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PHOTOREFRACTIVE SURGERY WITH EXCIMER LASER AND ITS IMPACT ON THE DIAGNOSIS AND FOLLOW-UP OF GLAUCOMA. A REVIEW

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SUMMARY

Excimer laser refractive surgery is a procedure performed worldwide to solve refractive errors and reduce dependence on glasses or contact lenses. There has been an increase in the number of procedures performed around the world. Myopia is the most common indication for corneal photorefractive surgery. Myopic patients have a higher risk of developing some type of glaucoma in their lifetime, such as primary open-angle glaucoma and others. Refractive surgery ablates central corneal stromal tissue, altering its thickness and biomechanics, which in turn makes it difficult to accurately measure intraocular pressure (IOP), since it underestimates it. This underestimation of IOP may delay the diagnosis of de novo glaucoma in patients with a history of refractive surgery. Each patient who wishes to undergo corneal refractive surgery should undergo a thorough glaucoma examination in order to monitor and detect the possible development and / or progression of glaucoma. A very useful practical approach is to perform a series of IOP measurements before and after surgery, when the eye is already stable, and the difference between the averages of the two sets of readings can then be used as a personalised correction factor for postoperative IOP monitoring in that eye. Also, if there is any suspicion of a possible glaucoma, paraclinical tests, such as coherent optical tomography of the retinal nerve fibre layer (RNFL), visual fields and photos of the optic nerve should be requested.
All this data prior to refractive surgery should be provided to these patients, so that they can save it and give it to their treating ophthalmologists in the future.
Key words: excimer laser, LASIK, SMILE, refractive surgery, glaucoma

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INTRODUCTION

Excimer laser refractive surgery in recent decades has become a widely performed procedure throughout the world, to solve a wide range of refractive errors and reduce dependence on glasses or contact lenses. With constant technological developments and advances in surgical techniques, there has been a steady increase in the number of people who have undergone photorefractive procedures worldwide. This procedure generates a change in corneal curvature, increasing or decreasing it, to correct hyperopic or myopic defects, respectively [1–5].

Myopia has a prevalence with great geographic variability, from 15 to 49 % in various areas of the world [6–8]. As moderate or severe myopia significantly affects quality of life by altering distance vision and making the individual highly dependent on optical correction, patients who undergo refractive surgery are often myopic young adults, who have a higher risk of developing at some po-

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int in their lives not only primary open-angle glaucoma (double or triple the risk) [1,9–13], but also secondary glaucomas, such as pigmentary [11,12] and steroid-induced [1]. Hyperopic patients, on the other hand, will present a future risk of angle-closure glaucoma [12]. For these reasons, it is, in the first instance, very important to educate both myopic and hyperopic patients that, although they have obtained good refractive results and enjoy good vision after refractive surgery, they still require ophthalmological evaluations to look for other long-term risks, such as glaucoma [1,14].

Refractive surgery with excimer laser affects the corneal biomechanics. The layered construction of the cornea and interlaminar adhesions are determinants of corneal rigidity. Thus, simply separating the corneal stroma into two layers, as in the creation of flaps during laser-assisted in situ keratomileusis (LASIK), significantly reduces tissue stiffness and may explain in part the post-LASIK intraocular pressure (IOP) underestimation seen with the Goldmann Applanation Tonometer [15]. It was calculated using a mathematical model that postoperative tensile strength is less affected after small incision lenticule extraction (SMILE), than after photorefractive keratotomy (PRK), or after LASIK [16]. However, this has not been confirmed clinically. Using the biomechanical parameters determined by the Ocular Response Analyser (ORA), i.e. corneal hysteresis and corneal resistance factor, in a meta-analysis it was found that corneal biomechanical strength was effectively preserved significantly better after SMILE than either after LASIK or Femtosecond LASIK (FS-LASIK), as predicted by the model. However, on the other hand, the SMILE impact on biomechanics was similar to PRK and laser-assisted sub-epithelial keratectomy (LASEK). Indeed, PRK and LASEK exhibited less reduction in corneal biomechanical strength than SMILE, although without reaching a statistically significant difference [2].

In addition, excimer laser corneal refractive surgery ablates stromal tissue to achieve curvature change and refractive correction. In myopic patients, this ablation is performed in the central area. In hyperopes, tissue ablation occurs in the mid-periphery. This focal thinning of the cornea also changes its biomechanics. Secondarily, it alters the precision of the IOP measurement, especially with applanation tonometers. Goldman tonometry has been widely shown to underestimate IOP after corneal photorefractive surgery [17,19,20–38]. This underestimation of IOP may at some point delay the diagnosis of de novo glaucoma in patients with a history of refractive surgery [39–44]. Another critical point is when the glaucoma patient wants refractive surgery [41,42].

IOP remains the only modifiable risk factor for glaucoma, and the unreliable measurements achieved with Goldmann Applanation tonometry may therefore represent a challenge in monitoring glaucoma progression and response to treatment in patients after refractive surgery [1,36,39–44].

For at least two decades it has been considered that photorefractive surgery is relatively contraindicated when there is any suspicion of glaucomatous involvement of the optic nerve, or in the presence of a filtering bleb due to surgery for previous glaucoma. This is particularly true for LASIK because, during the procedure, transient, but very high, peaks of intraocular pressure are reached [42].

Moreover, glaucoma patients are more likely to experience steroid-induced IOP elevation, medications which are commonly used after corneal refractive surgery, and the risk is higher following surface ablations, since in such cases they are prescribed for a longer time (weeks to months) [38,45].

It is essential, in order to avoid an increase in risks in patients who are candidates for photorefractive surgery, to carry out a very complete preoperative evaluation to rule out the presence of glaucoma, and also for this information to serve as a reference for long-term monitoring.

In this review, we want to emphasise the most important aspects to be taken into account in the evaluation in three different settings. The first scenario is the young patient with a diagnosis of suspected glaucoma or glaucoma who desires refractive surgery. The second scenario is the patient who attends the consultation with a history of photorefractive surgery and is found to have a suspicion of glaucoma, or a definite diagnosis of the condition. Finally, we will review some complications following LASIK related to high IOP.

PATIENTS SEEKING REFRACTIVE SURGERY

As in any other surgery, an individual analysis of the risks and benefits of the procedure should be made. Although the main interest of the refractive surgeon when examining a candidate is to rule out keratoconus or subclinical keratoconus, [46] it is also very important to evaluate in particular the possible existence of glaucoma, and to determine if there is a family history, as this would justify a much more detailed preoperative evaluation. If there are clear or highly suspicious signs of glaucomatous damage, a very careful study is mandatory prior to surgery. There can potentially be a contraindication for refractive surgery [1,14,40–43].

In cases with any suspicious finding, it is suggested that baseline measurements be established of diurnal IOP, thickness of the retinal nerve fibre layer (RNFL), visual fields and photographs of the optic nerve, as part of the preoperative study. It is very important to warn the patient about the possibility of glaucoma in the future [1,14,40,41,43]. A disadvantage of optical coherence tomography, in terms of obtaining information on the thickness of the nerve fibre layer, is that the databases of these devices (although constantly enriched) include a limited number of people, and the "unusual discs" (tilted discs, such as those of high myopia) are excluded from these databases. Unfortunately, many candidates for refractive surgery have "unusual" looking optical discs that cannot be accurately compared to "normal" optical

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discs in databases. In these cases, digital photography of the optic disc and comparison with future photos will provide valuable information about changes in both the optic nerve and the retinal nerve fibres [43].

A complete ophthalmological evaluation is essential, including gonioscopy and fundus under pupillary dilation. Assessment of the anterior chamber angle is of particular importance in hyperopes older than 40 years; cases of acute primary angle closure have been reported immediately following LASIK [47]. On the other hand, as mentioned above, evaluation of the optic nerve in myopia is often challenging due to the tilt of the nerve head along with the characteristic peripapillary atrophy.

The evaluation of the visual fields with automated systems should be part of preoperative tests in patients undergoing refractive surgery, when there is any type of suspicion of a possible glaucoma. The risk-benefit ratio must be discussed in detail with the patient, before he/she can make a decision to undergo the refractive procedure [1,14]. In cases of risk, by race, family history, or borderline intraocular pressure, even if they are not diagnosed with glaucoma, the results of the preoperative automated perimetry must be given to the patients, so that they are available as a reference for the treating physician who in future attempts to identify new visual field defects that may be related to glaucoma.

As mentioned above, it is very important to inform all refractive surgery candidates about the increased risk of myopic patients to suffer from open-angle glaucoma and, for hyperopic patients, about the greater chances of developing narrow-angle glaucoma, in the following decades. This is often forgotten by refractive surgeons, and results in patients being unaware of this issue.

It is clear that the structural alterations of the cornea after photorefractive surgery, which include a decrease in central corneal thickness in myopic ablations, have an impact that can be clinically significant in the precise measurement of IOP. Thorough documentation and record keeping of the preoperative condition of the eye is important. Future management of glaucoma, if it occurs, will be greatly facilitated by this information. Then it would be very helpful if a copy of the preoperative notes, or a specially designed form that contains the relevant information, is given to the patient for his/her records, so that he/she can provide it to anyone who is evaluating him / her for a possible glaucoma in the future. [1,14,38].

PATIENTS WITH HISTORY OF CORNEAL REFRACTIVE SURGERY WITH EXCIMER LASER

The first important point to be emphasised is that every ophthalmologist should directly question any adult patient about a past history of excimer laser refractive surgery. Often patients do not report it spontaneously, because if one or two decades have passed, they may not have it very present in their memory. In addition, at the slit lamp there are no corneal signs that indicate that a surface ablation was performed in the past. Also, in LASIK cases, the visualisation of the edge of the flap can be very difficult. If this past history is not identified, the ophthalmologist can be confident that a borderline value of tonometry is normal for that eye, when in fact it may be 3 or 4 mmHg higher.

Multiple studies have confirmed that central corneal thickness effectively influences the measurement of IOP with applanation tonometry [1,14]. This is a critical factor in ablative corneal refractive surgery, which, along with other biomechanical changes induced by the procedure, affects the measurement of the IOP after the procedure. The underestimation of IOP after photorefractive surgery using Goldmann applanation tonometry, has been documented in many studies [17,18–20,23,24,27–29,31,32,35–38].

Schipper and co-authors in 1995 reported that there was a decrease of 2 to 3 mmHg in the value found with applanation tonometry in the central area of the cornea, after myopic ablation with PRK, but that this decrease was not found when taking the pressure measurement in the temporal periphery of the cornea [17]. Similarly, in 2001 Park et al. [18] and also Rashad & Bahnassy [35] found less underestimation of the IOP when measured in the nasal peripheral cornea than in the central area. Therefore, the possibility of measuring the IOP in the periphery with an applanation tonometer, although technically challenging, seemed to be a plausible partial solution in these patients. However, as recently mentioned by De Bernardo et al. [26], 25 years ago when Schipper et al. published their study, although they did not mention the optical zones of corneal ablations used, most probably they were 4.00 to 5.00 mm, as it was the standard at that time. Currently, optical zones are usually between 6.50 to 7.00 mm and total ablation can reach a 9.00 mm diameter. Therefore, it is almost impossible to measure the IOP in a non-treated corneal area. Indeed, the differences between postoperative central and peripheral IOP measurements found by Park et al., [18] who used ablation zones 5.30 to 6.80 mm, and by Rashad & Bahnassy, [35] who mentioned an optical zone between 5.00 to 6.00 mm (both studies performed some years later than the study by Schipper et al.) were less noticeable. This might possibly be related to the change of the optical zones that occurred in the period of time between the studies [17,18,35].

In 1998 Rosa et al. published the results of their study where they used the fellow eye as control in 87 patients who underwent photorefractive keratectomy. They found a statistically significant difference (underestimation) in the IOP measured with applanation tonometer in the treated eye (from 17.7 ±2.8 mmHg before to 11.9 ±2.7 one month after surgery) and not in the fellow non-treated eye (17.1 ±3.5 mmHg to 16.7 ±3.1 one month later) [36].

Several researches during the last 15 years have found that non-contact pneumatonometry (air-puff) also exhibited a large reduction after LASIK [27–30,33].

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In a population study with a very large sample, almost 175 000 eyes, Schallhorn et al., using non-contact tonometry (air-puff pneumotonometer), in patients with both myopic and hyperopic refractive errors undergoing LASIK and PRK, found in the 4 groups of patients, a decrease in the measured IOP. The postoperative IOP of hyperopic eyes experienced a smaller underestimation than in myopic eyes, both for PRK and LASIK. Patients undergoing LASIK had a greater decrease in IOP [30].

On the other hand, some newer devices have been found to be less error-prone. Kaufmann et al. found a reduction of about 3.0 mmHg after LASIK with the applanation tonometry, but no change when measured with Pascal dynamic contour tonometer® (DCT; SMT Swiss Microtechnology AG, Port, Switzerland) [31]. Other researchers have found similar results [34,48]. This tonometer has a concave surface at the tip to avoid tangential or bending forces acting within the contact area. A miniaturised piezoelectric pressure sensor enables IOP measurement to be obtained.

The Corvis ST® is a device that comprises an air pulse indentation system and ultra-high speed Scheimpflug technology to monitor the corneal deformation response. It provides the in vivo characterisation of the corneal biomechanical properties and appears to cause less underestimation in postoperative IOP measurement compared to the Goldman tonometer [20,43]. Recently Chen et al. found that the underestimation of IOP measured using the Corvis ST® was on average slightly more than 1.0 mmHg in cases of Femtosecond laser-assisted Lasik, and close to zero after transepithelial photorefractive keratectomy; while using the applanation tonometer the magnitudes were more than 3.0 mmHg and almost 2.0 mmHg, respectively. In this study they also found that the underestimation of applanation - measured IOP readings were larger with LASIK, followed by SMILE, and the smallest differences were observed in Trans-epithelial PRK cases [20].

Table 1 summarises the findings of some selected studies on the underestimation of IOP after corneal photorefractive surgery.

Many formulas have been designed in order to calculate the real IOP based on postoperative IOP measurements, some of which are shown in Table 2. In 2016 De Bernardo et al., after testing several of these formulas in a group of 121 eyes of patients who underwent PRK, concluded that the best results were obtained by applying the formulas of Rashad, Chihara, Rosa and Duch [25,28,35–37]. However, the first two require knowledge of the intraocular pressure measured before refractive surgery, which is rarely available. Then, they suggested that, for a patient with a history of corneal photorefractive surgery, without having the data of previous intraocular pressure, the best approximation to calculate the real IOP measured with an applanation tonometer in the postoperative period would be to take the average of the formulas of Rosa and Duch. On the other hand, if the IOP data prior to refractive surgery are known, a good approximation can be obtained with an average of the Rashad and Chihara formulas [25].

In a study by Li et al. [49] that compared IOP changes after SMILE and FS-LASIK, the Ehlers [50] and Shah [51] formulas (both calculated to adjust IOP to pachymetry but not specifically designed for refractive surgery cases) were very close to preoperative IOP for both surgeries, with IOP variation approximately 1 mmHg. 6 months after the procedure; the change in Goldmann-correlated IOP, as determined by ORA device, was higher in FS-LASIK cases than in SMILE.

A very useful practical approach, suggested about 15 years ago by Bashford et al., but unfortunately seldom put into practice, is that in patients undergoing photorefractive surgery, a series of IOP measurements are performed before surgery and another series after the procedure, when the eye is already stable (i.e. one month or later post-surgery). The difference between the averages of the two sets of readings can then be used as a personalised correction factor for future IOP monitoring in that eye, clearly explaining it to the patients and providing this information in writing (or by other means e.g. e-mail) so that they can save it and give it to their treating ophthalmologists in the future [38].

INTRAOCULAR PRESSURE-RELATED COMPLICATIONS OF CORNEAL REFRACTIVE SURGERY

Increased IOP in the postoperative period of LASIK can lead to a spectrum of clinical manifestations, ranging from no corneal signs, to conditions such as pressure-induced stromal keratitis (PISK) or fluid interface syndrome (IFS), for which the name post-LASIK edema-induced keratopathy (PLEK) has been proposed [45,52].

In IFS there is a visible, although sometimes very subtle, accumulation of fluid in the interface between the LASIK flap and the underlying stromal bed, usually presenting between 10 days and 2 months after the procedure. This condition is preceded by an oedema located at the interface, but which does not form a pocket of free fluid, and is manifested as a granular haze in that area. In this state, this complication is known as PISK. The underlying cause is the presence of some degree of corneal oedema in these patients. This is usually secondary to the increase in IOP due to sensitivity to steroids, within several weeks post-LASIK [45,52]. However, the presence of ocular hypertension is not indispensable, since these clinical pictures have also presented not in the early postoperative period, but rather late, following dysfunction of the corneal endothelium after intraocular surgery in eyes with a past history of LASIK [53]. As already mentioned, since the trigger factor in these complications is corneal oedema, whether secondary to elevated IOP or endothelial failure, the name post-LASIK oedema-induced keratopathy (PLEK) has

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Table 1. Selected studies, pre and post corneal refractive surgery tonometry

First author / Year	Type of surgery	Type of refractive error corrected	Sample size (eyes)	Tonometer type	Magnitude of IOP underestimation (mmHg)
Schipper 1995[16]	PRK	M	64	Applanation (central cornea)	2.1*
				Applanation (temporal cornea)	0.4*
Park 2001[17]	Lasik nasal hinge	M	83	Applanation (central cornea)	3.9 ±2.0
				Applanation (nasal cornea)	2.0 ±2.8
Rashad & Bahnassy 2001[34]	Lasik	M	166	Applanation (central cornea)	3.69 ±1.63
				Applanation (nasal cornea)	2.39 ±1.71
Agudelo 2002[18]	Lasik	M	100	Applanation (central cornea):	
		H		Myopic Lasik	2.75 ±3.3
				Hyperopic Lasik	2.28 ±2.43
Kaufmann 2003[30]	Lasik	M	62	Applanation (central cornea)	3.00 ±1.9
				Dynamic Contour Tonometer	-0.20 ±1.5
Chihara 2005[27]	Lasik	M	100	Applanation (central cornea)	2.9 ±3.1
				Non-contact pneumatonometer (air-puff)	5.1 ±2.6
Yang 2006[28]	Lasik – nasal hinge	M	386	Non-contact pneumatonometer (air-puff)	5.9 ±0.16
Kohlhaas 2006[22]	Lasik	M	101	Applanation (central cornea)	3.56
Silva, 2011[23]	Lasik	M	15	Applanation (central cornea)	4.5 ±2.1
Schallhorn 2015[29]	Lasik	M	174 666	Non-contact pneumatonometer (air-puff):	
	PRK	H		Myopic Lasik	4.6 ±2.4
				Myopic PRK	3.2 ±2.5
				Hyperopic Lasik	2.3 ±2.3
				Hyperopic PRK	0.8 ±2.5
Lin 2016[32]	FS-Lasik	M	1228	Non-contact pneumatonometer (air-puff)	FemtoLasik = 6.4*
	Lasik		704		Lasik = 6.6*
Bahadir Kilavuzoglu/ 2018[26]	Lasik –superior hinge	M	425	Non-contact pneumatonometer (air-puff)	4.6 ±2.3
Helmy & Hashem 2020[31]	Lasik	M	300	Applanation (central cornea)	4.0 ±1.75

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Table 1. continue

First author / Year	Type of surgery	Type of refractive error corrected	Sample size (eyes)	Tonometer type	Magnitude of IOP under-estimation (mmHg)
Chen 2020[19]	FS-Lasik	M	50	Applanation (central cornea):	
	SMILE		50	FS-Lasik	3.38 ±2.76
	tPRK		44	SMILE	2.83 ±2.08
				tPRK	1.78 ±2.29
				Dynamic Contour Tonometer:	
				FS-Lasik	1.87 ±1.95
				SMILE	2.11 ±2.27
				tPRK	0.64 ±2.34
				ORA:	
				FS-Lasik	3.94 ±1.70
				SMILE	3.08 ±1.53
				tPRK	2.77 ±1.84
				Corvis ST:	
				FS-Lasik	1.21 ±1.72
				SMILE	1.46 ±1.43
				tPRK	0.18 ±1.63

Table 2. Selected published formulas for the calculation of post-photorefractive surgery corrected IOP

First Author / Year	Formula	Conventions
Rosa /1998[35]	IOP = (IOPmeasured) + (0.025* ΔCCT) + (0.34* SE-ac)	ΔCCT = Change in central corneal thickness
		SE-ac = Spherical equivalent attempted correction
Rashad & Bahnassy 2001[34]	IOPpost = 0.987 + 0.627 x IOPpre + 0.0143 x ΔCCT + 0.03044 x age	ΔCCT = Change in central corneal thickness
Duch 2001[36]	Underestimated value applanatic tonometry = 1.59 + 0.019* ΔCCT	ΔCCT = Change in central corneal thickness
Chihara 2005[27]	Underestimated value applanatic tonometry = -6.455 + (0.596* IOP pre)	
Yang /2006[28]	Predicted PIO = (0.5256 + (IOPpre*0.3220) + (CCT*0.0154) - (Kpre*0.0841) - (SEpre*0.2253) - (Ablation depth*0.0527) + (Male = 0.6917/ Female = 0) + (>30 years = 0.6085/ ≤ 30 years = 0) + 1.073)	CCT = Central corneal thickness
		Kpre = Preoperative mean keratometry
		SE = Spherical equivalent
Kohlhaas 2006[22]	Real IOP = Measured IOP + (540-CCT)/71 + (43 - K-value)/2.7+ 0.75	CCT = Central corneal thickness
		K-value = Mean keratometry
Bahadir Kilavuzoglu/ 2018[26]	Predicted IOP = 6.194 + (0.448)* (preop IOP) + (0.012)* (CCTpreop) + (0.554)* (SE-ac) – (1.009)* (OZ diameter)	CCTpreop= Preop. central corneal thickness
		OZ = optical zone
		SE-ac = Spherical equivalent attempted correction

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been suggested to include the whole spectrum of the condition [45]. Optical coherence tomography of the anterior segment is very useful to confirm the diagnosis of IFS, by observing the optically empty space below the flap [45,53]. It is very important to note that, due to the presence of fluid under the LASIK flap, the effective surface that contacts the applanation tonometer is thinner, resulting in artificially very low pressure readings when using this device to measure IOP in the centre of the cornea. This can cause ocular hypertension to be missed and therefore neither steroids are discontinued nor ocular hypotensive drugs are indicated, perpetuating the problem. Unfortunately, cases of blindness due to glaucomatous damage have been described in some of these patients, in whom IFS was not diagnosed until it was too late. Therefore, a high level of suspicion must be maintained in the early postoperative period of LASIK in a patient applying topical steroids with some visual disturbances and some haze in the flap interface [45]. Due to the huge underestimation of the central applanatic IOP, in IFS cases it is necessary to perform digital tonometry and additional peripheral measurements with the applanatic tonometer, outside the fluid pocket [53].

CONCLUSION

Glaucoma remains a relative contraindication for corneal refractive surgery, mainly due to problems with accurate postoperative surveillance [1]. Preoperative glaucoma risk assessment should be meticulously performed in all patients before refractive procedures, even in those who are very young adults.

Complete information on the IOP before and after the excimer laser procedure, as well as information on the corrected refractive error, and the depth of the planned ablation, must be provided in writing to all patients, who must be informed in full of their increased risk of future glaucoma and the difficulty in determining IOP [1,38].

All adults attending ophthalmological consultation should be questioned about a history of refractive surgery, and if so, tonometers that are less affected by these changes (Pascal® or Corvis ST®) should be used. Alternatively, a compensatory formula should be applied to try to establish the true IOP more accurately.

The refractive surgeon should be aware that there are some rare complications after LASIK, such as IFS, which, if overlooked, can lead to severe glaucoma damage to the optic nerve.

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