All-Femtosecond Laser Keratorefractive Surgery

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Abstract During the last few years, refractive lenticule extraction (ReLEx) has been introduced as a new approach in the field of keratorefractive surgery. In contrast to previous treatments, ReLEx is an all-femtosecond laser treatment where a refractive lenticule is created within the intact cornea. The lenticule can be removed using a flap-based approach (ReLEx flex), but in its latest evolution (ReLEx smile), the lenticule is extracted through a small peripheral incision, leaving most of the anterior stroma untouched. In theory, this approach should spare most of the corneal nerves and minimize the biomechanical impact of the procedure. Clinical studies have shown the safety and the visual and refractive outcomes after ReLEx to be as good as after FS-LASIK. The current article aims to provide an up-to-date overview of all-femtosecond laser keratorefractive surgery with particular emphasis on the most current of approach, ReLEx smile.

Keywords Myopia · Astigmatism · Laser in situ keratomileusis (LASIK) · Keratorefractive surgery · Femtosecond laser · Refractive lenticule extraction (ReLEx)

Introduction

Excimer Laser Keratorefractive Surgery

During the last 20 years, the excimer laser has dominated the field of keratorefractive surgery, initially with surface

ablation procedures such as photorefractive keratectomy (PRK) and later with the flap-based laser in situ keratomileusis (LASIK). Due to excellent patient satisfaction, high precision, and very good safety [1, 2], LASIK has become one of the most frequently performed surgical procedures worldwide. LASIK is performed as a two-stage procedure, which involves the cutting of a flap in the anterior stroma followed by excimer laser photoablation of stromal tissue. Within the last decade, femtosecond lasers have mostly replaced manual microkeratomes for cutting of the LASIK flap (FS-LASIK). Although this may have improved the clinical outcome [3], the procedure still has potential weaknesses. First, flap-related complications such as traumatic flap dislocation [4], reduced corneal sensitivity due to severed stromal nerves [5], and surgically induced ectasia due to loss of biomechanical strength [6] remain significant challenges. Second, several factors may influence the precision of the photoablative procedure, including corneal hydration, room humidity, patient age, parallax error, and laser fluency [7, 8]. Furthermore, in surface ablation procedures, postoperative wound healing may cause stromal haze formation and affect the long-term stability of the obtained refractive correction, with myopic regression as a well-known complication of high myopic corrections [9].

All-Femtosecond Laser Keratorefractive Surgery

Within the last few years, surgical extraction of a refractive lenticule, or ReLEx[®], has evolved as a new treatment in the field of keratorefractive surgery. Presently, the Visumax[®] femtosecond laser (Carl Zeiss Meditec) is the only platform to offer this treatment. The 500-kHz Visumax laser generates very fast pulses (10^{-15} s) in the near-infrared spectrum. Depending on the specific laser settings, each pulse

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conveys approximately 150 nJ, which causes localized photodisruption at the focal point. The generated plasma expands, creating a cavitation bubble and, as individual cavitation bubbles fuse, the stroma is cut with a minimum of collateral damage. The Visumax uses a high numerical aperture, concave contact glass to focus the laser pulses with very high precision. Thus, laser spots of approximately 1- μm diameter are placed with a defined distance of 2–5 μm in a spiral pattern. To ensure centration on the visual axis, the patient fixates on a blinking light, and suction is applied at the limbus to maintain stability of the eye. Initially, the posterior surface of the lenticule is cut, followed by creation of the anterior surface, which is slightly enlarged in diameter to facilitate surgical manipulation. Depending on the method used to access the lenticule, ReLEx can be divided into ReLEx flex, in which a LASIK-like flap allows surgical removal of the lenticule, and ReLEx smile, in which a small incision (approximately 2–4 mm in length) is created for manual lenticule extraction. A blunt spatula is used to break any remaining tissue bridges after the laser treatment, and the lenticule is grasped and removed with a pair of forceps.

For further details on the surgical approach, please refer to Sekundo et al. [10], Shah et al. [11], and Vestergaard et al. [12].

In contrast to LASIK, ReLEx represents a one-laser approach, where the critical laser treatment is performed on the intact cornea rather than on exposed corneal stroma. Consequently, the potential variability associated with the excimer laser photoablation is avoided. In addition, the minimally invasive ReLEx smile treatment have several theoretical advantages over flap-based treatments, including very little trauma to the corneal surface, less corneal denervation, and better biomechanical strength due to an almost intact anterior stroma. Since the first introduction of ReLEx, the repetition rate of the Visumax laser has been increased from 200 to 500 kHz, and the settings for laser spot size, energy, and distance have been optimized, changes that may have had a significant impact on the clinical outcome after surgery. Furthermore, the flap-based ReLEx flex represents an evolutionary step before ReLEx smile and is today primarily used as an introductory step for new ReLEx surgeons. Due to these changes, the present review focuses primarily on studies concerning ReLEx smile. However, the number of clinical publications on ReLEx is still very limited, with only approximately five papers reporting on the outcome after ReLEx smile and fewer than 20 papers investigating ReLEx flex, many of which consider the initial 200-kHz Visumax. Thus, where appropriate, significant studies on ReLEx flex are incorporated.

At present, the Visumax allows myopic corrections up to –10 diopters (D) spherical equivalent (SE) correction, with

an astigmatic component of up to 5 D. Hyperopic treatments are not available at the moment, although one study has reported on the outcome of hyperopic ReLEx flex [13]. The Visumax laser is CE (Conformité Européenne) marked and is currently being evaluated in clinical studies for the approval of ReLEx by the FDA (US Food and Drug Administration).

Clinical Results

Refractive Outcome

Overall, ReLEx has been reported to have high refractive predictability (Table 1). In the largest report to date on ReLEx smile in 670 myopic eyes 3 months after surgery, the mean error in SE refraction was -0.25 ± 0.44 D, with 80 % of eyes within ± 0.50 D and 94 % within ± 1.0 D [14•]. We recently extended this evaluation to the first 1,574 eyes 3 months after ReLEx smile and found a similar mean error of -0.15 ± 0.50 D with 77 % of eyes within ± 0.50 D and 95 % within ± 1.0 D [31]. Other reports on ReLEx smile [11, 12, 15, 16] and 500-kHz ReLEx flex [17–21] have found very similar refractive outcomes in smaller numbers of patients.

The refractive stability after ReLEx smile has not been extensively investigated. However, in one study on 279 eyes with high myopia, refraction was found to be stable from 1 to 3 months after surgery, although a minor regression of -0.15 D was observed during the first month [12]. One other study on 54 eyes found no regression during the first 6 months after surgery [15]. Similarly, no regression has been found during the first 3–6 months after 500-kHz ReLEx flex [17, 18, 20, 21] or for 1 year after 200-kHz ReLEx flex [22, 23].

Interestingly, the refractive predictability after ReLEx smile has been found to be unrelated to the degree of the attempted myopic correction [14•]. This stands in contrast to excimer-based treatments, which show decreasing precision with increasing myopic correction [24]. Furthermore, other parameters including preoperative corneal power, patient age, and gender have been found to have very limited impact on the refractive outcome after ReLEx smile [14•].

Correction of high astigmatism has not yet been systematically evaluated after ReLEx. Only one paper on 200-kHz ReLEx flex contains a rigorous evaluation of the outcome after cylinder correction [25]. An undercorrection of approximately 10 % was reported; however, the average preoperative cylinder was only 0.96 ± 0.87 D, and the population skewed toward low corrections, making it difficult to extrapolate to high astigmatisms. Recently, we evaluated correction of myopic astigmatism with ReLEx

Table 1 Overview of studies on refractive lenticule extraction (ReLEx) reporting refractive outcome, visual outcome, and safety, based on the surgical approach

200 kHz ReLEx flex	Study method	Number of eyes	Follow-up period (months)	Refractive outcome	Regression	Visual outcome	Two-line loss in CDVA (%)
Sekundo et al. [10]	Prospective study	10	6	40 % within $\pm$ 0.5D	None	90 % UDVA $\geq$ 20/40	None
Blum et al. [22]	Prospective study	108	6	75 % within $\pm$ 0.5D	None	73 % UDVA $\geq$ 20/20	0.9
Kunert et al. [25]	Retrospective study	182	6	77 % within $\pm$ 0.5D	Not reported	75 % UDVA $\geq$ 20/20	2
Gertner et al. [23]	Case control series. ReLEx flex vs. FS-LASIK	44	12	84 % within $\pm$ 0.5D	0.14D	68 % UDVA $\geq$ 20/20	None
500-kHz ReLEx flex							
Ang et al. [20]	Prospective study	33	3	82 % within $\pm$ 0.5D	None	65 % UDVA $\geq$ 20/20	None
Kamiya et al. [18]	Prospective study	38	6	100 % within $\pm$ 0.5D	None	87 % UDVA $\geq$ 20/20	8
Vestergaard et al. [17]	Case control series. ReLEx flex vs. FS-LASIK	80	3	83 % within $\pm$ 0.5D	None	88 % UDVA $\geq$ 20/25	3.8
Kamiya et al. [19]	Case control series. ReLEx flex vs. FS-LASIK	43	3	84 % within $\pm$ 0.5D	Not reported	98 % UDVA $\geq$ 20/20	None
Demirok et al. [21]	Paired eye study. ReLEx flex vs. FS-LASIK	14	6	86 % within $\pm$ 0.5D	None	95 % UDVA $\geq$ 20/25 (by 1 month)	None
200-kHz ReLEx smile ^a							
Sekundo et al. [16]	Prospective study	91	6	80 % within $\pm$ 0.5D	None	84 % UDVA $\geq$ 20/20	2.2
Shah et al. [11]	Prospective study	51	6	91 % within $\pm$ 0.5D	None	79 % UDVA $\geq$ 20/25	2
ReLEx smile							
Hjortdal et al. [14]	Prospective study	670	3	80 % within $\pm$ 0.5D	Not reported	84 % UDVA $\geq$ 20/25	2.4
Vestergaard et al. [12]	Prospective study	279	3	77 % within $\pm$ 0.5D	0.15D	73 % UDVA $\geq$ 20/25	0.4
Zhao et al. [15]	Prospective study	54	6	93 % within $\pm$ 0.5D	None	98 % UDVA $\geq$ 20/20	None

CDVA corrected distance visual acuity, UDVA uncorrected distance visual acuity

^a The early ReLEx smile procedures were performed with two large (60°) incisions (one superior and one inferior)

smile in 775 eyes, of which 106 eyes had an astigmatism of 2.50 D or more. On average, 95 % were within ± 1.0 D of the attempted spherical equivalent correction three months after surgery. However, a significant astigmatic undercorrection was observed, with an average error of treatment of 0.17 ± 0.42 D in low astigmatism and 0.59 ± 0.65 D in high astigmatism [26].

At present, only one study has examined hyperopic treatment (average SE refraction $+2.8 \pm 1.3$ D) with 200-kHz ReLEx flex [13]. After 9 months, only 64 % of patients had a postoperative refraction within ± 1.0 D of that attempted, and there was significant regression of the effect during the first 6 months after surgery. Thus, it still remains to be determined whether ReLEx eventually will allow safe and predictable hyperopic treatments.

Visual Outcome

In the first clinical studies, ReLEx flex was reported to have delayed visual recovery in comparison with FS-LASIK [11, 27]. However, later studies suggested that the laser scanning pattern and energy had an impact on the lenticule surface quality and the immediate postoperative outcome [28, 29, 30]. Subsequent changes in the laser scanning trajectory and energy delivery appear to have eliminated the problem with postoperative visual recovery.

Three studies have examined the uncorrected distance visual acuity (UDVA) after 500-kHz ReLEx smile for myopia and report 73–100 % of patients as having an UDVA of 20/25 or better 3–6 months after surgery (Table 1) [12, 14, 15]. Similar results have been reported for 500-kHz ReLEx flex [17–21], and the procedure has been found to be on par with the outcome after FS-LASIK [17, 21]. The efficacy index 3 months after ReLEx smile (postoperative UDVA/preoperative CDVA) has been found to be 0.90 ± 0.25 , indicating that a patient on average can expect a postoperative UDVA of 90 % of their preoperative CDVA [14].

Safety and Complications

The induced change in corrected distance visual acuity (CDVA) may be used as an indicator for the overall safety of a refractive surgical procedure. In general, loss or gain of two or more lines on the Snellen visual acuity card is considered significant and noticeable for the patient.

Most existing studies on ReLEx flex or ReLEx smile are too small to properly evaluate the safety of the procedure, and the frequency of a two-line loss in CDVA has been reported to lie between 0 and 8 % (Table 1) [10, 11, 15–21]. In one study on 279 eyes after ReLEx smile, 0.4 % of eyes were reported to have a loss of two or more lines [12]. In contrast, a 2.4 % risk of a two-line loss was found in 670 eyes by Hjortdal et al. [14]. However, in the same study, a

safety index (CDVA before/CDVA after surgery) of 1.07 ± 0.22 was found, indicating that CDVA on average increased after surgery, as would be expected because of the image magnification of myopic keratorefractive procedures. In a recent single-center study, the safety and complications of 1,574 ReLEx smile procedures were evaluated after 3 months [31]. CDVA was found to have improved with two or more lines in 3.4 % of eyes, whereas 1.5 % of eyes had experienced a loss of two or more lines. Yet, at a late follow-up visit, all patients with a loss in visual acuity had recovered to within one line of the preoperative value. The surgeon learning curve and the laser settings were found to be important parameters for the postoperative visual recovery. Overall, safety after ReLEx smile appears to be on par with that reported after FS-LASIK [1, 3], although recovery may be prolonged in a few cases.

Endothelial changes after ReLEx have not been systematically evaluated. Only one study on 38 eyes has reported endothelial cell counts and found that ReLEx flex induced no significant changes in endothelial cell density [18].

A variety of peri- and postoperative complications have been reported after ReLEx smile. The most frequently reported perioperative complications include tears at the incision and minor abrasions, whereas decentration, suction loss, difficulties removing the lenticule, and cap perforation may rarely occur [11, 12, 16, 17, 25]. Frequent postoperative complications include dry eye, microstriae, and increased interface scatter, whereas rare complications include keratitis, interface inflammation, epithelial ingrowth, and monocular ghost images [17, 18, 25]. Recently, we found irregular postoperative topography in 18 of 1,574 eyes, giving rise to ghost images in six cases [31]. Topography-guided PRK was performed in four of these eyes, ameliorating the symptoms in three cases. In another recent paper, a lenticule remnant was documented to be the cause of postoperative monocular double vision [32]. Postoperative ectasia has not been reported after ReLEx smile; however, one case has been documented after a flap-based ReLEx flex treatment [22].

Overall, ReLEx smile appears to be a technically more demanding surgical procedure than LASIK, introducing new potential complications related to the extraction of the refractive lenticule. Still, despite a relatively high frequency of peri- and postoperative complications, the visual outcome is reported to be good, with minimal risk of loss in CDVA on the long term.

Higher Order Aberrations (HOAs) and Contrast Sensitivity

Only three studies have compared the induced HOAs after ReLEx flex and LASIK [19] or FS-LASIK [17, 23]. In these studies, both ReLEx flex and LASIK were found to

increase the total corneal or whole-eye HOAs; however, ReLEx flex induced less spherical aberration than LASIK. Furthermore, in LASIK the induced HOAs were found to increase with the degree of attempted refractive correction, whereas in ReLEx flex no such correlation was found [19]. Parallax error during excimer laser photoablation has been suggested as an explanation for the observed differences in induced spherical aberration after LASIK and ReLEx flex [19]. As of yet, no studies have reported changes in HOAs after ReLEx smile with the 500-kHz Visumax laser.

Contrast sensitivity after ReLEx has been examined in one retrospective, comparative study on 200-kHz ReLEx flex and FS-LASIK. Both procedures showed a similar increase in photopic contrast sensitivity after 1 year; however, ReLEx flex also showed an improvement in mesopic contrast that was not found after FS-LASIK [23]. Presently, changes in contrast sensitivity have not been evaluated after ReLEx smile.

Based on the relatively few comparative studies on HOAs and contrast sensitivity, ReLEx appears to be on par with or better than LASIK; however, studies on ReLEx smile are lacking.

Corneal Sensitivity and Tear Secretion

Three studies have examined the corneal sensitivity after ReLEx smile in comparison with a flap-based treatment [33•, 34, 35]. In a randomized paired-eye study, Demirok et al. demonstrated less reduction in corneal sensitivity after ReLEx smile than after FS-LASIK, although sensitivity had fully normalized in both groups by 6 months [34]. In another randomized paired-eye study, the corneal nerve density and number of long nerve fibers were higher after ReLEx smile than after ReLEx flex [33•]; accordingly, sensitivity was better after ReLEx smile. Finally, in a comparative study on ReLEx smile, ReLEx flex, and FS-LASIK, better sensitivity was found at all time points for up to 3 months after ReLEx smile [35].

Two studies have performed a paired-eye evaluation of the postoperative tear secretion after ReLEx smile in comparison with a flap-based treatment [33•, 34]. In both studies, no significant differences in tear osmolarity, tear secretion rate, and tear meniscus height were observed. However, one study found a slight difference in the postoperative tear-film break-up time in favor of ReLEx smile [33•].

Overall, the minimally invasive ReLEx smile causes less damage to corneal nerves than flap-based treatments, resulting in better postoperative sensitivity. However, the nervous changes appear to have only minimal measurable impact on the postoperative tear secretion.

Corneal Biomechanics and Sublayer Thickness

In ReLEx smile, most of the anterior stroma remains intact after surgery. Since the cornea is biomechanically strongest in the anterior part [36], it would theoretically be more robust after ReLEx smile than after a flap-based treatment where most of the anterior lamellae are severed. Thus, ReLEx smile-treated corneas may be hypothesized to be more resistant to trauma and less prone to developing postoperative keratectasia, and they have been suggested to be even stronger than PRK-treated corneas [37•]. Furthermore, it has recently been speculated that the refractive lenticule should be removed deeper within the stroma to increase the postoperative corneal strength [37•]. Although this might be advantageous from a biomechanical point of view, many factors could affect the outcome, including endothelial safety, the quality of the laser cut in deeper stroma, and the relative front- and back-surface changes. Thus, the optimal depth of the refractive lenticule still remains to be determined.

At present, only one study has been published on the biomechanical properties after ReLEx smile in comparison with FS-LASIK using the Ocular Response Analyzer [38]. This paired-eye, randomized study found no differences in corneal hysteresis (CH) or corneal resistance factor (CRF) 6 months after surgery. In a comparable study on ReLEx smile and ReLEx flex, we similarly found no difference between the methods regarding CH and CRF [39]. However, in a small comparative study on ReLEx smile, ReLEx flex, and FS-LASIK, we recently found the biomechanical response, as measured with the Corvis ST, to be more abnormal after a flap-based treatment than after ReLEx smile [40]. Overall, the biomechanical changes after ReLEx smile are still unclear, and there is a considerable need for further studies.

A planar and uniform flap is generally considered important in flap-based keratorefractive surgery, and three studies have found the cap to be of nearly uniform thickness and similar to the flap after ReLEx flex or FS-LASIK [15, 41, 42]. Furthermore, in one study, no significant changes were observed in central cap or stromal bed thickness for 6 months after surgery [42]. We recently evaluated corneal sublayer thicknesses after ReLEx smile and ReLEx flex [39] and found no significant difference in cap or stromal bed thickness 6 months after surgery. However, as seen after other myopic keratorefractive procedures [43, 44], a compensatory epithelial hyperplasia was observed.

Retreatment

Although ReLEx has been found to have a high refractive predictability, some patients have a postoperative residual

refractive error due to over- or undercorrection [14••]. In flap-based treatments, an excimer-based enhancement procedure can be performed after lifting the flap [45]. However, retreatment after ReLEx smile is more complicated.

Possible approaches may include PRK or LASIK, whereas a new ReLEx procedure may be more unpredictable due to multiple dissection planes within the cornea. Presently, no systematic clinical evaluation of ReLEx smile enhancements has been published. However, one study has reported on successful topography-guided PRK in ReLEx smile patients with postoperative irregular astigmatism [31], and another has reported on successful FS-LASIK in a patient with perioperative suction loss [46]. Furthermore, in a rabbit model, the conversion of a ReLEx smile cap to a flap has been demonstrated, allowing subsequent intrastromal photoablation [47]. Still, the optimal approach for ReLEx smile enhancements needs to be established.

Experimental Studies

In excimer laser keratorefractive surgery, the energy delivered to the cornea may promote subsequent inflammation and wound repair [48]. In contrast to the excimer laser, femtosecond lasers deliver only minimal amounts of energy to surrounding tissue [49], suggesting that the femtosecond laser may induce less postoperative wound repair. In accordance, a recent study in rabbits has demonstrated ReLEx flex to induce less wound healing and inflammation than FS-LASIK, particularly after high myopic corrections [49]. Whether this observation has any clinical consequence remains to be determined; however, wound repair after LASIK and, in particular, PRK has been extensively investigated and is known to influence the postoperative outcome [48, 50, 51].

Extracting an intact stromal lenticule from the cornea opens new interesting possibilities in keratorefractive surgery. First, if the extracted tissue can be successfully preserved, the surgical procedure may in theory be reversed at a later time point by reimplantation of the lenticule. Second, the lenticule could, speculatively, be used to change the refraction in another individual, for example, by implanting a myopic lenticule in the stromal pocket of a hyperopic patient, a procedure that in Europe at least would require permission from national authorities. In a recent study, refractive lenticules from rabbit eyes were demonstrated to have an intact collagen structure and viable keratocytes after 1 month cryopreservation [52]. Other studies in rabbits and primates have shown

successful cryopreservation and later reimplantation of a stromal lenticule [53–55]. Furthermore, in primates, the procedure was shown to induce little postoperative wound repair, and keratocyte repopulation could be observed after 16 weeks [46]. Thus, although further studies are needed, lenticule reimplantation or transplantation from one patient to another may become reality in the near future.

Conclusion

Several studies have shown that the refractive and visual outcomes after ReLEx smile and ReLEx flex are as good as after FS-LASIK, and ReLEx has even been indicated to induce fewer HOAs. Furthermore, ReLEx smile has been shown to be as safe as LASIK, although the procedure may be technically more demanding and have a different variety of complications.

The minimal impact on the anterior stroma in ReLEx smile represents the most interesting aspect of the new procedure. Thus, stromal nerves are spared, and ReLEx smile has been convincingly demonstrated to cause less denervation and have better sensitivity than flap-based treatments. Yet, the impact on postoperative tear secretion and dry-eye symptoms remains unclear. Due to the intact anterior stromal lamellae, the cornea may be stronger after ReLEx smile than after a flap-based treatment. However, biomechanical differences have proven elusive and have not yet been positively confirmed.

In its current state, ReLEx smile has been shown to be a reliable, efficient, and safe procedure for myopic corrections. Correction of myopic astigmatism also appears promising, but hyperopic treatments need further evaluation, and the long-term outcome and biomechanical properties of ReLEx smile remain undetermined. Furthermore, compensation for eye rotation as well as aspheric or custom lenticule profiles is still not available. Thus, in complicated cases with irregular corneas, the excimer laser is still the only valid option. In contrast, ReLEx may allow exciting new treatments including reimplantation or transplantation of refractive lenticules, and it is of considerable interest to see the further evolution of ReLEx over the coming years.

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- Of importance,
- Of major importance

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