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ORIGINAL RESEARCH

Comparison of corneal biomechanics after myopic small-incision lenticule extraction compared to LASIK: an ex vivo study

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Purpose: To investigate ex vivo potentially different corneal biomechanical properties after small-incision lenticule extraction (SMILE) versus LASIK for myopic correction.

Methods: Thirty human donor corneas were subjected to either myopic SMILE or femtosecond laser-assisted LASIK. Donor corneas were assigned to six investigative groups: Group A, –3.00 D (diopters) SMILE; Group B, –8.00 D SMILE; Group C, –3.00 D LASIK; and Group D, –8.00 D LASIK. Additionally, two control groups were formed: Group E, SMILE and Group F, LASIK. All groups consisted of five corneas, randomly allocated. The corneas in the control groups were subjected to the corresponding femtosecond-laser lamellar cuts but not to tissue removal. Evaluation of biomechanical tensile strength was conducted by biaxial force application. Primary outcome measures were stress at 10% and 15% strain, and Young's modulus at 10% and 15% strain.

Results: In SMILE, the average relative difference (Δ) of the four outcome measures was –34.46% for –3.00 D correction versus control Group E and –49.34% for –8.00 D correction versus control Group E. In LASIK, average Δ was –24.88% for –3.00 D correction versus control, and –52.73% for –8.00 D correction versus control. All these differences were statistically significant; SMILE compared to LASIK for the same myopic correction appears to result in more biomechanical reduction for –3.00 D corrections by –26%, while a nonstatistically significant difference was noted in –8.00 D corrections.

Conclusion: Both SMILE and LASIK procedures do substantially alter corneal biomechanical properties, and the degree of tensile strength reduction is statistically significantly correlated to the extent of myopic correction. Additionally, SMILE procedure seems to result in more tensile strength reduction in lower myopic corrections compared to LASIK, and similar tensile strength reduction to LASIK in higher myopic corrections when compared to LASIK.

Keywords: SMILE, femto-second LASIK, myopic LASIK, corneal biomechanics, Young's modulus, corneal stress–strain, shear strength, tensile strength

Introduction

Small-incision lenticule extraction (SMILE) procedure[1,2] is a new method of intrastromal keratomileusis that seems to be a viable alternative for refractive correction, since numerous recent studies validate its safety and efficacy, even when compared to LASIK procedure the current laser refractive procedure of choice to treat myopia.[3,4]

SMILE is a new single femtosecond laser "flapless" procedure that involves the creation of an intrastromal lenticule between two photo disruption planes that is mechanically removed through a small corneal incision tunnel of 2–3 mm diameter typically created superotemporally.[5]

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On the other hand, LASIK procedure involves two distinct steps: the creation of the flap (corresponding to a lamellar cut typically 110–140 μm within the cornea) by either a mechanical microkeratome or a femtosecond laser (usually operating at 1,056 nm),[6] followed by the refractive part, the ablative removal of stromal tissue from the exposed bed under the lifted flap using an excimer laser (usually operating at 193 nm).[7]

The removal of corneal tissue by either procedure inevitably leads to reduction of corneal tensile strength.[10,11] Both procedures alter corneal biomechanical properties that are thought to play an important role in the development of post-LASIK ectasia, but the nature of each procedure may produce different biomechanical effects. First, it is known that vertical cuts have more biomechanical impact than horizontal cuts. In SMILE significantly less anterior cornea is subjected to transverse separation, since side cut diameter is 2–3 mm (50°) compared to LASIK where flap diameter is of 300°, that is, 360° minus only the hinge. Additionally, it is also known that anterior stromal lamellae are stronger than posterior stromal lamellae, and the anterior 40% of the central corneal stroma constitutes the strongest region of the cornea, whereas the posterior 60% of the stroma is at least 50% weaker. In SMILE, since the anterior stroma remains uncut and the tissue is removed from deeper stromal layers than in LASIK, the strongest part of the stroma continues to contribute to the strength of the cornea postoperatively.

In this study, we attempted to comparatively evaluate the changes in corneal biomechanical properties ex vivo following either SMILE (Visumax Laser; Carl Zeiss Meditec AG, Jena, Germany) or Femtosecond LASIK (FS200 & EX500 Lasers; Alcon Surgical, Fort Worth, TX, USA) for high or low myopic correction.

Materials and methods

This laboratory (ex vivo) study received approval by the Ethics Committee of Laservision.gr Clinical Research Eye Institute. Thirty human donor corneas were used in this study, which were obtained for research purposes from the Eye Bank for Sight Restoration Inc. (New York, NY, USA), an accredited member of the Eye Bank Association of America. The corneas were donated by 30 different organ donors (17 males and 13 females), whose mean age was 60.9±10.1 years (range 46–78 years). The corneas were stored in OptiSol (Bausch & Lomb, Rochester, NY, USA) solution and were maintained at 4°C.

Sample preparation

The human donor corneas were randomly assigned to six investigative groups (n=5 each) which were subjected to the following myopic simulated treatments: Group A, –3.00 D SMILE; Group B, –8.00 D SMILE; Group C, –3.00 D LASIK; and Group D, –8.00 D LASIK. Two control groups were formed (also n=5 each), one for each procedure, Group E, control group for SMILE, and Group F, control group for LASIK. The corneas in these control groups were subjected to the corresponding femtosecond laser lamellar cut at 140 μm depth and "smile" side cut for SMILE cases, and to the corresponding 110 μm LASIK flap cut in LASIK cases, but not to any tissue removal.

During the procedures, the corneas were mounted on artificial anterior chamber (Baron; Katena Products, Inc., Denville, NJ, USA). In either procedure, suction was manually activated, and centration was manually achieved during the femtosecond laser step.

SMILE procedures were performed using the 500 kHz VisuMax femtosecond laser (Carl Zeiss Meditec AG). Software version 1.16 was used to plan the procedures, choosing an optical zone of 6.50 mm, a cap diameter of 7.50 mm at 140 μm depths, and a lenticule cut diameter of 5.32 mm. For the –3.00 D corrections (Group A), the maximum lenticule thickness was 64 μm (minimum 15 μm). For the –8.00 D corrections (Group B), the maximum lenticule thickness was 136 μm (minimum 15 μm). The two lenticule interfaces (upper and lower) were manually separated through a 2 mm lateral "tunnel" incision in an upper/lower order. The lenticule was then extracted using microforceps via this incision. The corneas, in the control group for SMILE (Group E), were subjected to the two lamellar cuts and manual separations corresponding to the –3.00 D correction, but the lenticule was not removed.

The LASIK procedure was performed using the WaveLight Refractive Suite™, namely: 1) the FS200 femtosecond laser (Alcon Surgical) for the creation of a 110 μm thick, 8.0 mm diameter corneal flap, followed by 2) the WaveLight EX-500 excimer laser (Alcon), employing the "Wavefront Optimized" procedure for the ablative tissue removal. Optical zone diameter was 6.50 mm. For the –3.00 D corrections, the maximum ablation depth was 45.51 μm, while for the –8.00 D corrections it was 114.71 μm. The flaps were then repositioned in place. The corneas in the control for LASIK (group-F) were subjected to flap creation, which was subsequently lifted and repositioned without any ablative excimer laser tissue removal.

Following the operations, the cornea specimens were stored back into OptiSol and maintained at 4°C until testing. To obtain central corneal thickness, contact ultrasound pachymetry was employed prior to the following tensile strength testing (PachPen; Accutome Inc., Malvern, PA, USA).[8] All cornea specimens were then trephined by a 9.50 mm round punch at their center section.

Tensile strength testing

The Biotester 5000 System (CellScale Biomaterials Testing, Waterloo, ON, Canada) was used to provide biaxial load cell-based in-plane tensile tests. The specimens were fixed (randomly orientated) on a 4×5-tine rake arrangement (Figure 1) at their center 3.5×3.5 mm square section. The tines were of 250 µm diameter and spaced apart by 0.7 mm. Shear rate was fixed to 4.16 µm/s. The specimens on the fixation unit were submerged in an isotonic saline bath (9 mg/mL sodium chloride solution; B. Braun Melsungen AG, Melsungen, Germany), temperature controlled at 37°C for 5 minutes before testing to allow for temperature stabilization, as well as during testing to eliminate any temperature-related variability. Testing was performed until the first sign of slippage, indicated by an abrupt change in the force–strain curve, displayed real-time in the system monitor.

The following data time (s), x and y size (µm) x- and y-axis displacement (µm), x- and y-applied force (mN), and x and y strain (unitless) were recorded every second. An integrated CCD camera, capturing still images at a 1,280×960 pixel resolution, facilitated the precise x- and y-displacement measurement. Data were processed by custom software (LabJoy v. 9.05; CellScale Biomaterials Testing).[9]

For Groups C, D, and F corneas (LASIK treated), the flap remained positioned on the stromal bed to maintain similar thickness and thus reduce comparison bias with the SMILE-treated corneas (Groups A, B, and E).

Data evaluation

For data evaluation, the following definitions have been adopted: strain, the unitless relative elongation ($\Delta x/l$ or $\Delta y/l$), where (l) is the initial dimension of 3.5 mm, expressed as percentage and stress, a pressure metric, as the applied force F divided by the cross-section (A) of the corneal specimen test area (F/A) (F/A, units = mN/mm^2 = kPa = 10^3 Pa; MPa = 10^6 Pa, where Pa stands for Pascal, SI unit for pressure). Cross-section of the test area (A) was defined by 3.5 mm x- (or y-, respectively) width multiplied by the measured central corneal thickness. Stress at 10% and 15% strain was recorded.

Figure 1 Fitting of the corneal specimen on the BioTester device rake battery just prior to testing.

Young's modulus (also known as stress/strain ratio) is associated with tissue resistance to tensile strains. It is defined as the ratio of stress to strain applied to the tissue, and is also consequently expressed in units of pressure (MPa $=10^6$ Pa). To calculate Young's modulus, two-dimensional graphs were constructed by plotting stress in the vertical axis versus strain in the horizontal. Linear regression fitting using the SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA) was applied on the linear section of the loading curve to calculate, by means of the slope function (gradient), the stress–strain ratio. Young shear modulus E was calculated as the gradient at the vicinity of 10% and 20% strain on the stress–strain graph.

Specifically, for all 60 data sets (6 groups ×5 specimens each ×2 data sets per specimen, one for the x- and one for the y-dimension):

1. The values for stress at 10% and 15% strain were recorded.
2. The values for Young's modulus were calculated at 10% and 15% strain. For the 10% calculation, the data range was selected to correspond to strain extending from 7% to 13%, and for the 15% calculation, to strain extending from 12% to 18%.

Results

Donor data of the tissue used, provided by the Eye Bank, were recorded and analyzed: mean donor age at the time of cornea harvest was 59.4±12.8 years for Group A, 62.5±6.9 years for Group B, 58.5±14.2 years for Group C, 64.2±5.8 years for Group D, 54.7±12.1 years for Group E, and 63.9±8.5 years for Group F. No statistically significant difference between the groups was noted.

Mean central corneal thickness as measured prior to the tensile strength testing was 663.3±32.7 µm in Group A, 549±26.0 µm in Group B, 674.7±51.5 µm in Group C, 553.9±25.9 µm in Group D, 699.4±33.9 µm in Group E, and 692.4±21.7 µm in Group F. The distinct data sets collected during the tensile measurements on each cornea specimen were on average 230±30 (range: 137–255). Average displacement was 983.0±76.1 µm (range: 795–1,062), mean maximum applied force was 4,266.0±694.3 mN (range: 3,428–5,740), and maximum strain was 24.6%±1.7% (range: 20.3–26.3).

Examples of stress–strain curves are shown in Figure 2. For the calculation of Young's modulus, 65 distinct data pairs (vertical axis: stress and horizontal axis: strain) contributed to each slope function derivation. The average coefficient of determination (R^2) of the trend lines was 0.994±0.004 (range: 0.987–0.998).

Table 1 provides stress and Young's modulus results from all six groups (Figure 3), comparatively analyzed in Table 2. Within the same procedure (eg, within SMILE or LASIK), the corneas that received the larger myopic correction (–8.00 D) displayed more tensile strength reduction compared to the smaller myopic correction (–3.00 D) by all metrics. More precisely, within SMILE procedure, the average tensile strength reduction Δ (numeric average of the four metrics: Young's modulus @ 10%, Young's modulus @ 15%, stress @ 10%, and stress @ 15%, Table 2) for the –3.00 D correction (Group A) was –34.46% when compared to the SMILE control (Group E), and for the –8.00 D correction (Group B) it was –49.34% also when compared to SMILE control (Group E). Compared to the –3.00 D correction (Group A), the –8.00 SMILE correction (Group B) had on average –22.70% reduced corneal biomechanical metrics. All these differences were statistically significant.

Within LASIK, the average Δ of the –3.00 D correction (Group C) was –24.88%, when compared to the LASIK control (Group F) and –52.73% for the –8.00 D correction (Group D), again statistically significant. Compared to the –3.00 D correction (Group C), the –8.00 D LASIK correction (Group D) had on average –37.07% reduced corneal biomechanical metrics.

Discussion

Both SMILE and LASIK procedures have performed well in studies in all measures of safety, efficacy, and predictability for myopia correction.[10] Despite their common objective, there are fundamental operating differences between these two procedures. SMILE, a relatively newer and evolving procedure, has been so far employed for the correction of myopia and/or myopic astigmatism in the range of –3 to –10 Ds,[11] while LASIK has a broader treatment range, including higher amounts of myopia, as well as the correction of hyperopic refractive errors.[12,13] In addition, LASIK may be applied for customized treatments where centration can be actively controlled and cyclorotation compensated and where wavefront and/or topographic data can be incorporated in the tissue pattern planned for removal,[14] and potentially has the benefit of vast surgical and research experience.

The potential obvious advantages of SMILE over LASIK apart from biomechanics include reduced dependence on environmental factors that may influence excimer stromal ablation, such as laser fluence variability and stromal hydration, reduced possibility for operating room airborne foreign-body interface contamination, and potentially reduced postoperative dry-eye symptoms.[15] In terms of

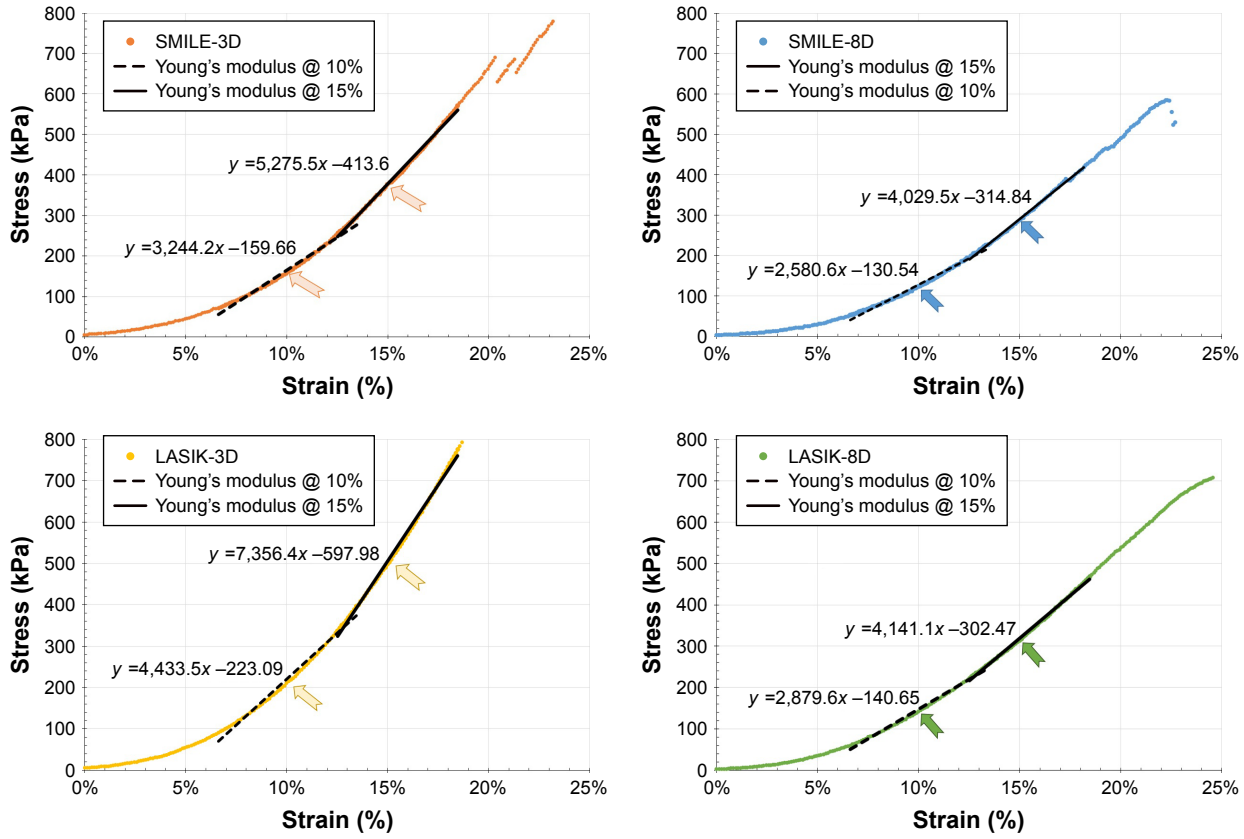

Figure 2 Young's modulus *E* linear regression fitting performed on stress–strain curves.
Notes: Data illustrate stress (shear force ÷ cross-section, expressed in kPa) versus relative displacement (strain, reported as %). From left to right, top to bottom, Group A (SMILE-3D), Group B (SMILE-8D), Group C (LASIK-3D), and Group D (LASIK-8D). Young's modulus corresponds to the slope, which is indicated by the numeric factor preceding variable *x* in each trend-line function per group, expressed in kPa and converted to MPa in the data listed in Table 1.
Abbreviation: SMILE, small-incision lenticule extraction.

Table 1 Comparative tensile measurements between the six groups

Metric	Young's modulus @ 10% (MPa)	Young's modulus @ 15% (MPa)	Stress @ 10% (kPa)	Stress @ 15% (kPa)
Group E SMILE control				
Mean	5.09	8.17	248	580
SD	±0.78	±0.92	±54	±75
Group A SMILE-3D				
Mean	3.24	5.28	160	376
SD	±0.85	±1.06	±66	±98
Group B SMILE-8D				
Mean	2.58	4.03	123	287
SD	±0.55	±0.81	±35	±72
Group F LASIK control				
Mean	5.63	9.34	266	632
SD	±0.65	±0.91	±68	±92
Group C LASIK-3D				
Mean	4.43	7.36	210	498
SD	±0.81	±1.16	±77	±108
Group D LASIK-8D				
Mean	2.88	4.14	142	313
SD	±0.59	±0.48	±47	±69

Note: Data represent mean and standard deviation between all corneas within each group.
Abbreviations: SD, standard deviation; SMILE, small-incision lenticule extraction.

corneal sensation and dry eye outcomes, some studies, as well as our own unreported to-date experience, have shown equivalence – if not superiority – of SMILE over LASIK.[16–18]

This study focuses mainly on the investigation of the degree of reduction in corneal biomechanical strength as a result of either SMILE or LASIK. Its importance derives from the fact that significant loss of corneal strength in large myopic corrections may lead to refractive regression,[19] and/or possibly iatrogenic ectasia.[20–22] In LASIK, barring the ablated tissue significance, the flap creation itself further contributes to reduction of corneal strength since, despite it still being attached to the "processed" stroma, it may no more conduce to the biomechanical strength of the underlying stroma.[11,12] In SMILE, in theory, the cornea should be less affected compared to any given LASIK or photorefractive keratectomy (PRK) procedure, as most of the anterior stromal lamellae remain intact above the cavity created by the extracted lenticule,[10,13] keeping in mind the depth dependence of transverse shear modulus of the cornea (stronger at the anterior third).[23–25]

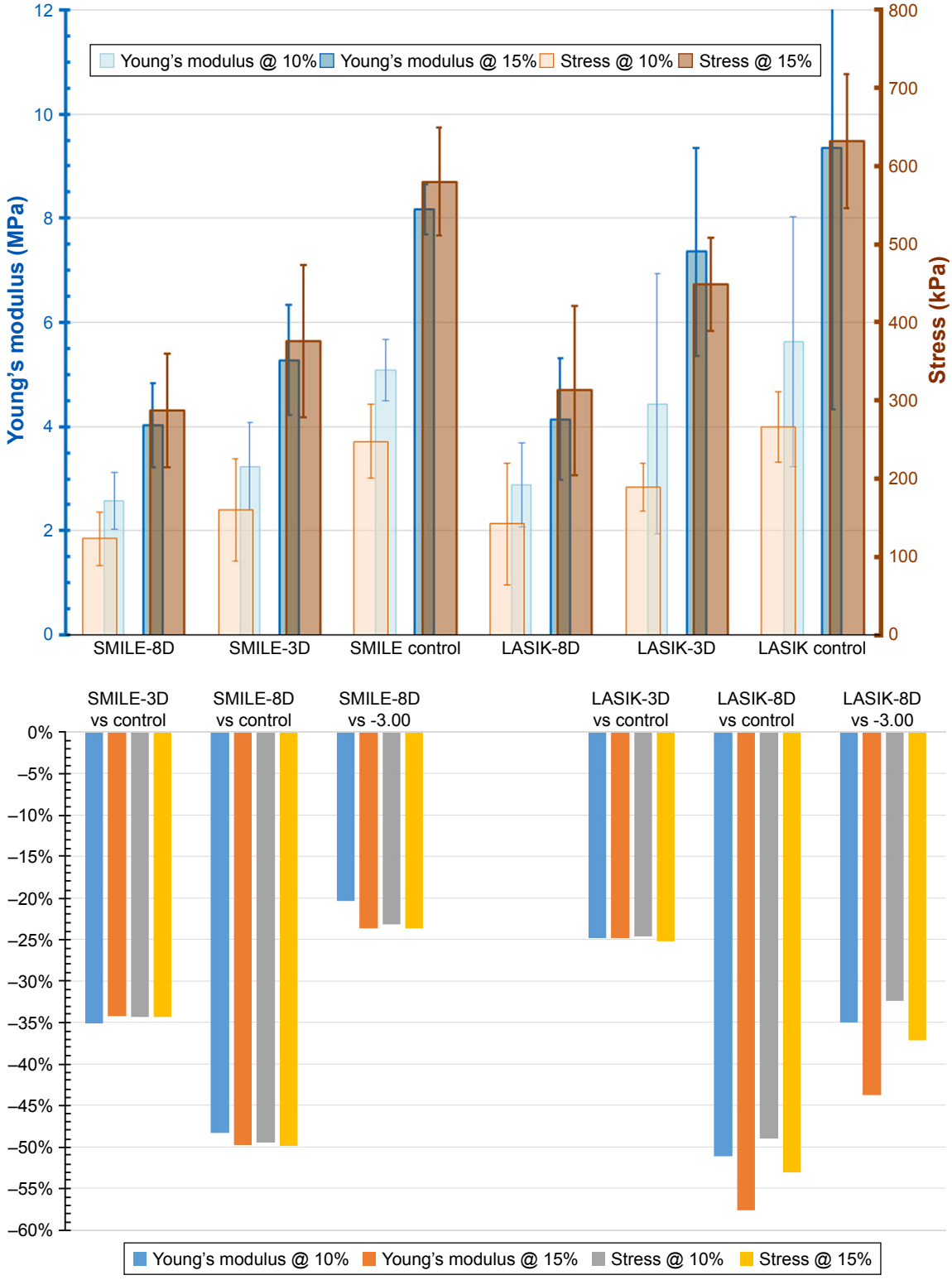

Figure 3 Summary of biomechanical tensile test differential results per group studied.
Note: Young's modulus (units MPa) and stress results (units kPa) calculated at 10% and 15% strain.
Abbreviation: SMILE, small-incision lenticule extraction.

These effects have been described or hypothesized,[13,26] but to the best of our knowledge, no experimental or clinical evidence on this aspect has been presented in the peer-reviewed literature.

In this study, we conducted a human ex vivo comparative investigation of the potential in-plane tensile strength reduction in corneas subjected to either SMILE or femtosecond laser-assisted LASIK as in vivo biomechanical

Table 2 Comparative analysis of tensile results

	Young's modulus @ 10% (MPa)	Young's modulus @ 15% (MPa)	Stress @ 10% (kPa)	Stress @ 15% (kPa)	Average Δ
Δ within procedure					
SMILE-3D vs control	−36.3%	−35.4%	−35.5%	−35.2%	−35.6%
SMILE-8D vs control	−49.3%	−50.7%	−50.4%	−50.5%	−50.2%
SMILE-8D vs -3.00	−20.4%	−23.6%	−23.1%	−23.7%	−22.7%
LASIK-3D vs control	−21.3%	−21.2%	−21.1%	−21.2%	−21.2%
LASIK-8D vs control	−48.9%	−55.7%	−46.6%	−50.5%	−50.4%
LASIK-8D vs -3.00	−35.1%	−43.7%	−32.4%	−37.1%	−37.1%
Δ between same dioptric correction					
SMILE-3D vs LASIK-3.00	−27%	−28%	−24%	−24%	25.9%
SMILE-8D vs LASIK-8.00	−10% (*)	−3% (*)	−13% (*)	−8% (*)	−8.7% (*)

Notes: Δ: relative (%) difference between metrics; *difference was not statistically significant ($P>0.05$). Average Δ is the numeric average of the four metrics (Young's modulus @ 15%, stress @ 10%, and stress @ 15%).
Abbreviation: SMILE, small-incision lenticule extraction.

measurements, in our experience, have shown low specificity and sensitivity. To the best of our knowledge, this is the first experimental investigation of this issue.

All the samples used, as well as the procedures implemented, were as closely matched as possible. The corneal samples had no statistically significant age, gender, or race difference; the operations were designed in a way they would reflect current clinical standards in our practice: the upper lamellar dissection in SMILE was created at 140 µm, and the femtosecond LASIK flap was created at 110 µm, exactly as in our clinical practice. To evaluate the effect on corneal biomechanical properties, we used biaxial stress–strain measurements,[27,28] which may be superior to corneal strip extensiometry used in earlier experiments considering the nonuniform topographic distribution of the corneal strength profile.[29,30] Thus, the orientation of the cornea specimens during the tensile measurements was intentionally random, to exactly address the fact that the in-plane biomechanical properties may naturally vary along different corneal meridians because of the known anisotropic differences of corneal collagen.[31–33]

The data in this study suggest that SMILE and LASIK appear to result in statistically similar tensile strength reduction for higher myopic corrections (–8.00 D); however, LASIK appears to result in less corneal strength reduction in smaller myopic correction (–3.00 D).

These admittedly unexpected results may be attributed to a number of significant differences between the two procedures. SMILE results in more tissue removal, due to the minimum additional 15 µm tissue dissected, independent of the amount of myopia corrected. In the –3.00 D SMILE corrections, the maximum lenticule thickness was 64 µm and in the –8.00 D corrections, 136 µm. Additionally, the tissue removal starts "deeper" at 140 µm in comparison to LASIK ablation starting at 110 µm. On the other hand, in LASIK, in the –3.00 D corrections, the maximum ablation depth was 45.51 µm, and in the –8.00 D corrections, 114.71 µm. These differences exist despite the same 6.50 mm optical zone for all procedures performed. These data correspond to an average of 19.5 µm per diopter of removed tissue in SMILE, compared to an average of 14.74 µm per diopter of ablated tissue in LASIK.

Another possible factor contributing to differences in tissue loss and resulting tensile strength reduction changes is the possible uncertainty of the depth of the lamellar cut produced by the femtosecond laser. The precision of the achieved depth (thickness) of femtosecond-created LASIK flap has been reported in the peer-review literature,[34] to be in the vicinity of ±3 to ±5 µm.[35] The variability in the maximum ablated tissue by the excimer laser also constitutes an independent factor.[36]

In SMILE procedure, there are two such femtosecond laser lamellar dissections, the upper and the lower, separated by a minimum 15 µm plus the necessary, nomogram-recommended maximum lenticule thickness. For example, the upper interface may be 140 µm within the cornea and the lower interface up to 280 µm within the cornea (140+136 µm, in the example of –8.00 D). This factor may introduce a large deviation between the programmed and achieved thickness of the removed tissue, for two reasons: first, the need for two lamellar dissections introduces a possible deviation of the maximum lenticule thickness, which may cumulatively result in the order of ±10 µm. Second, the depth for the very deep lamellar cut may not be as precise as for a typically anterior flap cut. These issues, of course, deserve a thorough investigation, which is outside the scope of this work.

Limitations of our study may include limited statistical power due to the sample size as well as acceptance of a basic

assumption that the in-plane tensile strength testing (eg, along the *x* and *y* dimensions) corresponds to in vivo biomechanical behavior of the cornea.[37] A laminar tissue such as the corneal stroma could potentially have very high tensile strength due to the contribution of the collagen fibers (fibrils) and yet be very weak in shear strength due to little interweaving. However, testing the corneal samples of a thickness in the order of 500 µm (0.5 mm) cross-section with a shearing approach was not possible using the technique employed in this study and would require torsional rheometry techniques.[30] Additional studies with differentiation of myopic correction applied and depth of lenticule may be warranted to validate and further investigate the findings of this preliminary study. Evaluation of transverse shear biomechanical strength aspect may also contribute to this issue.

Conclusion

According to our study, both SMILE and LASIK procedures do substantially alter corneal biomechanical properties, and the degree of tensile strength reduction is statistically significantly correlated to the extent of myopic correction. Additionally, SMILE procedure seems to result in more tensile strength reduction in lower myopic corrections and similar tensile strength reduction in higher myopic corrections when compared to LASIK, ex vivo, a finding that could be partly attributed to differences of tissue loss existing between the two techniques.

Disclosure

The author holds consultant/advisory positions at Alcon/WaveLight, Allergan, Avedro, i-Optics, Keramed, Zeiss, and ISP Surgical. The author reports no other conflicts of interest in this work.

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