A Comparison of Corneal Biomechanical Properties of Chronic Smokers and Non-Smokers Using the Ocular Response Analyzer

Abstract

We compared the biomechanical properties of corneas in eyes of healthy chronic smokers and non-smokers. In this prospective, comparative, and cross-sectional study, 50 eyes of 50 healthy chronic smokers (Study group) and 50 eyes of 50 age-matched, healthy non-smokers (Control group) were enrolled. The corneal hysteresis (CH) and corneal resistance factor (CRF) were measured into two groups using the Ocular Response Analyzer (ORA). Differences in the corneal biomechanical properties were determined using an independent-samples t test. Urine samples were collected to measure urinary levels of cotinine. Correlations between the number of cigarettes smoked per day, smoking duration, age, and CH-CRF values in the smokers group were also evaluated. Mean CH was 10.63±2.08 (SD) mmHg and 10.57±1.45 mmHg and the mean CRF was 10.53±1.81 mmHg and 10.27±1.77 mmHg in the smoker and control groups, respectively (p>0.05). CH and CRF were not correlated with the number of cigarettes smoked per day, smoking duration, or age. The findings indicate that cigarette smoking does not affect corneal biomechanical parameters such as CH and CRF. In addition, CH and CRF are not affected by the number of cigarettes smoked per day, smoking duration, or age.

Keywords

Cigarette Smoking; Corneal Hysteresis; Corneal Resistance Factor; Chronic Smoking; ORA

Abbreviations

ORA: Ocular Response Analyzer; CH: Corneal Hysteresis; CRF: Corneal Resistance Factor; IOPcc: Corneal-compensated IOP; IOPg: Goldmann-related Intraocular Pressure; IOP: Intraocular Pressure; CCT: Central Corneal Thickness; AL: Axial Length

Introduction

Chronic smoking has negative effects on the ocular surface; chronic smokers had lower Schirmer scores in the corneas [1], a higher degree of squamous metaplasia [2,3], a higher grade of lipid layer changes in tears [3], and lower tear film break-up time compared with non-smokers [1-4]. Smoking also affects tear secretion and protein components in tears [5,6]. Furthermore, cigarette smoking may be harmful to the corneal endothelium. In our previous study, we found a significant decrease in the percentage of hexagonal cells in chronic smokers [1]. In addition to these findings, another study showed that smoking may inhibit or suppress the triggering factors of keratoconus and lead to a decreased rate or reduced severity of keratoconus [7]. All of these findings indicate that smoking influences biochemical processes and may change the biomechanics of the cornea.

The Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments) allows us to perform in vivo evaluation of corneal biomechanical parameters such as corneal hysteresis (CH) and corneal resistance factor (CRF), using a non-contact rapid air pulse. CH measures the viscous damping of the cornea, and CRF is most often associated with the viscous and elastic resistance inherent to the cornea [8,9]. Hafezi [10] reported that chronic smoking increases corneal rigidity in a statistically significant manner. However, this article will be the first to evaluate biomechanical properties in the corneas of chronic smokers by distinguishing objectively between smokers and nonsmokers. Thus, the purpose of the present study was to investigate the effects of chronic cigarette smoking on the corneal biomechanical parameters of healthy chronic smokers and non-smokers using the ORA.

Material and Methods

Study Design

This prospective and comparative study was carried out at the Ophthalmology Department at Istanbul Kanuni Sultan Suleyman Education and Research Hospital. The research adhered to the tenets of the Declaration of Helsinki, and a detailed written informed consent was taken before each individual's participation in the study.

Subjects

Included in the study group were 50 eyes of 50 healthy chronic smokers who had been smoking at least 30 cigarettes per day for at least 10 years and had no other systemic or ocular disease. As a control group, 50 eyes of 50 age-matched, healthy non-smokers were studied. None of the control subjects had actively smoked cigarettes or had a history of passive smoke exposure at home or at work in the current study.
Study participants with any of the following conditions were excluded from the study: a best-corrected visual acuity less than 20/20, history of contact lens use, use of any eye medications, past ocular surgery, or laser therapy, specific occupations associated with dry eye, high refractive errors, and systemic diseases such as diabetes mellitus and hypertension.

**Urinary Cotinine Concentration**

To distinguish objectively between smokers and nonsmokers, it was necessary to determine the level of cotinine in the urine. Cotinine, the major metabolite of nicotine, has a half life of 24 hours and is readily detectable in the smoker's urine even several days after the smoker has terminated smoking. Urine samples were collected in clean plastic containers to measure urinary levels of cotinine [11], and the basic technique used was based on spectrophotometric assessment at wavelength 532 nm. Laboratory workups were performed in the laboratory of the Kanuni Sultan Suleyman Education and Research Hospital. The influence of diuresis on urinary cotinine concentrations was corrected using the method described by Thompson [12]. Jatlow [13] have suggested the usefulness of urinary cotinine as an objective validation of the history of smoking.

**Examination Protocol and Measurements**

All participants underwent a detailed ophthalmologic examination including the following: spheric equivalent, best-corrected visual acuity, slit lamp examination, IOP measurement using pneumotonometer, dilated fundus examination, central corneal thickness (CCT) measurement with ultrason pachymetry, and axial length (AL) measurements with the ultrasonic axial scan. After a complete ophthalmologic examination, patients with a suspicion of corneal disorder such as early keratoconus were examined, and corneal topography measurements were performed to exclude any form of keratoconus.

The corneal biomechanical parameters were measured by an experienced clinician using Reichert Ocular Response Analyzer Software 3.01 while the patient was sitting comfortably in a chair located in a special room. Three replicate measurements with ORA were acquired for each eye. If poor-quality waveforms were located in a special room. Three replicate measurements with ORA were acquired for each eye. If poor-quality waveforms were obtained, they were deleted, and a new measurement was taken and the mean values of each parameter were used for statistical analysis. The clinician was masked in terms of study group. All measurements were performed between 9:00 am and 12:00 pm to avoid diurnal variations.

**Statistical Analysis**

All statistical tests were performed using SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 16. The normality of the data was confirmed using the Kolmogorov-Smirnov test (p>0.05). Independent Student t test was used to compare variables between groups. Correlations between mean level of CH· CRF values and mean level of the other ocular factors were evaluated by Pearson's correlation. A p value of <0.05 was considered significant.

## Results and Discussion

### Demographic Findings

In this study, 50 eyes of 50 healthy chronic smokers admitted to our department were included. As a control group, 50 eyes of 50 age-matched, healthy non-smokers were included. The mean ± SD age of the included subjects was 36.28±5.91 years (range 28-48) and 35.02±5.83 years (range 27-49 years) for the smokers group and the non-smokers group, respectively (p >0.05). On average, smokers smoked 16.70±8.00 (range 10-30) cigarettes per day and had been smoking for 12.20±3.01 (range 10-20) years. The characteristics of the two groups of subjects are shown in (Table 1). There were no statistically significant differences between the two groups with regard to gender, AL, and CCT distributions (p>0.05).

Cotinine levels in the urine were 44.2±9.8 ng/ml in non-smokers and 2439±451 ng/ml in smokers (p<0.05). These data clearly indicate that the smokers were accurately selected, because the urine cotinine concentration in nonsmokers is normally below 500 ng/ml [14].

### Biomechanical Parameters (CH and CRF)

Table 2 shows the comparison of mean ORA measurements in smokers and non-smokers groups. Mean CH and CRF values

### Table 1: The demographic and clinical characteristics of participants.

|          | *Smokers* | *Non-smokers* | *P-Value* |
|----------|-----------|---------------|-----------|
| Eyes, n  | 50/50     | 50/50         |           |
| Gender, n| Female    | Male          |           |
| Age, years| Mean±SD   | Mean±SD       | p-Value   |
|          | Range     | Range         |           |
| Spherical equivalent, D | Mean±SD     | Mean±SD       | p-Value   |
|          | Range     | Range         |           |
| Axial length, mm| Mean±SD    | Mean±SD       | p-Value   |
|          | Range     | Range         |           |
| CCT, µm  | Mean±SD   | Mean±SD       | p-Value   |
|          | Range     | Range         |           |
| Cotinine, ng/mL| Mean±SD | Mean±SD       | p-Value   |
|          | Range     | Range         |           |

n: Number of Eyes; AL: Axial Length; CCT: Central Corneal Thickness; SD: Standard Deviation; D: Diopter; *: Independent Student t test

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in the eyes of chronic smokers were not significantly different from those in age-matched non-smokers (p > 0.05). The IOPg and IOPcc, which were measured with ORA, did not differ between the smokers and non-smokers (p > 0.05).

Correlation Analyses

A correlation analysis was performed between the number of cigarettes smoked per day, smoking duration, age, and ORA parameters in the smokers group. The CH and CRF values were not associated with the number of cigarettes smoked per day, smoking duration, or age (Table 3). There is a strong relationship between smoking and a number of common eye diseases. Ophthalmologic disorders associated with cigarette smoking include cataract, age-related macular degeneration, retinal ischemia, glaucoma, anterior ischemic optic neuropathy, Graves’ ophthalmopathy, and tobacco-alcohol amblyopia [15-16].

Cigarettes contain a number of heavy metals and toxic chemicals that may have many adverse effects on several organs, including the eye [17]. Furthermore, some of these substances may have an influence on the cornea via their effects on collagen stability. Baker showed that formaldehyde which is a main toxic product of cigarette smoke, increases collagen cross-linking [18].

Cigarette smoking is associated with a higher prevalence of nuclear cataract [19]. Smoking also leads to a protein modification in the human lens and accelerates cataract development [19-21]. Recently, another link was found between smoking and hyperopia [22]. All of these demonstrate that smoking influences biochemical processes and may change the biomechanics of the cornea [2].

A previous study showed that cigarette smoke contains glyco-toxins, which are highly reactive glycation products that can rapidly induce the formation of advanced glycosylation end-products (AGEs) on proteins in vitro and in vivo and cause DNA mutations in vitro [23]. However, during cigarette smoking, nitrogen oxides and nitrite are released at a high level, which also may increase collagen cross-links [24-25].

Table 2: Comparison of mean ORA measurements in smokers and non-smokers groups.

| Variable | Smokers | Non-smokers | p-value* |
|----------|---------|-------------|----------|
| CH, mmHg | 10.63±2.08 | 10.57±1.45 | 0.864 |
| MeanzSD  | 5.70-16.30 | 7.60-13.60 | 0.864 |
| CRF, mmHg| 10.53±1.81 | 10.27±1.77 | 0.473 |
| MeanzSD  | 7.80-14.90 | 6.60-13.40 | 0.473 |
| IOPg, mmHg| 15.92±3.46 | 15.29±3.33 | 0.354 |
| MeanzSD  | 8.00-23.80 | 11.00-25.50 | 0.354 |
| IOPcc, mmHg| 14.61±3.15 | 13.95±2.97 | 0.289 |
| MeanzSD  | 8.70-21.80 | 9.30-21.10 | 0.289 |

CH: Corneal Hysteresis; CRF: Corneal Resistance Factor; IOPcc: Corneal-Compensated IOP; IOPg: Goldmann-Related Intraocular Pressure; ORA: Ocular Response Analyzer; SD: Standard Deviation; *: Independent Student t test

Table 3: Results of correlation analyses for ORA measurements in chronic smokers

| Variable | Age (y) | Number of smoking (d) | Smoking duration (y) |
|----------|---------|-----------------------|---------------------|
| CH       | r       | p         | Age (y) | Number of smoking (d) | Smoking duration (y) |
|          | -0.068  | 0.637     | 0.189   | 0.189                 | 0.032               |
| CRF      | r       | p         | 0.005   | 0.974                 | 0.085               |
|          | 0.085   | 0.556     | 0.098   | 0.499                 |
| IOPg     | r       | p         | -0.070  | 0.631                 | -0.261              |
|          | 0.067   | -0.084    | 0.056   | 0.561                 |
| IOPcc    | r       | p         | -0.061  | 0.673                 | -0.085              |
|          | 0.558   | 0.000     | 0.997   | 0.032                 |

CH: Corneal Hysteresis; CRF: Corneal Resistance Factor; IOPcc: Corneal-Compensated IOP; IOPg: Goldmann-Related Intraocular Pressure; ORA: Ocular Response Analyzer; d: Day; y: Year; p: Pearson correlation test

Recently, an epidemiologic study showed that the by-products of cigarette smoke may lead to cross-linking of collagen, which in the cornea may prevent the development and progression of keratoconus [7]. However, in that study patients with keratoconus were aware of the disease and may have tried to maintain a healthy lifestyle, for example, without smoking. A weakness of the study is the lack of a population control. Hafezi [10] reported that the eyes of chronic smokers indicated significantly increased corneal rigidity. Cigarette smoking represents a source of AGEs, which act similarly to the sugar aldehydes in the formation of AGEs in diabetes [26-27]. Several previous studies have investigated the corneal biomechanical properties related to diabetes mellitus [28-31]. Kotecha et al. [28] reported that CRF was significantly greater in the eyes of diabetic patients, and that there were no significant differences in CH between patients with diabetes mellitus and those without diabetes mellitus. Goldich et al. [29] showed that CH and CRF in the eyes of those with diabetes were significantly higher than in those without diabetes. In contrast to these studies, Sahin [30] found that CH was significantly lower in diabetic patients, whereas CRF was not significantly different from that of control subjects. Kara [31] reported that diabetes mellitus does not affect corneal biomechanical parameters such as CH and CRF in children.

As mentioned above, there have been controversial studies published on corneal biomechanical changes and the literature includes only one study on the effects of chronic smoking on corneas using ORA [10]; however, there have been no studies of corneal biomechanical parameters in chronic smokers that have distinguished this group objectively from non-smokers. In our study, we investigated the corneal biomechanical parameters such as CH and CRF in chronic smokers by measuring the amount of cotinine in the urine. Our data suggest that no differences exist in corneal biomechanical properties between chronic smokers and non-smokers. We also found that CRF and CH values were not associated with the number of cigarettes smoked per day, smoking duration, or age of the smoker.

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Conclusion

The present study showed that the corneal biomechanical parameters such as CH and CRF of chronic smokers are similar to those of healthy non-smokers. The number of cigarettes smoked per day, smoking duration or age do not seem to be associated with CH and CRF in chronic smokers. From this point of view, further studies are needed to elucidate the exact relationship of CH and CRF to smoking and systemic diseases.

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