Concurrent laser-assisted in situ keratomileusis with high-fluence cross-linking versus laser-assisted in situ keratomileusis only in treatment of hyperopia
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Purpose
To compare refractive and corneal structural stability after laser-assisted in situ keratomileusis (LASIK) with and without concurrent prophylactic high-fluence cross-linking in the treatment of hyperopia.

Patients and methods
In an interventional prospective nonrandomized comparative study, 50 eyes of 25 patients with hyperopia (+1 D to +6 D) or hyperopic astigmatism (up to 4 D) underwent customized LASIK with concurrent prophylactic high-fluence cross-linking in the right eye (group A) and customized LASIK only in the left eye (group B). Main outcome measures included postoperative uncorrected visual acuity (UCVA), manifest and cycloplegic refractive spherical equivalent, keratometric readings, and spherical aberrations throughout the 2 years of postoperative follow-up.

Results
There were statistically significant changes in all studied parameters between preoperative and postoperative follow-up at 3 months, 1 year, and 2 years in both groups, and these changes remained stable in group A throughout the follow-up period. UCVA was statistically significantly better in group A compared with group B at 3 months (P=0.02). In group B, UCVA was highly statistically significant better at 1 year compared with that at 3 months (P=0.005).

Conclusion
LASIK with concurrent prophylactic high-fluence has better visual outcomes and stability compared with LASIK alone in the treatment of hyperopia.

Keywords: collagen cross-linking and laser-assisted in situ keratomileusis reoperations, hyperopia, laser-assisted in situ keratomileusis, post-laser-assisted in situ keratomileusis regression

Introduction
Laser-assisted in situ keratomileusis (LASIK) is the most commonly practiced refractive surgical procedure. Its use in the treatment of hyperopia and hyperopic astigmatism is safe, predictive, and efficient [1–3]. LASIK ablation in hyperopia involves an annular area in the corneal periphery. The required refractive effect is attained by inducing relative flattening at the periphery of the cornea together with a concomitant relative steepening of its center (optical area). There are many recent innovations in LASIK technology; however, it still has some limitations. The late regression is the most important limitation after treatment of hyperopia [4]. LASIK induces weakening of the anterior corneal layers and decreases the overall corneal rigidity, and this can explain refractive regression [5–7] Improving corneal biomechanics may be helpful to overcome this concern. LASIK treatment in hyperopia has an intrinsic biomechanical reaction, which leads to progressing flattening of the central cornea. So, concurrent prophylactic high-fluence cross-linking (CXL) with LASIK reduces this intrinsic progressive flattening by reinforcing the biomechanical properties of the cornea. This offers more stability and enables to treat higher degrees of hyperopia [8]. CXL is currently widely used in the treatment of primary and post-LASIK ectasia [9,10].

In this study, the results of LASIK were compared with those of LASIK with concurrent prophylactic high-fluence CXL in treatment of hyperopia regarding efficacy, spherical aberrations, and refractive and keratometric stability over the period of 2 years.
Patients and methods

Study design
This was a prospective, nonrandomized, comparative, interventional, case series study. The study was approved by the local ethical committee of Faculty of Medicine, Minia University, and was adherent to the Tenets of the Declaration of Helsinki. Informed written consent was taken from all patients for the surgical procedure and for inclusion in the study after comprehensive explanation of the aim of the study, benefits, and all possible risks.

Fifty eyes of 25 patients with age ranged between 18 and 58 years were included in the study. The patients included four males and 21 females with bilateral hyperopia or hyperopic astigmatism. They underwent customized LASIK with concurrent prophylactic high-fluence CXL in the right eye (group A) and customized LASIK only in the left eye (group B). Both groups were further divided into two subgroups. Eyes with spherical equivalent below +3 D were allocated in groups A1 and B1, whereas those with spherical equivalent equal to or above +3 D were allocated in groups A2 and B2. Inclusion criteria included patients with hyperopia +1 D to +6 D or hyperopic astigmatism up to 4 D with stable refraction. Patients younger than 18 years were excluded from this study. Moreover, patients with previous intraocular or corneal surgery, active corneal disease, irregular corneas or abnormal corneal topography including keratoconus or keratoconus suspects, dry eye, and any other ocular comorbidities all were excluded as well.

Main outcome measures were evaluated preoperatively and at 3 months, 1 year, and 2 years postoperatively and included Log–Mar uncorrected visual acuity (UCVA), manifest refractive spherical equivalent (MRSE), cycloplegic refractive spherical equivalent (CRSE) by autorefractometer, keratometry measurements using oculus pentacam (OCULUS Inc., Waltham, MA, USA), and spherical aberrations at 4 mm and at maximum pupil diameter using iDESIGN advanced wave scan system, which utilizes a high-definition Hartmann-Shack Wavefront sensor.

Surgical technique
All surgeries were performed using STAR S4 IR Excimer Laser with optical zone of 6 mm and ablation zone of 9 mm.

For eyes in group A, after the laser ablation, the flap was folded onto itself and protected with a dry Wexel sponge, and then one drop of Vibex Rapid (Avedro Inc., Waltham, Massachusetts, USA), consisting of 0.10% saline-diluted riboflavin in a slightly hypotonic solution, mixed with ocular viscoelastic devices, was carefully spread over the bare stromal bed with an irrigating cannula for one minute. Following stromal soaking, the flap was properly repositioned into place, and the residual riboflavin was washed. This was followed by application of UVA fluence of 30 mW/cm² for 80 s (overall energy of 2.4 J/cm²) delivered by the KXL CXL system (Avedro Inc.).

Postoperative treatment included topical moxifloxacin 0.5% eye drops, a combination of topical dexamethasone and tobramycin eye drops four times daily for 2 weeks, and topical tear substitute for 4 weeks.

Statistical analysis
SPSS for Windows software (version 20.0.; SPSS Inc.) was used. Data were normally distributed and tested by Shapiro–Wilk normality test. The parametric test was used for statistical analysis. A paired sample t test was used in the same group between preoperative and postoperative data and independent sample t test between the two groups. P value was considered significant if it was less than 0.05.

Results
In group A, the Log–Mar UCVA was 0.63±0.31 preoperatively with a statistically highly significant change to be 0.34±0.17, 0.37±0.24, and 0.38±0.28 at 3 months, 1 year, and 2 years postoperatively, respectively (P=0.0001). MRSE was 2.7±1.9 D preoperatively with a statistically highly significant decrease postoperatively to +0.3±0.9, +0.4±0.9, and +0.7±0.8 D after 3 months, 1 year and 2 years, respectively (P=0.0001). CRSE was +1.1±0.7, +1±0.8, and +1.1±1 D for the 3 months, 1 year, and 2 years postoperatively, respectively, compared with +3.3±2 D preoperatively (P=0.0001). Medium keratometry was 46.1±2, 45.9±1.9, and 45.8±2.1 D at 3 months, 1 year, and 2 years postoperatively, respectively, compared with 43.6±1.6 D preoperatively (P=0.0001). Spherical aberration at 4 mm was −0.08±0.1, −0.09±0.1, and −0.08±0.1 for the 3 months, 1 year, and 2 years postoperatively, respectively, compared with 0.04±0.03 preoperatively (P=0.0001).

Spherical aberration at maximum pupil diameter was −0.2±0.3, −0.2±0.2, and −0.2±0.2 for the 3 months, 1 year, and 2 years postoperatively, respectively, compared with 0.2±0.1 preoperatively (P=0.0001). All data remained stable during the follow-up period.
for 2 years, indicating visual, refractive, and keratometric stability in group A.

Group A was subdivided into subgroups A1 for eyes with less than +3 D preoperative spherical equivalent and included 14 eyes and subgroup A2 for those ≥+3 D preoperative spherical equivalent and included 11 eyes.

At 3 months postoperative, UCVA Log–Mar was significantly better (0.014) in the subgroup A1 (0.27 ±0.15) compared with subgroup A2 (0.47±0.22). Coma, spherical aberration at 4 mm, and spherical aberrations at maximum pupil diameter, were significantly better in subgroup A1 than subgroup A2 and were 0.025, 0.001, and 0.002, respectively. At 1 year postoperatively, UCVA Log–Mar was significantly better (0.006) in the subgroup A1 (0.25±0.15) than in subgroup A2 (0.51±0.28). Coma, trefoil, spherical aberrations at 4 mm, and spherical aberrations at maximum pupil diameter were significantly better in subgroup A1 than subgroup A2 and were 0.030, 0.017, 0.003, and 0.006, respectively. At 2 years postoperatively, UCVA Log–Mar was significantly better (0.036) in the subgroup A1 (0.24±0.14) than in subgroup A2 (0.51 ±0.33). Trefoil, spherical aberrations at 4 mm, and spherical aberrations at maximum pupil diameter were significantly better in subgroup A1 than subgroup A2 and were 0.046, 0.001, and 0.007, respectively.

In group B, preoperative UCVA Log–Mar was 0.62 ±0.19 compared with of 0.51±0.31, 0.42±0.28, and 0.45±0.28 for the 3 months, 1 year, and 2 years postoperatively, respectively (P=0.06). UCVA was significantly better at 1 year than 3 months (P=0.005), which means visual instability during the follow-up period in group B. MRSE was +0.6±0.8, +0.7±0.9 D, and +1±0.8 D at 3 months, 1 year, and 2 years postoperatively, respectively, compared with +2.7 ±1.7 D preoperatively (P=0.0001). CRSE was +1.2 ±0.9, +1.2±0.9, and +1.3±0.9 D at 3 months, 1 year, and 2 years postoperatively, respectively, compared with +3.3±1.8 D preoperatively (P=0.0001). Medium keratometry was 45.7±2.1, 45.6±1.9, and 45.7±2.06 D, for the 3 months, 1 year, and 2 years postoperatively, respectively, compared with 43.6±1.6 D preoperatively (P=0.0001). Spherical aberration at 4 mm was -0.05±0.1, -0.05±0.1, and -0.06±0.1 for the 3 months, 1 year, and 2 years postoperatively, respectively, compared with 0.05±0.03 preoperatively (P=0.0001). Spherical aberration at maximum pupil diameter was -0.2±0.3, -0.2±0.3, and -0.2±0.2 for the 3 months, 1 year and 2 years postoperatively, respectively, compared with 0.2±0.1 preoperatively (P=0.0001).

Group B was subdivided into subgroups B1 for eyes with less than +3 D preoperative spherical equivalent and included 14 eyes and subgroup B2 for those more than or equal to +3 D preoperative spherical equivalent and included 11 eyes. At 3 months postoperative, no significant difference in UCVA in both subgroups was seen. Coma, spherical aberration at 4 mm, and spherical aberrations at maximum pupil diameter were significantly better in subgroup B1 than subgroup B2 and were 0.002, 0.008, and 0.002, respectively. At 1 year postoperative, no significant difference in UCVA in both subgroups was seen. Coma and spherical aberrations at maximum pupil diameter were significantly better in subgroup B1 than subgroup B2 and were 0.018. UCVA was significantly better in subgroup B2 at 1 year (0.49 ±0.27) than at 3 months (0.6±0.34), with P value of 0.026.

Regarding the comparison between groups A and B, UCVA was significantly better in group A than group B at 3 months with a P value of 0.02. UCVA was significantly better in subgroup A1 than subgroup B1 at 3 months with P value of 0.047. A detailed comparison between preoperative and postoperative data in both groups is presented in Table 1, and spherical equivalent in both groups is presented in Fig. 1.

**Discussion**

There is a marked improvement in diagnostic tools and in excimer laser technology; however, LASIK induces several biomechanical alterations [8]. It results in stromal weakening and reduces corneal rigidity [5,6]. Hyperopic regression after LASIK was documented in previous studies [11,12]. This occurs mainly within the first year after treatment [3,13–15]. In the studies of Waring et al. [15] and de Ortuea and Arba Mosquera [13], most of the hyperopic shift occurred during the first 3 months. Plaza-Puche et al. [14] reported a significant regression in the first postoperative 12 months (P<0.01) with more stable refraction thereafter (P=0.08).

CXL is a very effective innovation in the field of preservation of corneal stability and can reduce post-LASIK refractive regression. Adding more stiffness to the cornea, which has been mechanically compromised by LASIK, through CXL may reduce the adverse
effects associated with biomechanical weakening. The introduction of accelerated CXL with higher irradiance (30 mW/cm²) in cases with keratoconus and postoperative corneal ectasia has been proved to be effective at stabilizing and reducing corneal curvature. Studies have documented that accelerated CXL is as effective as conventional CXL for corneal stabilization with a high safety profile [16–18]. Combining CXL with LASIK (LASIK Xtra) can reestablish corneal strength, increase the accuracy of refractive error correction, maintain the stability of visual results, and potentially decrease regression. Regarding LASIK in hyperopia, it was suggested that it induces progressive flattening of the central area of the cornea, which may be notable up to 5 years postoperatively. Therefore, LASIK with concurrent high-fluence CXL may counteract this flattening and prevent regression in patients with hypermetropia [8]. Few articles have studied the procedure of hyperopic LASIK with prophylactic CXL [19,20]. Kanellopoulos and Kahn [19] reported that after 2-year follow-up of 34 hyperopic patients treated using LAISK Xtra, more cases with refractive regression were observed in the no-CXL group (+0.72±0.19 D) versus the CXL group (+0.22±0.31 D) (P=0.0001).

Table 1 Comparison between preoperative and postoperative data in both groups

|                  | Preoperative | 3 months | 1 year | 2 years |
|------------------|--------------|----------|--------|---------|
|                  | Group A      | Group B  | Group A| Group B |
| UCVA (Log-Mar)   | 0.63±0.31    | 0.62±0.19| 0.34±0.17| 0.51±0.31|
| Spherical equivalent | 2.7±1.9     | 2.7±1.7  | 0.3±0.9 | 0.6±0.8 |
| Cycloplegic spherical equivalent | 3.3±2       | 3.3±1.8 | 1.1±0.7 | 1.2±0.9 |
| BCVA (Log-Mar)   | 0.28±0.16    | 0.23±0.14| 0.35±0.02| 0.4±0.2  |
| K1               | 42.8±1.8     | 42.7±1.6 | 45.6±1.9| 45.3±2.1 |
| K2               | 44.4±1.6     | 44.5±1.9 | 46.5±2.1| 46.2±2.2 |
| Km               | 43.6±1.6     | 43.6±1.6 | 46.1±2 | 45.9±2.1 |
| High order aberrations % | 12±10.5    | 10.2±6.2 | 52±18 | 48.7±21.8 |
| Spherical aberrations at 4 mm | 0.04±0.03  | 0.05±0.3 | 0.08±0.05| 0.05±0.10 |
| Spherical aberrations at maximum pupil diameter | 0.2±0.1 | 0.2±0.1 | 0.2±0.3 | 0.2±0.3 |

BCVA, best-corrected visual acuity; UCVA, uncorrected visual acuity.

Figure 1

Spherical equivalent t in both group pre and post. Operatives.
In the current study, 50 eyes of 25 patients with mean age of 35.6±12.1 years, comprising four males and 21 females, with bilateral hyperopia or hyperopic astigmatism underwent customized LASIK with concurrent prophylactic high-fluence CXL in the right eye (group A) and customized LASIK only in the left eye (group B). UCVA, CRSE, MRSE, keratometric measurements, spherical aberrations at 4 mm, and maximum pupil size were evaluated preoperatively and at 3 months, 1 year, and 2 years postoperatively. In both groups, UCVA, MRSE, CRSE, medium keratometry, spherical aberration at 4 mm, and maximum pupil size were significantly changed postoperatively compared with preoperative values. In group B, UCVA was significantly changed at 1 year compared with 3 months \( (P=0.005) \), indicating unstable visual acuity during the first year in the no-CXL group. UCVA was significantly better in hyperopic LASIK with concurrent prophylactic high-fluence CXL group at 3 months \( (P=0.02) \) and remains stable till 2 years postoperatively. No regression on topographic \( k \) values (means) was observed in both groups. Safety and efficacy were better in group A than group B during the follow-up period.

To the best of our knowledge, no previous studies have compared spherical aberrations in both procedures. Spherical aberrations were studied at 4 mm and at maximum pupil diameter. No significant difference was noted between both groups regarding this issue.

Our results demonstrated better visual stability, safety, and efficacy in hyperopic LASIK with concurrent prophylactic high-fluence CXL. However, larger series with longer follow-up are needed to prove this procedure as an effective procedure to prevent hyperopic regression with good refractive, visual, and keratometric stability.

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**Conflicts of interest**
There are no conflicts of interest.

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