Changes in Ocular Surface and Corneal Epithelial Thickness with Systemic Isotretinoin Treatment

Sistemik İzotretinoin Tedavisinin Oküller Yüzey ve Kornea Epiteli Kalınlığı Üzerine Etkisi

Özet amaç: Sistemik izotretinoin tedavisi alan hastalarda ön segment optik koherens topografi (OS-OKT) ile mekere kornea epiteli kalınlığı (MKEK), göz filminde kornea epiteli kalınlığı (GYKEK) ve ortalama mekere korneal kalınlık (MKK) ölçülmesindeki değişimlerin değerlendirilmesi. Gereç ve Yöntemler: Sürekli nodülöz akne ve derin cilt enfeksiyon hastaları için izotretinoin tedavisine yanıt vermediğinde kullanılması önerilen ve FDA tarafından onaylanan izotretinoin, geniş bir mekere kornea epitheli kalınlığı (MKEK), göz filminde kornea epitheli kalınlığı (GYKEK) ve mekere korneal kalınlık (MKK) ölçülmesindeki değişimlerin değerlendirilmesi amaçlanmıştır. 

Metyhod: 17 kadın ve 15 erkek hastanın (64 göz) 1. ayda çıkartılan ölçümler kullanılarak, 2. ayda mekere kornea epitheli kalınlığı, göz filminde kornea epitheli kalınlığı ve ortalama mekere korneal kalınlık değerlerinin ortalamaları hesaplandı. 

Sonuç: Oral izotretinoin tedavisi, kornea epitheli kalınlığı ve orantılı optik koherens tomografi (OS-OKT) ile mekere kornea epitheli kalınlığı, göz filminde kornea epitheli kalınlığı ve ortalama mekere korneal kalınlık değerlerinin azaltılmasına yol açtı. 

Anahtar Kelimeler: Oral izotretinoin tedavisi; kornea epitheli kalınlığı; ortalama mekere korneal kalınlık; ortalama mekere korneal epitheli kalınlığı; göz filminde kornea epitheli kalınlığı; ortalama mekere korneal kalınlık; mekere korneal epitheli kalınlığı; posterokorneal epitheli kalınlığı; mekere korneal kalınlık.
mon side effects on the eye. These effects usually clear away after cessation of the drug.4

Optical coherence tomography (OCT) was applied to investigate the possible side effects of oral isotretinoin on the retinal nerve fiber layer and ganglion cell complex, previously.5-7 This device has been widely used for detecting many pathologies especially diseases affecting retinal layers and optic nerve in ophthalmology because it is non-invasive, non-contact, reliable and well-tolerated by patients. Anterior segment OCT (AS-OCT) has been used for ocular surface disorders, in recent years. Obtaining ‘optical biopsies’ of anterior segment lesions and different ocular surface are probable with this device.8 Corneal epithelial thickness (CET) can also be measured by AS-OCT and even the tear film layer might be distinguished in high resolution AS-OCT.9 The alterations in CET measured by AS-OCT according to dry eye disease were reported, previously.9,10 As mentioned above, oral intake of isotretinoin might cause dry eye disease (DED) and the effects of this drug on ocular surface had been investigated by using Schiempflug based topography and meibography devices.11-13

The purpose of this research was to assess the changes in central corneal epithelial (CET), tear film corneal epithelial thickness (TCET) and mean central corneal thicknesses (CCT) determined by AS-OCT. The alterations in CET measured by AS-OCT due to systemic isotretinoin use. Tear film break-up time (BUT), Schirmer test and ocular surface disease index (OSDI) score were also assessed as secondary objective of this study. For aught we know, this is the first research assessing the influence of systemic isotretinoin on corneal epithelial thickness measured by AS-OCT.

**MATERIAL AND METHODS**

This research was directed by the Ophthalmology and Dermatology Departments. First confirmation from the Institutional Review Board (71522473/050.01.04/117) was retrieved and informed consent was taken from all patient. This research was conducted according to the Declaration of Helsinki.

Patients who had severe nodulocystic acne disease and evaluated in our clinic prior to oral 0.5-1 mg/kg/day isotretinoin treatment were recruited in this current study. Patients who had the Meibomian gland disease, DED and other ocular surface diseases, previous ocular surgery were not included in this study. Besides, patients who used contact lenses within three months and especially had systemic autoimmune diseases were excluded. Complete ophthalmic evaluation, including best corrected visual acuity (BCVA), intraocular pressure (IOP) measurement by non-contact tonometer (Nidek, TONOREF II), slit-lamp biomicroscopic exam for anterior segment and fundus evaluation were made. Tear film BUT and Schirmer tests were performed. Patients were administered the OSDI questionnaire to evaluate DED-related symptoms. Then mean central CET, TCET and mean CCT were measured by using AS-OCT. This detailed examination was performed four times: prior to systemic isotretinoin intake, one month, three and six months after the initiation of treatment.

Tear film BUT was measured after a drop of 2% fluorescein was instilled. The time between the last blink and the appearance of dry spot was evaluated two times and the average value was obtained and recorded.14

Schirmer test was applied with a topical anesthetic agent (proparacaine HCl, Alcaine). Schirmer strips were inserted in the inferior fornix, and the patients closed their eyes for 5 minutes, then the wet part of the strip was read and noted.14

Cirrus enhanced depth imaging OCT (EDI-OCT, Carl Zeiss Meditec, Dublin, CA, USA) was performed to get high resolution anterior segment images. Images with signal strength of ≥8 were evaluated. The mean CCT and central CET were evaluated manually with the markers supplied by the AS-OCT software. The markers were located vertical to the ocular surface epithelium from a side just near the tear film (first hyperreflective layer) to the Bowman membrane (third hyperreflective layer) for measuring TCET and then they were placed from the second hyperreflective layer (the beginning of epithelium) to the third hyperreflective layer as Bowman membrane to measure central CET and finally the whole thickness of central cornea was measured. All measurements were performed manually by one
examiner (N.Ö.A) from five varied locations of every central image and the mean value was used for statistical analysis.

Statistical analysis was applied by SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). The variables were investigated using analytical methods (Shapiro-Wilk’s test) to determine whether or not they were normally distributed. Descriptive analyses were presented using mean and standard deviation for normally distributed variables. A one-way repeated measures ANOVA was conducted to compare the effect of systemic isotretinoin use on CET, TCET, CCT, tear film BUT, Schirmer test and OSDI score measurements prior to and first, third, sixth months of treatment. The significance level was evaluated as $\alpha = 0.05$.

**RESULTS**

Sixty four eyes of 17 female and 15 male subjects were recruited. The mean age of patients was 17.5 ± 2.3 years. The mean BCVA measured by Snellen chart was 0.9±0.02 decimal. The mean IOP was 16.8± 2.1 mm Hg.

The results of mean central TCET, CET and CCT were summarized in Table 2.

The mean CCT decreased gradually during the initial three months of the treatment and a rise was seen on the sixth month of treatment ($p= 0.001, p<0.001$).

The mean TCET did not change with the treatment on the following sixth months of treatment ($p= 0.154, p= 0.423$).

The mean central CET increased on the first month and decreased on the third month and increased again on the sixth month of the treatment ($p= 0.046, p= 0.006$).

The measurements of tear film BUT, Schirmer test and OSDI score outcomes were revealed in Table 1. Tear film BUT decreased gradually with isotretinoin treatment during initial six months ($p= 0.001$). The Schirmer test did not statistically change with treatment during six months ($p= 0.191$). The OSDI scores gradually increased during the initial six months ($p<0.001$).

| TABLE 1: | The mean tear film BUT, mean Schirmer test and the mean OSDI score values prior to treatment, in the first, third and sixth months of isotretinoin treatment. |
|----------|--------------------------------------------------------------------------------|
| Months   | Tear film BUT (second) | Schirmer test (mm) | OSDI Score |
| Prior    | 23.2±5.9 (*p=0.146)   | 28±7.8 (*p=0.110) | 6.3±2.2 (*p=0.633) |
| 1 month  | 16.5±5.6 (*p=0.068)   | 24.3±12.6 (*p=0.090) | 9.5±3.3 (*p=0.057) |
| 3 months | 12.2±6.3 (*p=0.057)   | 25.6±10.6 (*p=0.055) | 18.9±7.2 (*p=0.512) |
| 6 months | 8.7±7.3 (*p=0.063)    | 20.3±13.8 (*p=0.110) | 21.7±9 (*p=0.056) |

* Shapiro-Wilk’s test (Test of Normality).

| TABLE 2: | The mean CCT, mean TCET and the mean CET values prior to treatment, in the first, third and sixth months of isotretinoin treatment. |
|----------|--------------------------------------------------------------------------------|
| Months   | Mean CCT (µ) | Mean TCET (µ) | Mean CET (µ) |
| Prior    | 565.7±16.4 (*p=0.128) | 59.7±3.2 (*p=0.068) | 47±1.8 (*p=0.101) |
| 1 month  | 556.5±10.5 (*p=0.101) | 60.5±3.9 (*p=0.055) | 50.5±3.9 (*p=0.225) |
| 3 months | 554.5±11.6 (*p=0.125) | 57±2.1 (*p=0.078) | 46.5±3.3 (*p=0.168) |
| 6 months | 558.7±14.7 (*p=0.211) | 59.5±3.3 (*p=0.067) | 48±2.1 (*p=0.098) |

CCT: central corneal thickness; TCET: tear and corneal epithelial thickness; CET: corneal epithelial thickness.

*Shapiro-Wilk’s test (Test of Normality).
Table 3 revealed p values analyzed by using repeated measures of ANOVA test. According to these analyses, the mean tear film BUT was lower on the sixth month of treatment than prior to treatment. The change was mainly seen in the initial three months. The statistically significant change in the mean CCT was seen on the first month of the treatment (p= 0.004). The statistically significant alteration in the mean CET was seen in the initial three months.

**DISCUSSION**

In this current study, the effects of oral isotretinoin treatment on ocular surface were investigated. The mean CCT, TCET, CET values measured by AS-OCT were evaluated, in addition the mean tear film BUT, Schirmer test, OSDI scores were investigated. Egger had reported the decline in tear film BUT in most cases treated with oral isotretinoin. A pathological decrease of tear film BUT was realized in 69.1 % of patients.15 Karalezli et al. found that the mean tear film BUT and Schirmer test results decreased during oral isotretinoin treatment and OSDI scores, impression cytology scores increased with treatment.16 Polat et al. also found decrease in Schirmer test with treatment.17 In our study, the decline during the initial six months in tear film BUT and an increase in OSDI scores were observed. But the Schirmer test was not changed during treatment. In fact, we have already known that isotretinoin affects mainly sebaceous gland activity so the decline in tear film BUT and the stability of the Schirmer test might be expectable.2,3 The controversy with other reports might be explained by different sample sizes, dosage of the drug and different timing of Schirmer tests.

As mentioned above, studies investigated the effect of oral isotretinoin on impression cytology to find out changes in ocular surface. Karalezli et al. and de Queiroga et al. found alterations in conjunctival epithelium.16,18

A few study focused on the mean CCT and anterior segment changes with the treatment. Yuksel et al. obtained statistically significant difference in the mean CCT between baseline and at the sixth month of treatment.11 The mean CCT decreased gradually during the initial 6 months and correlated with meibomian gland disease score. Cumurcu et al. evaluated changes in anterior segment parameters as mean CCT, anterior chamber depth (ACD), anterior chamber angle (ACA), lens thickness (LT), pupil size and found statistically significant changes in mean CCT, ACD, LT and keratometric rates.13 Tear film osmolarity is also an important issue for DED and tear hyperosmolarity is in the definition of DED according to DEWS II report.19 Deinema et al. found decrease in CCT with increase in tear hyperosmolarity.20 In our study, the mean CCT was measured by AS-OCT and was found to decrease, especially in the first month of the treatment and continued to decline during six months of the treatment.

Both impression cytology and Schiempflug based corneal tomography provide detailed information about ocular surface. Therewithal, AS-OCT provides high resolution imaging. Kal et al. evaluated tear meniscus measured by AS-OCT in advanced renal failure subjects and thought that AS-OCT was useful for evaluating tear meniscus.21 El- Fayoumi et al. evaluated cornea and corneal epithelial thickness in addition to tear meniscus height in patients with rheumatoid arthritis and found thinner epithelial and corneal thicknesses in these patients.22 Çakır et al. found improvement in central corneal epithelial thickness measured by AS-OCT in dry eye patients.

| Table 3: Repeated measures of ANOVA test analysis results. Changes in tear film BUT, Schirmer tests, OSDI scores, mean CCT, TCET and CET values by months. |
|---|---|---|---|---|---|---|
| Months | BUT (p-value) | Schirmer (p-value) | OSDI (p-value) | Mean CCT (p-value) | Mean TCET (p-value) | Mean CET (p-value) |
| 0-1 months | 0.022 | 0.167 | <0.001 | 0.004 | 0.644 | 0.041 |
| 1-3 months | 0.023 | 0.460 | <0.001 | 0.086 | 0.058 | 0.010 |
| 3-6 months | 0.203 | 0.091 | <0.001 | 0.113 | 0.083 | 0.111 |
| 0-6 months | <0.001 | 0.079 | <0.001 | <0.001 | 0.423 | 0.006 |

BUT: break up time; OSDI: ocular surface disease index; CCT: central corneal thickness; TCET: tear and corneal epithelial thickness; CET: corneal epithelial thickness.
In conclusion, we have already known that the oral isotretinoin treatment might dry eye during the therapy. This current study revealed that this treatment might affect the mean CET and CCT measured by AS-OCT. Future studies performed with larger sample sizes and by using more sophisticated AS-OCT types would be more informative about this topic.

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**Conflict of Interest**
No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

**Authorship Contributions**

**Idea/Concept:** Nilgün Özkan Aksoy, Bahar Sevimli Dikicier; **Design:** Nilgün Özkan Aksoy, Bahar Sevimli Dikicier; **Control/Supervision:** Erkan Çelik; **Data Collection and/or Processing:** Nilgün Özkan Aksoy, Burçin Çakır, Bahar Sevimli Dikicier; **Analysis and/or Interpretation:** Nilgün Özkan Aksoy, Burçin Çakır; **Literature Review:** Nilgün Özkan Aksoy, Burçin Çakır, Bahar Sevimli Dikicier; **Writing the Article:** Nilgün Özkan Aksoy, Burçin Çakır, Bahar Sevimli Dikicier; **Critical Review:** Bahar Sevimli Dikicier, Erkan Çelik.

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