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CLINICAL STUDY

The changes in corneal biomechanical parameters after phototherapeutic keratectomy in eyes with granular corneal dystrophy

K Kamiya, K Shimizu and F Ohmoto

Abstract

Purpose **To assess corneal biomechanical changes in eyes undergoing phototherapeutic keratectomy (PTK) and to investigate the relationship of PTK with corneal thickness.**
Methods **We examined 36 eyes of 23 patients undergoing PTK for the treatment of granular corneal dystrophy (GCD). Corneal hysteresis (CH) and corneal resistance factor (CRF) were measured with an Ocular Response Analyzer™ before and 3 months after surgery. We also investigated the relationships between corneal biomechanical parameters and central corneal thickness before and after surgery.**
Results **The CH was significantly decreased from 10.2 ± 2.2 to 8.7 ± 1.8 mm Hg after PTK (Wilcoxon signed-rank test, $P < 0.001$), as was the CRF, from 10.3 ± 2.0 to 8.5 ± 1.8 mm Hg ($P < 0.001$). We found a significant correlation between both CH and CRF and the central corneal thickness before surgery (Pearson correlation coefficient $r = 0.37$, $P = 0.03$ for CH, $r = 0.51$, $P = 0.002$ for CRF) and 3 months after surgery ($r = 0.54$, $P = 0.001$ for CH, $r = 0.74$, $P < 0.001$ for CRF).**
Conclusions **PTK induces a significant decrease in the biomechanical parameters of the cornea. The corneal thickness may play some role in corneal biomechanics even in eyes with GCD.**
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Keywords: corneal biomechanics; corneal hysteresis; corneal resistance factor; corneal thickness; PTK

Department of Ophthalmology, University of Kitasato School of Medicine, Kanagawa, Japan

Correspondence: K Kamiya, Department of Ophthalmology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555, Japan
Tel: +81 42 778 9012;
Fax: +81 42 778 9920.
E-mail: kamiyak-tky@umin.ac.jp

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Introduction

The purpose of phototherapeutic keratectomy (PTK) is to remove diseased corneal tissue and increase corneal transparency by surgical laser photoablation. PTK as well as other excimer laser refractive surgery (eg, photorefractive keratectomy (PRK) and laser *in situ* keratomileusis (LASIK)) can affect the structural integrity of the cornea by the stromal tissue removal and loss of Bowman's membrane, and there is therefore, theoretically, a risk of corneal biomechanical weakening after both surgical procedures. Actually, it has been shown that the corneal biomechanical parameters were significantly decreased after LASIK.[1–3] Although PTK usually requires less laser ablation of the corneal stroma than is needed by other excimer laser surgery, the biomechanics of the cornea before PTK may have already been more affected by histopathological deformation than that of normal eyes before keratorefractive surgery. In addition, the presence of iatrogenic ectasia after PTK has also been documented.[4] Thus, it is of clinical importance to assess the corneal biomechanical changes after excimer laser surgery, but these have not so far been studied in the case of PTK. The purpose of this study is twofold: to quantitatively assess the biomechanical changes of the cornea in eyes with granular corneal dystrophy (GCD) that undergo PTK, and to investigate the relationship of the biomechanical parameters with the central corneal thickness in such eyes.

Materials and methods

We prospectively studied 36 eyes of 23 consecutive patients (male, 5; female, 18;

Table 1 Patient demographic data

	Demographic data
Age (years)	69.6 ± 6.8 (range, 52–81)
Sex (Male/Female)	5:18
Central cornea thickness (μm)	545.1 ± 41.0 (479–616)
Intraocular pressure (mm Hg)	15.8 ± 3.8 (range, 9–23)
Corneal hysteresis (mm Hg)	10.2 ± 2.2 (range, 6.2–15.6)
Corneal resistance factor (mm Hg)	10.3 ± 2.0 (range, 6.3–15.8)

69.6 ± 6.8 years of age, mean ± s.d.) (range, 52–81 years) undergoing PTK for the treatment of GCD. The central corneal thickness before PTK was 545.1 ± 41.0 μm (479–616 μm). The intraocular pressure was 15.8 ± 3.8 mm Hg (range, 9–23 mm Hg). Preoperative patient demographics are summarised in Table 1.

Phototherapeutic keratectomy was performed using the VISX Star S2 excimer laser system (VISX Inc., Santa Clara, CA, USA) with the following parameters: wavelength, 193 nm; fluency, 160 mJ/cm^2; repetition rate, 10 Hz; ablation zone diameter, 5.0 mm; transition zone, 0.5 mm; and ablation depth, 45–50 μm based on the clinical appearance of the depth of pathology from the preoperative slit-lamp evaluation. We used the transepithelial technique for corneal epithelium removal. Postoperatively, steroidal (0.1% fluorometholone, Flumetholone™ Santen, Osaka, Japan) and antibiotic (levofloxacin, Cravit™ Santen, Osaka, Japan) medications were topically administered four times daily for 1 week, together with a soft contact lens, with the dose being steadily reduced thereafter.

We also measured the biomechanical parameters of the cornea, namely, corneal hysteresis (CH) and corneal resistance factor (CRF), using the Ocular Response Analyzer™ (ORA: Reichert Ophthalmic Instruments, Depew, New York, USA) before and 3 months after surgery.[1] This device uses a rapid air impulse to deform the cornea, and the shape changes are monitored by an electro-optical system.[1] The air puff induces two applanations, inward and outward, of the cornea. The air deforms the cornea through an initial applanation event (peak 1), then beyond it into a concavity, and gradually subsides, allowing the cornea to rebound through a second applanation (peak 2). CH is calculated as difference between pressures (mm Hg) where the infra-red peaks 1 and 2 occur. The CRF is calculated as a linear function of P1 and P2, based on the results of a large-scale clinical data analysis, according to the manufacturer.[5] We carried out this measurement three times to ensure consistent signal quality and to look for consistent signal morphology and measurement values, and the average value was used for statistical analysis according to the manufacturer's instructions. The central corneal thickness was also measured using an ultrasound

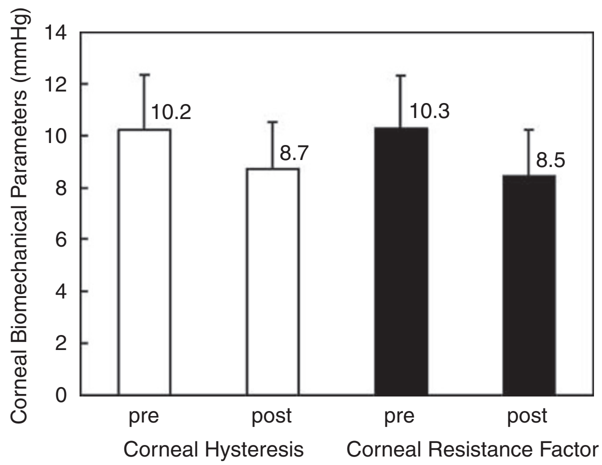

Figure 1 Graph showing a significant decrease in corneal hysteresis (CH) and corneal resistance factor (CRF) after phototherapeutic keratectomy (PTK) ($P < 0.001$, Wilcoxon signed-rank test). Bar represents SD.

pachymeter (DGH-500, DGH Technologies, Exton, USA) before and 3 months after surgery. Additionally, to assess the repeatability of the measurements of this device, we made three consecutive measurements of CH and CRF with this device in 18 eyes with granular dystrophy before surgery at the same time of day on 2 days. We evaluated the repeatability of the two measurements by Bland–Altman plots as described previously.[6] Informed consent was obtained from all patients. The study adhered to the tenets of the Declaration of Helsinki. Institutional review board approval was not required for this study, because the ORA has been widely used as a non-contact tonometer, which is considered to be a routine part of a postoperative examination in a clinical setting.

All statistical analyses were performed using StatView version 5.0 (SAS, Cary, USA). The results are expressed as mean ± SD, and a P-value of less than 0.05 was considered statistically significant.

Results

After PTK, the CH was decreased significantly from 10.2 ± 2.2 mm Hg (mean ± SD) (range, 6.2–15.6 mm Hg) to 8.7 ± 1.8 mm Hg (range, 5.1–13.8 mm Hg), (Wilcoxon signed-rank test, $P < 0.001$) (Figure 1); and the CRF also showed a significant decrease from 10.3 ± 2.0 mm Hg (range, 6.3–15.8 mm Hg) to 8.5 ± 1.8 mm Hg (range, 5.0–12.0 mm Hg) ($P < 0.001$) (Figure 1). The central corneal thickness was reduced significantly from 545.1 ± 41.0 μm (range, 479–616 μm) to 485.9 ± 46.0 μm (range, 423–591 μm) ($P < 0.001$). There were weak, but significant, correlations between CH and the central corneal thickness before (Pearson correlation coefficient

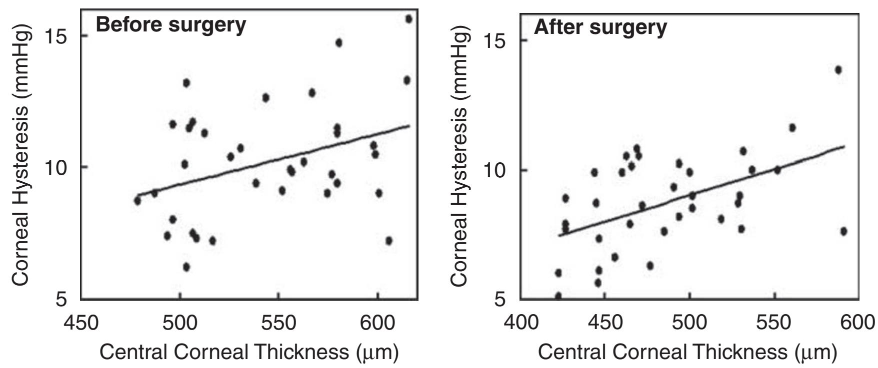

Figure 2 Scatter plot showing a weak, but significant correlation between corneal hysteresis (CH) and central corneal thickness before (Pearson correlation coefficient $r = 0.37$, $P = 0.03$) and 3 months after surgery ($r = 0.51$, $P = 0.002$).

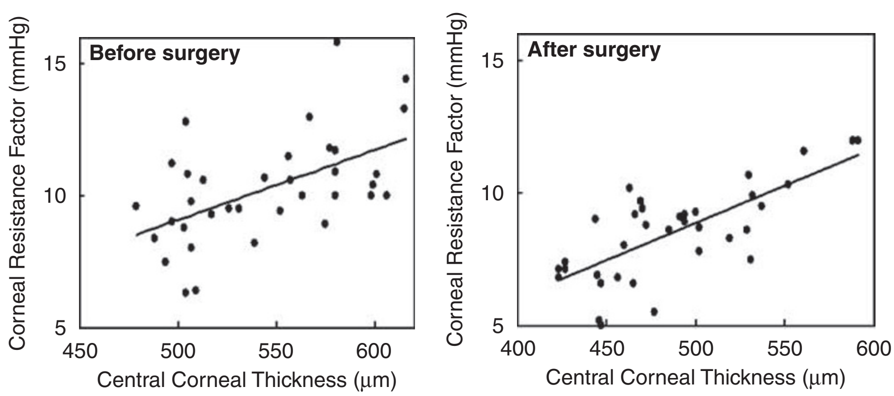

Figure 3 Scatter plot showing a modest significant correlation between corneal resistance factor (CRF) and central corneal thickness before (Pearson correlation coefficient $r = 0.54$, $P = 0.001$) and 3 months after surgery ($r = 0.74$, $P < 0.001$).

$r = 0.37$, $P = 0.03$) and 3 months after surgery ($r = 0.51$, $P = 0.002$) (Figure 2), and modest significant correlations between CRF and the central corneal thickness before ($r = 0.54$, $P = 0.001$) and 3 months after surgery ($r = 0.74$, $P < 0.001$) (Figure 3). There was no significant association between patient age and CH ($r = -0.11$, $P = 0.54$), or between age and CRF ($r = -0.21$, $P = 0.23$) before surgery. Iatrogenic keratectasia did not occur in any case during the observation period. Bland–Altman plots indicate that the mean difference between the two measurements with ORA ($\pm$95% limits of agreement; LoA) was 0.0 ± 0.7 mm Hg (-1.5 to 1.4 mm Hg) for CH, and 0.1 ± 0.7 mm Hg (-1.2 to 1.4 mm Hg) for CRF (Figure 4).

Discussion

In this study, we showed that PTK significantly decreased both CH and CRF, indicating that PTK, which requires surgical removal of the diseased cornea, may induce a significant reduction of the biomechanical characteristics of the cornea just as LASIK can.[1–3] To our knowledge, this is the first report to evaluate the biomechanical changes of the cornea after PTK. This assessment is clinically important for the dissemination of this surgical technique, especially in consideration of the occurrence of iatrogenic keratectasia in post-PTK eyes.[4] Moreover, both CH and CRF are significantly correlated with the central corneal thickness before and after PTK, suggesting that the preoperative and postoperative corneal thickness may play some role in these biomechanical characteristics of the cornea even in eyes with GCD. Our results also indicate that CRF may reflect the overall rigidity of the cornea, depending on CCT more correctly than CH does even in eyes with GCD, as evidenced by the higher correlation coefficient of CCT before and after PTK. With regard to CCT, Lu *et al*[7] showed that there was no significant correlation between CH and CCT induced by wearing soft contact lenses during eye closure. Kirwan *et al*[8] also stated that the lowest postoperative CH was recorded in an eye with a postoperative CCT of 517 μm, suggesting that factors in addition to CCT may play a role in corneal biomechanics. On the other hand, Lam *et al*[9] reported that CH was positively associated with CCT in normal eyes. Broman *et al*[10] showed that CH was significantly correlated with CCT with a modest correlation coefficient in patients

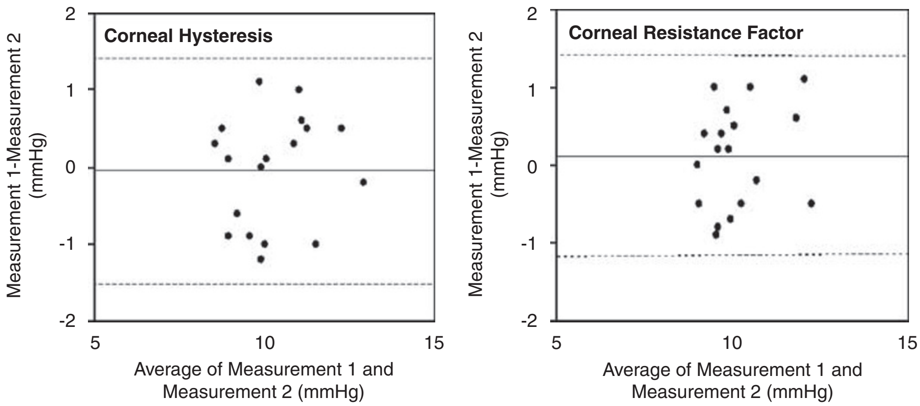

Figure 4 Bland–Altman plots represent the difference between two measurements divided by the mean between these measurements. The solid lines represent the mean differences of three consecutive measurements of corneal hysteresis (CH) and corneal resistance factor (CRF); the dotted lines, the upper and lower borders of the 95% limit of agreement (mean difference ± 1.96 multiplied by SD of the mean difference).

presenting at a glaucoma clinic. Shah *et al*[11] also showed that CH increased with increasing CCT in normal eyes, but the correlation was moderate. We have already shown that CCT was the most relevant factor affecting CH as well as CRF, suggesting that CCT may play an important role in the biomechanics of the cornea.[12]

The diseased cornea of granular dystrophy may affect the biomechanical strength of the cornea, possibly as a result of histopathological deterioration in the collagen lamellae[13] or in the Bowman's layer.[14] Szentmáry *et al*[13] reported that the collagen lamellae in the anterior stroma of eyes with granular dystrophy showed a rather irregular and loose architecture and were interspersed with small vascular inclusions between the collagen fibers. They also showed that Bowman's layer was absent in the laser-treated area, and that the architecture of the subepithelial stromal collagen lamellae was irregular.[13] Seitz *et al*[14] stated that the breaks of Bowman's layer were found in 68% of specimens with GCD. Miyata *et al*[4] first described a case of progressive corneal ectasia following PTK for the treatment of band keratopathy. They stated that it occurred even though the residual corneal thickness was greater than 500 μm, which, as the fully acceptable thickness, was usually deemed to avoid iatrogenic ectasia in normal eyes. Considering that the amount of laser ablation (45–50 μm) in PTK was smaller than that in other excimer laser surgery, such as PRK or LASIK, there is some possibility that the biomechanical strength of the cornea may have already been weakened by histopathological deformation. However, this assumption may be contradicted by the results of our present and previous studies that showed that the preoperative biomechanical properties of eyes with GCD (10.2 ± 2.2 mm Hg for CH, 10.3 ± 2.0 mm Hg for CRF, 545.1 ± 41.0 μm) are very similar to those of normal eyes having similar corneal thickness (10.2 ± 1.3 mm Hg for CH, 10.2 ± 1.7 mm Hg for CRF, 540.4 ± 31.0 μm).[12] Our findings may support the view that the biomechanical parameters of GCD are not influenced by its histopathological deformation. We need further investigations to confirm whether or not its deformation may influence the biomechanical characteristics.

In this study, we found no significant association between patient age and biomechanical parameters in eyes with GCD, possibly because of the small sample size ($n = 36$) and the narrow range of patient ages (from 52 to 81 years). We have already demonstrated that the eyes of older volunteers have shown a tendency to have a lower CH value.[12] Moreover, Kotecha *et al*[15] reported in a study of patients attending the Glaucoma Research Unit that CH was dependent on age. Ortiz *et al*[2] also reported that the CH value was lower in older eyes, and the difference between the youngest age group (9–14 years) and the oldest age group (60–80 years) was statistically significant. Elsheikh *et al*[16] showed using experimental means that the CH area was significantly larger with decreased age. By contrast, Kirwan *et al*[17] reported that CH in children was similar to that reported in adults. We cannot deny the possibility that patient age may play some role in the biomechanical properties of the cornea even in eyes with GCD. Further investigations are required to clarify this point.

It has been shown that the decrease in CH was not statistically different after LASIK and laser-assisted subepithelial keratectomy (LASEK), indicating that LASIK involving a thin 120-μm flap did not induce additional biomechanical change.[8] On the other hand, in our preliminary data, LASIK decreased CH and CRF significantly more than PRK (data not shown). This may be due to the fact that LASIK requires not only surgical tissue removal but also flap creation, whereas PRK requires tissue removal only. In addition, LASIK ablates more of the deeper layers of the corneal stroma than PRK, which may contribute to the greater damage to the corneal nerves evident after LASIK because these are transected at a deeper plane of the cornea. In this study, PTK appeared to result in less decrease in CH and CRF than LASIK as in previous studies, possibly because the amount of laser ablation in PTK is smaller than that in LASIK. We should be aware that it is still difficult to directly compare the effects of the different surgical procedures on corneal biomechanics, because these biomechanics were influenced by many factors such as the amount of laser ablation, age, or race.

In light of the increasing number of reports of iatrogenic keratectasia after excimer laser surgery, such as PRK, LASIK, or PTK, it is clinically important to assess the postoperative biomechanical changes of the cornea. The ORA (Reichert Ophthalmic Instruments) has been developed to assess the biomechanical properties of the cornea.[1] It has been shown that there were no significant differences of CH or CRF in post-LASIK patients with or without keratectasia.[18,19] The values of CH and CRF may be useful when used in conjunction with other parameters such as aberrometry or the morphology of the signals. As indicated in Figure 4, Bland–Altman plots show that the mean difference between two consecutive measurements with ORA (±95% LoA) was 0.0 ± 0.7 mm Hg (−1.5–1.4 mm Hg) for CH, and 0.1 ± 0.7 mm Hg (−1.2–1.4 mm Hg) for CRF. The ±95% LoA with granular dystrophy was slightly wider than those with normal eyes in our present and previous studies.[7,12] Although the repeatability of the measurement with GCD appeared to be slightly inferior to those with normal eyes, we consider that this device offers reasonable repeatability even in the evaluation of the biomechanical properties with GCD.

The study assessed the biomechanical parameters of the cornea before and 3 months after surgery. It has been shown that it took 3–6 months to develop a clinically apparent ectasia after PTK.[4] In light of a considerable number of case reports of late-onset keratectasia,[20–22] it is confidently assumed that biomechanical deformation slowly develops over time, and then progresses rapidly after a certain threshold is passed. In addition, the recurrence of the diseased cornea has been reported in the late postoperative period after PTK.[23–30] More prolonged observation is necessary to ascertain whether iatrogenic keratectasia or the recurrence of the disease after PTK occurs in the late postoperative period.

In summary, we showed that the biomechanical parameters of the cornea were significantly decreased after PTK in eyes with GCD, possibly because of the surgical removal of the diseased corneal tissue. Moreover, these biomechanical parameters were significantly associated with the central corneal thickness, not only before surgery but also after it, suggesting that the corneal thickness may play some role in the corneal biomechanics, even in eyes with a diseased cornea. A further study with greater numbers of patients is required to confirm these preliminarily findings.

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