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ORIGINAL ARTICLE

Investigation of dry eye parameters in patients with age-related macular degeneration undergoing repeated intravitreal injections

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Abstract

Purpose: This study aims to investigate the effects of repeated intravitreal injections on dry eye parameters in patients with age-related macular degeneration (AMD).

Methods: The study evaluated 139 eyes of 139 naive patients with neovascular AMD (nAMD) who received at least three intravitreal injections having normal break time and no fluorescein staining before the injections (Group 1) and 80 healthy control eyes of 80 individuals (Group 2). Patients with systemic conditions contributing to dry eye, fewer than three injections, a history of ocular surgery, pre-existing dry eye disease, or autoimmune diseases were excluded from the study. Ophthalmological examinations were conducted 1 month after the last injection, assessing meibomian gland loss, non-invasive tear break-up time, and corneal epithelial mapping, and compared with the control group. Data were analyzed using Jamovi statistical software, with a $p<0.05$ considered significant.

Results: Group 1 (139 patients, mean age 68.3±8.58 years) showed significant differences in lower eyelid meibomian gland atrophy, non-invasive tear break-up time, and corneal epithelial thickness in the inferior, inferior nasal, and inferior temporal regions compared to Group 2 (81 individuals, mean age 67.3±4.92 years). Correlation analysis revealed statistically significant relationships between the total number of injections and the percentage of atrophy of the lower eyelid meibomian glands ($p<0.001$), non-invasive tear break-up time ($p<0.001$), and corneal epithelial thickness in the inferior ($p=0.01$) and inferior nasal regions ($p=0.04$).

Conclusion: Repeated intravitreal injections in patients with nAMD are associated with significant atrophy of the lower eyelid meibomian glands, reduced non-invasive tear break-up time, and thinner inferior corneal epithelial thickness, suggesting a potential contribution to dry eye development. Clinicians should consider these findings to optimize treatment protocols and implement preventive measures to enhance ocular health in patients undergoing intravitreal therapy for AMD.

Keywords: Age-related macular degeneration; dry eye disease; intravitreal injections; meibomian gland atrophy; tear break-up time.

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Age-related macular degeneration (AMD) is one of the leading causes of vision loss among the elderly population worldwide.[1] This progressive ocular condition affects the macula, leading to a gradual decline in central vision. Neovascular AMD (nAMD) is a subtype characterized by the growth of new and abnormal blood vessels in the macular region. The advent of intravitreal injections, particularly with anti-vascular endothelial growth factor agents, has revolutionized the management of nAMD, providing significant improvements in visual acuity and quality of life.[2] Two treatment protocols are employed in intravitreal injection therapy. The "Treat and Extend" protocol involves administering injections at frequent intervals (typically monthly) for a specified initial period, with the interval between injections being gradually extended as the patient's condition stabilizes. The "Pro Re Nata" protocol involves administering intravitreal injections as needed based on disease activity.[3] The repetitive nature of these injections raises concerns about potential side effects on the ocular surface, particularly the development of dry eye disease.[4]

Dry eye disease is a multifactorial disorder characterized by the loss of tear film homeostasis and ocular surface inflammation. Symptoms can range from mild irritation and discomfort to severe ocular pain and visual disturbances, significantly impacting patients' daily activities and overall quality of life.[5] Given the chronic nature of AMD and the necessity for repeated intravitreal injections, it is crucial to understand the impact of these treatments on ocular surface health.

This study aims to investigate the effects of repeated intravitreal injections on dry eye parameters in patients with nAMD. By systematically evaluating various clinical indicators of dry eye disease, we aim to provide comprehensive insights into the prevalence and severity of dry eye in this patient population. Furthermore, understanding these relationships may guide clinicians in optimizing treatment protocols and implementing appropriate preventive measures to enhance the overall ocular health of patients undergoing intravitreal therapy for nAMD.

Materials and Methods

This study evaluated 139 eyes of 139 naive patients with a diagnosis of nAMD who received at least three intravitreal injections having normal break time and no fluorescein staining before the injections (Group 1), and 80 healthy eyes of 80 individuals (Group 2). Patients with systemic conditions such as diabetes that could contribute to dry eye, those who received fewer than three intravitreal injections, those with a history of ocular surgery, those with pre-existing dry eye disease, or any autoimmune diseases potentially associated with dry eye were excluded from the study. If both eyes of the individuals included in the study meet the inclusion and exclusion criteria, only the right eye was included in the study. To prevent endophthalmitis, povidone-iodine (PI) (10%) was applied to the ocular surface for 3 min before the injection, after which the ocular surface was washed and the injection was performed. A topical antibiotic (ofloxacin, 4 times daily) was administered for 1 week following the injection. Detailed ophthalmological examinations were conducted 1 month after the last injection for the patients included in the study. Post-injection parameters were measured 1 month after the last injection. Meibomian glands in the upper and lower eyelids were examined using Sirius (CSO, Florence, Italy). Meibomian gland loss was evaluated using a scoring system called meiboscore, which assessed gland loss as a percentage (Fig. 1). The evaluation of meibomian gland loss was performed by a masked researcher (M.K.). Non-invasive tear break-up time was measured in seconds using the same corneal topography device. (Fig. 2) Corneal epithelial mapping was assessed using optical coherence tomography (RTVue-XR, Optovue Inc., USA) (Fig. 3). Written informed consent was obtained from all participants, and approval was received from the Local Ethics Committee of Ankara Etlik City Hospital (No: AEŞH-EK1-2023-059). The study adhered to the principles of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using Jamovi statistical software version 2.3.26.0 (Internationally developed open-source project). After checking the distribution and variance of the data using

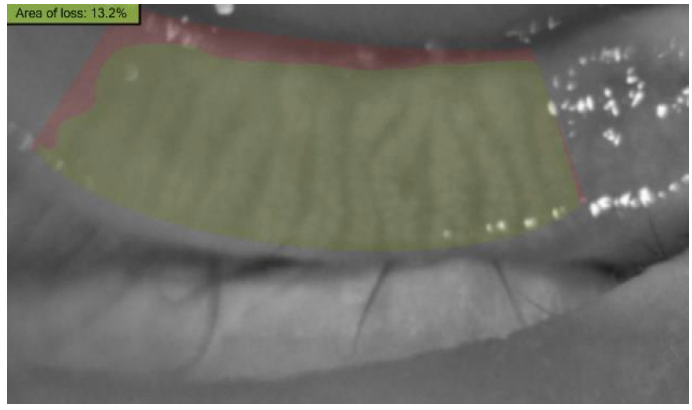

Fig. 1. Meibography image demonstrating the estimation of the meibomian gland atrophy percentage in the lower eyelid.

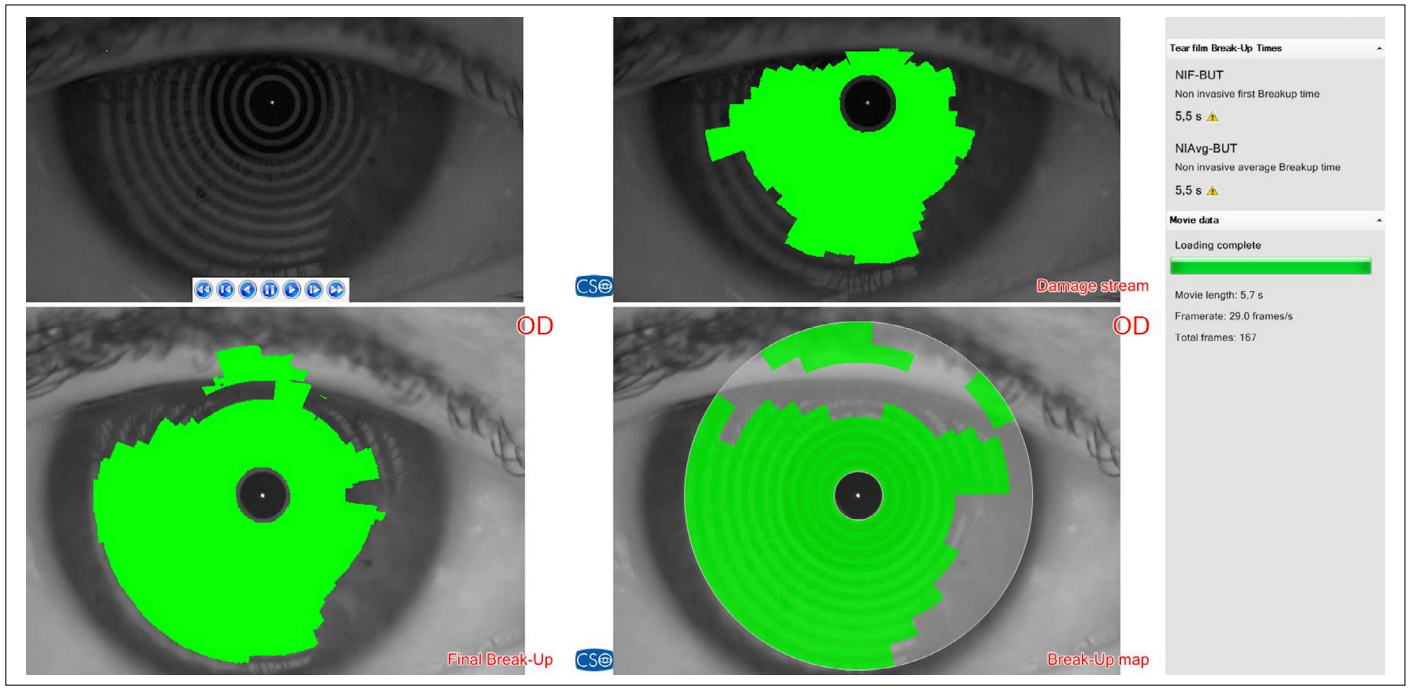

Fig. 2. The demonstration of the non-invasive break-up time calculation via corneal topography device.

the Shapiro–Wilk test and Levene's test, parametric data between the two groups were compared using Student's t-test or Mann–Whitney U test, while non-parametric data comparisons were made using the Chi-square test. Pearson correlation analysis was used for correlation analysis. A $p<0.05$ was considered statistically significant.

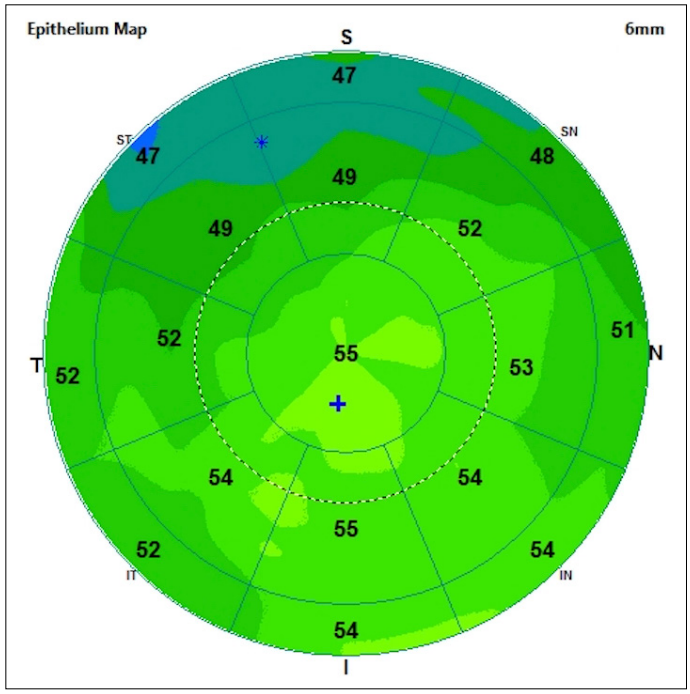

Fig. 3. The epithelial thickness map over the central cornea with a diameter of 6 mm measured by the optical coherence tomography device is shown.

Results

In the intravitreal injection group (Group 1), there were 139 patients with a mean age of 68.3±8.58 years (min: 50 years, max: 93 years) (76 males, 63 females). In the control group (Group 2), there were 81 individuals with a mean age of 67.3±4.92 years (min: 60 years, max: 84 years) (46 males, 35 females). There were no significant differences between the two groups in terms of mean age and gender distribution ($p=0.57$ and $p=0.76$, respectively). The average number of injections in Group 1 was 6.19±4.53 (minimum 3, maximum 28).

There were no significant differences between Group 1 and Group 2 in terms of pachymetry, percentage of atrophy of the upper eyelid meibomian glands, and corneal epithelial thickness in the superior, superior-nasal, superior temporal, nasal, temporal, and central regions ($p=0.21$, $p=0.30$, $p=0.58$, $p=0.12$, $p=0.15$, $p=0.09$, $p=0.11$, and $p=0.06$, respectively). However, there were statistically significant differences in the percentage of atrophy of the lower eyelid meibomian glands, non-invasive tear break-up time, and corneal epithelial thickness in the inferior, inferior nasal, and inferior temporal regions ($p=0.046$, $p=0.002$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively) (Table 1).

Correlation analysis showed statistically significant relationships between the total number of injections and the percentage of atrophy of the lower eyelid meibomian glands,

Table 1. Comparison of two groups regarding meibomian gland dysfunction percentage, non-invasive break-up time, pachymetry, and corneal epithelial thickness

	Group 1	Group 2	P
Pachymetry	533.33±33.78	543.47±84.66	0.21
NIBUT	6.99±3.33	8.89±4.34	0.002*
SMGD %	21.95±8.84	20.70±7.64	0.30
IMGD %	24.47±10.77	21.42±9.15	0.046*
CCET	54.08±4.09	54.47±1.90	0.06
NCET	52.97±3.42	52.86±1.54	0.09
TCET	52.37±3.44	52.49±1.75	0.11
SCET	51.53±2.52	51.72±2.35	0.58
SNCET	52.71±2.07	52.75±1.46	0.12
STCET	51.17±2.66	51.68±2.14	0.15
ICET	52.73±4.88	55.14±2.98	<0.001*
INCET	53.01±4.81	55.26±2.94	<0.001*
ITCET	52.47±5.07	54.69±3.04	<0.001*

NIBUT: Non-invasive break-up time; SMGD: Superior meibomian gland dysfunction; IMGD: Inferior meibomian gland dysfunction; CCET: Central corneal epithelial thickness; NCET: Nasal corneal epithelial thickness; TCET: Temporal corneal epithelial thickness; SCET: Superior corneal epithelial thickness; SNCET: Superior nasal corneal epithelial thickness; STCET: Superior temporal corneal epithelial thickness; ICET: Inferior corneal epithelial thickness; INCET: Inferior nasal corneal epithelial thickness; ITCET: Inferior temporal corneal epithelial thickness. *: Mann–Whitney U test.

Table 2. Correlation analysis between intravitreal injection numbers, dry eye parameters, and corneal epithelial thickness

	Number of total intravitreal injections
Non-invasive break-up time	
Pearson's r	−0.440
P	<0.001
Inferior meibomian gland dysfunction %	
Pearson's r	0.612
P	<0.001
Inferior corneal epithelial thickness	
Pearson's r	−0.213
P	0.01
Inferior nasal epithelial thickness	
Pearson's r	−0.173
P	0.04
Inferior temporal corneal epithelial thickness	
Pearson's r	−0.165
P	0.053

non-invasive tear break-up time, and corneal epithelial thickness in the inferior and inferior-nasal regions (p<0.001, p<0.001, p=0.01, and p=0.04, respectively) (Table 2).

Discussion

This study investigated the impact of repeated intravitreal injections on the development of dry eye in patients with nAMD. Our findings demonstrate that patients receiving intravitreal injections have significantly lower eyelid meibomian gland atrophy, shorter non-invasive tear break-up time, and thinner inferior corneal epithelial thickness compared to the control group. These results are consistent with previous studies reported by Laude et al.[6] and Kıyat et al.[4] Laude et al.[6] reported an increase in ocular surface disease and dry eye symptoms in a substantial portion of cases following intravitreal injections. Similarly, Kıyat et al.[4] found an increase in meibomian gland dysfunction and dry eye symptoms in patients with nAMD receiving intravitreal injections compared to the control group. The significant difference in lower eyelid meibomian gland atrophy and its correlation with injection frequency suggests that intravitreal injections may contribute to meibomian gland dysfunction. As known, meibomian gland dysfunction is a leading cause of evaporative dry eye disease.[7]

PI is an antiseptic widely used before intravitreal injections due to its broad-spectrum antimicrobial effects. PI applied to the ocular surface can disrupt the tear film, potentially shortening the tear break-up time. In a study involving patients undergoing repeated intraocular injections, repeated application of PI caused cytotoxic damage to the ocular surface, resulting in goblet cell loss and squamous metaplasia in epithelial cells.[8] The mucus layer is crucial for the stability of the tear film. Given these reported effects, it is conceivable that PI may exacerbate dry eye symptoms or worsen existing dry eye disease. Especially in patients exposed to repeated intravitreal injections, the cumulative effect of PI could increase the risk of dry eye. However, it remains unclear whether PI alone causes dry eye or to what extent it contributes to its development. Short-term applications of PI (e.g., pre-operative disinfection) have been shown not to cause significant dry eye symptoms, to markedly reduce conjunctival bacterial flora, and not to lead to long-term adverse effects on the ocular surface.[9] In experimental settings, PI has been found to cause temporary ocular surface changes, but these effects are usually reversible and do not indicate chronic dry eye development. For instance, short-term PI exposure in rabbit models did not result in long-term ocular surface damage.[10]

PI may cause meibomian gland dysfunction by damaging the cells within the glands or by occluding their ducts, leading to increased tear evaporation and dry eye symptoms. A study has found that repeated applications of PI and antibiotics resulted in the loss of meibomian

glands and deterioration in ocular surface parameters.[11] In cases where intravitreal injections were performed, there was a significant increase in the rate of meibomian gland loss in both the upper and lower eyelids and higher Ocular Surface Disease Index (OSDI) scores.[11] Given PI's effectiveness in reducing the risk of infection, its use during intravitreal injections is indispensable. However, measures can be taken to minimize the risk of developing dry eye. Studies have shown that lower concentrations of PI (e.g., 1% or 0.66%) may be as effective for pre-operative disinfection as higher concentrations (e.g., 5%) and are associated with fewer side effects.[10,12] After applying PI, it should be thoroughly rinsed with sterile saline. Post-injection, artificial tear drops can be used to support the tear film. Patients with risk factors for dry eye (e.g., those with a previous diagnosis of dry eye) should be closely monitored. Further research is needed to determine whether PI triggers dry eye or to what extent it contributes to its development.

Topical antibiotic drops used after injections and their preservatives, particularly with long-term use, may cause or exacerbate dry eye. Preservatives such as benzalkonium chloride in eye drops can disrupt the corneal epithelium and tear film, leading to dry eye symptoms and ocular surface damage. This includes increased corneal epithelial cell apoptosis and inflammation.[13] Datta et al. demonstrated that benzalkonium chloride causes mitochondrial dysfunction in human corneal epithelial cells and reduces the number of conjunctival goblet cells.[14] Research has shown that preservative-free eye drops are more effective than preserved drops in reducing eye inflammation and increasing antioxidant activity in tears. This leads to significant improvements in dry eye symptoms, tear film break-up time, and overall ocular surface health.[15] The use of topical antibiotic drops after injection, particularly in cases with risk factors (e.g., pre-existing dry eye, contact lens users, elderly patients), may increase the risk of dry eye. Prolonged use of antibiotic drops can further elevate the risk of dry eye by increasing exposure to preservatives.[15] Consequently, topical antibiotic drops and their preservatives can be factors that cause or exacerbate dry eye. Therefore, especially in at-risk patients, it is important to prefer preservative-free drops, use antibiotics for a short duration, and support with artificial tear drops.

In our study, a significant reduction in inferior corneal epithelial thickness was observed. We hypothesize that pre-operative PI and the accumulation of post-operative topical antibiotics predominantly in the lower fornix may contribute to the decrease in inferior epithelial thickness. There are articles in the literature investigating corneal epithelial thickness in dry eye patients with varying results.[16-18] In a study using Fourier-domain optical coherence tomography to assess corneal epithelial thickness in dry eye patients, the upper corneal epithelium was found to be thinner compared to healthy individuals, but no statistical difference was noted in central and inferior epithelial thickness.[16] The epithelial thickness profile in dry eye cases is more irregular compared to healthy individuals. The variance and range of epithelial thickness profiles are significantly higher in dry eye patients, and these parameters show a strong correlation with dry eye symptoms.[17] Liu and Pflugfelder found that central and mid-peripheral corneal thickness in dry eye patients was significantly reduced compared to healthy eyes.[18]

A key finding of our study is the significant relationship between the total number of injections and lower eyelid meibomian gland atrophy, non-invasive tear break-up time, and inferior corneal epithelial thickness. This finding suggests that repeated injections may have a cumulative effect and that a higher number of injections could be associated with more severe dry eye symptoms. The prevalence and severity of dry eye syndrome in postmenopausal women increase with age. For example, the prevalence of dry eye in women aged 66–70 was found to be 61.9%.[19] In addition, dry eye symptoms were observed to be more common and severe in postmenopausal women compared to premenopausal women.[20] Hormonal changes may affect tear film production and stability, leading to dry eye syndrome. In our study, women were the majority in both groups and the mean age was over 65. This may have influenced our results to show that dry eye is increasing. On the other hand, common risk factors for both nAMD and dry eye disease include aging, smoking, and systemic conditions such as obesity and high cholesterol levels.[21,22] These shared risk factors suggest a possible overlap in the etiology of both diseases. The association between nAMD and dry eye disease is underscored by shared mechanisms of oxidative stress, inflammation, and immune system involvement.[23]

Our study has some limitations. First, it is a retrospective study, which limits our ability to draw definitive conclusions about causality. Second, we did not assess dry eye symptoms but focused on objective measurements. Future studies should prospectively evaluate both dry eye symptoms and objective measures in larger cohorts. In addition, not examining dry eye parameters before injections is another limitation of our study.

Conclusion

This study suggests that repeated intravitreal injections may contribute to the development of dry eye in patients with nAMD. Developing strategies to prevent and manage dry eye in these patients is important.

Ethics Committee Approval: Written informed consent was obtained from all participants, and approval was received from the Local Ethics Committee of Ankara Etlik City Hospital (No: AEŞH-EK1-2023-059). The study adhered to the principles of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: B.K., S.I.K., M.K., A.S.D., O.C.; Design: B.B.K., S.I.K., M.K., A.S.D., O.C.; Supervision: B.K., S.I.K., M.K., A.S.D., O.C.; Resource: B.K., M.K.; Materials: B.K., M.K.; Data Collection and/or Processing: B.K., S.I.K., M.K.; Analysis and/or Interpretation: B.K., S.I.K., A.S.D.; Literature Search: B.K., S.I.K., M.K.; Writing: B.K., S.I.K.; Critical Reviews: B.K., S.I.K., A.S.D., O.C.

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