

# Effect of Refresh Plus<sup>®</sup> preservative-free lubricant eyedrops on tear ferning patterns in dry eye and normal eye subjects

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**Purpose:** To evaluate the tear ferning patterns in dry eye and normal eye subjects in the 3 hours following application of Refresh Plus<sup>®</sup> preservative-free lubricant eyedrops.

**Methods:** Thirty men with dry eye (mean age 22.14±2.34 years) and 30 age-matched men with normal eyes (mean age 23.91±3.24 years) were enrolled. Eyes were classified as normal or dry based on their Ocular Surface Disease Index score, tear meniscus height, and noninvasive tear breakup time. The tear ferning test was performed before and 30, 60, 120, and 180 minutes after application of a Refresh Plus eyedrop into the right eye in each subject.

**Results:** There was a significant change in tear ferning grade after application of Refresh Plus eyedrops ( $P=0.02$ , Wilcoxon test) in the group with dry eye, but not in the normal eye group ( $P=0.19$ , Wilcoxon test). The correlation of tear ferning grade was moderate ( $r=0.484$ ,  $P=0.049$ ) at 60 minutes after application of the eyedrops and strong at 120 minutes ( $r=0.560$ ,  $P=0.019$ ) and 180 minutes ( $r=0.726$ ,  $P=0.001$ ). There was also a strong correlation ( $r=0.865$ ,  $P=0.001$ ) between tear ferning grades obtained 120 and 180 minutes after application. In the normal eye group, there was a moderate ( $r=0.407$ ,  $P=0.029$ ) correlation between tear ferning grades obtained before and 60 minutes after application of the eyedrops. There was also a strong correlation ( $r=0.532$ ,  $P=0.003$ ) between tear ferning grades obtained 120 and 180 minutes after application.

**Conclusion:** Tear ferning patterns improved significantly after application of Refresh Plus preservative-free lubricant eyedrops in subjects with dry eye. Artificial tears containing sodium carboxymethylcellulose, such as Refresh Plus, can be used to improve tear ferning patterns in dry eye for at least 3 hours.

**Keywords:** dry eye, eyedrops, tear film, tear meniscus height

## Plain language summary

This study was performed to determine the effect of Refresh Plus<sup>®</sup> preservative-free lubricant eyedrops on ocular tear film in patients with dry eye.

Tear ferning patterns obtained in subjects with dry eye improved significantly during 3 hours of observation after application of Refresh Plus preservative-free lubricant eyedrops. There was some improvement in the quality of tear ferning after application of artificial tears in normal eye subjects but the change was not statistically significant.

Artificial tears containing sodium carboxymethylcellulose, such as Refresh Plus, can improve ocular tear film in patients with dry eye for at least 3 hours after instillation.

## Introduction

Tear film is a thin moist layer that covers and moisturizes the surface of the cornea.<sup>1</sup> Upon blinking, the tear film spreads over the cornea to avoid drying of the ocular surface.<sup>2</sup>

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Various factors affect the rate of spontaneous eye blinking, including stability of the tear film, thickness of the lipid layer, composition of meibum produced by the meibomian gland, and the eye-drying rate.<sup>3,4</sup> Blink rate has been found to depend on age and high in infants and adults up to the age of 25 years.<sup>5,6</sup> In adults, the meibum is less saturated, more oily, less ordered, and contains flexible chains of lipids, whereas in infants the meibum is highly saturated, stiff, and contains waxy lipids.<sup>7</sup> Furthermore, there is more meibum in the lipid reservoir in adults than in infants.<sup>8</sup> This explains why adults up to the age of 25 years have a higher rate of spontaneous eye blinking (15–30 blinks per minute) than infants (approximately four blinks per minute).<sup>9</sup>

Dry eye is a common ocular surface disorder that develops because of instability within the tear film, and causes uncomfortable symptoms in 5%–50% of the population worldwide.<sup>10</sup> Dry eye can be caused by a high tear-evaporation rate, a deficiency in tear secretion, or both.<sup>10</sup> Furthermore, a change in osmolarity of the ocular surface may occur, which can lead to apoptosis of cells on the epithelial surface and consequent loss of goblet cells that produce mucin.<sup>11,12</sup> The symptoms of dry eye have a considerable impact on quality of life.<sup>13</sup> Therefore, it is important to detect this condition as early as possible for optimal management.<sup>14</sup> Given that eye dryness is complex and affected by a number of parameters, a combination of diagnostic tests, along with dry-eye questionnaires, such as the Ocular Surface Disease Index (OSDI), are needed for diagnosis. For example, tear-evaporation rate,<sup>15</sup> Schirmer's test,<sup>16</sup> phenol red thread,<sup>16</sup> tear meniscus height (TMH),<sup>17</sup> noninvasive tear breakup time (NITBUT),<sup>18</sup> osmolarity,<sup>19</sup> and the tear ferning (TF)<sup>20,21</sup> test can be used to detect dry eye. Artificial tears can be used to lubricate the tear film and relieve some of the uncomfortable symptoms associated with moderate dry eye.<sup>22,23</sup>

Previous studies shown that the TF test can be used to assess the quality of tears in subjects with dry eye, including smokers,<sup>24</sup> those with diabetes,<sup>25</sup> subjects with normal eyes after consumption of a single dose of hot green tea<sup>26</sup> or peppermint,<sup>27</sup> and after oral vitamin A supplementation for 3 consecutive days.<sup>28</sup> The aim of the present study was to compare TF patterns in the 3 hours following application of Refresh Plus<sup>®</sup> (Allergan, Marlow, UK) preservative-free lubricant eyedrops in dry- and normal eye subjects.

## Methods

### Subjects

Thirty men with dry eye (mean age 22.14±2.34 years) and 30 age-matched normal eye men (mean age 23.91±3.24 years)

were enrolled. A slit lamp was used to examine abnormalities of the eyelids, eyelashes, conjunctiva, cornea, and iris. Subjects with no eyelid or lash abnormalities, those who had recently undergone ocular surgery or were receiving ophthalmic medication, contact-lens wearers, smokers, and patients with diabetes, anemia, or a thyroid disorder were excluded. OSDI and TMH scores and NITBUT test results were used to classify subjects as having or not having dry eye. The study was approved by the College of Applied Medical Sciences Ethics Committee, King Saud University and performed according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each study participant before commencement of the research. All tests were performed by the same examiner in an environment that was controlled for humidity (<40%) and temperature (23°C).<sup>25</sup> After subjects had completed the OSDI questionnaire, the TMH, NITBUT, and TF tests were performed, with a 10-minute interval between each test.

### Refresh Plus preservative-free lubricant eyedrops

Refresh Plus preservative-free lubricant eyedrops (30 single-use containers each containing 0.4 mL; Allergan, Marlow, UK) are aqueous-based artificial tears. The drops contain sodium carboxymethylcellulose (CMC) 0.5% as the active ingredient, as well as sodium lactate and various electrolytes, including sodium chloride, potassium chloride, magnesium chloride, and calcium chloride. They can be used to relieve symptoms of dry eye, ie, irritation, burning, and discomfort.<sup>22</sup>

### Ocular Surface Disease Index

The OSDI was completed by each study participant first, and a score <13 was considered as normal eye.<sup>29</sup>

### TMH and NITBUT tests

The TMH and NITBUT tests were performed in each subject's right eye after completion of the OSDI, with a 5-minute interval between the two tests. Both tests were performed using a Keratograph 4 system (Oculus, Wetzlar, Germany). Fluorescein was added to the subject's eye. For the NITBUT test, the subject was asked to refrain from blinking while the tear film was observed.<sup>30</sup> A yellow barrier filter was used to enhance the visibility of tear-film breakup. TBUT was recorded as the number of seconds that elapsed between the last blink and the appearance of the first dry spot in the tear film. The inferior TMH images

were captured and measured perpendicularly to the lid margin at the central point relative to the pupil center using an integrated ruler. Both tests were performed three times and average measurements recorded. The eye was defined as normal if the tear height in the lower lid was  $>0.2$  mm for TMH and the TBUT was  $>10$  seconds for NITBUT measurements.

## Tear ferning test

A tear sample (1  $\mu$ L) was collected from the lower meniscus of the right eye in each subject using a glass capillary tube (10  $\mu$ L; Sigma-Aldrich; St Louis, MO, USA). The tear sample was dried at 23°C for 10 minutes at a humidity of  $<40\%$ . A DP72 microscope (10 $\times$  magnification; Olympus, Tokyo, Japan) was used to observe and capture the tear ferns. Each TF pattern was graded according to the 5-point TF-grading scale using increments of 0.1.<sup>21</sup> The TF test was repeated for each subject at 30, 60, 120, and 180 minutes after application of the artificial eyedrops.

## Statistical analysis

Data were tabulated using Excel (Office 2010; Microsoft, Redmond, WA, USA) and analyzed using SPSS version 22 (IBM, Armonk, NY, USA). The Spearman correlation coefficient was used to investigate relationships among the obtained data. Correlation coefficients was considered small (0.10–0.29), moderate (0.30–0.49), or large (0.50–1).<sup>31</sup>

## Results

Data collected from all tests were found not to be normally distributed ( $P<0.05$ , Kolmogorov–Smirnov test); therefore, the median (IQR) was used to represent the average values. Median (IQR) scores for the OSDI and TMH, NITBUT, and TF tests in dry- and normal eye groups are shown in Table 1. There were significant differences ( $P<0.05$ , Wilcoxon test) in the OSDI scores and NITBUT measurements between dry- and normal eye subjects, but not significant between-group differences for TMH scores ( $P>0.05$ , Wilcoxon test). In the dry-eye group, there were significant differences ( $P<0.05$ , Wilcoxon test) in TF grades obtained at the five different time points after administration of the eyedrops, but not in the normal eye group ( $P>0.05$ , Wilcoxon test).

Examples of the five TF images obtained from dry- and normal eye subjects before and 30–180 minutes after application of artificial tears are shown in Figure 1. Box plots for the TF scores on the tests are shown side by side for the dry- and normal eye groups in Figure 2.

**Table 1** Median OSDI scores and TMH, NITBUT, and TF test results in dry eye and normal eye subjects

Test	Median (interquartile range)	
	Dry eye (n=30)	Normal eye (n=30)
OSDI score*	18.10 (9.90)	9.00 (10.21)
TMH (mm)	0.23 (0.08)	0.26 (0.07)
NITBUT (seconds)*	13.21 (2.29)	6.31 (4.30)
TF0 grade*	2.80 (1.05)	1.00 (0.50)
TF30 grade*	2.00 (2.10)	0.80 (0.50)
TF60 grade*	1.50 (1.80)	0.80 (0.50)
TF120 grade*	1.00 (2.00)	0.80 (0.80)
TF180 grade*	1.10 (1.70)	0.80 (0.50)

**Notes:** \* $P<0.05$ . TF0-180, TF scores obtained 0-180 minutes after application of eyedrops.

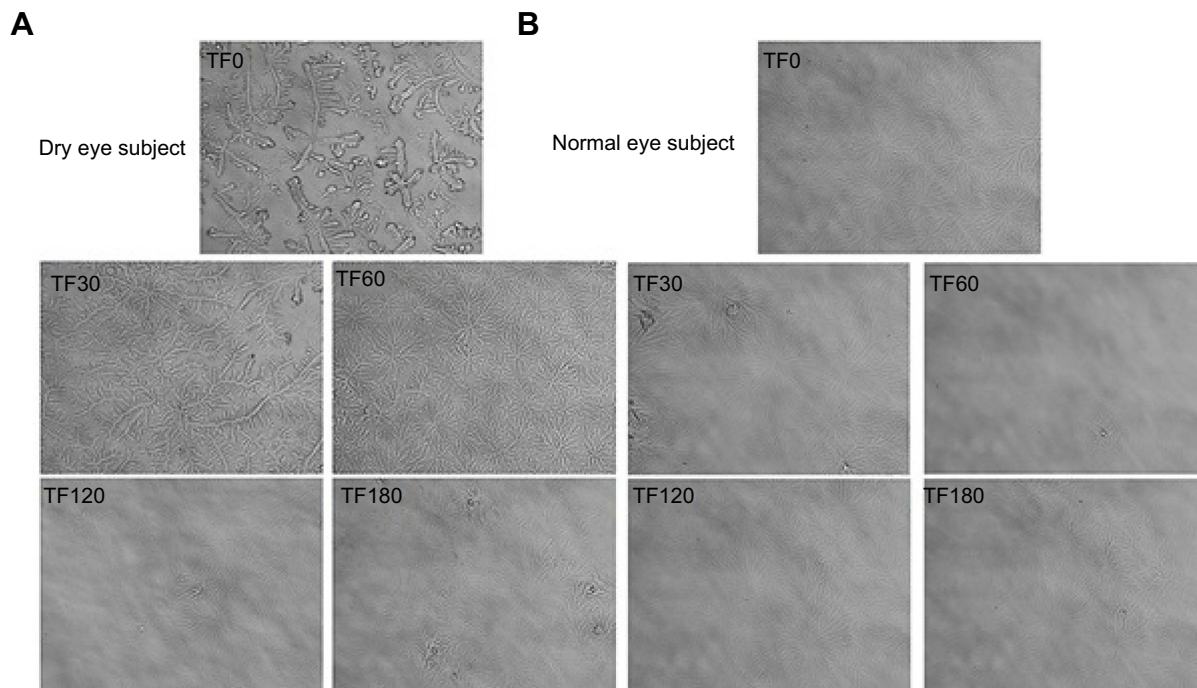
**Abbreviations:** OSDI, Ocular Surface Disease Index; NITBUT, noninvasive tear breakup time; TF, tear ferning; TMH, tear meniscus height.

Correlations between scores from the OSDI and TMH, NITBUT, and TF tests in dry- and normal eye groups are shown in Tables 2 and 3, respectively. In the group of subjects with dry eye, the correlation between the TF grades obtained before and after application of the eyedrops was moderate ( $r=0.484$ ,  $P=0.049$ ) at 60 minutes and strong at 120 minutes ( $r=0.560$ ;  $P=0.019$ ) and 180 minutes ( $r=0.726$ ,  $P=0.001$ ). There was a strong correlation ( $r=0.865$ ,  $P=0.001$ ) between TF grades obtained 120 and 180 minutes after application of the eyedrops. There was also a strong negative correlation ( $r=-0.542$ ,  $P=0.025$ ) between OSDI scores and TF grades obtained 60 minutes after application.

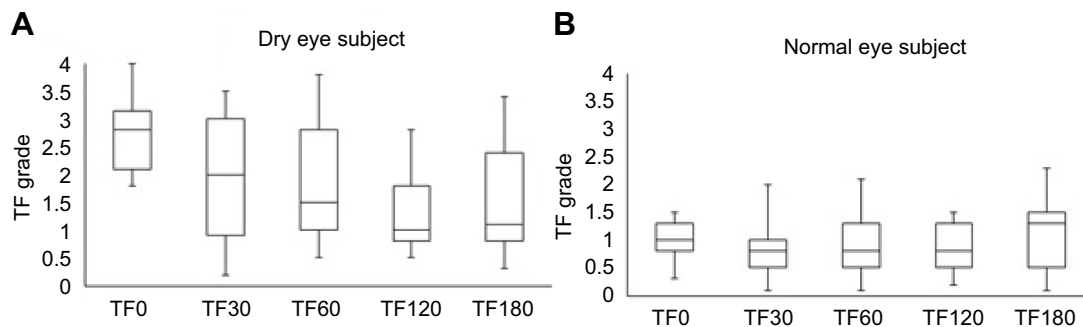
For normal eye subjects, there was a moderate correlation ( $r=0.407$ ,  $P=0.029$ ) between TF grades obtained before and 60 minutes after application of the eyedrops and a strong correlation ( $r=0.532$ ,  $P=0.003$ ) between those obtained 120 and 180 minutes after application. Furthermore, there was a moderate correlation ( $r=0.425$ ,  $P=0.022$ ) between TMH and NITBUT values.

## Discussion

Dry eye is a common ocular problem that causes various uncomfortable symptoms. Artificial tears are the first choice for management of symptoms of dry eye. Indeed, most of the ocular discomfort, ie, inflammation, burning, itching, and dryness, can be relieved by the use of eye lubricants.<sup>32</sup> Various types of eye lubricants with different pH, viscosity, physical, and chemical properties are available. Lubricants with a certain pH might be suitable for some but not all individuals with dry eye.<sup>33</sup> Furthermore, artificial tears contain different active ingredients, preservatives, electrolytes, and polymers in varying concentrations.<sup>22</sup> The different



**Figure 1** Tear ferning (TF) images obtained before and after application of eyedrops in the right eye of (A) a dry-eye subject and (B) a normal eye subject. **Notes:** TF0-180, TF scores obtained 0-180 minutes after application of eyedrops.



**Figure 2** Box plots for tear ferning (TF) test scores in (A) dry-eye subjects and (B) normal eye subjects. **Notes:** TF0-180, TF scores obtained 0-180 minutes after application of eyedrops.

types of artificial tears also vary in their mode of action.<sup>32</sup> For example, eyedrops containing hydrogel in borate solution tend to create a viscous matrix within the eye in which the comfort effect lasts longer when compared with other types of artificial tears.<sup>34</sup> Another mechanism involves augmentation of some tear components and improvement in the thickness of the lipid layer.<sup>35</sup>

In the present study, Refresh Plus preservative-free lubricant eyedrops were used to improve the TF grade and decrease the symptoms of dry eye. These drops contain CMC 0.5% and have a pH of 6.5 and an osmolarity of 276 mmol/kg.<sup>32</sup> There was a significant ( $P < 0.05$ ) improvement in TF grade obtained in subjects with dry eye after

application of a single drop of these artificial tears that lasted for at least 3 hours. Lubricants containing CMC are known to improve the stability of tear film and increase the density of goblet cells.<sup>36,37</sup> For example, Optive eyedrops, which contain sodium CMC 0.5% and glycerin 0.9%, can be used to relieve the symptoms of eye dryness.<sup>38,39</sup> High-viscosity or gel-like artificial eyedrops are preferred by many patients with dry eye, because they have a longer ocular residence time.<sup>40</sup> It has been reported that Refresh Plus eyedrops can significantly reduce the epithelial defects produced during laser in situ keratomileusis ( $P = 0.020$ ).<sup>41</sup> Another study showed that use of Refresh Plus eyedrops led to significantly lower average ocular

**Table 2** Correlations between OSDI scores and TMH, NITBUT, and TF test results in subjects with dry eye — *r* (*P*-value)

Test	OSDI	TMH	NITBUT	TF0	TF30	TF60	TF120	TF180
OSDI	1 (—)	-0.222 (0.392)	-0.358 (0.158)	-0.193 (0.459)	-0.446 (0.073)	-0.542 (0.025)	-0.100 (0.703)	-0.043 (0.870)
TMH	-0.222 (0.392)	1 (—)	-0.060 (0.818)	-0.032 (0.902)	-0.217 (0.403)	-0.094 (0.719)	0.020 (0.939)	-0.168 (0.519)
NITBUT	-0.358 (0.158)	-0.060 (0.818)	1 (—)	0.166 (0.525)	0.449 (0.070)	0.302 (0.239)	0.296 (0.248)	0.086 (0.744)
TF0	-0.193 (0.459)	-0.032 (0.902)	0.166 (0.525)	1 (—)	-0.085 (0.744)	0.484 (0.049)	0.560 (0.019)	0.726 (0.001)
TF30	-0.446 (0.073)	-0.217 (0.403)	0.449 (0.070)	-0.085 (0.744)	1 (—)	0.159 (0.542)	-0.074 (0.777)	-0.160 (0.538)
TF60	-0.542 (0.025)	0.094 (0.719)	0.302 (0.239)	0.484 (0.049)	0.159 (0.542)	1 (—)	0.503 (0.040)	0.449 (0.070)
TF120	-0.100 (0.703)	0.020 (0.939)	0.296 (0.248)	0.560 (0.019)	-0.074 (0.777)	0.503 (0.040)	1 (—)	0.865 (0.001)
TF180	-0.043 (0.870)	-0.168 (0.519)	0.086 (0.744)	0.0726 (0.001)	-0.160 (0.538)	0.449 (0.070)	0.865 (0.001)	1 (—)

**Notes:** TF0-180, TF scores obtained 0-180 minutes after application of eyedrops.

**Abbreviations:** OSDI, Ocular Surface Disease Index; NITBUT, noninvasive tear breakup time; TF, tear ferning; TF30, TMH, tear meniscus height.

**Table 3** Correlations between OSDI scores and TMH, NITBUT, and TF test results in normal eye subjects — *r* (*P*-value)

Test	OSDI	TMH	NITBUT	TF0	TF30	TF60	TF120	TF180
OSDI	1 (—)	-0.142 (0.463)	-0.233 (0.225)	-0.029 (0.882)	-0.134 (0.489)	0.083 (0.667)	0.107 (0.581)	-0.020 (0.918)
TMH	-0.142 (0.463)	1 (—)	0.425 (0.022)	-0.036 (0.853)	-0.173 (0.368)	-0.003 (0.987)	-0.038 (0.843)	0.194 (0.312)
NITBUT	-0.233 (0.225)	0.425 (0.022)	1 (—)	-0.075 (0.699)	0.094 (0.626)	0.104 (0.592)	-0.034 (0.859)	0.052 (0.789)
TF0	-0.029 (0.882)	-0.036 (0.853)	-0.075 (0.699)	1 (—)	0.174 (0.368)	0.407 (0.029)	0.226 (0.239)	0.105 (0.587)
TF30	-0.134 (0.489)	-0.173 (0.368)	0.094 (0.626)	0.174 (0.368)	1 (—)	0.320 (0.091)	-0.042 (0.828)	0.048 (0.805)
TF60	0.083 (0.667)	-0.003 (0.987)	0.104 (0.592)	0.407 (0.029)	0.320 (0.091)	1 (—)	0.429 (0.020)	0.391 (0.036)
TF120	0.107 (0.581)	-0.038 (0.843)	-0.034 (0.859)	0.226 (0.239)	-0.042 (0.828)	0.429 (0.020)	1 (—)	0.532 (0.003)
TF180	-0.020 (0.918)	0.194 (0.312)	0.052 (0.789)	0.105 (0.587)	0.048 (0.805)	0.391 (0.036)	0.532 (0.003)	1 (—)

**Notes:** TF0-180, TF scores obtained 0-180 minutes after application of eyedrops.

**Abbreviations:** OSDI, Ocular Surface Disease Index; NITBUT, noninvasive tear breakup time; TF, tear ferning; TF30, TMH, tear meniscus height.

surface-staining scores following laser in situ keratomileusis in patients with myopia when compared with those obtained by Bion tears ( $P=0.015$ ).<sup>42</sup>

Eyedrops containing sodium hyaluronate 0.1%–0.3% have been found to be more effective than saline for reducing the symptoms of dry eye and improving NITBUT



scores in subjects with moderate eye dryness.<sup>43</sup> Insertion of a cross-linked hyaluronic acid gel (0.2 mL) in the lower eyelid led to improvements in corneal fluorescein staining, increased TBUT scores, and improved Schirmer's test results in subjects with dry eye.<sup>44</sup> A combination of artificial tears containing a CMC salt and hyaluronic acid was found to be more effective in the management of symptoms of dry eye than eyedrops containing either ingredient alone.<sup>45–47</sup> This combination lead to high shear viscosity and reduced stickiness and blur during blinking.

This study had some limitations, including a limited sample size and inclusion of only male subjects. Furthermore, the effect of artificial tears was observed for only 3 hours and only one type of artificial tears was used. Moreover, the possibility of a confounding effect of environmental factors, such as sunlight and extremes of humidity and temperature, immediately prior to taking part in the study cannot be excluded. Therefore, a further study is needed to test the longer-term effects of various type of artificial tears on tear film in a larger number of subjects with and without dry eye.

## Conclusion

TF patterns obtained from subjects with dry eye improved significantly after application of Refresh Plus preservative-free lubricant eyedrops. There was some improvement in the quality of TF after application of artificial tears in normal eye subjects but the change was not statistically significant. Artificial tears containing sodium CMC, such as Refresh Plus, can be used to improve TF patterns in subjects with dry eye for at least 3 hours.

## Abbreviations list

CMC, carboxymethylcellulose; NITBUT, noninvasive tear breakup time; OSDI, Ocular Surface Disease Index; TF, tear ferning; TMH, tear meniscus height.

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## Disclosure

The authors report no conflicts of interest in this work.

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