear fluid cannot be uniformly deposited across the cornea, which results in an area lacking in aqueous coverage corresponding to characteristic TFBU. This BUP, which occurs during eye opening, is termed “area break” (AB).\textsuperscript{16,17} Using fluorescein, in the severest form of ADDE, upward movement of fluorescein-stained aqueous tears cannot be confirmed, while only the severe ocular surface epithelial damage and the lower height of the TM can be observed. However, in relatively less severe cases, upward movement of fluorescein-stained aqueous tears can be observed just within the inferior part of the cornea (may be appropriately coined as “partial AB”). Also, in partial AB as well, severe punctate staining of the ocular surface epithelium within the palpebral zone may be seen.

In mild to moderate ADDE cases, at the thinner aqueous TF area in the lower part of the cornea that is susceptible to TFBU, TFBU is likely to occur during the upward movement of aqueous tears owing to the simultaneous action of this upward movement and TF thinning induced by the lower TM,\textsuperscript{18} which appeared as a line-like BUP when using fluorescein. We coined this BUP, which is seen after the eye is opened, as “line break” (LB).\textsuperscript{16,17} Theoretically, this BU is facilitated by the greater suction effect\textsuperscript{16,17} and thinner aqueous TF\textsuperscript{50} in cases with less aqueous tear volume. Around LB, corneal epithelial damage is generally observed together with conjunctival epithelial damage within the interpalpebral zone. In SBUTDE,\textsuperscript{1,2} a case with LB sometimes occurs with rapid expansion of the BU region, together with no or minimal corneal epithelial damage and apparently normal height of the lower TM. In our current thinking, this BUP might be associated with decreased corneal wettability\textsuperscript{31–33} rather than aqueous tear deficiency, and DE with this BUP should be properly classified as DWDE, not as ADDE. In this type of DE, owing to the decreased wettability of possibly the inferior part of the cornea, aqueous deposition is less than normal, in spite of normal meniscus tear volume, and this may be why LB with its rapid expansion is likely to occur. However, further study is needed to support this theory.

TF BUPS in DWDE

Even when the aqueous tear volume is sufficient, accelerated TFBU can occur, probably in relation to decreased corneal wettability.\textsuperscript{31–35} This BU can be seen (1) instantaneously during eye opening at the deposition process of aqueous tears on the cornea, and/or (2) during the upward spread of the TFLL after the eye is opened, during which process a dimple\textsuperscript{4,25} passes over the cornea and BU occurs when the dimple passes over the corneal surface, at which point the wettability is impaired. The former BUP is coined as “spot break” (SB)\textsuperscript{16,17} owing to the spot-like appearance of the BU, and the smaller SB is likely to be erased during the upward movement of aqueous tears after the eye is opened. The latter BUP is coined as “dimple break” (DB),\textsuperscript{17} because the BU occurs at the dimple site. The underlying mechanism of SB and DB is presumably the contamination of the corneal surface by the TFLL that results in decreased wettability.\textsuperscript{31–35} Therefore, SB and/or DB can be
corneal epithelial damage, which is generally thought to be associated with DWDE. RB is thought to be associated with increased evaporation DE. RB must occur after the cessation of UMF. LB is generally accompanied by superficial DB is thought to be associated with mild to moderate ADDE. DB is diagnosed as an irregular but vertical line–like shape during UMF within the zone closer to the central part of the cornea, within which fluorescein intensity becomes decreased with time until the cessation of UMF; LB is thought to be associated with mild to moderate ADDE. DB is diagnosed as an irregular and indefinite shape whose typical place for the BU to occur generally differs with cases and with each blink; RB is thought to be associated with increased evaporation DE. RB must occur after the cessation of UMF; LB is generally accompanied by superficial corneal epithelial damage at the lower part of the cornea. However, LB can occur with rapid expansion of the BU with minimal or no superficial corneal epithelial damage, which is generally thought to be associated with DWDE.

**TF BUPs in IEDE**

Even in normal eyes, when the eye is kept open for a longer time, after the complete establishment of TF BU, DB can occur, probably owing to evaporation. TFLL and secretory mucin (MUC5AC) are thought to be components of the TF, contributing to the suppression of evaporation and stability of TF after its establishment, and insufficiency of those components would result in earlier TFBU, even after the complete establishment of TF owing to facilitated evaporation. It should be kept in mind that currently, the capability of TF to resist evaporation and the evaporation-suppressive action of the TFLL are controversial, both in clinical and in vitro studies, and precise clarification of these phenomena is a topic for future research. We coined this TFBU as “random break” (RB), because in RB the portion and shape of the BU is not likely to be reproducible. In RB, it should be noted that the BU is observed after the cessation of the upward movement of fluorescein-stained aqueous tears after the eye is opened, which corresponds to the timing after complete establishment of precorneal TF after the cessation of upward spread of the TFLL. Even when RB is seen, if the BU area expands rapidly, it is reasonably suggested that decreased wettability, probably due to the impairment of membrane-associated mucins (especially MUC16), is also associated; and if we consider the treatment for RB with rapid expansion, not only the facilitated evaporation but also the decreased wettability should be considered. The BUPs, their characterization as a DE subtype, insufficiency of components, and the possible selection of topical treatments are summarized in the Table.

**Recent Advancements in Eye Drops for TFOT**

It should be noted that 3% diquafosol sodium (DQS) eye drops, which produced a paradigm shift in our approach to DE in Japan, can enhance the production of aqueous fluid, evaluated for the first in the human eye via meniscometry, from the conjunctival epithelium and secretory mucin (MUC5AC) from the conjunctival goblet cells. Moreover, DQS eye drops can enhance the expression of membrane-associated mucins (MUC1, MUC4, and MUC16) of the corneal surface epithelium. Considering that artificial-tear eye drops and hyaluronic-acid eye drops can only increase tear volume for up to 5 and 10 minutes, respectively, the effect of DQS for increasing tear volume as long as 30 minutes is expected to be effective for treating ADDE via the longer enhancement of...
<table>
<thead>
<tr>
<th>Cornea</th>
<th>Subtype</th>
<th>Pathophysiology</th>
<th>Supplementation of Aqueous Fluid</th>
<th>Supplementation of Secretory Mucin</th>
<th>Supplementation of Membrane-Associated Mucins</th>
<th>Pathology</th>
<th>Interpretation of the Insufficient Components</th>
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<tr>
<td>Lower</td>
<td>ADDE</td>
<td>Severe aqueous deficiency</td>
<td>None/ADDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>Area-like</td>
<td>X~Δ, quick; SA, slow and limited within the lower part of the cornea. X cannot be observed. Epithelial damage is common to Asian countries and is also related to abnormalities in secretory and membrane-associated mucins.</td>
</tr>
<tr>
<td>Upper</td>
<td>ADDE</td>
<td>Mild to moderate aqueous deficiency</td>
<td>None/ADDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>Spot-like</td>
<td>Δ, severe; SA, rapid expansion.</td>
</tr>
<tr>
<td>Lower</td>
<td>ADDE</td>
<td>Decreased corneal wettability</td>
<td>None/ADDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>Random break</td>
<td>X~Δ, quick; SA, slow and limited within the lower part of the cornea. X cannot be observed. Epithelial damage is common to Asian countries and is also related to abnormalities in secretory and membrane-associated mucins.</td>
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<tr>
<td>Upper</td>
<td>ADDE</td>
<td>Decreased corneal wettability</td>
<td>None/ADDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>None/DWDE Supplementation</td>
<td>Line-like</td>
<td>Δ, severe; SA, rapid expansion.</td>
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**TFOD and TFOT in Asian Countries and Concomitant Therapy to TFOT**

In Asian countries where DQS has gradually become available, which can enhance the production of conjunctival goblet cells,58 and it can also supplement membrane-associated mucins59 of the corneal surface epithelium. Therefore, DQS and RBM are excellent eye drops for the treatment of DE related to abnormalities in secretory and membrane-associated mucins.
2016 version of a new definition of DE in Japan. It is a translation in Japanese from that of the Asia Dry Eye Society. In Western countries, on the other hand, DQS and/or RBM eye drops are not available, and the idea of TFOD and TFOT might possibly be less favored. However, in Western countries, there has been an advancement in prescription anti-inflammatory eye drops other than steroids to treat DE. In the United States and in various European countries, cyclosporine eye drops are available, and in the United States, in addition to cyclosporine, lifitegrast, an inhibitor of intercellular adhesion molecule-1, has become available for the treatment of DE. In Japan, we do not deny the importance of anti-inflammatory therapy for DE. The Japanese theory is based on the idea that the inflammation is not the cause, but the result of a vicious cycle (Fig. 1) between TFBU and damaged corneal surface epithelium. Therefore, steroid eye drops are often used together with the TFOT, for example, at the start of TFOT and at exacerbation of the symptoms. As an alternative treatment to TFOT, for severe ADDE cases presenting AB, even at present, punctal occlusion of both the upper and lower puncta is essential, together with artificial tear eye drops, and this results in stable TF via the establishment of precorneal TE. Moreover, for DE cases with meibomian gland dysfunction (MGD), for which RB is expected, topical therapy as TFOT and treatment for MGD (such as using warm compress, lid hygiene, and antibiotic eye drops) must be adopted.

**Future Directions**

In Japan, great attention has been paid to the instability of TF as a visible core mechanism of DE. This concept has been adopted by Asian countries, and it is clinically and practically useful to diagnose and treat DE. TFOD and TFOT are the ideal methods for a clinician to diagnose DE subtype through BUPs with a different pathophysiology, only using sodium fluorescein, and to choose the best treatment for DE available in each country. In future studies, it should first be validated whether or not TFOT proposed by theoretically supported TFOD is also practically useful, even in the other countries, and the possible limitations of the methods should be elucidated and improvements proposed. Moreover, if this concept works properly, a noninvasive method for TFOD other than using fluorescein, such as the use of an interferometer, should be explored for easier screening of DE subtype.

As another direction of TFOD, the relationship between TFOD and blink-related friction should be elucidated. TF instability is the manifestation of DE in an open eye, and it is usually only viewed from the perspective of TF’s preventing the desiccation of the ocular surface epithelium. However, to comprehensively understand the pathophysiology, ocular manifestations, and symptoms of DE, attention should be focused on blink-related friction as another important mechanism of DE (Fig. 4). Tears are known to act as a lubricant, with their shear-thinning property being important to reduce friction.

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*Figures* 2 and 3. The detailed concept of TFOT version 1 produced by the Dry Eye Society of Japan. TFOT illustrates the target for therapy and possible candidates for topical eye therapy currently available in Japan and elsewhere to improve TF stability. However, for the selection of the most effective topical therapy, TFOD is essential to detect the insufficient component needed for the ocular surface to stabilize the TF and to classify the DE subtype. Reprinted from http://www.dryeye.ne.jp/tfot/index.html, with permission from Dry Eye Society.
friction during blinking. However, in DE, owing to quantitative and/or qualitative abnormalities in tears, increased blink-related friction may also become the cause for a vicious cycle between the lid-wiper region\(^66,67\) and the eyeball surface. Friction-related ocular surface diseases (OSDs), such as lid-wiper epitheliopathy,\(^66\) superior limbic keratoconjunctivitis,\(^68-71\) and filamentary keratitis,\(^72,73\) are known to be sometimes associated with DE, especially in ADDE cases. Moreover, other than these blink-related OSDs, conjunctivochalasis,\(^74-76\) which is highly prevalent in elderly people,\(^75\) is known to enhance not only TF instability, but also blink-related friction, and is thought to modify the ocular surface

![Diagram showing various intrinsic and extrinsic risk factors affecting DE](image)

**Figure 4.** Stratified structure of DE. To comprehensively understand DE, TF breakup and increased friction are taken into consideration as the major mechanisms of DE. The former mechanism is common to any type of DE when the eye is kept open. The latter mechanism is that which during blinking may be more important in aqueous-deficiency DE. Various intrinsic and extrinsic risk factors flow into the two mechanisms, which form the vicious cycle (VC), from which symptoms result while presenting ocular surface manifestations of DE.

![Diagram showing implementation of TFOD and TFOT in Japan](image)

**Figure 5.** An example of implementation of TFOD and TFOT in Japan. In Japan, DE is diagnosed from symptoms and abnormal fluorescein breakup time (FBUT, ≤5 seconds). For TFOD, the first step is the classification of the DE subtypes (ADDE, DWDE, or IEDE) based on major BUPs. In this classification, SBUTDE is thought to correspond to DWDE and IEDE. Based on BUPs and/or DE subtypes, components that are insufficient and should be supplemented can be suggested as the target for TFOT. AT, artificial tears; HA, hyaluronic acid; PP, punctal plug; RE, rapid expansion.
manifestations and symptoms in DE. In our recent report on TFOD, we have excluded DE cases accompanied by the above-described friction-related OSDs in order to analyze only the relationship between BUPs and objective signs and subjective symptoms. Therefore, in a future study, the association of friction-related OSDs with DE subtype should be elucidated. Furthermore, blink-related friction must be related to ocular surface inflammation. Therefore, a comprehensive understanding of the relationship between TF instability, increased friction, and inflammation must also be a target for further investigation.

In TFOT, DQS and RBM eye drops are useful, as they both increase secretory mucins. However, the action by which this increase is achieved may differ. DQS can increase MUC5AC within 5 minutes. In contrast, RBM may increase the secretory mucin gradually via the increase of goblet cells, and this might be the reason why there have been reports that RBM can effectively treat friction-related OSDs. Considering that the increased secretory mucin may increase the viscosity of tears, there must be cases in which the use of DQS results in increased friction, leading to the exacerbation of the accompanied friction-related OSDs in ADDE. Therefore, from the point of blink-related friction, there must be cases in which concomitant use of a TF stabilizer such as DQS and a lubricant such as RBM results in improvement in signs and symptoms of DE. Further study is necessary to elucidate the optimal treatment for DE, while being based on TFOD via the consideration of increased friction as another mechanism of DE.

**Conclusions**

The new concepts of TFOD and TFOT opened another field for the diagnosis and therapy for DE, based on the dynamics of precorneal TF. According to this concept, using fluorescein is all that is needed to look through the DE subtype via the classification of BUPs and to propose the appropriate choice of topical therapy based on the instability of TF as a core mechanism for DE (Fig. 5). Moreover, this concept appears to be very useful and practical for clinicians. Although TFOD and TFOT are concepts first established in Japan, the commercial availability of both DQS and RBM has been found to be favorable, and the availability of DQS is now expanding from Japan to Asian countries in combination with the concept of TFOT. Currently, this concept still requires further investigation; however, future study is expected to deepen our understanding of DE.

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**References**


Corrected March 4, 2019: In Figure 2, reading left to right, top to bottom, the labels were changed from A, B, E, C, D, F to A, B, C, D, E, F The order of the six images was not changed.