

# Changes in Corneal Biomechanical Properties Following Hemodialysis in Non-Diabetic End Stage Renal Disease

## Diyabetik Olmayan Son Dönem Böbrek Hastalığında Hemodiyaliz Sonrası Kornea Biyomekanik Özelliklerinde Görülen Değişiklikler

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### ABSTRACT

**Purpose:** The aim of this study was to evaluate changes in corneal biomechanical properties following hemodialysis using an ocular response analyzer (ORA) in non-diabetic end stage renal disease

**Materials and Methods:** We included one eye of 50 non-diabetic chronic renal failure patients (25 females and 25 males) with a mean age of  $56.94 \pm 9.95$  years (range 36-80 years) in this cross-sectional study. Corneal compensated intraocular pressure (IOPcc), corneal hysteresis (CH) and the corneal resistance factor (CRF) were measured for included the eye of each participant using an ORA before and after hemodialysis. Central corneal thickness (CCT), blood pressure, plasma osmolality and plasma colloid osmotic pressure were also measured before and after the hemodialysis session. A paired samples t-test and Pearson's correlation analysis were carried out for statistical analysis.

**Results:** The mean CCT, IOPcc, CH and CRF of the patients before hemodialysis were  $550.20 \pm 19.64$   $\mu$ m,  $16.84 \pm 3.20$  mmHg,  $10.68 \pm 2.41$  mmHg and  $11.36 \pm 2.50$  mmHg, respectively. The mean CCT, IOPcc, CH and CRF of the patients after hemodialysis were  $547.30 \pm 19.83$   $\mu$ m,  $15.61 \pm 2.77$  mmHg,  $11.38 \pm 2.91$  mmHg and  $11.37 \pm 2.96$  mmHg, respectively. The mean plasma osmolality, plasma colloid oncotic pressure and mean arterial pressure (MAP) of the patients before hemodialysis were  $309.12 \pm 9.10$  mOsm/L,  $23.86 \pm 1.49$  mmHg and  $99.74 \pm 12.84$  mmHg, respectively. The mean plasma osmolality, plasma colloid oncotic pressure and mean arterial pressure (MAP) of the patients after hemodialysis were  $293.74 \pm 8.82$  mOsm/L,  $28.72 \pm 2.19$  mmHg and  $87.53 \pm 10.98$  mmHg, respectively. Significant changes occurred in IOPcc, CH, mean arterial pressure, serum osmolality and plasma colloid oncotic pressure (p values of 0.006, 0.036, <0.001, <0.001 and <0.001, respectively). There was no significant difference in the CRF or CCT values before and after hemodialysis (p values of 0.980 and 0.084, respectively). There were significant moderate correlations between differences in IOPcc and CH ( $r = -0.369$ ,  $p = 0.008$ ) and MAP and CH ( $r = 0.355$ ,  $p = 0.011$ ).

**Conclusion:** Hemodialysis did not alter CCT and CRF but caused a significant IOP decrease and CH increase in non-diabetic chronic renal failure patients that need be taken into account during the evaluation of IOP in hemodialysis patients.

**Key Words:** Corneal hysteresis, Corneal resistance factor, Hemodialysis, Intraocular pressure, Ocular response analyzer.

### ÖZ

**Amaç:** Diyabetik olmayan son dönem böbrek yetmezliği olan hastalarda oküler cevap analizörü kullanarak (OCA) hemodiyalizi takiben korneanın biyomekanik özelliklerinde görülen değişimleri değerlendirmek

**Gereç ve Yöntem:** Bu kesitsel çalışmaya ortalama yaşları  $56.94 \pm 9.95$  yıl olan 50 diyabetik olmayan kronik böbrek yetmezliği olan hastanın (25 erkek ve 25 kadın) tek gözleri dahil edildi. Korneal kompanse göz içi basıncı (GİBkk), korneal histerezis (KH) ve korneal direnç faktör (KDF) hemodiyaliz öncesi ve sonrası OCA kullanılarak ölçüldü. Aynı zamanda santral korneal kalınlık (SKK), kan basıncı, plazma osmolalitesi ve plazma kolloid onkotik basınç hemodiyaliz öncesi ve sonrası ölçüldü. İstatiksel analiz için eşleştirilmiş örneklem t-testi ve Pearson korelasyon analizi kullanıldı.

**Bulgular:** Hemodiyaliz öncesi hastaların ortalama SKK, GİBkk, KH ve KDF değerleri sırasıyla  $550.20 \pm 19.64$   $\mu$ m,  $16.84 \pm 3.20$  mmHg,  $10.68 \pm 2.41$  mmHg ve  $11.36 \pm 2.50$  mmHg, hemodiyaliz sonrası hastaların ortalama SKK, GİBkk, KH ve KDF değerleri sırasıyla  $547.30 \pm 19.83$   $\mu$ m,  $15.61 \pm 2.77$  mmHg,  $11.38 \pm 2.91$  mmHg ve  $11.37 \pm 2.96$  mmHg olarak ölçüldü. Hemodiyaliz öncesi hastaların ortalama plazma osmolalitesi, plazma kolloid onkotik basınç ve ortalama arteriyel basınç (OAB) değerleri sırasıyla  $309.12 \pm 9.10$  mOsm/L,  $23.86 \pm 1.49$  mmHg ve  $99.74 \pm 12.84$  mmHg, hemodiyaliz sonrası hastaların ortalama plazma osmolalitesi, plazma kolloid onkotik basınç ve OAB değerleri sırasıyla  $293.74 \pm 8.82$

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mOsm/L,  $28.72 \pm 2.19$  mmHg ve  $87.53 \pm 10.98$  mmHg olarak ölçüldü. GİBkk, KH, OAB, plazma osmolalitesi ve plazma kolloid onkotik basınçta önemli değişiklikler meydana geldi. (p değerleri sırasıyla, 0.006, 0.036, <0.001, <0.001 ve <0.001). Hemodiyaliz öncesi ve sonrası KDF ve SKK değerleri arasında önemli bir fark yoktu. (p değerleri sırasıyla, 0.980 ve 0.084). GİBkk ve KH ( $r = -0.369$ ,  $p = 0.008$ ) ve OAB ve KH ( $r = 0.355$ ,  $p = 0.011$ ) arasında önemli orta derecede ilişki mevcuttu.

**Sonuç:** Hemodiyaliz, GİB değerlendirilmesinde dikkate alınması gereken diyabetik olmayan son dönem kronik böbrek yetmezliği olan hemodiyaliz hastalarında SKK ve KDF'de değişikliğe neden olmamaktadır fakat önemli derecede GİBkk'da azalma, KH'de artışa sebep olmaktadır.

**Anahtar Kelimeler:** Korneal histerezis, Korneal direnç faktör, Hemodiyaliz, Göz içi basıncı, Oküler cevap analizörü.

## INTRODUCTION

Hemodialysis is an important and by far the most common treatment for end-stage renal failure. A wide range of ocular involvement in chronic renal failure patients treated with maintenance hemodialysis has been reported, including refractive changes, conjunctival calcium deposits, band keratopathy, dry eye, lenticular opacities and changes in intraocular pressure (IOP).<sup>1</sup>

Changes in IOP during or after hemodialysis have also been widely reported in the literature. The effects of hemodialysis on IOP are still unclear. However, various studies have reported different and conflicting findings; some indicate that IOP may increase,<sup>2,3</sup> while others indicate that it may decrease.<sup>4</sup> The two procedures in a hemodialysis session, ultrafiltration and dialysis, have opposing effects on IOP: dehydration tends to lower IOP, whereas a decrease in serum osmolality increases IOP.<sup>5</sup> Hemodialysis also induces a considerable change in central corneal thickness (CCT).<sup>6,7</sup>

The Goldmann applanation tonometer (GAT) is still the gold standard device for tonometry. However, GAT measurements are affected by central corneal thickness (CCT) and corneal rigidity.<sup>8</sup> The relationship between corneal biomechanical properties and IOP is even more important today due to the increasing number of refractive surgeries performed on corneal tissue, which can alter CCT and corneal biomechanical factors. New tonometry devices are being developed that are purportedly less affected by CCT and other corneal biomechanical properties.

The ocular response analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY/USA) measures corneal biomechanical factors and provides an IOP that is less affected by corneal properties. Corneal hysteresis (CH) is the direct measurement of the corneal biomechanical properties and therefore may represent the effect of corneal resistance on IOP measurements better than CCT alone.<sup>9</sup> Another corneal biomechanical property measured by the ORA is the corneal resistance factor (CRF), an indicator of overall corneal resistance. It has been reported that the corneal compensated IOP (IOPcc) is not affected by CRF. However, CRF has been reported to significantly correlate with CCT, and CH has been reported to have higher reproducibility

than CRF.<sup>10,11</sup> IOPcc and CH were constant throughout the day with no significant diurnal variation.<sup>12,13</sup> The corneal compensated intraocular pressure (IOPcc) is obtained from the difference between the 2 applanation pressures using the formula  $P2 - kP1$ , where P1 and P2 are the first and second applanation pressures, respectively, and k is a constant. As the difference between P1 and P2 is related to the corneal biomechanical properties, the value of IOPcc is intended to represent a measure of IOP that is free of corneal influence.<sup>14</sup>

Alterations in ocular parameters such as CH and CRF before and after hemodialysis have been studied in only one previous report, which primarily only focused on changes in IOP.<sup>15</sup> The current study was designed to evaluate IOPcc, CH and CRF before and after hemodialysis using the ORA and their relation with plasma osmolality, plasma colloid oncotic pressure and mean arterial pressure.

## MATERIALS AND METHODS

Fifty patients with chronic end-stage renal failure (stage 5: creatinine clearance <15 ml/min) who participated in the hemodialysis program of the Malatya State Hospital Hemodialysis Unit were included in this cross-sectional study. The exclusion criteria included the presence of the following: spherical and/or cylindrical refractive errors above  $\pm 3$  diopters, a narrow iridocorneal angle, corneal pathology, cataract affecting optical clarity, glaucoma, uveitis, prior ocular surgery, optic neuropathy and diabetic retinopathy. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of local ethic committee. All patients signed the informed consent form before the initiation of the study.

A detailed ophthalmologic examination including best corrected visual acuity and an anterior segment and fundus examination were performed for each patient. IOPcc, CH and CRF measurements were taken 30 min before and after hemodialysis by the ORA, and CCT was measured using an ultrasonic pachymeter that was attached to the ORA. The mean of three consecutive measurements was used for assessment. The measurements were performed before and after hemodialysis by the same physician.

Patients underwent uniform 4 h, high-flux hemodialysis

with total body heparinization. The blood pump speed was between 180-200 ml/min, and the dialysate flow rate was 500 ml/min. The dialysate contents were as follows: Na<sup>+</sup>, 140<sup>+</sup> mEq/l; K<sup>+</sup>, 2 mEq/l; Ca<sup>+</sup>, 2.5 mEq/l; Mg<sup>+</sup>, 1 mEq/l; and Cl<sup>-</sup>, 106.5 mEq/l. Plasma osmolality, plasma colloid oncotic pressure and mean arterial pressure were measured for each patient before and after hemodialysis. Plasma osmolality was calculated using the formula  $P_{osm} = Na^+ \times 2 + BUN / 2.8 + Glucose / 18$ . Plasma colloid osmotic pressure was calculated using the following formula: plasma colloid osmotic pressure = 5.5 X the concentration of plasma albumin + 1.4 X the concentration of plasma globulin. The mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

The data were analyzed using the SPSS statistical package, version 17.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to check the normality of the sample distribution. For general statistical reporting, the mean values of each data set were calculated with the SD. A paired samples t-test was used to compare the IOPcc, CH, CRF measurements before and after the hemodialysis session. The level of statistical significance was set at  $p < 0.05$ .

## RESULTS

Fifty patients [25 (50%) females and 25 (50%) males] with a mean of age  $56.94 \pm 9.95$  years participated in this study. Gonioscopy using a Goldmann three-mirror lens revealed that all of the patients had wide angles of grade 3 or higher.

The CCT, CH, CRF, IOPcc, plasma osmolality, plasma colloid oncotic pressure and mean arterial pressure values before and after hemodialysis are shown in Table 1. Significant changes were observed in CH, plasma osmolality, plasma colloid oncotic pressure and mean arterial pressure, but no significant change occurred in CCT or CRF (Table 1).

The mean differences and percent changes (%) for CH, CRF, CCT and IOPcc after hemodialysis were  $0.646 \pm 2.193$  mmHg (8.87%),  $0.324 \pm 2.787$  mmHg (3.28%),  $-2.90 \pm 11.566$   $\mu$ m (0.51%) and  $-1.086 \pm 3.053$  mmHg (5.39%), respectively. The mean differences (percentage) in mean arterial pressure, plasma osmolality and plasma colloid osmotic pressure after hemodialysis were  $-12.748 \pm 7.406$  mmHg (11.86%),  $-15.38 \pm 8.616$  mOsm/L (4.94%) and  $5.266 \pm 1.304$  mmHg (7.40%), respectively.

There were moderate but significant correlations between the percentage differences in CH and CRF ( $r = 0.579$ ,  $p < 0.001$ ), CH and IOPcc ( $r = -0.369$ ,  $p = 0.008$ ) and CH and MAP ( $r = 0.355$ ,  $p = 0.011$ ). However, we did not observe correlations between the percentage differences in CH, CRF, CCT, IOPcc, MAP, plasma osmolality or plasma colloid oncotic pressure [the range of r values was (-)0.245-263, and the range of p values was 0.065-0.996].

A linear regression analysis demonstrated a moderate and significant association between the percentage differences in CH and CRF [odds ratio (OR) = 0.410, 95% confidence interval (CI) 0.246–0.573;  $p < 0.001$ ].

**Table 1.** Effect of hemodialysis on the studied parameters of the patients.

Parameter	Mean	SD	Range	p*
IOPcc before HD (mmHg)	16.84	3.20	9.3-21.8	0.006
IOPcc after HD (mmHg)	15.61	2.77	9.3-20.9	
CCT before HD ( $\mu$ m)	550.20	19.64	510-590	0.084
CCT after HD ( $\mu$ m)	547.30	19.83	510-595	
CH before HD (mmHg)	10.68	2.41	6.4-15.9	0.036
CH after HD (mmHg)	11.36	2.50	7.4-16.8	
CRF before HD (mmHg)	11.38	2.91	6.7-17.3	0.980
CRF after HD (mmHg)	11.37	2.96	5.3-18.1	
Plasma osmolality before HD (mOsm/L)	309.12	9.10	298-325	<0.001
Plasma osmolality after HD (mOsm/L)	293.74	8.82	275-311	
MAP before HD (mmHg)	99.74	12.84	73-113	<0.001
MAP after HD (mmHg)	87.53	10.98	60-110	
PCOP before HD (mmHg)	23.86	1.49	21.1-26.9	<0.001
PCOP after HD (mmHg)	28.72	2.19	23.9-28.8	

\* Paired samples t-test

**CCT:** central corneal thickness, **CH:** corneal hysteresis, **CRF:** corneal resistance factor, **HD:** hemodialysis, **IOPcc:** corneal compensated intraocular pressure, **MAP:** mean arterial pressure, **PCOP:** plasma colloid oncotic pressure.

A linear regression analysis also demonstrated a weak but significant association between the percentage differences in CH and IOPcc (OR= -0.294, 95% CI, -0.439– -0.150;  $p < 0.001$ ).

## DISCUSSION

We demonstrated that significant changes occur in IOP and corneal biomechanical properties following hemodialysis in patients with chronic end-stage renal failure. Although the change in CCT that we observed was small (3  $\mu\text{m}$ ), this finding highlights the ability of hemodialysis to influence ocular rigidity as a biomechanical parameter, which is primarily dependent on the properties of the corneoscleral shell.

IOP is the most important known risk factor for glaucoma and is still the only parameter for which treatment has been demonstrated to decrease glaucoma progression. Corneal parameters, particularly CCT, affect IOP measurement.<sup>16</sup> In recent years, corneal biomechanical parameters and CCT have been shown to affect IOP measurements.<sup>14</sup> Congdon et al.<sup>16</sup> reported an association between glaucomatous damage and CH, and they stated that the progressive visual field could be associated with low hysteresis independently of CCT. It was shown that a lower CH is significantly associated with a smaller rim area and volume, a thinner retinal nerve fiber layer and a large linear cup-to-disc ratio, independent of disc size, corneal thickness, intraocular pressure and age.<sup>17</sup> Brown et al. reported that IOP measurement obtained using a self tonometer, similar to GAT, were more influenced by overall corneal biomechanics than CCT.<sup>18</sup> In the current study, despite the small change in CCT, there were significant changes in CH and IOPcc, which might support the assertion that CH is independent of CCT but is affected by IOP.

The use of ORA to assess corneal biomechanical properties was recently introduced. It allows for the measurement of IOP, CH and CRF. CH, which is calculated as the difference between the two pressure values at two applanation processes, is related to the viscoelastic behavior of the corneal tissue. The CRF, which is calculated as a linear function of the two pressures associated with the two applanation processes, is an indicator of overall corneal resistance.<sup>10</sup> Corneal biomechanical evaluation may be valuable for the preoperative screening of refractive surgery candidates, avoiding misinterpretation of the IOP and helping to differentiate between healthy and abnormal corneas.<sup>19,20</sup>

The ORA determines the biomechanical properties of the cornea during the rapid motion of the cornea in response to an air impulse and uses this information to adjust the IOP measurements. Previous investigations have demonstrated changes in corneal biomechanical properties, as assessed by

the ORA, in patients with keratoconus and Fuchs' corneal dystrophy after refractive procedures such as LASIK and in patients with diabetes mellitus.<sup>10,21</sup> With respect to corneal changes, some studies in chronic renal failure patients have revealed that CCT is not affected after hemodialysis.<sup>22,23</sup> Dinç et al.<sup>6</sup> demonstrated a significant decrease in CCT after hemodialysis and reported that corneal thickness measured using ultrasound pachymetry decreased significantly during hemodialysis; however, as in the current study, they also failed to demonstrate a significant correlation between the decreases in IOP and CCT.

There are conflicting reports about the effects of hemodialysis on IOP; some reports have shown an IOP increase,<sup>2</sup> some have shown an IOP decrease,<sup>4</sup> and some have shown no significant change in IOP.<sup>22</sup> Hemodialysis appears to have different and even opposing effects on IOP. Dehydration due to excess fluid loss following hemodialysis causes a decrease in IOP. However, reduction in serum osmolality causes an increase in IOP.<sup>5</sup> Hemodialysis treatments lasted around 4 hours so another factor about these conflicting results might be diurnal variation of IOP. However, it was reported that IOPcc and CH were constant throughout the day with no significant diurnal variation.<sup>12,13</sup> This suggests IOPcc might be more reliable parameter in hemodialysis patients especially with glaucoma.

To our knowledge, this study is the first that determine changes in corneal biomechanical properties before and after hemodialysis. In a previous study, CH and IOPcc values did not differ significantly after hemodialysis in a small group of end-stage renal disease patients.<sup>15</sup> The difference between the results of the studies could not be explained because only ocular parameters studied in the previous study despite the similarities between the study groups and the sample size of previous report might not be sufficient to determine the effect of hemodialysis on CH and IOPcc. In the current study, the mean IOPcc was found to decrease significantly after hemodialysis ( $p=0.006$ ), and the mean CH was found to increase significantly after hemodialysis ( $p=0.036$ ). We believe that increased plasma colloid osmotic pressure played a role in the IOP decrease or that the effect of increased plasma colloid osmotic pressure exceeded the effect of decreased plasma osmolality on IOP. We determined a weak but significant association between the percentage differences in CH and IOPcc. In agreement with our results, a previous study has reported a relationship between IOP and CH as well as a possible remodeling response of the cornea to IOP, which could affect CH.<sup>24</sup> The positive correlation between CH and MAP may be a factor for the change in biomechanical properties of cornea after hemodialysis. However, there was no statistically significant difference in CRF measurements before and after hemodialysis.

There were some limitations to this study. Due to similar age and ethnicity of the patients who underwent hemodialysis, the generalizability of these results to all CRF patients being treated with hemodialysis is tenuous.

In summary, this study revealed hemodialysis may induce changes in corneal biomechanical properties. After hemodialysis patients had lower IOPcc and higher CH levels. There was positive correlation between CH and MAP and this correlation may indicate change in blood pressure can be related to effect of hemodialysis on corneal biomechanical properties. Hemodialysis may induce changes in IOPcc and CH. Further research is required to fully determine the effect of hemodialysis on IOP and corneal biomechanical properties.

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