

A Review of Corneal Biomechanics after LASIK and SMILE and the Current Methods of Corneal Biomechanical Analysis

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Abstract

Corneal refractive surgeries for the correction of myopia, hyperopia, astigmatism and hyperopia are quick and effective procedures, and have been growing in popularity over the last two decades. However, post-surgery corneal ectasia remains one of the most feared surgical complications. This is where the biomechanical integrity of the cornea begins to fail, with progressive thinning of the stroma, steepening of the cornea, irregular astigmatism, and decreased distance visual acuity. Laser-assisted *in-situ* keratomileusis (LASIK) is currently the most common refractive surgery procedure. It uses a femtosecond laser or a microkeratome to cut a thin flap on the surface of the cornea. Corneal tissue is then photoablated to correct the refractive error and the flap is then replaced at the end of the procedure. Newer techniques such as small incision lenticule extraction (SMILE) make use of a small incision only, without flap creation, and a lenticule is extracted to correct the refractive error. The avoidance of flap creation should theoretically maintain the integrity of the anterior corneal region and lower the risk of corneal ectasia, but there have been few clinical studies to date that compare the corneal biomechanical outcomes of different procedures. In this review, we highlight the biomechanical differences in outcomes between LASIK and SMILE, as well as explain some of the *in vivo* and *in vitro* techniques to investigate corneal biomechanical parameters.

Keywords: LASIK; SMILE; Femtosecond; Corneal biomechanical analysis; Biomechanics

Introduction

Corneal refractive surgeries have risen in popularity in recent years as it offers a long-term solution to myopia, hyperopia, astigmatism and presbyopia, and is generally viewed as safe and effective. Laser-assisted in-situ keratomileusis (LASIK) is one of the most common laser surgeries offered, which involves creating a corneal flap and then ablating the underlying corneal tissue, before replacing the flap. The most feared complication of these procedures is the risk of corneal ectasia, where there is progressive breakdown of corneal structure, thinning of corneal stroma and progressive astigmatism, eventually leading to reduced visual acuity. This prompts us to consider the biomechanical effects of refractive surgery on the cornea. Here, we review the literature on corneal biomechanical parameters, how these are measured, and how they could add to the predictability of refractive surgery outcomes. We also look at a newer technique called small incision lenticule extraction (SMILE), a theoretically less damaging procedure, and compare this to LASIK in terms of biomechanical stability. Our search was carried out in EMBASE from 1980 onwards, date of search 3rd August 2015. The search strategy is summarized in Appendix 1

Corneal Structure

The biomechanical structure and function of the cornea is highly dependent on its constitutive elements, their mechanical properties, and a myriad of biological processes. The microstructure of the corneal stroma is composed of 300 to 500 lamellar sheets, each of which

consists of thin collagen fibrils that stretch from limbus to limbus. The fibrils in each sheet are arranged parallel to one another and are evenly spaced. Glycosaminoglycans fill the spaces between the fibrils and lamellae. The normal corneal structure confers the critical optical property of transparency while providing adequate mechanical integrity needed to maintain anterior corneal curvature over a wide range of loads and hydration levels [1]. Alterations of this structural equilibrium have direct visual consequences. This is especially relevant in diseases such as keratoconus and postoperative corneal ectasia after refractive surgery.

Laser-assisted in-situ keratomileusis

Corneal refractive surgery has transformed the management of refractive error, and has gained considerable popularity in the last two decades. Laser-assisted in-situ keratomileusis (LASIK) is the most common refractive surgery procedure, as it has faster visual recovery and is nearly painless compared to the older photorefractive keratectomy (PRK) [2]. In LASIK, a femtosecond laser or a microkeratome is used to cut a thin flap on the surface of the cornea. This flap is then peeled back and ultraviolet energy from an excimer laser is focused directly onto the corneal stroma to photoablate tissue in a pattern to correct the refractive error; the flap is then replaced at the end of the procedure. The mechanical microkeratome uses a shear force with an oscillating blade, which moves through the cornea in a torsional movement [3]. The femtosecond laser uses a longer wavelength than excimer laser, and even shorter pulses, to photodisrupt the cornea by focusing at a predetermined depth with a diameter of 1 μm , which can expand to 2 to 3 μm [4]. Each of these laser pulses creates an expanding bubble of CO₂ gas and water, that can cleave the tissue and create a plane of separation. The pulses are

scanned in a spiral or raster pattern and are placed next to each other to create a resection plane [5].

Side effects of LASIK

With a mechanical microkeratome, complications following flap creation have been reported. These include epithelial sloughing, epithelial defects, free/partial flaps, and button holes [6,7]. The femtosecond laser produces fewer complications in comparison to the microkeratome [8]. Dry eye symptoms are common after both methods of LASIK, with symptoms peaking at 1 week to 3 months after surgery. Dry eye symptoms are also more common with the microkeratome than with the femtosecond laser created flaps, and in patients with an unstable tear film [9].

Post-LASIK corneal ectasia is the most feared late complication of the procedure. It is defined as biomechanical failure of the cornea, with progressive thinning of the stroma, steepening of the cornea, irregular astigmatism, and decreased distance visual acuity. The incidence of post-LASIK ectasia is estimated to be 0.66% [10]. Corneal topography can be used to identify pre-operative patterns that could indicate suspicious corneas that may be at higher risk of developing corneal ectasia. Risk factor indices to detect corneal abnormalities have been developed by several authors including Maeda et al. [11] and Rabinowitz et al. [12]. In these indices, subjective analyses of topography are combined with patient clinical information. The Ectasia Risk Scoring System (ERSS) by Randleman et al. [10] is based on a corneal topography score, central corneal thickness, degree of pre-operative myopia, residual stromal bed thickness, and patient age. The scoring system was developed based on a retrospective case-control study, which evaluated Placido disc-based corneal topography, central corneal thickness, the level of myopic correction, residual stromal bed thickness, and the patient's age. The ERSS, however, lacks sensitivity in predicting the risk of post-operative ectasia, with 4 to 8% of false negatives, and other reported cases of ectasia after LASIK in patients with no identifiable risk factors [13,14]. Other predictors of ectasia risk include the "Ambrosio 2" scale, which is an absolute scale developed from curvature and pachymetric maps [15], the belin-ambrosio enhanced ectasia display (BAD) which combines elevation and pachymetric evaluations to produce a tomographic display of the cornea structure [15], and the percent thickness altered (PTA) [16] which combines the flap thickness and ablation depth as a percent of total corneal thickness and recommends a level less than 40% to reduce post-operative ectasia risk.

Because of the risk of corneal ectasia as well as the influence on stable post-operative shape, corneal biomechanics is rapidly becoming recognized as a major contributor to refractive surgery outcomes. The organized collagen fibres running along the lamellae of the cornea relax toward the periphery when cut [17] and the decreased lamellar tension allows peripheral expansion which leads to biomechanical central flattening [18]. In LASIK, flaps are created to be 100 to 140 microns thick, which sever the stronger anterior cornea collagen fibres. Therefore, the flap is likely to decrease the biomechanical stability of the cornea [17]. In a study using radial shearing speckle pattern interferometry (RSSPI) to measure corneal strain on donor human corneas, it has been shown that horizontal delamination incisions, where only the stromal bed was cut, resulted in less loss of structural integrity than vertical side cuts through the lamellae. The use of angulated side cuts, where the stromal diameter of the flap exceeded the epithelial diameter, also increased structural integrity [19]. Thus,

the more vertical the cut made in LASIK, the greater the number of lamellae cut, the weaker the biomechanical stability of the cornea.

Refractive lenticule extraction

Refractive lenticule extraction (ReLEx) is a newer form of refractive surgery. It is a generic term referring to various procedures that involve removal of a lenticule of stroma, with the first clinical outcomes of femtosecond laser intrastromal extraction (FLEX) published in 2003 [20]. Refractive lenticule extraction (ReLEx) describes intrastromal keratomileusis without the use of an excimer laser or microkeratome. In ReLEx flex (FLEX) [21], a refractive lenticule of stroma is cut with two passes using a femtosecond laser, allowing access to dissection and manual removal of the lenticule. A LASIK-like flap is used to access the stromal lenticule. In small incision lenticule extraction (SMILE), instead of a flap, only a single incision is made. The lenticule is extracted from an arcuate side incision, as small as 1mm, made close to the edge of the lenticule. This maintains the integrity of the anterior corneal region with the avoidance of the creation of a flap [22]. Compared to flap-related procedures, SMILE should therefore reduce the side effects associated with flap creation such as corneal denervation, dry eyes, epithelial instability, and should also theoretically have greater relative biomechanical strength. However, research is ongoing to generate clinical evidence of these predictions.

This review seeks to illustrate the importance of biomechanical assessment in refractive surgery, and also to compare the biomechanical effects on the cornea after SMILE and LASIK. Although the literature is limited in this area, there is much scope for further research.

Corneal biomechanical parameters

Hundreds of collagen lamellae traverse the cornea and are in tension due to loading by the intraocular pressure. Disruption of these fibres by a refractive procedure results in loss of tension and corneal expansion peripheral to the disruption [22]. This produces biomechanical central flattening in the anterior cornea which is the mechanism underlying astigmatism correction secondary to arcuate keratotomy, as well as the hyperopic shift in photo-ablative keratectomy [23]. In the anterior stroma, greater collagen interweaving and increased numbers of transverse fiber elements result in an exponential decrease in elasticity from the stronger anterior to the weaker posterior stroma [24]. Thus, the depth-dependent biomechanical properties of the cornea would be substantially altered after refractive surgery. Inter-lamellar cohesive strength increases with age, and varies by meridian. In a study on human eye bank corneas, mean cohesive strength in the inferior periphery was found to be only two thirds the strength observed in the nasal or temporal periphery, and was also significantly less than the strength of the superior periphery. Unsurprisingly, the inferior cornea is where corneal steepening in corneal ectasia is most likely to occur [25].

Despite the advances and availability of corneal refractive surgery, the biomechanical properties of the pre and post-operative cornea are not well characterized. The biomechanical properties of corneal tissue determine how it will respond and deform when placed under stress, and this process depends on the biomechanical properties of the cornea.

Mathematical modeling corneal tensile strength

The cohesive tensile strength of the cornea is a reflection of how strongly the stromal lamellae are held together, and this decreases from anterior to posterior cornea. A LASIK flap thickness is normally planned to be 110 μm , and a SMILE cap thickness approximately 120-160 μm . From this principle, a mathematical model based on depth-dependent tensile strength was produced by Randleman et al. They predicted that the post-operative stromal tensile strength would be greater after SMILE than LASIK since the anterior lamellae would remain intact, under the assumption that the SMILE procedure was with a 130- μm anterior depth and LASIK with a 110- μm flap [24]. Using a mathematical model, Reinstein et al. predicted that post-operative tensile strength was greater after SMILE than after LASIK, and that the SMILE lenticule thickness could be approximately 100 μm greater than the LASIK ablation depth and still have equivalent corneal strength [26].

Ocular Response Analyser (ORA)

The Ocular Response Analyzer (ORA, Reichert, Inc., Depew, NY) is a noncontact tonometry method designed to provide a more accurate *in vivo* measurement of IOP through compensation for corneal properties. The ORA has a precisely metered air pulse and a quantitative electro-optical system that monitors the deformation of the cornea through the reflection of infrared light to a detector. After alignment to the corneal apex, the air puff is initiated. The air pump is controlled relative to the first applanation signal. The air pressure forces the cornea to deform inward, passing first applanation, when the pressure (P1) is registered and the air pump receives a signal to shut down. However, the air pressure continues to increase through inertia in the piston, and the cornea deforms into a slight concavity until the air pressure reaches a maximum. As pressure decreases, the cornea gradually recovers its normal configuration, passing through a second applanation state at pressure (P2). Thus, the maximum applied pressure is dependent on the timing of the first applanation event. Both applanation events are registered by a peak on the infrared signal detector, so that two independent pressure values are recorded. The difference between the 2 pressures is called corneal hysteresis (CH) and reflects the viscoelastic nature of the cornea. If the cornea were purely elastic, the difference in pressures between the loading pathway and the unloading pathway would be zero [27]. Hysteresis is the result of energy dissipation in the tissue when external forces (the air-puff) cause deformation and this dissipated energy cannot be recovered when the forces are removed. Thus, CH is a reflection of the energy loss due to viscous damping in the cornea [28]. Unlike CH, Corneal Resistance Factor (CRF), another parameter measured by the ORA, was empirically determined to have maximum correlation with pachymetry. However, CRF is not equivalent to elasticity as is commonly presumed, but is a function of P1 and P2. Both CH and CRF are related to central corneal thickness, with CRF having a stronger relationship, and both are reduced in keratocous and corneal ectasia [29].

CorVis ST (CST)

The CorVis ST (Dynamic Scheimpflug Analyzer) is a new noncontact tonometry system integrated with an ultra-high speed Scheimpflug camera. It was introduced by Oculus in 2010 as a method of analyzing corneal biomechanical response and IOP *in vivo*. It employs a similar air puff deformation technique, but with a fixed maximum air pressure of 25 kPa. It uses a high-speed Scheimpflug

camera, which acquires images at 4330 frames per second, to monitor a single cross-sectional plane of the deforming horizontal meridian. This imaging process allows for dynamic inspection of the deformation process during non-contact tonometry. The recording starts with the cornea in its natural convex shape. The air pulse then forces the cornea inward (ingoing phase) through applanation (first applanation) into a concavity phase until it reaches the highest concavity and maximum deformation. There is an oscillation period before the outgoing phase. The cornea then undergoes a second applanation before returning to its natural convex shape. The timing and pressure of the air puff at the first and second applanations and at the highest concavity moments are recorded. IOP is also calculated based on the timing of the first applanation event. Similar to Goldmann tonometry, the IOP measurement is influenced by both stiffness and thickness [30].

Other parameters include maximum deformation amplitude (maximum amplitude at the apex (highest concavity), first applanation time (time from initiation until the first applanation), highest concavity time (time from initiation until highest concavity is reached), second applanation time (time from initiation until the second applanation), first and second applanation length (flattened surface length at first and second applanation), central concave curvature radius at highest concavity and of the normal cornea, velocity inward (corneal speed at the first applanation) and velocity outward (corneal speed at the second applanation) [31].

The ORA and CorVis ST are reliable techniques for *in vivo* measurement of IOP and the only commercial devices for assessment of biomechanical response parameters, but nonetheless are only able to analyze the cornea in a two dimensional plane.

Newer techniques that are emerging can characterize corneal properties in 3D, including supersonic shear imaging [32], corneal optical coherence elastography [33], and Brillouin light scattering microscopy [34].

In supersonic shear imaging, a 15 MHz linear probe is used to perform conventional ultrasonic imaging of the cornea. An ultrasonic sequence combines the generation of a remote perturbation in the cornea and ultrafast (20,000 frames per second) ultrasonic imaging of the resulting corneal displacements that evolves into a shear wave propagation, whose local speed is directly linked to local elasticity. A quantitative high-resolution map of local corneal elasticity can be provided by this dedicated sequence of ultrasonic waves [32]. In the cornea, supersonic shear wave imaging has been used to assess corneal stiffening in experimental models of corneal collagen cross-linking [35]. With SSI, it has been shown in an *ex vivo* study on porcine eyes that iontophoresis-assisted trans-epithelial corneal collagen cross-linked corneas exhibited increased resistance to pressure rise, indicating stiffening [35].

Optical coherence elastography is a novel method where OCT is used to measure corneal elasticity. Displacement of intra-corneal optical features generated by an externally applied force, tracked with a cross-correlation algorithm, can non-destructively estimate local and directional corneal material properties [33]. This method has been mostly used in studies comparing various corneal collagen cross-linking approaches, where authors showed that the biomechanical stiffening effect produced by trans-epithelial benzalkonium chloride-EDTA (BAC-EDTA) riboflavin-UVA crosslinking was greater than the standard epithelium-off riboflavin-UVA crosslinking in animal models [36].

Brillouin light microscopy is a non-invasive method that does not require structural or mechanical deformations of the cornea. Spontaneous Brillouin scattering arises from the interaction of an externally applied light source and natural sound waves that are inherently present in the cornea. By detecting the spectral shifts in the scattered light, which are in the order of 10 GHz, the cornea's biomechanical properties can be determined at microscopic spatial resolution without any physical contact [34]. Brillouin microscopy has been used to study the mechanical differences in keratoconic versus normal corneas in *ex vivo* human tissue, and has shown that in keratoconus, mechanical loss is primarily concentrated within the area of the keratoconic cone [37]. Outside of this area of local pathology, the biomechanical properties of the keratoconic cornea are similar to a normal cornea.

These methods can all be used to measure biomechanical parameters *in vivo*, but studies so far have only been done on animal models or *ex vivo* human tissue. With more research, these techniques can theoretically be used to assess biomechanical properties clinically, and the effects of refractive surgery might be investigated in the future, including the *in vivo* measurement of post-operative corneal biomechanics in SMILE and LASIK.

There have been recent studies that compared corneal biomechanical parameters of SMILE to other refractive surgical

techniques, and some of these have not found an observable preservation of biomechanical response parameters using SMILE [38-41], likely due to tissue removal with the lenticule. In a study, CH and CRF of patients undergoing FLEX in one eye and SMILE in the other were prospectively compared using the ORA in a clinical trial of 35 patients [38], which showed no significant differences at 6 months after surgery. A case series comparing these same parameters also showed no significant differences at 1 week and 3 months after surgery. However, since CH and CRF are both viscoelastic parameters, simultaneous changes in viscosity may mask changes in elasticity. A more recent prospective study used ORA to compare the biomechanical parameters of the cornea after SMILE and LASIK. There were 187 patients who had undergone SMILE and 79 patients with LASIK. The authors showed that in patients with myopia greater than -6.00 dioptres, the CH, CRF, p1 and p2 area decreased more after LASIK than after SMILE [42]. Greater amplitude of the two infrared applanation peaks was associated with a stiffer cornea [28], leading to the conclusion that SMILE produces a stiffer cornea than LASIK. With lower myopic corrections, there was no significant difference in these parameters, similar to previous studies [39,40]. This was likely due to small difference in the reduction in mechanical weakness between the two procedures that was beyond the sensitivity of the device. However, in higher myopes, with increased tissue removal the changes were larger and thus differences, detectable.

Ref.	Author, year	Method	Sample	Outcome
38	Vestergaard AH et al. 2014	Prospective, randomized, single-masked clinical trial. Included patients treated for moderate to high myopia with FLEX in one eye and SMILE in the other	35 patients, 70 eyes	No significant differences between FLEX and SMILE at 6 months in terms of pachymetry, CH and CRF
39	Agca A et al. 2014	Prospective comparative case series. One eye of each patient was treated with SMILE, and the fellow eye with femto-LASIK	30 patients, 60 eyes	No differences between femto-LASIK and SMILE treatments at 6 months in terms of postoperative CH or CRF.
40	Penderson IB et al. 2014	Retrospective evaluation of corneal biomechanical properties after LASIK, ReLEx flex, and ReLEx SMILE using Corvis ST and ORA on patients treated for high myopia (-10.5 to -5.5 diopters) more than one year previously	LASIK (35 eyes), ReLEx flex (31 eyes), and ReLEx smile (29 eyes). A control group included 31 healthy eyes	LASIK and ReLEx flex and the flap-free ReLEx smile result in similar reduction in corneal biomechanics when evaluated by Corvis ST and ORA.
41	Shen Y et al. 2014	Retrospective study measuring corneal deformation parameters using CorVis ST between groups	17 eyes of 17 patients after SMILE, 18 eyes of 18 patients after LASEK, 17 eyes of 17 patients after femtosecond LASIK	No significant difference in deformation amplitude and applanation time (applanation 1) between the LASEK and SMILE groups nor between the SMILE and femtosecond-LASIK groups. 3 months after surgery
42	Wang D et al. 2014	Prospective study. Patients grouped according to SMILE or LASIK and -6.00 diopters (D) or less (> -6.00 D) or myopia greater than -6.00 D (>-6.00 D). CH, CRF, and 37 waveform parameters were recorded using ORA and compared preoperatively and at 1 week and 1 and 3 months postoperatively.	187 eyes had SMILE, 79 eyes had LASIK	In myopia greater than -6.00 D, the CH, CRF, p1area, and p2area decreased significantly more in LASIK than in SMILE
43	Wu D et al. 2014	Prospective comparative case series. Patients had SMILE or femtosecond LASIK. CH, CRF and 37 other biomechanical waveform parameters were quantitatively assessed with the Ocular Response Analyzer preoperatively and 1 week and , 3, and 6 months postoperatively.	40 eyes had SMILE, 40 eyes had femtosecond LASIK	CH and CRF values in the SMILE Group were significantly higher than those in the femtosecond LASIK group 3 months and 6 months postoperatively

Table 1: Summary of recent papers comparing biomechanical outcomes of LASIK techniques versus SMILE.

In another prospective comparative case series comparing SMILE and LASIK using ORA to measure CH and CRF, Wu et al. showed that

there were significantly less viscoelastic changes after SMILE than after LASIK at 3 and 6 months postoperatively [43]. The difference in results

between the two ORA studies is mainly due to the different study populations. In the Agca study [39] the mean myopia was -3.62 (1.79) hence may have been too small to be able to detect a difference between the two groups while in the Wu et al. study the mean myopia was -5.71 (1.19).

Shen et al. used the CorVis ST and found that there was no significant differences in the deformation amplitudes and appplantation time between SMILE and femtosecond (FS)LASIK at 3 months after surgery [41]. However, this was a retrospective study with a small group of patients, likely underpowered to detect a difference. In addition, pre-operative biomechanical parameters in the study populations were not captured by the CorVis ST retrospectively.

The theoretical differences in corneal stress distribution between LASIK and SMILE have also been compared in a computational modeling study, using a finite-element anisotropic collagen fiber-dependent model of refractive surgery [44]. The authors created patient specific corneal models for LASIK and SMILE, and compared the stress distribution between these models and against a geometry analog model that served as a control. They showed that the stress distribution was similar between the SMILE simulations and the control model with greater stress anteriorly than posteriorly, whereas LASIK repeatedly showed decreased stress in the flap anteriorly and increased stress in the residual stromal bed, compared to the control model. They also showed that an increased flap thickness or lenticule depth caused greater residual stromal bed stress in LASIK compared to SMILE. This theoretical analysis suggests that SMILE could maintain a biomechanically stronger anterior corneal region than LASIK, and that the residual stromal bed in an equivalent LASIK eye, would carry greater stress since the region of the flap is biomechanically weaker, thus driving the stress posteriorly.

Conclusion

Corneal biomechanics is an important consideration in refractive surgery, as the cornea is inevitably altered biomechanically, and there is a risk of corneal ectasia after any refractive surgery. The emergence of non-invasive methods of studying biomechanical changes after these procedures are useful in comparing different methods of refractive surgery. SMILE is the latest non-flap based method in refractive surgery, and its preservation of the anterior cornea without creating a flap seems to be superior at conserving biomechanical stability at higher degrees of myopia than LASIK. Further clinical work to support the modelling should confirm this hypothesis.

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