# Evolution of corneal thickness and optical density after laser in situ keratomileusis versus small incision lenticule extraction for myopia correction

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(n=39 per group) was performed. Anterior segment optical coherence tomography (MS39) images were collected at each postoperative visit (1 day, 1 week and 1 and 3 months) and flap/cap thicknesses were measured. Using ImageJ software, three regions were defined to measure OD (in grayscale units: flap/cap stroma, residual stromal bed (RSB) and all stroma (including flap/capstroma, surgical interface and RSB).

Results Mean central thickness significantly increased during the 3-month follow-up in both LASIK (5.43  $\pm 4.23 \ \mu$ m; p=0.0118) and SMILE (2.76 $\pm 5.61 \ \mu$ m; p=0.0118), with differences between both techniques statistically significant (p=0.020). All OD values showed a statistically significant reduction during SMILE follow-up: cap  $48.96 \pm 5.55$  versus  $44.95 \pm 5.41$  (p=0.19×10<sup>-6</sup>), RSB 50.26±7.06 versus 45.42±7.53 (p=0.00005), total stroma 50.34 $\pm$ 6.49 versus 45.46 $\pm$ 6.96 (p=0.5 $\times$ 10<sup>-5</sup>) at 1 day and 3 months, respectively, whereas no statistically significant changes were found during LASIK follow-up. No significant differences were observed in OD values between both techniques at any time point, although SMILE showed a tendency for higher OD values than LASIK within the first postoperative month. Visumax presented a tendency for thicker caps than target  $(11.48 \pm 7.85 \ \mu m)$ , but not for flaps (2.73±8.93 µm) (p=0.00003). **Conclusions** Both LASIK flaps and SMILE caps show a significant postoperative rethickening. SMILE corneas present higher optical densities than LASIK corneas in the early postoperative period, with a significant decrease thereafter and up to 3 months. These findings correlate with the delayed visual recovery observed after SMILE.

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# ABSTRACT

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**Purpose** To compare the thickness and stromal optical density (OD) evolution of the flap and cap after femtosecond (FS-LASIK; Visumax) and small incision lenticule extraction (SMILE), respectively, for myopia

**Methods** A prospective study comprising 78 eyes

# INTRODUCTION

Corneal refractive surgery has evolved in the recent years, and despite laser-assisted in situ keratomileusis (LASIK) being the most commonly performed procedure, small incision lenticule extraction (SMILE) is progressively gaining popularity.<sup>1</sup> In contrast with femtosecond laser-assisted LASIK (FS-LASIK), that involves excimer laser ablation beneath a corneal flap dissected with a FS laser, SMILE is a flap-free intrastromal refractive procedure where

a FS laser dissected lenticule is extracted through a small corneal incision.<sup>1</sup> The latter has the potential advantages of less iatrogenic dry eye,<sup>2</sup> lower laser energy requirements,<sup>3</sup> fewer induced higher-order aberrations,4 reduced corneal inflammation and keratocyte damage,<sup>5</sup><sup>6</sup> and lower suction intraocular pressure during the FS laser procedure.<sup>7</sup> On the other hand, most studies report a slower visual recovery after SMILE when compared with LASIK.<sup>1 8</sup> This could be related to the increased trauma to the surrounding tissue during manual lamellar dissection within the cornea during SMILE, and also due to a possible difference on the smoothness of the resultant residual stromal bed (RSB). Visumax FS laser platform (Zeiss, Germany), in contrast to other FS laser platforms, uses a curved coupling contact glass interface with the cornea, leading to very little corneal distortion when securing the eye. However, these low-pressure curved patient interfaces (instead of high-pressure flat ones) have been associated with an early transient increase in corneal optical density (OD), cornea oedema and slightly thicker LASIK flaps than target,<sup>9</sup> what could also justify the slower visual recovery after SMILE.

The purpose of the current study is to prospectively analyse the evolution of the OD and thickness of LASIK flaps and SMILE caps created with the Visumax FS laser platform in order to evaluate the influence from its curved low-pressure glass interface and the one from the extrasurgical manipulation during SMILE cases.

# MATERIALS AND METHODS

This prospective, observational, single-centre study comprised 78 eyes of 42 consecutive patients who underwent FS-LASIK (n=39) or SMILE (n=39) for the correction of myopia, with or without astigmatism. Both LASIK flaps and SMILE lenticules were performed with the Visumax 500 kHz (Carl Zeiss Meditec AG) FS laser, and excimer ablations were done with the sixth-generation Amaris 750 excimer laser (Schwind Eve-Tech-Solutions, Germany). All patients provided written informed consent, and institutional review board approval from our institution was obtained. The study was performed in accordance with the tenets of the Declaration of Helsinki.

As this is a study regarding LASIK flap and SMILE cap morphology and OD, refractive status is not considered as an outcome; thus, surgical indication was not randomised. Nevertheless, inclusion criteria were myopia with or without astigmatism; RSB>300  $\mu$ m and percentage of tissue ablation <40% for FS-LASIK; RSB under the cap >250  $\mu$ m for SMILE; central corneal thickness >480 microns and soft contact lenses discontinuation for at least 2 weeks before surgery. Exclusion criteria were unstable refraction, previous ocular surgery, topographic suspicion of keratoconus, ocular disease and systemic disorders that could influence wound healing, such as diabetes and connective tissue disorders.

Preoperative examinations included measurement of uncorrected and corrected (manifest and cycloplegic) distance visual acuity, combined Scheimpflug and anterior segment optical coherence tomography (AS-OCT) topography (MS39, CSO, Italy), AS-OCT imaging (MS39), slit-lamp biomicroscopy, Goldmann tonometry and funduscopy.

All procedures were done by two experienced surgeons (JLAdB and ILA). A povidone-iodine solution was applied to the skin and the conjunctiva (diluted at 5%), and a sterile surgical drape and a speculum were positioned. Topical lidocaine 2% was used in every surgery for anaesthesia. For LASIK surgery, the Visumax FS laser used the following parameters: a circle pattern using a bed energy of 200 nJ, a spot and line separation of 4 µm and a targeted flap thickness of 110 µm (33 eyes) or 100 µm (6 eyes). After lifting the flap, excimer laser ablation was done, programming an optical zone larger or equal to the pupillary size. Then, stroma was rinsed with balance salt solution and the flap was repositioned with a cannula. At the end of the surgery, regular antibiotic and anti-inflammatory drops were instilled. For SMILE surgery, the Visumax FS laser used the following parameters: a circle pattern using a pulse energy of 120 nJ, spot spacing of 3.8 µm (for the lenticule), a lenticule diameter of 6.5 mm and a targeted cap thickness of 120 µm. After creating the lenticule, superficial and deep interfaces were dissected and the lenticule extracted through an anterior side cut of 2.3 mm. The same antibiotic and anti-inflammatory drops were instilled at the end of the surgery.

All patients were instructed to apply topical antibiotic and steroid drops (tobradex, Alcon) 5 times per day for the first week, and only artificial tears were continued thereafter as needed. Postoperative examinations were scheduled for 1 day, 1 week, 1 month and 3 months postoperatively. The same experienced optometrist (MC-C) performed anterior segment OCT in every follow-up visit with the MS39 (software Phoenix v3.7.0.18). The same ophthalmologist (AP-F) measured the flaps and caps in an AS-OCT section in a horizontal meridian in the centre of the cornea in each follow-up visit. Following the same method as in prior studies of the same group,<sup>9–11</sup> 17 flap thickness data points were measured in the horizontal meridian of the cornea (centre of flap/cap, 0.5 mm, 1 mm, 1.5 mm, 2 mm, 2.5 mm, 3 mm, 3.5 mm and 4 mm nasally and 0.5 mm, 1 mm, 1.5 mm, 2 mm, 2.5 mm, 3 mm, 3.5 mm and 4 mm temporally).

For assessing flap and cap morphology and thickness evolution during the follow-up, we evaluated five parameters: the mean central thickness (MCT: mean value of the centre and 0.5 mm nasally and temporally), the mean total thickness (MTT: mean value of the 17 points measured), the SD of the MTT, the flap or cap thickness range (difference between the thickest and thinnest point) and the flap/cap thickness homogeneity (CTH or FTH: difference between the thickness of two points located symmetrically at 2 mm from the centre).

The OD of the corneal stroma is assessed to describe the quality and behaviour of the corneal tissue after surgery, as in other studies of this group.<sup>9-11</sup> We used Image] (version 1.49 u, National Institutes of Health) for the analysis of the AS-OCT images of the operated corneas, as previously described.9-11 Therefore, at each follow-up visit, the best AS-OCT image obtained (the one with less noise, ie, the most homogeneous black fundus and without apex optical reflections or artefacts) was chosen. The region of interest manager was used to delimitate, in the central 2 mm area, the stroma included in the flap or cap and in the RSB, excluding the flap or cap interface (as it could overestimate density). In this study, as interface inflammatory reaction might be different in LASIK and in SMILE, OD was also measured in the central 2 -mm area including the interface (total OD). In every case epithelium, Bowman layer, Descemet membrane and endothelium were excluded from the analysis, as they are hyper-reflective in AS-OCT and could be a source of bias. Then, OD was measured in grayscale units (GSU), that is automatically generated by the software, ranging from 0 (white) to 255 (black). Thus, OD of the corneal tissue is a surrogate of the corneal backscatter.

StatPlus:mac Pro (v6.1.5.1, AnalystSoft) was used for data analysis. A sample size of 30 eyes per group was expected to detect differences in flap thickness of 2.5  $\mu$ m, 80% of the time with a p value of 0.05. Statistical comparisons were made using unpaired two-tailed Student's t-test, and analysis of variance (ANOVA) for repeated measures as needed. P<0.05 was considered statistically significant. Data is expressed as mean±SD (range).

# RESULTS

Table 1 summarises OD evolution. No statistically significant differences were found between LASIK and SMILE at any time point during the follow-up. The ANOVA for repeated measures showed a statistically significant change during the SMILE follow up for the cap OD ( $p=0.19\times10^{-6}$ ), RSB OD (p=0.00005) and total OD ( $p=0.5\times10^{-5}$ ), whereas no significant changes were found during LASIK follow-up. A relative change in SMILE cap OD of -8.19% is seen from 24 hours to 3 months postoperative, -9.63% for the SMILE RSB OD and -9.69% for the SMILE total OD. In LASIK, there was a smaller relative change in OD, with -3.05% for the stroma of the flap, -4.98% for the LASIK RSB and -4.79% for the LASIK total OD. Figure 1 shows the evolution of OD in both LASIK and SMILE. It is evident that total OD and RSB OD in SMILE are higher than LASIK OD values during the first week, but then they decrease progressively until the end of the follow-up, staying above every LASIK value except

Table 1 Optical density evolution in grayscale units (GSU)												
	24 hours		1 week			1 month			3 months			
	SMILE	LASIK	P value	SMILE	LASIK	P value	SMILE	LASIK	P value	SMILE	LASIK	P value
FLAP/CAP OD (GSU)	48.96±5.55	48.56±4.98	0.737	49.15±4.69	49.23±4.97	0.941	47.38±4.49	47.90±5.05	0.633	44.95±5.41	47.08±5.74	0.096
RSB OD (GSU)	50.26±7.06	49.24±6.19	0.499	50.87±6.45	49.59±6.56	0.391	48.66±6.09	48.17±6.89	0.745	45.42±7.53	46.79±6.86	0.400
Total OD (GSU)	50.34±6.49	49.52±5.99	0.566	50.92±5.86	49.83±6.27	0.428	48.65±5.70	48.18±6.53	0.743	45.46±6.96	47.15±6.28	0.265

FLAP/CAP OD, optical density of the stroma contained in the flap or cap; LASIK, laser-assisted in situ keratomileusis; OD, optical density; RSB OD, residual stromal bed optical density; SMILE, small incision lenticule extraction; total OD, total optical density of the stroma including interface.



**Figure 1** Optical density evolution of the different areas analysed in the central 2 mm of the anterior segment optical coherence tomography slice. CAP, density of the stroma included in the cap thickness; FLAP, density of the stroma included in the flap thickness; LASIK, laser-assisted in situ keratomileusis; LASIK RSB, density of the stroma under the interface; LASIK total, total density of the overall stromal tissue including interface; SMILE RSB, density of the stroma under the interface; SMILE RSB, density of the stroma under the interface; SMILE rotal, total density of the stroma under the interface; SMILE total, total density of the stroma under the interface.

in the last follow-up visit, where SMILE actually shows lower OD values than LASIK.

Regarding flap thickness, statistically significant changes are seen in the MCT and the MTT for both LASIK flap and SMILE cap, as a certain thickening of the flap and the cap is observed (table 2). This MTT increase (1 week vs 3 months postoperative) was statistically higher in LASIK (5.43  $\pm 4.23 \ \mu$ m) than in SMILE (2.76 $\pm 5.61 \ \mu$ m) (p=0.020). As seen in this table, no significant changes have been found for the rest of LASIK or SMILE analysed parameters during the entire follow-up (figure 2A). Table 3 shows cap and flap changes in homogeneity during the 3-month follow-up period. No significant changes were found during the follow-up in both cases, but comparison between CTH and FTH showed a statistically significant difference between both values at 1-month (p=0.02) and 3-month follow-up visits (p=0.046), obtaining a worse homogeneity within SMILE caps (figure 2B).

To assess accuracy of the FS laser platform, difference between targeted flap/cap thickness and MCT was  $2.73\pm8.93 \ \mu m$  (range:  $-15 \ to +19$ ) for LASIK flaps and  $11.48\pm7.85 \ \mu m$  (range:  $-4.33 \ to +28.33$ ) for SMILE caps (p=0.00003). If two sets of LASIK flaps are considered regarding the targeted flap thickness of 100  $\mu m$  or 110  $\mu m$ , then mean difference with the targeted flap

thickness is  $9.05 \pm 6.76 \,\mu\text{m}$  (0–19) for the thinner flaps (n=6) and  $1.58 \pm 8.87 \,\mu\text{m}$  (range: -15 to +18) for the regular 110  $\mu\text{m}$  flaps (n=33).

### DISCUSSION

To the best of our knowledge, this is the first study accurately describing the evolution of the corneal OD after SMILE and after Visumax-assisted LASIK. This statement is supported by the fact that all previous related studies looked at the corneal densitometry measured only with a Scheimpflug topographer (Pentacam, Oculus, Germany)<sup>12-14</sup>; however, in our study, we used a modern combined spectral-domain OCT and Placido-disk topographer (MS39, CSO, Italy) that provide the highest axial image resolution among commercially available AS-OCTs. AS-OCT technology overcomes Scheimpflug imaging, as it allows for an accurate measure of the corneal stroma, excluding the analysis of epithelium, Bowman's layer, Descemet membrane and endothelium, that is hyper-reflective in AS-OCT and so a potential source of bias. Also, AS-OCT allows for a better stratification of different sections within the stroma, being able to measure not only its whole thickness, but also above and beneath the surgical plane, excluding any potential bias induced from the interface.

While previous evidence could not find significant differences in postoperative corneal densitometry after LASIK and SMILE, concluding that the delayed visual recovery seen in SMILE is not related to changes in corneal density,<sup>12–14</sup> we have observed a statistically significant reduction of all SMILE OD parameters (about 10% improvement) during the follow-up period (table 1 and figure 1). This finding, not observed in any of LASIK OD parameters (about 5% improvement), could justify SMILE's delayed visual recovery by reflecting a progressive improvement in corneal stroma transparency. Although we could not demonstrate statistically significant differences between both techniques at any time point, there was an obvious tendency for worse total OD values at the early postoperative in SMILE (mainly at the expense of the RSB OD; table 1), showing a progressive improvement after the first postoperative month, ending with even better values than LASIK at the end of the follow-up (figure 1). A larger study sample could prove this worse early postoperative OD in SMILE in comparison with LASIK, correlating with the observed significant progressive improvement when SMILE values are analysed alone. Nevertheless, our data demonstrates that, after 3 months, OD of the anterior corneal stroma is equal with both techniques, correlating with their equivalent efficacy and safety outcomes.<sup>1</sup> As previously discussed, it has been suggested that curved low-pressure coupling contact glass interfaces (as the one obtained with Visumax) associate with an early transient increase in corneal OD.9 Thus, considering that all LASIK and SMILE procedures were performed using the same technology in the current study, any difference in OD between

Table 2	hickness evolution of flaps and caps							
	24 hours	1 week	1 month	3 months	P value			
MCT FLAP	105.29±8.92 (90–127)	104.99±7.37 (88.67–124.67)	107.52±7.33 (95.33–126)	111.19±8.54 (94.33–128)	0.11×10 <sup>-6</sup>			
MCT CAP	127.07±8.42 (111.33–147)	129.98±10.84 (114.67-158)	128.77±9.15 (114–154.33)	131.00±7.83 (115.67–148.33)	0.0118			
MTTFLAP	113.11±5.87 (102.82–125.70)	111.71±5.22 (98.24–120.24)	114.12±4.57 (105.33–126.67)	117.14±5.93 (101.71–125.5)	0.12×10 <sup>-11</sup>			
MTTCAP	132.18±6.11 (121.73–144.76)	131.92±6.85 (116.12–143.67)	133.07±7.08 (120.56-147.22)	134.69±6.15 (122.50–148.12)	0.0014			
SDFLAP	7.55±2.24 (3.48–13.63)	7.61±2.03 (4.45–12.21)	7.49±2.03 (4.24–11.73)	7.42±2.22 (3.34–13.95)	0.945			
SDCAP	7.38±2.08 (3.38–11.77)	7.89±2.10 (4.41-14.38)	7.88±2.64 (3.52–14.38)	7.25±2.63 (2.98–13.14)	0.241			
RANGE FLAP	27.51±8.72 (11–42)	26.44±6.52 (17-42)	26.51±7.44 (14–43)	26.23±7.38 (14–43)	0.769			
RANGE CAP	25.97±7.55 (12-44)	28.23±9.05 (15-58)	27.64±9.40 (13-58)	26.15±9.30 (9–49)	0.421			

MCT, mean central thickness; MTT, mean total thickness; Range, difference between the thicker and thinner point; SD, SD of the MTT.

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**Figure 2** (A) Cap and flap mean total thickness (MTT) evolution during the entire follow-up. MTT: mean thickness considering all points measured with the AS-OCT slice. (B) Evolution of cap and flap thickness homogeneity (CTH & FTH) during the 3-month follow-up. Homogeneity: difference of the thickness in two symmetrical points at 2 mm from the centre of the flap or cap.

<b>Table 3</b> Flap and cap homogeneity: differences of thickness between2 points at 2 mm from the centre nasally and temporally								
	24 hours	1 week	1 month	3 months	P value			
FTH	7.21±5.86 (0–21)	6.79±5.84 (0–25)	6.31±4.95 (0–21)	6.28±5.79 (0–29)	0.831			
CTH	8.41±5.47 (2–21)	7.79±5.68 (0–23)	9.77±7.67 (0–26)	9.43±7.79 (0–26)	0.271			

CTH, cap thickness homogeneity; FTH, flap thickness homogeneity.

both techniques could only be explained by the different degree of intraoperative trauma to the corneal stroma.

Although we have previously studied LASIK flap OD provided by other FS laser platforms using the same methodology,<sup>9–11</sup> we have not been able to directly compare those outcomes with the ones provided in the current study as different OCT technologies have been used for the OD measurement.

Reinstein et al were the first to describe, by the use of highfrequency digital ultrasound, the progressive thickening of the cornea after central myopic ablations due to the compensatory effect of the corneal epithelium (mean epithelial thickening up to 5 µm from 1 day to 1 month postoperative, and an additional 1 µm from 1 month to 3 months postoperative).<sup>15</sup> In the same direction as Reinstein and other authors, <sup>15</sup><sup>16</sup> we have observed a statistically significant progressive thickening of both LASIK flap and SMILE cap during the follow-up (table 2 and figure 2A). Interestingly, this increase was significantly higher after LASIK (about 5 µm) than after SMILE (about 3 µm). This smaller thickening after SMILE could be related to a real smaller epithelial remodelling or to an associated limited stromal deswelling that could be masking an equivalent epithelial thickening. Further investigation is needed if the biomechanics of the cap in comparison to the flap could influence on this remodelling, as the flap is a 'free-floating' piece of tissue in contrast to the cap, which is all around still anchored and may influence the capacity of the collagen fibres to reorganise anteriorly (gaining thickness). Nevertheless, these findings are in contrast with previous studies of our group,<sup>9-11</sup> where we could not demonstrate these changes in the LASIK flap thickness (with other FS laser platforms) during the follow-up, suggesting that modern AS-OCT technology might be superior to other spectraldomain AS-OCT technology used in those studies in order to accurately measure small corneal thickness changes.

Regarding Visumax accuracy in obtaining flap/cap thicknesses close to target, we observed a tendency to create thicker SMILE caps (+11.48 µm), with dispersion from target significantly higher than the one observed for LASIK flaps  $(+2.73 \mu m)$ . This accuracy is similar to the one reported by Reinstein et al using high-frequency digital ultrasound for Visumax-LASIK flaps (+2.3  $\mu$ m),<sup>17</sup> but worse than the one they reported for SMILE (between -2.3 and +6.5  $\mu$ m).<sup>18</sup> In contrast with previous literature, Visumax-LASIK flap thickness accuracy was similar to the one reported previously by our group with other laser platforms with high-pressure flat interfaces,<sup>9</sup> not confirming our previous statement about the superiority of these flat interfaces compared with the lowpressure curved ones for the specific case of Visumax laser platform. However, we should take into account that use of different imaging technology could have biased this conclusion. Finally, flap and cap thickness homogeneity did not change during the follow-up, but SMILE caps showed a significantly worse homogeneity than LASIK flaps (figure 2B). This finding may be explained by the fact that, in SMILE, FS laser first performs the deep (and refractive) cut of the lenticule, continuing with the superficial and nonrefractive cut (parallel to the corneal surface) that corresponds to the cap. The high pressure created by the gas within the deep stroma during the FS laser photodisruption may induce an uneven compression to the anterior cornea when the anterior cut is being performed, thus inducing some heterogeneity in the thickness of the cap. This does not happen in LASIK flaps, where the FS laser spots are only focused in one dissection plane.

In conclusion, both SMILE caps and LASIK flaps show a significant rethickening during the follow-up. To the best of our knowledge, this study shows for the first time that SMILE corneas present higher densities during the early postoperative period, with a significant decrease thereafter and up to 3 months, whereas LASIK corneas show a non-significant decrease in OD. This early OD rise, and subsequent improvement, is likely related to the delayed visual recovery seen after SMILE and might be related to an increased surgical manipulation.

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Data availability statement All data relevant to the study are included in the article

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**Clinical science** 

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