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Tear clearance measurement in patients with dry eye syndrome using quantitative lacrimal scintigraphy

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Objective: The aim of this study was to evaluate the tear clearance in patients with dry eye syndrome using quantitative lacrimal scintigraphy. ***Materials and Methods:*** We investigated 21 patients (42 eyes; 18 women, 3 men; mean age, 63.19 ± 13.33 years) with dry eye syndrome. Additionally, for the sake of comparison, 12 normal subjects of the same age group (24 eyes; 10 women, 2 men; mean age, 68.25 ± 2.63 years) were included. Lacrimal scintigraphy, Schirmer-1 test, BUT, and rose bengal ocular surface vital staining were performed in these cases. ***Results:*** According to the results of lacrimal scintigraphy, the mean value of T1/2 was 4.16 ± 1.22 minutes and the mean value of RI was 14.15% ± 2.30% in normal subjects. However, in patients with dry eye syndrome, these values were 20.59 ± 1.97 minutes and 55.64% ± 6.90%, respectively. Consistent with the results of ophthalmologic tests, the mean Schirmer-1 value was 12.46 ± 2.10 mm, the mean value of BUT was 14.36 ± 3.40 seconds, and the mean staining value of the rose bengal was 1.98 ± 0.80 in normal subjects, whereas these values were 1.36 ± 0.49 mm, 5.46 ± 1.33 seconds, 6.62 ± 0.86, respectively, in patients with dry eye syndrome. When we compared the results of lacrimal scintigraphy and the results of ophthalmologic tests, an inverse correlation was noted between both the T1/2 and RI values and both the Schirmer-1 and BUT values in all subjects ($p < 0.001$). However, there was a greater positive correlation between the rose bengal ocular surface staining value and both the T1/2 and RI values in all cases ($p < 0.001$). ***Conclusion:*** In the current study, it was concluded that although the lacrimal drainage system was normal, tear clearance was significantly delayed in dry eye patients. With this study, we have shown that quantitative lacrimal scintigraphy, which is an objective, practical, and noninvasive method, appears to be useful for the assessment of the tear clearance in patients with dry eye syndrome.

Key words: lacrimal scintigraphy, Tc-99m pertechnetate, tear clearance, dry eye syndrome.

INTRODUCTION

DRY EYE is a chronic disease in which an unstable tear film inadequately supports the health of the ocular surface epithelium. It affects 10% of the general population between the ages of 30 to 60 years. However, prevalence increases to 15% of people over 65 years.[1] Formerly, it was thought that a simple lack of tear production caused dry eye. But, later on, it was claimed that any abnormality in the ocular hydrodynamic system which includes tear distribution, evaporation and drainage leads to this condition as well as aqueous tear deficiency.[2]

The patients with dry eye typically complain of sensations of burning, grittiness, foreign body sensation and actual dryness. These symptoms are usually increased by wind, air condition, prolonged staring (reading or computer use) and other conditions that lead to a decrease in the blink rate or an increase in evaporation rate. Tearing, which is a paradoxical symptom, sometimes appears in patients with dry eye syndrome owing to reflex tearing. In patients with more severe dry eye, intermittent or

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continuous blurring of vision may arise due to damage in the central corneal epithelium as well as changes in the quality of tears.[3]

The diagnostic approach to patients with symptoms of dry eye is to carefully examine each portion of the anatomy that contributes to the tear film. Therefore, in this approach, the lids are evaluated for position, tone, blink rate, completeness of closure, and presence or absence of inflammation. Tear meniscus and conjunctiva are evaluated using slit-lamp examination to determine any abnormalities. The stability of tear film is assessed by the tear break-up time test (BUT). The corneal epithelial surface is evaluated by ocular surface vital staining test using rose bengal or fluorescein vital dye. Tear production is evaluated by Schirmer-1 test. The effects of chronic tear dysfunction are evaluated in a fine hazy scarring of the basement membrane and even the deeper Bowman's layer of the cornea. Tear osmolarity, corneal sensation, and conjunctival tissue may also be assessed in these patients.[3,4]

Additionally, the lacrimal gland ocular surface integrated unit, which is composed of the tear secretion by the lacrimal glands and ocular surface epithelia, fluid transudation through the conjunctiva, tear evaporation, tear drainage through the nasolacrimal system and corneal and conjunctival permeability, is evaluated. Since this unit regulates both tear production and the ocular hydrodynamic system, which play an important role in the pathogenesis of dry eye, this evaluation is essential not only to diagnose dry eye syndrome but also to evaluate the ocular surface and to assess the effectiveness of therapies in dry eye patients in the follow-up period. In order to evaluate the lacrimal gland ocular surface integrated unit globally, tear clearance measurement is performed.[4–10]

Clinically, a common way to measure the tear clearance is to judge the speed of disappearance from the ocular surface of exogenously added fluorescein. By introducing dye into the conjunctival sac and determining the rate at which its color fades, clinicians can measure tear secretion indirectly and tear drainage directly. To measure the clearance of fluorescein instilled into the tears, two main techniques are available. The first technique is a routine test that uses Schirmer test strips to collect fluorescein-stained tears and then to evaluate the strip visually. Although, this technique is simple and inexpensive, several problems, that can lead to inaccurate assessment of tear fluorescein concentration, occur. The first problem is that it is difficult to compare the color on the strip with photographic standards of liquid fluorescein of different concentrations. The second one is that the intensity of the fluorescein color on the strip is affected by the length of strip wetting. For example, a tear fluorescein concentration of 250 units appears different on a strip wet 4 mm than on a strip wet 30 mm. Moreover, it does not provide a quantitative measurement of the tear fluorescein concentration. In the other technique, the tear fluorescein concentration is measured using a fluorometer. However, it is not practical for routine use.[2,10–12] For these reasons, physicians need an accurate, more-practical, and objective methods to evaluate tear clearance.

Lacrimal scintigraphy is a noninvasive, more practical, safe, objective, and physiological method of evaluating patency of the lacrimal system. In addition to simple image enhancement, quantitative assessment of the rate of drainage and measurement of tear clearance can be obtained from each palpebral aperture. Although, lacrimal scintigraphy has been used to assess the tear dynamics in various eye diseases for more than 30 years,[13–15] as far as we know there has not been any study focusing in the tear clearance measurement using this technique in patients with dry eye syndrome until now.

The aim of this study was to evaluate the tear clearance in patients with dry eye syndrome using quantitative lacrimal scintigraphy.

MATERIALS AND METHODS

In this study, we investigated 42 eyes of 21 patients who had complained of dry eye symptoms and had been diagnosed with aqueous tear deficiency at Baskent University, Medical Faculty Department of Ophthalmology. Eighteen of the patients were females and 3 of the patients were males with a mean age of 63.19 ± 13.33 years. The mean duration of dry-eye symptoms was 3.4 ± 1.2 years in these patients. Patients with other systemic or ocular diseases that might change the ocular surface, or those with eyelid abnormalities, mechanical problems, history of previous drug use, contact lens use, punctal occlusion, the use of eye-drops (other than nonpreserved artificial tears), ocular surgery, or co-existence of severe blepharitis or meibomitis were excluded from the study.

In order to make a comparison, 12 normal subjects (24 eyes) of the same age group (10 women, 2 men; mean age, 68.25 ± 2.63 years) with no history of any eye disease, ocular surgery, use of eye drops, or symptoms of ocular irritation, and who had normal external eye examination were included.

All patients with dry eye syndrome and normal cases underwent lacrimal scintigraphy and ophthalmologic tests including Schirmer-1, BUT, and ocular surface vital staining using rose bengal.

This research was conducted by medically qualified personnel in strict accordance with the guidelines of the Baskent University Medical Faculty Institutional Review Board, regarding the Tenets of the Declaration of Helsinki. All patients and normal subjects were informed about the study protocol.

Lacrimal scintigraphy: Lacrimal scintigraphy was performed using a dual head gamma camera (e-Cam, Siemens, Germany) with a low-energy all-purpose collimator. All patients were seated in front of the collimator and were instructed to continue blinking and breathing

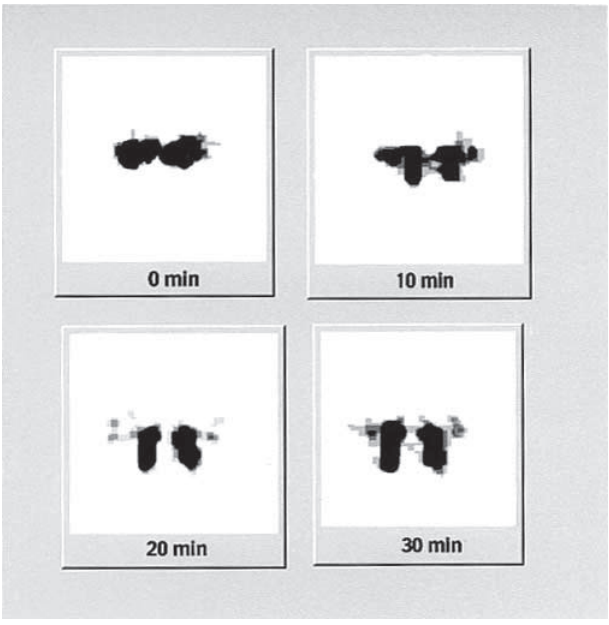

Fig. 1 Lacrimal scintigraphy in a normal subject.

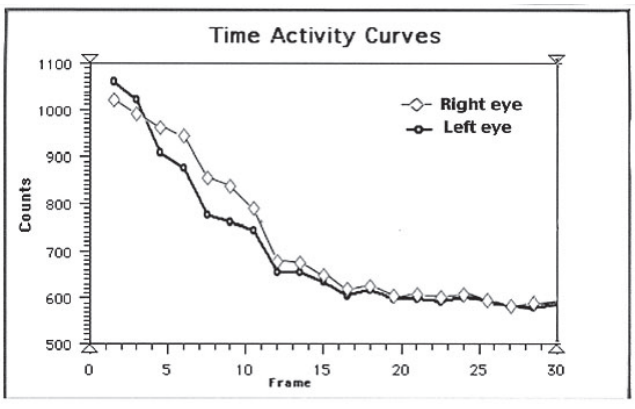

Fig. 2 Time-activity curves in the same case in Figure 1.

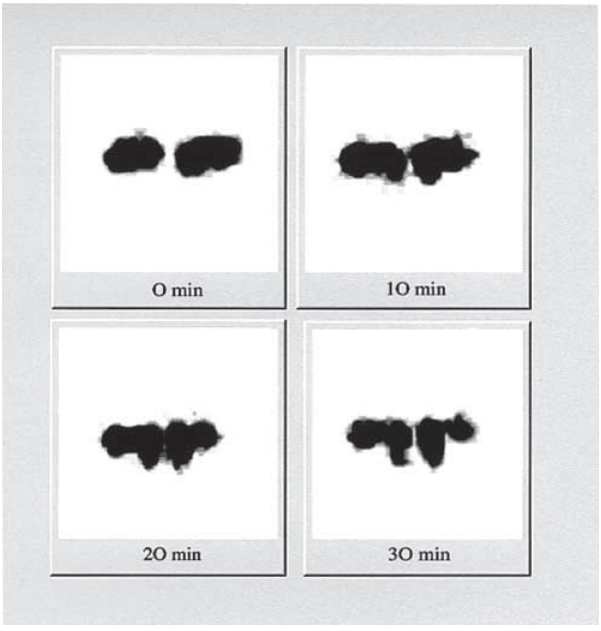

Fig. 3 Lacrimal scintigraphy in a patient with dry eye syndrome.

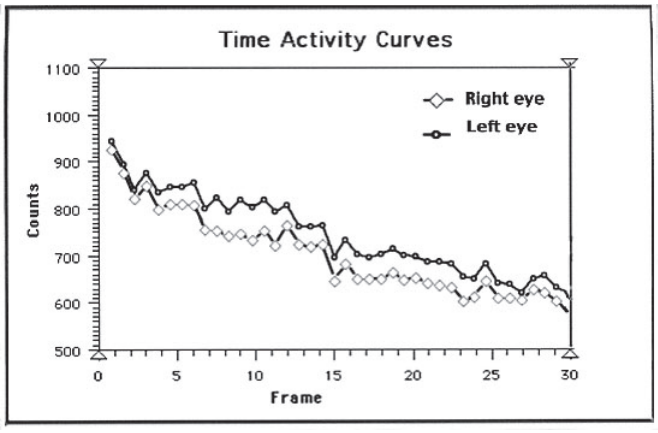

Fig. 4 Time-activity curves in the same patient in Figure 3.

normally while 7.4 MBq of Tc-99m pertechnetate in approximately 25 μl of isotonic saline was instilled with a pipette simultaneously into both eyes at the lateral canthi. Dynamic images of eyes were recorded every 30 seconds for 30 minutes using a 64 × 64 matrix. Images were then evaluated quantitatively. For quantitative analysis, one region of interest was defined on each side outlining the inner canthus of the palpebral aperture and counts were obtained. Using commercial software, these counts were corrected for decay of the radioisotope, and then a time-activity curve was obtained (Figs. 1–4). Values for half time of tear clearance (T1/2), which is the time to half of maximum activity from the palpebral aperture, and retention index (RI), which is the percentage of remaining activity on the ocular surface at the end of the dynamic study were calculated using this curve. To calculate these parameters, the radioactivity of the first frame was assumed to be 100% of the instilled dose.

BUT test: No topical anesthesia was administered. A drop of 2% sodium fluorescein solution was instilled with an eyedropper, and using the cobalt blue light of the slit-lamp, the time between the last blink and the first appearance of a dark spot was measured. This procedure was repeated 3 times, and the average value was recorded. A BUT value less than 10 seconds was considered abnormal.

Schirmer-1 test: One drop of 0.5% proparacaine hydrochloride was instilled in each eye for topical anesthesia. In a dimly lit room, a standard Schirmer strip (Alcon Laboratories, Fort Worth, Texas, USA) was placed in the inferolateral one third of the lower eyelid. Care was taken to prevent the paper from contacting the cornea. After 5

minutes, the level of strip wetting (in millimeters) was measured. A level greater than 5 mm was considered normal.[16]

Rose bengal ocular surface vital staining test: Rose bengal strips (Barnes-Hind, Akorn, Inc., Abita Springs, La., USA) were used by applying unpreserved saline to the impregnated strip and touching the wet strip to the inferior palpebral conjunctiva. As the dye may be irritating in the patient with dry eye, a drop of topical anesthetic was instilled before applying the dye. After 15 seconds, stained areas in the conjunctiva were examined by light passed through a green filter. Results were evaluated using a grading system developed by Van Bijsterveld.[17] According to this system, each eye was scored separately. Nasal bulbar conjunctival staining, temporal bulbar conjunctival staining, and corneal staining were graded on a four-tier scale: 0: no staining, 1: mild staining, 2: moderate staining, 3: extensive staining.

Statistical tests: One way analysis of variance (ANOVA) and Student t tests were used for the comparison of the results in dry eye patients with the normal subjects. Pearson test was used for correlations. All analyses were performed using the statistical package SPSS 11.5 for Windows, and a value for p less than 0.05 was considered statistically significant.

RESULTS

Results of lacrimal scintigraphy: In normal subjects, the variety of T1/2 values was 3–6 minutes and the mean value of this parameter was 4.16 ± 1.22 minutes. Additionally, in this group, the RI values were observed as 12–17% and the mean value of RI was 14.15% ± 2.30%.

On the other hand, in patients with dry eye syndrome, the range of T1/2 values was 16–25 minutes and the mean value of T1/2 was 20.59 ± 1.97 minutes. Furthermore, in these patients, the RI values were 40–69% and the mean value of RI was 55.64% ± 6.90% (Figs. 5–6).

In the statistical analysis, it was found that there was a significant difference between patients with dry eye syndrome and normal subjects with regard to values for T1/2 and RI ($p < 0.0001$). It was also found a positive correlation between the T1/2 values and the RI values in all dry eye patients and normal subjects ($p < 0.01$, $r = 1$).

Results of ophthalmologic tests: In normal subjects, the mean value of Schirmer-1 was 12.46 ± 2.10 mm. In these subjects, the mean value of BUT was 14.36 ± 3.40 seconds, the mean staining value of the rose bengal was 1.98 ± 0.80.

However, in patients with dry eye syndrome, the mean value of Schirmer-1 was 1.36 ± 0.49 mm, the mean value of BUT was 5.46 ± 1.33 seconds, and the mean value of the rose bengal staining was 6.62 ± 0.86.

There was a statistically significant difference between patients with dry eye syndrome and normal subjects with regard to the results of Schirmer-1, BUT, and rose bengal tests ($p < 0.0001$).

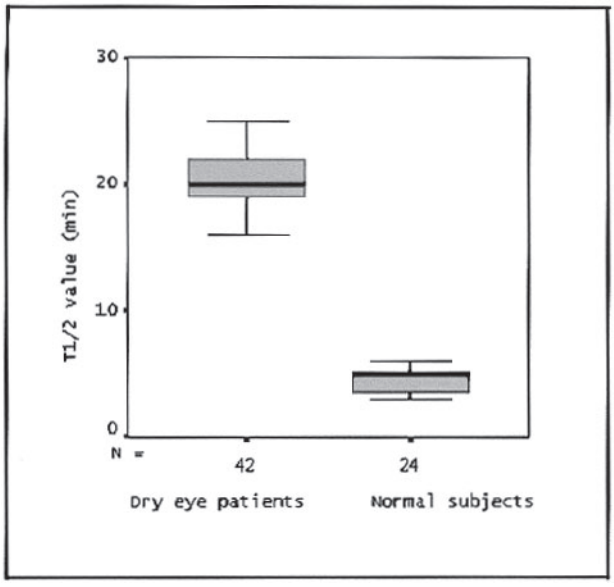

Fig. 5 The scatter of T1/2 values in dry eye patients and normal subjects.

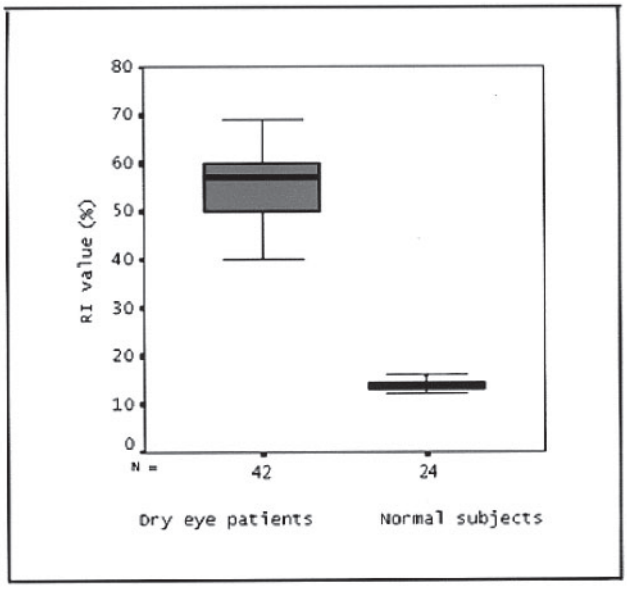

Fig. 6 The scatter of the values of RI in dry eye patients and normal subjects.

When we compared the results of lacrimal scintigraphy with the results of ophthalmological tests in dry eye patients and normal subjects, we found an inverse correlation between both the T1/2 and RI values and both the Schirmer-1 and BUT values in dry eye patients and normal subjects ($p < 0.001$, $r = -1$) whereas there was a greater positive correlation between the rose bengal ocular surface staining value and both the T1/2 and RI values in all cases ($p < 0.001$, $r = 1$).

DISCUSSION

Dry eye is a complicated ocular surface disorder. Previously, clinicians performed only traditional diagnostic tests such as BUT, the Schirmer-1, and ocular surface dye staining, to evaluate dry eye patients. Later on, they realized that an algorithm using many diagnostic tests was better for identifying a patient's eye condition than a single test alone. Many recent diagnostic tests have improved sensitivity and specificity over these conventional tests.[4,5]

One of these recent techniques is tear clearance measurement. Though this is a new method, it is performed routinely to evaluate dry eye patients in many centers, because it is a unique way to assess the integrity of the integrated lacrimal unit, globally and dynamically.[18,19]

Clinically, tear clearance is measured by the decay of the tear fluorescein concentration over time. It can be performed *in vivo* or in collected tears. Assessment of the tear fluorescein concentration is made with Schirmer's strips or a fluorometer. However, these two evaluation techniques have some disadvantages as mentioned above.[11,12] Because of these inconveniences, accurate, more practical, objective, and quantitative methods are needed to evaluate tear clearance.

Lacrimal scintigraphy which was first described in 1972 is a noninvasive, easy, quantitative, and physiologic method to assess the lacrimal system. Although, fine anatomic detail is not available as it is in contrast dacryocystography, physiological assessment is more accurate in scintigraphy because no instrumentation is necessary. Moreover, this method provides better contralateral comparison. Despite the fact that lacrimal scintigraphy has been used to evaluate the tear dynamics in different eye diseases for a long time,[13–15,20] there has not been much scintigraphic research about dry eye patients.

One of the scintigraphic studies was performed by Greaves et al.[21] They compared the precorneal residence of an artificial tear preparation in patients with dry eye and normal subjects using lacrimal scintigraphy. In their study, the artificial tear solution was radiolabeled with Tc-99m diethylenetriaminepentaacetic acid (DTPA). They found that precorneal clearance of the artificial tear solution was found to follow bi-exponential kinetics in all subjects with no significant differences in clearance kinetics between the two study populations. In a few other scintigraphic studies, investigators have performed similar research using various drugs which have been used to treat dry eye.[22–24]

Different from the studies above-mentioned, we used quantitative lacrimal scintigraphy to measure the tear clearance in patients with dry eye syndrome. In order to evaluate the tear clearance, we used T1/2 and RI parameters. We found that in all of the patients with dry eye, tear clearance from the palpebral aperture was significantly delayed when compared with normal subjects ($p < 0.0001$). In dry eye patients, the mean T1/2 value was 20.47 ± 2.21 minutes and the mean value of RI was 56.16% ± 9.20%. However, these values in normal subjects were 4.16 ± 1.22 minutes and 14.15% ± 2.30%, respectively.

We were not able to compare our results with those of other scintigraphic studies, since to our knowledge, this study is the first, related to this topic. Therefore, we compared our results with the results of clinical studies in which fluorescein dye disappearance technique was used for calculating tear clearance. Macri et al. measured fluorescein tear clearance in patients with dry eye syndrome and in healthy controls using a fluorometer.[12] In their study, the mean tear fluorescein clearance was 90.70 ± 63.30 optical density (OD) in healthy subjects. Conversely, this value was 3707 ± 4824 OD in patients with aqueous tear deficiency. They concluded that tear clearance delayed more in dry eye patients compared with healthy subjects ($p < 0.0001$). Sorbara et al. compared the tear clearance rate in dry eye patients and normal subjects using fluorescein dye disappearance technique.[25] They found that there was a statistically significant difference in the tear clearance rates between dry eye patients and normal subjects ($p < 0.0001$). This rate was 4.89 ± 2.74%/min in patients with dry eye syndrome whereas 11.85 ± 3.31%/min in normal cases. Other clinical studies have also shown similar results which correlated with our findings.[2,11]

In our study, we also compared the results of lacrimal scintigraphy with those of ophthalmological tests. An inverse correlation was observed between both the T1/2 and RI values and the Schirmer-1 value in dry eye patients and normal subjects ($p < 0.001$, $r = -1$). Like our results, in the other study which was carried out by Alfonso et al., they concluded that significantly higher tear fluorescein clearance and lower Schirmer-1 test values were found in dry eye patients than in normal subjects.[11] When our study and other clinical studies[5,11] were taken into consideration, it was concluded that the reason for delayed tear clearance in dry eye syndrome might be reduced tear volume.

When we compared the rose bengal staining value and both the T1/2 and RI values, we found that there was a positive correlation between the results of these parameters in all dry eye patients and normal subjects ($p < 0.001$, $r = 1$). This correlation was inverse between the BUT and both the T1/2 and RI values in all cases ($p < 0.001$, $r = -1$). We observed that in dry eye patients, high rose bengal staining value, low BUT value, and delayed tear clearance, all of which indicate the severity of ocular surface disease, coexisted.

Like our results, many clinical studies demonstrated that delayed tear clearance shows a positive correlation with the severity of corneal epithelial disease.[2,11,12] Macri et al. assessed the correlation between tear fluorescein clearance with irritation symptoms, ocular surface vital staining with fluorescein, corneal and conjunctival

sensitivity in normal cases and dry eye patients.[12] It was found that there was a positive correlation between the clearance and irritation symptoms, fluorescein staining values, corneal, conjunctival sensitivity scores in all patients ($p < 0.0001$). Tsubota et al. investigated the correlation between tear function tests and ocular surface integrity in dry eye patients.[26] They also observed a similar correlation between the results of tear clearance, BUT, ocular surface vital staining with rose bengal and fluorescein as we found ($p < 0.005$).

The exact mechanism by which reduced tear clearance from the ocular surface leads to corneal epithelial disease has not been established in dry eye patients; however, reduced tear clearance appears to promote ocular surface inflammation. As a result, accumulation of pro-inflammatory cytokines, proteolytic enzymes, and cytotoxic factors in the tear fluid develops. Two such factors whose concentrations have been found to increase as tear clearance decreases are the interleukin-1 and the matrix metalloproteinase MMP-9. Increased or uncontrolled activity of these factors is capable of initiating an inflammatory cascade on the ocular surface.[19,20] According to these studies mentioned above, it is considered that reduced tear clearance can be an indirect measure of inflammation on the ocular surface. This inflammation may escalate as retained inflammatory factors in the tear fluid recruit inflammatory cells onto the ocular surface and stimulate the production of additional inflammatory mediators by the ocular surface epithelia and infiltrating inflammatory cells.[22–24,26,27] This may change the treatment approach in these patients.

As a result, in this study, we demonstrated that tear clearance significantly decreased in patients with dry eye syndrome although the lacrimal drainage system was entirely normal. From the findings of this study, it can be concluded that quantitative lacrimal scintigraphy—an objective, practical, and noninvasive method—appears to be useful in the evaluation of tear clearance in patients with dry eye syndrome.

REFERENCES

1. Dursun D, Wang M, Monroy D, Li D, Lokeshwar BL, Stern ME, et al. A mouse model of keratoconjunctivitis sicca. *IOVS* 2002; 43 (3): 632–638.
2. Tsubota K. Tear dynamics and dry eye. *Retinal and Eye Research* 1998; 17 (4): 565–596.
3. Terry MA. Dry eye in the elderly. *Drugs and Aging* 2001; 18 (2): 101–107.
4. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye. *Cornea* 2000; 19 (5): 644–649.
5. Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing film disorders known to cause ocular irritation. *Cornea* 1998; 17: 38–56.
6. Gilbard JP, Farris RL, Santamaria IJ. Osmolarity of tear microvolumes in keratoconjunctivitis sicca. *Arch Ophthalmol* 1978; 96: 677–681.
7. McCollum CJ. Rapid assay of lactoferrin in keratoconjunctivitis sicca. *Cornea* 1994; 13: 505–508.
8. Danjo Y. Ocular surface damage and tear lactoferrin in dry-eye syndrome. *Acta Ophthalmol* 1994; 72: 433–437.
9. Yen MT, Pflugfelder SC, Feuer WJ. The effect of punctal occlusion on tear production, tear clearance, and ocular surface sensation in normal subjects. *Am J Ophthalmol* 2001; 131: 314–323.
10. Prabhasawat P, Tseng SCG. Frequent association of delayed tear clearance in ocular irritation. *Br J Ophthalmol* 1998; 82: 666–675.
11. Alfonso A, Monroy D, Stern ME, Feuer WJ, Tseng SCG, Pflugfelder SC. Correlation of tear fluorescein clearance and Schirmer test scores with ocular irritation symptoms. *Ophthalmol* 1999; 106 (4): 803–810.
12. Macri A, Ronaldo M, Pflugfelder S. A standardized visual scale for evaluation of tear fluorescein clearance. *Ophthalmol* 2000; 107 (7): 1338–1343.
13. Hurwitz JJ, Kirsch J. Nuclear lacrimal scanning. In: *The lacrimal system*, Hurwitz JJ (ed), Philadelphia; Lippincott-Raven, 1996: 73–81.
14. Kersten RC, Bartley GB. Evalution and management of the tearing patients. *Basic and Clinical Science Course* 1999–2000; 7: 231–255.
15. Amanat LA, Hildrict TE. Lacrimal scintigraphy: II. Its role in the diagnosis of epiphora. *Br J Ophthalmol* 1983; 67: 720–728.
16. Dursun D, Ertan A, Bilezikci B, Akova YA, Pelit A. Ocular surface changes in keratoconjunctivitis sicca with silicone punctum plug occlusion. *Current Eye Research* 2003; 26: 263–269.
17. Van Bijsterveld OP. Diagnostic tests in sicca syndrome. *Arch Ophthalmol* 1969; 82: 10–14.
18. O'Rourke J. Measurement of anterior chamber dynamic functions. In: *Nuclear ophthalmology dynamic function studies in intraocular disease*, Philadelphia; WB Saunders Company, 1976: 23–50.
19. de Paiva CS, Pflugfelder SC. Tear clearance implications for ocular surface health. *Exp Eye Res* 2004; 78: 395–397.
20. Heyman S, Katowitz JA. Dacryoscintigraphy. In: *Pediatric Nuclear Medicine* (2nd ed), Treves ST (ed), New York; Springer-Verlag, 1995: 121–134.
21. Greaves JL, Wilson CG, Galloway NR, Birmingham AT, Olejnik O. A comparison of the precorneal residence of an artificial tear preparation in patients with keratoconjunctivitis sicca and normal volunteer subjects using gamma scintigraphy. *Acta Ophthal* 1991; 69: 432–436.
22. Zhu Y, Wilson CG, Meadows D, Olejnik O, Frier M, Washington N, et al. Dry powder dosing in liquid vehicles: ocular tolerance and scintigraphic evaluation of a perfluorocarbon suspension. *Int J Pharm* 1999; 191 (2): 79–85.
23. Wilson CG, Zhu YP, Frier M, Rao LS, Gilchrist P, Perkins AC. Ocular contact time of a carbomer gel (GelTears) in humans. *Br J Ophthalmol* 1998; 82 (10): 1131–1134.
24. Snibson GR, Greaves JL, Soper ND, Prydal JI, Wilson CG, Bron AJ. Precorneal residence times of sodium hyaluronate solutions studied by quantitative gamma scintigraphy. *Eye* 1990; 4: 594–602.
25. Sorbara L, Simpson T, Vaccari S, Jones L, Fonn D. Tear

turnover rate is reduced in patients with symptomatic dry eye. *Contact Lens Anterior Eye* 2004; 27: 15–20.
26. Tsubota K, Kaido M, Yagi Y, Fujihara T, Shimmura S. Diseases associated with ocular surface abnormalities: the importance of reflex tearing. *Br J Ophthalmol* 1999; 83: 89–91.
27. Pflugfelder SC, Solomon A, Dursun D, Li D. Dry eye and delayed tear clearance: "A call to arms." *Adv Exper Med Biol* 2002; 506: 739–743.