Recent advances in technology and our understanding of corneal physiology have led to a rapid progression in available corneal and refractive surgical procedures. In contrast to the past, penetrating keratoplasty is no longer the only intervention of choice. Lamellar keratoplasty has gained a renewed interest and newer approaches, such as phototherapeutic keratectomy, laser-assisted in situ keratomileusis, intrastromal corneal ring segments, corneal collagen crosslinking, deep anterior lamellar keratoplasty and endothelial keratoplasty, are improving and becoming increasingly popular. This article is intended to be an overview of the modern corneal procedures, divided into three categories: anterior cornea, including those involving the epithelium, Bowman’s layer and anterior stroma; stromal; and posterior cornea, including those involving the posterior stroma, Descemet’s membrane and endothelium. Newer and experimental corneal procedures are also discussed.

Keywords: corneal collagen crosslinking • corneal surgery • endothelial keratoplasty • intrastromal corneal ring segments • lamellar keratoplasty • keratoprosthesis • refractive surgery
Anterior corneal procedures

Excimer laser-assisted procedures

Photorefractive keratectomy

Since the first excimer laser ablations were performed on human eyes by McDonald et al. [1] and Seiler et al. [2] in 1988, photorefractive keratectomy (PRK) initially became one of the most popular refractive surgeries, correcting simple and compound myopic astigmatism, and simple and compound hyperopic astigmatism (Figure 1) [3–5].

Like all refractive surgeries, PRK is performed using topical anesthesia. Since the precise corneal epithelial thickness is unknown, the epithelium is typically first removed either mechanically, with or without the use of alcohol, or with the excimer laser. Epithelial removal allows for accurate stromal ablation with the excimer laser, which is preprogrammed with the patient’s specific refraction and optical treatment zone. Owing to the central corneal abrasion, patients often experience significant tearing, photophobia and discomfort during the early postoperative period. Topical antibiotics, steroids and NSAIDs are used along with a bandage contact lens (BCL) that remains on the eye until the epithelial defect is healed.

Sight-threatening complications have been reported in as few as 1–2% of patients undergoing PRK [6]. Haze formation and scarring associated with regression of refractive effect, light scatter and irregular astigmatism is one of such complications [7] that has significantly decreased [8] since the use of mitomycin C was popularized by Majmudar and Epstein in 2000 [9]. Although potential toxicity to the epithelial, stromal and endothelial keratocytes exists with mitomycin C use [10–14], the use of mitomycin C in refractive surgery is supported by the current literature [15].

Decentration of the ablation zone can lead to disturbing visual sequelae, including irregular astigmatism, persistent halo and monocular diplopia [7]. It is a rare complication now owing to the use of the eye-tracking device and the close monitoring of the patient’s fixation by the surgeon. Halos, glare and diurnal visual fluctuation were previously common occurrences that generally subsided within 6 months following the operation [16]. They are now uncommon owing to advances in techniques, especially with customized ablation.

Laser-assisted in situ keratomileusis

Initially described by Pallikaris et al. in 1990, laser-assisted in situ keratomileusis (LASIK) has become the most commonly performed corneal refractive surgical procedure (Figure 1). It combines photoablation using the excimer laser and an intrastromal surgical technique that preserves the integrity of the outer cornea [17].

In LASIK, a corneal flap consisting of the epithelium and part of the stroma is made with either the microkeratome or the femtosecond (FS) laser. With the microkeratome, the flap can range from 130 to 160 µm deep [3], depending on the degree of refractive correction required. With the FS laser, the flap is created by delivering laser pulses at a predetermined stromal depth, usually between 100 and 110 µm deep. The flap is hinged in both cases.

After the corneal flap is made and flipped back to expose the stroma, the excimer laser beam is applied to the stromal bed in a fashion similar to that in PRK. The corneal flap is replaced after the ablation by accurately realigning the fiduciary lines made with radial keratotomy or custom LASIK markers prior to the procedure [18], although this is now less frequently performed with the use of the FS laser.

The advantages and limitations of LASIK are well documented, especially in comparison to PRK. A Cochrane collaboration methodology meta-analysis/systemic review conducted by Shortt et al. [19,20] concluded that LASIK is safer and more accurate than PRK, with less postoperative pain and more rapid visual recovery (2–3 days with LASIK and 4–15 days with PRK) [21]. The amount of haze and regression is also less with LASIK, especially in patients with severe myopia [22]. However, some studies found LASIK to be associated with more complaints of dry eye, worse contrast...
sensitivity and night vision, inferior correction of high-order aberrations (HOAs), flap complications and, arguably, an increased risk of corneal ectasia [23–26].

Flap complications caused by the microkeratome are well documented, occurring in up to 3% of cases, and are related to the surgeon’s experience with using a microkeratome [27,28]. Incomplete flap creation or failure of the microkeratomes to stop at the hinge results in a free flap [29]. Other complications include buttonholes, short flaps, blade marks and irregular cuts. These can mostly be managed by repositioning the flap and deferring photoablation, with no significant loss of best-corrected visual acuity (BCVA). The most devastating complication is intraocular penetration from a misassembled microkeratome [30]. Postoperative flap-related complications include loss or dislocation of the flap, which can result from incomplete adherence of the flap to the stromal bed, leading to significant haze formation. Other flap-related complications include diffuse lamellar keratitis (‘shifting sands of the Sahara’) [31], epithelial ingrowth (Figure 2) and wrinkling of the flap.

Many refractive surgeons have turned to the FS laser for flap creation to minimize complications and improve surgical outcome. A poll taken in 2006 found that over 30% of all LASIK flaps were made with the FS laser under such monikers as ‘IntraLASIK’, ‘all-laser LASIK’ and ‘bladeless LASIK’ [32]. The major advantages of FS laser flap creation over the mechanical microkeratome are:

- Reduced intraoperative flap complications;
- Stronger flap adhesion, which is likely to reduce trauma-associated flap dislocation and, possibly, the risk for corneal ectasia;
- Improved flap strength and less variable central corneal thickness;
- Capability of cutting thinner flaps (90 µm) to accommodate thin corneas and/or high refractive errors;
- Fewer induced HOAs;
- Reduced LASIK-related dry eyes [32–46].

Corneas that underwent FS laser-assisted LASIK have also been found to be biomechanically similar to those that underwent PRK [47].

The use of FS lasers in LASIK is not without complications. Earlier models have been shown to lead to an increased incidence of diffuse lamellar keratitis [48] and a greater risk for haze development [49], which is likely to result from the induced inflammatory response [50]. More recent models, such as the 60- and 150-kHz lasers, induce a much smaller inflammatory response [51].

A unique side effect of the FS laser is transient light-sensitivity syndrome, which is known for intense photophobia with good uncorrected distance visual acuity and an unremarkable slit-lamp examination at 2–6 weeks after uneventful LASIK [52]. Similarly, it is associated with the earlier models but rarely with the later models, and is postulated to have an inflammatory origin with a good response to steroid treatment [45,52].

**Figure 1. Anatomic overview of various corneal procedures.** (A) Layers of the cornea. (B) Location and depth of corneal involvement of various procedures. DALK: Deep anterior lamellar keratoplasty.
phototherapeutic keratectomy

Figure 2. Post-laser-assisted in situ keratomileusis epithelial ingrowth at the flap–stromal interface.

Courtesy of Allan Slomovic (University of Toronto, ON, Canada).

An alternative approach termed epipolis LASIK (epi-LASIK) was introduced by Pallikaris et al. [58]. It involves epithelial separation by mechanical means using a subepithelial separator similar to a blunt microkeratome. The theoretical advantage of epi-LASIK over LASEK is that the epithelial layer is separated from the stroma without the use of alcohol, which is potentially toxic to the epithelium and corneal stroma [59–61]. By creating a corneal epithelial flap, LASEK/epi-LASIK can be seen as a hybrid of PRK and LASIK that may address the discomfort and delayed recovery associated with PRK while eliminating virtually all flap-related complications of LASIK [56,62–66]. Some studies have found less corneal haze [67,68] and decreased levels TGF-β1 [67]. However, other investigators found no difference between PRK and LASEK with regards to pain, recovery time, final visual outcome and patient preference [69]. When compared with LASIK, patients who underwent LASEK had more pain with the early postoperative period and an increased time to visual stabilization [70].

Phototherapeutic keratectomy

Phototherapeutic keratectomy (PTK) has been investigated since 1988 and was approved by the US FDA in 1995 for the treatment of anterior corneal disorders. It is best suited to pathological processes in the anterior 10–20% of the corneal stroma, specifically anterior stromal scars, dystrophies, elevated corneal lesions and infectious keratitis [71,72]. PTK can be an alternative to lamellar keratoplasty or penetrating keratoplasty (PKP) in many cases [72]. Simple PTK, or PTK without the use of adjuncts, is very similar to PRK. Corneal thickness and the depth of pathology are estimated preoperatively using various techniques. The epithelium and anterior stroma are ablated with an excimer laser up to a certain percentage of this estimated depth. The effect of the laser treatment is then assessed using a slit-lamp microscope and ablation is repeated if necessary. This shoot-and-check technique is continued until the bulk, but not necessarily all, of the pathological process is removed. The tendency is to keep ablating until all the opacities have been removed, but that often results in a deep ablation with significant induced corneal flattening and excessive corneal haze [73]. BCL is applied immediately post-treatment.

Simple PTK is a safe procedure that is most effective for those with a smooth corneal surface [74–77]. For those with an irregular corneal surface, this surface contour is duplicated deeper into the corneal tissue with simple PTK, owing to the flat-beam profile and beam homogeneity of the excimer laser. A variety of techniques are used to overcome this hurdle. If the epithelium is loose and irregular, it is removed mechanically. Elevated lesions may be debulked with a blade or ‘chipped away’ with the laser using small spot sizes.

The use of masking/modulating agents can also be helpful. These substances protect depressions on the corneal surface so that elevations are ablated preferentially. Some of these agents, such as artificial tears and tetracaine [78–80], are simply applied frequently onto the corneal surface during treatment. Others, such as BioMask [81,82] and Photo-Ablatable Lenticular Modulator [83], are applied to the cornea in situ and moulded with a rigid contact lens in its liquid state. As the agent solidifies, its bottom surface fills the corneal surface irregularities while its upper surface reproduces the inner surface of the contact lens [81,84]. Most recently, wavefront or topography-guided corneal ablation has become a popular means of reducing or eliminating corneal surface irregularity [85,86]. PTK is also successful in treating calcificant, recurrent corneal erosions [87]. After all the loose epithelium is debrided, the Bowman’s layer is ablated uniformly to just 5–6 μm deep.

In summary, PTK is a very safe and versatile technique that is quite effective at treating a wide variety of anterior corneal lesions. Moreover, if unsuccessful, an anterior lamellar graft can often be performed. For these reasons, PTK is frequently the procedure to attempt before going onto a corneal transplant.

Nonexcimer laser procedures

Bowman’s layer transplantation

The development of haze in the anterior corneal stroma following surface ablation with an excimer laser is likely to result from an abnormal wound-healing response. Since subepithelial stromal scarring does not occur in the presence of the Bowman’s layer, Melles and colleagues hypothesized that scar excision followed by isolated Bowman’s layer transplantation would restore a clear cornea and improve visual acuity [88]. He recently reported the first isolated donor Bowman’s layer transplantation and concluded that persistent subepithelial haze after excimer laser surface ablation unresponsive to retreatment may be effectively managed with superficial scar dissection followed by Bowman’s layer transplantation. No recurrent scarring was noted over 6 months in their published case. This technique may be an alternative to anti-proliferation agents, deep anterior lamellar keratoplasty (DALK) or PKP for this particular indication.
Automated anterior lamellar keratoplasty

By contrast with PKP [87], automated anterior lamellar keratoplasty (ALK) is a procedure in which only part of the cornea anterior to the Descemet's membrane (DM) is replaced by donor corneal tissue [89,90]. Over the past decade, lamellar keratoplasty has gained a renewed interest owing to advances in microkeratomes and FS lasers [91].

Indications for automated ALK are opacities or irregularities in the anterior to mid-stromal region of the cornea, ranging from herpetic scarring to anterior stromal dystrophies [92]. Lamellar keratoplasty has many advantages over PKP [92]. First, the anterior chamber is not entered in lamellar keratoplasty, reducing the risk of expulsive hemorrhage or endophthalmitis. Second, the corneal endothelium is not transplanted, decreasing the risk of graft rejection. Last, the recovery is shorter postoperatively, and visual rehabilitation is faster. When compared with other lamellar techniques, automated ALK is a procedure of relative ease with rapid visual recovery [91].

Deep anterior lamellar keratoplasty

In situations where the pathological process is in the deep stromal area but does not affect the endothelium, one must increase the depth of the keratectomy (Figure 1). In DALK, the recipient is prepared by excising a corneal disc spanning the thickness of the entire stroma, without DM. A donor button with its DM stripped off is sutured into the recipient bed (Figure 3).

It is not easy to dissect the cornea down to the DM since the depth of dissection, relative to the corneal thickness, is difficult to visualize, resulting in possible DM microperforation [93]. Several techniques have been advocated to overcome this hurdle. All of them focus on facilitating the identification of DM and/or the predescemetic plane to obtain a smooth deep surface with uniform thickness. Sugita and Kondo proposed the use of hydrodelamination, whereby a saline solution is injected into the stroma with a blunt needle [94]. The stroma whitens when the solution penetrates between the collagen fibers, allowing for easy identification and removal. Melles and Manche both proposed a technique where viscoelastic material is forced through the posterior stromal lamellae, causing the DM to separate and the overlying tissue is then excised [95–99]. Alternatively, several authors [90,100–102], including Anwar and Teichmann who ultimately modified it [103,104], proposed the so-called big-bubble technique using air to delaminate the corneal stroma and to separate it from the DM.

Deep anterior lamellar keratoplasty was historically associated with poor postoperative visual acuity. Causes included graft–host interface haze and/or vascularization, graft-surface irregularities and/or astigmatism, and persistent epithelial defects [105]. Graft–host interface haze is especially problematic when DM visualization was inadequate intraoperatively and a layer-by-layer dissection was necessary [103], leaving the host bed with too much residual stroma [106]. With recent surgical advances, DALK has been shown to offer functional results comparable with, or better than, those with PKP, while avoiding the problems associated with transplanted donor endothelium [107–115].

The popularization of DALK has also opened up the possibility of using only the stromal layer of a donor cornea, hence reducing dependence on a donor with a high endothelial cell count.

Last, FS lasers have recently been employed in a variation of the big-bubble technique. In separate studies, Farid et al. [116] and Price et al. [117] used the FS laser to create a zigzag incision in the donor cornea and recipient bed during the step of partial trephination instead of a calibrated guided trephine system as originally described by Anwar and Teichmann [104]. Theoretically, this technique minimizes the risk of DM perforation by allowing for precise depth visualization for air-needle placement in the posterior stroma based on the lamellar and posterior laser cuts. The use of FS laser in DALK needs to be evaluated further.

Stromal procedures

Intrastromal corneal ring segments

Intrastromal corneal ring segments (ICRSs) are a relatively new form of additive keratorefractive surgery where one or two ring
segments are placed symmetrically or asymmetrically into mid-peripheral corneal tunnels created by manual mechanical dissection or with FS laser, resulting in corneal flattening and a reduction in irregular astigmatism (Figure 1) [118]. The magnitude of flattening is proportional to the thickness of the implant and inversely proportional to its diameter [119]. The main advantage over other modalities is that it is potentially reversible and adjustable, as it does not result in permanent corneal tissue destruction and distortion due to corneal wound healing [120]. The central cornea is also preserved, maintaining its prolate shape. Despite preliminary success, this indication was overtaken by LASIK.

The Keravision INTACS implants (Kera Vision Inc., CA, USA), currently approved for use in low-to-moderate myopic patients, received European CE certification in 1996 and FDA approval in 1999 [121]. They are composed of two 150° polymethylmethacrylate (PMMA) ring segments (Figure 4). The thickness of the rings required, ranging from 0.21 to 0.45 mm, depend on the level of the myopia. Currently, this method has FDA approval for the correction of low-to-moderate myopia (-1.00 to -3.00 D, with less than 1.00 D of coexisting astigmatism).

In 2000, Colin et al. reported the use of INTACS in keratoconus with an aim to delay or even avoid corneal grafts in ectatic corneal disease [122]. Since then, several studies have reported variable visual, refractive and keratometric changes (2.14–9.60 D) following INTACS implantation in keratoconic eyes [122–125]. Corneal irregularity is also reduced with INTACS, which may be reflected by reduction in HOAs and a corresponding improvement in BCVA [124]. ICRS in keratoconus have also been useful for improving contact lens tolerance [123,126,127].

The indications for ICRS in general (INTACS, Ferrara rings [Ferrara Ophthalmics, Brazil] and Kerarings [Mediphacos, Belo Horizonte, Brazil]) have since transitioned to the correction of ectatic corneal disorders such as keratoconus, pellucid marginal degeneration and post-LASIK ectasia. Ferrara et al. reported good outcomes for myopia with a different ring segment design called Ferrara rings, which has subsequently been adopted for use in ectatic corneal disorders [128].

Few cases of ICRS in pellucid-marginal degeneration have been reported. Central corneal flattening and reduction in spherocylindrical error has been demonstrated, along with improved contact lens tolerance [129–131]. Similar refractive changes have been noted in keratoconus and post-LASIK ectatic corneas following ICRS implantation. Central corneal flattening and reductions in spherocylindrical error have also been noted (Figure 5), with a corresponding improvement in BCVA [132,133]. Pinero also noted a reduction in coma-like aberrations and astigmatism, which led to a significant improvement in BCVA during a 2-year follow-up period [119]. This group also found more HOAs in eyes that underwent the mechanical procedure compared with a FS-assisted procedure in the initial postoperative period.

**Collagen crosslinking**

Until recently, treatments for conditions affecting the biomechanical strength of the cornea, namely ectatic corneal disorders, have been limited to ICRS and corneal grafting. Both treatments address only the consequences of progressive corneal weakening but not the basic defect within the cornea.
In 1997, early in vitro studies by Spoerl et al. showed the potential and advantages of a new technique, involving riboflavin (vitamin B2) and UVA (370 nm), to safely increase the stability of the cornea by artificially crosslinking corneal fibers without disadvantages such as scarring, decompensation and toxicity [134,135]. Corneal crosslinking (CXL) has since been shown clinically to increase the rigidity and structural integrity of the cornea, preventing progression to end-stage disease in various ectasias (Figure 1) [136–141].

As riboflavin is poorly absorbed through the corneal epithelial tight junctions [139,142,143], the cornea is generally de-epithelialized out to 7–9 mm. Ultrasound pachymetry is then performed at the thinnest point of the de-epithelialized cornea, to ensure a minimal corneal thickness of 400 µm. Riboflavin 0.1% solution is then applied to the cornea every 2–3 min for 30 min. Corneal saturation with riboflavin and its presence in the anterior chamber is monitored by slit-lamp biomicroscopy with cobalt blue light, where it is visible as a yellow flare (Figure 6A). The eye is then irradiated for 30 min with UVA (Figure 6B) with the continual application of riboflavin solution every 2–3 min.

After the treatment, antibiotic drops are instilled and a BCL is placed over the cornea until complete re-epithelialization, which is usually on day 3 post-treatment. Some authors advocate the use of a tapering regimen of topical steroids [144], while others believe steroids inhibit the crosslinking process [145].

Corneal crosslinking is a photochemical reactive process. The corneal stroma is saturated with riboflavin, which collects alongside the collagen to be crosslinked. Riboflavin absorbs UV light at 370 nm (absorption maxima of the riboflavin chromophore) in the presence of oxygen and induces new chemical bonds in the stromal collagen by the creation of free radicals. Riboflavin has two functions in the process of chemical crosslinking. First, it facilitates UVA absorption, absorbing approximately 95% of UVA [139] and thereby preventing damage to deeper ocular structures. Second, it produces oxygen free radicals, which are thought to induce collagen crosslinkage by increasing the formation of intrafibrillar and interfibrillar covalent bonds through the natural lysyl oxidase pathway [135]. Initially, CXL was thought to induce crosslinkage between the stromal collagen molecules, which subsequently increases the biomechanical stability of the corneal and its resistance to enzymatic digestion [146]. Recent studies suggest that, instead, CXL increases the number of crosslinking sites within the collagen molecule [147]. This process produces a rearrangement of corneal lamellae and a relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature.

The major indication for the use of CXL is to halt or reduce, but not reverse, the progression of corneal ectasias, such as keratoconus and pellucid marginal degeneration [135,137–140,148–150]. Clinical studies have shown stabilization of keratoconic eyes with no evidence of progression with up to 6 years follow-up and some slight regression of the ectasia by an average of 2D [138,139]. CXL is also effective in the treatment and prophylaxis of iatrogenic ectasia, resulting from excimer laser ablation [136,138]. For corneal edema due to endothelial decompensation, CXL has been reported to reduce corneal thickness and improve epithelial changes when used in combination with a dehydration agent such as 40% glucose [152–154]. Studies have also suggested that it may be used with success in bullous keratopathy [153,155–157]. CXL has been used in some cases to treat infectious keratitis or corneal ulceration with progressive melting unresponsive to medical treatment with good success [158–161]. Some success has been reported for combination therapy using ICRS implantation or limited topography-guided photoablation to reshape the cornea [162–166].

Corneal crosslinking has not been shown to induce endothelial injury. There has been no loss of corneal stromal transparency and no damage to deeper ocular structures provided the cornea is thicker than 400 µm [139,167,168]. A corneal thickness of less than 400 µm is, therefore, regarded as the absolute contraindication for the procedure.

After crosslinking, a transient loss of visual acuity with haze can be observed in some cases, which usually subsides completely during the first postoperative year. A loss of two or more Snellen lines at 6 months or 1 year after treatment is considered a complication, with a rate ranging from 1 to 3% [169]. Age over 35 years and...
BCVA better than 6 out of 7.5 are reported risks factors. Several cases of infectious keratitis have been reported post-CXL [170–172]. It is generally thought that the infectious agents were contracted in the early postoperative, rather than intraoperative, period as CXL kills bacteria and fungi. Pre-existing ocular surface conditions such as blepharitis should be aggressively treated before surgery to avoid such complications.

The use of CXL has become much more widespread and versatile as it emerges as a promising treatment for many corneal conditions. However, concerns regarding certain aspects of CXL have been raised. In particular, its effect on other ocular parameters such as tear function, corneal sensitivity, properties of conjunctival epithelium and goblet cells, and ocular surface limbal stem cell viability has been questioned. The long-term effect of UVA irradiation in possibly increasing the occurrence of metaplastic disorders of the ocular surface should also be further studied.

Thermal correction of presbyopia

Holmium: YAG laser thermal keratoplasty

Laser thermal keratoplasty (LTK) is a form of refractive surgery directed at the corneal stroma that is based on biomechanical principles very similar to conductive keratoplasty (CK; see later) [173,174]. Instead of delivery of heat by electrical conduction, a laser delivers the heat by thermal conduction. Otherwise, the objective of LTK is to stimulate shrinkage of the stromal collagen in a concentric pattern around the central cornea by the creation of leukoma footprints and thus achieve corneal steepening. Unlike CK, these footprints are in a conical shape, as thermal conductivity (unlike direct electrical conductivity) is attenuated as it passes from the corneal surface into the stroma [175]. The use of LTK has not been widespread owing to the significant regression of effect observed.

Conductive keratoplasty

Approved by the FDA for usage in 2002, CK is a laserless, non-lamellar modality for refractive surgery, primarily indicated for the management of low-to-moderate hyperopia (+0.75 to +3.00 D, with less than +0.75 D of coexisting astigmatism) [176]. By applying this outside of the visual axis, steepening of the central cornea is achieved to correct the hyperopia [177,178]. This has largely been replaced by newer techniques secondary to induced irregular astigmatism and regression of effect.

New approaches to the correction of presbyopia

Intrasomal correction of presbyopia

Intrasomal correction of presbyopia (INTRACOR) refers to a developing technique using FS to correct presbyopia in a minimally invasive manner [179,180]. In this procedure, FS pulses are delivered intrastromally, avoiding any disruption of Bowman’s layer and DM, with the objective of creating five concentric cylindrical rings around the line of sight. The intended result is to create a multifocal hyperprolate cornea by steepening the anterior corneal surface centrally, while flattening the cornea more peripherally. This procedure is indicated mainly for patients with only low hyperopia, myopia or astigmatism; the number, size and shape of the INTRACOR rings are determined based on the level of ametropia or cylinder. The benefits of this procedure are many, as it is fast and painless, with procedure time ranging from 18 to 30 s, and it is associated with very low intraoperative risk and postoperative complications, as it avoids the need for surface ablation or flap creation.

Since the introduction of this technique, only two studies evaluating the short-term outcome of the procedure have been published [179,180]. Each series reported uneventful surgeries for all cases, with no significant postoperative complications aside from slight disturbance in visual acuity in the immediate postoperative period. Long-term follow-up is required for its proper evaluation.

Posterior corneal procedures

Posterior lamellar keratoplasty & deep lamellar endothelial keratoplasty

Posterior lamellar keratoplasty is a surgical procedure that involves replacement of diseased posterior cornea with donor tissue while retaining the anterior corneal layers (Figure 1). The aim is to replace only the dysfunctional endothelial layer with healthy functioning endothelium, thus allowing for the clearing of the corneal edema.

Figure 7. Descemet stripping and endothelial keratoplasty versus penetrating keratoplasty. (A) Visante optical coherence tomography view of the corneal post-Descemet stripping and endothelial keratoplasty, and (B) post-penetrating keratoplasty.
In an early approach, Melles et al. described an approach to deep lamellar endothelial keratoplasty (DLEK) [97], in which intraocular air was used to support the donor tissue so as to avoid problems associated with corneal sutures. This technique was later modified by Terry and Ousley [181].

Many series have confirmed that endothelial keratoplasty produced viable postoperative endothelial cell count, did not induce corneal refractive changes, reduced astigmatism rates, and provided for earlier refractive stability and visual rehabilitation compared with conventional PKP surgery [182–190]. However, the average Snellen visual acuity attained was approximately 20/40–20/50, with few 20/20 results [182–190]. The limitation in postoperative visual acuity was thought to be likely due to the uneven donor–host interface. Descemet stripping and endothelial keratoplasty (DSEK) was then created with the aim to provide a smoother recipient bed.

**DSEK & Descemet stripping automated endothelial keratoplasty**

Melles et al. again revolutionalyzed the field by instituting a significant modification to the endothelial keratoplasty procedure. They described a technique, termed descemetochorix, to strip away the DM from a recipient cornea in order to provide a smoother recipient interface [191]. Price and Price popularized the technique in the USA, referring to it as DSEK (Figure 7) [192–194].

In DSEK, the donor corneal tissue is prepared as in endothelial keratoplasty. The cornea is dissected at 90% stromal depth in an artificial anterior chamber filled with air, using the technique described by Melles et al. (see posterior lamellar keratoplasty and DLEK) [195]. The center of the cornea is marked and a full-thickness button is made by trephination. The technique used by Price and Price for the recipient cornea is also similar to the DLEK surgery, except DM stripping is performed rather than posterior stromal dissection and removal [192,194]. The corneal epithelium is first marked to outline the area from which DM was to be removed. Through a temporal scleral tunnel as originally described [192,194], or a limbal or clear corneal incision similar to cataract surgery [196], the DM is scored along the perimeter of the area to be removed with a Price–Sinskey hook. Within this circumscribed area, the DM and diseased endothelium is then carefully stripped off the posterior stroma using a Descemet’s stripper and removed from the anterior chamber with forceps. The anterior corneal tissue of the donor button is removed and a small amount of viscoelastic is placed on the donor endothelium. The donor posterior lamella is folded on itself in a ‘taco’ configuration and placed into the recipient anterior chamber. The donor taco is unfolded and centered, and the temporal scleral incision is closed with one or more sutures. Air is injected into the recipient anterior chamber and left there for 5–8 min to promote donor tissue adherence. The ocular surface is massaged with a Lindstrom LASIK flap roller or a similar instrument while the anterior chamber is filled with air to help remove any residual fluid trapped in the donor–host interface. After the massage, three or four equally spaced small stab incisions are placed in the midperipheral recipient cornea down to the graft interface to drain residual trapped fluid. Most of the air in the anterior chamber is then removed and replaced with balanced salt solution, leaving a small air bubble. Patients are then instructed to lie facing the ceiling for 30–60 min to allow the remaining air to push the donor tissue against the recipient cornea.

In 2006, Gorovoy modified DSEK by replacing the manual stromal dissection of the donor cornea with an automated keratectomy dissection [197]. He termed this modification Descemet stripping automated endothelial keratoplasty (DSAEK). As this method avoids all manual lamellar dissections, Gorovoy hypothesized that the resulting smoother donor–host interface may decrease visual recovery time and increase visual quality. This hypothesis was confirmed by other authors [198,199]. However, the higher donor dislocation rate originally found by Gorovoy [197] was also echoed in the literature [199].

Current literature suggests that DSAEK appears to be effective for the treatment of endothelial diseases of the cornea [200]. Some reports have even suggested that DSAEK should replace
traditional PKP for surgical treatment of endothelial disease [199,201,202] as it seems to be similar to PKP in terms of surgical risks and complication rates [199,203], graft survival (graft clarity) and acuity [204–206], and endothelial cell loss [201,204,207,208]; and superior to PKP in terms of early visual recovery and refractive stability [202,209–211], postoperative refractive outcomes [199,212–215], wound and suture-related complications [216], and intraoperative and late choroidal hemorrhage risk [203,217,218]. A recent report by the American Academy of Ophthalmology concluded that the four most common complications of DSAEK are graft dislocation (Figure 8), endothelial rejection, graft failure and glaucoma, all of which do not seem to be detrimental to the ultimate visual recovery in most cases [200]. The report also stated that, as in any new technique, long-term prospective studies are needed to demonstrate acceptable complication rates and long-term endothelial cell survival post-DSAEK.

**DM endothelial keratoplasty**

In 2002, Melles et al. reported a human cadaver eye model in which the DM carrying healthy endothelial cells was transplanted through small scleral tunnels [219]. He subsequently termed the technique DM endothelial keratoplasty (DMEK) and reported its use in a patient with Fuchs’ endothelial dystrophy [220].

The donor tissue used in Melles’ et al. DMEK was cultured for 2 weeks before trephination and subsequent DM stripping with microforceps. Because of the elastic properties of the membrane, a ‘DM roll’ spontaneously formed with endothelium at the outer side. The DM roll was stored in organ culture medium until the time of transplantation. Melles then performed a procedure similar to DLEK (Melles’ technique), substituting the posterior stromal dissection in the recipient cornea with a descemetorhexis [191]. The donor DM roll was sucked into a custom-made injector after being stained with trypan blue. The roll was inserted into the recipient anterior chamber using the injector and gently spread out. Air was injected underneath the donor DM to oppose the tissue onto the recipient cornea. The anterior chamber was completely filled with air for 30 min, after which the air was replaced with liquid [220]. The patient’s visual acuity was reported to be 20/80 at 1 day and 20/20 at 1 week post-transplantation with no change in refraction.

Unlike other EK procedures, DMEK provides a near-normal restoration of the grafted cornea, which may result in faster and more complete visual rehabilitation [219]. Without the additional donor stroma, the visual performance of the eye is likely to be limited only to the preoperative condition of the recipient anterior cornea. DMEK may also be more suitable for modern anterior segment surgery as, with the small donor DM roll, the procedure can easily be performed through a clear corneal incision as that used in cataract surgery. However, other surgeons have found that DM is quite fragile, and manipulations of donor tissue that are reasonably well tolerated in the other endothelial keratoplasty surgeries result in wrinkles, folds, tears and unacceptable endothelial cell loss when applied to pure DM transplantation. Various modifications of carriers have been used in an attempt to overcome these challenges [221,222].

**Future trends**

Over the last decade, availability of donor tissue and repeated human graft failures has prompted the search for artificial corneal substitutes that would be compatible in human eyes. Several of these devices are available and in clinical use today. These range from completely synthetic devices such as the Boston Keratoprosthesis (Boston KPro; Massachusetts Eye and Ear Infirmary, MA, USA) to the completely biological tissue-engineered cornea.

**Boston KPro**

The Boston KPro received FDA approval in 1992 [223]. It is suitable for patients with repeated failed corneal grafts where further transplants are judged to be at high risk for failure. The optical component is made from PMMA. A corneal graft is sandwiched between this unit of front plate and stem, and a larger back plate (Figure 9). This device is then locked into place with a titanium ‘c-ring’ and sutured to the recipient’s eye (Boston KPro type I). Postoperatively, a continuous-wear BCL is placed on the cornea (Kontur Contact Lens Co., CA, USA), which is replaced every 3–4 months, and the patient is given a tapering regimen of antibiotic and steroid drops for life. As there is no reliable device to measure intraocular pressure in these patients, digital palpation and regular follow-up with visual fields and optic nerve evaluation is necessary to monitor glaucoma progression.

A pseudophakic eye with a well-positioned intraocular lens can be corrected with a KPro of a standard power. An aphakic eye requires a chosen power depending on the axial length of the eye. In patients with severe ocular surface disease, an anterior cylinder may be added to the KPro, which protrudes through a permanent tarsorrhaphy in patients with severe ocular surface disease (Boston KPro type II).

In 2005, Aquavella reported the result of their series of 25 patients with the Boston KPro type 1 [224]. All prostheses were retained with no extrusion. Almost half of the patients achieved vision of 20/25–20/200 in an average of 60 days. The first and largest multicenter study on the Boston KPro type 1 was published in 2006 [225]. A total of 141 procedures by 39 different surgeons were analyzed at 17 sites. Postoperative visual acuity improved to 20/200 in 57% of the cases. The graft-retention rate at 8.5 months was 95%. Other recent studies have demonstrated retention rates of 83–100%, with visual outcomes of at least 20/200 in 77–83% of patients [226,227].

**Osteo–odonto keratoprosthesis**

First described by Strampelli in 1963 [228], this device uses the patient’s own tooth root and surrounding alveolar bone to support an optical cylinder. Other biological support materials include cartilage [229] and tibial bone [230]. The first stage involves assembling the tooth–optic lamina and implanting this in a submuscular pouch of the lower lid in the fellow eye for 2–4 months. A full-thickness buccal mucous membrane graft is then harvested and sutured on the recipient eye. In the second stage, this device is retrieved and then implanted in the recipient eye that has had its lens and iris removed, and anterior vitrectomy following trephination. The buccal mucous membrane graft cover is
then repositioned and sutured into place. Surgical management is usually carried in a joint fashion with an ophthalmologist and maxillo–facial surgeon.

In 2005, Falcinelli reported on 181 patients with a median follow-up of 12 years [231]. The probability of retaining an intact osteo–odonto keratoprosthesis (OOKP) was 85% and the probability of retaining best postoperative visual acuity was 55.5% after 18 years. In 2008, Liu et al. reported on 36 patients with a mean follow-up of 3.9 years and found that OOKP retention rates approached 72%, with 61% retaining best-achieved vision during the follow-up period [232]. The same year, Tan et al. reported on 15 Asian patients with OOKP and showed a retention rate of 100% over 19.1 months [233].

**Biointegrable keratoprostheses:**

**AlphaCor™ & Pintucci keratoprosthesis**

The AlphaCor™ (Argus Biomedical, Perth, Australia) was developed in Australia and received FDA approval in 2003 [234]. It is composed of a clear central optical core and an opaque skirt made of a biocompatible polymer (poly-2-hydroxyethyl methacrylate) [235] joined by a polymer. The outer skirt is designed to facilitate colonization by invading keratocytes for integration with surrounding tissues. This device is implanted intrastromally following a careful lamellar dissection to 50% thickness and trephination of the central posterior lamella. In the second stage, performed 2–3 months later (to allow for biointegration), trephination is performed of the tissues superficial to the optic and removed to expose the optical zone [234,236]. In 2003, Hicks et al. reported retention rates of 62% over 2 years [236]. However, poor visual outcomes and late anterior stromal melts have limited the use of this device.

In 1979, Pintucci et al. used Dacron® as a skirt for a PMMA optic [237]. In the first stage, a mucous membrane graft is used to cover the eye following corneal debridement of the epithelium. The device is buried in a submuscular pouch in the lower lid for biointegration over at least 2 months. The device is then retrieved from the lower lid before implantation similar to that with OOKP. Pintucci et al. reported on 20 eyes with a mean follow-up of 58 months [237]. All achieved some improvement of vision, with 65% retaining this improvement for more than 2 years. In 2006, Maskati reported on 31 eyes, with 77% achieving an improvement in vision to greater than counting fingers at 1.5 m. Loss in vision was seen in seven eyes [238].

**New devices on the horizon**

With the growing need for a corneal substitute, there are a number of devices being developed. These range from supradescentic synthetic corneas [239,240] to natural corneal substitutes from recombinant human collagen [241–244]. Having a range of synthetic and artificial corneal substitutes within our armamentarium will allow visual rehabilitation of blindness due to corneal disease despite a shortage of donor corneas.

**Expert commentary**

Recent improvements of surgical techniques and advances in instrumentation have contributed to improved visual outcomes with various corneal procedures. This has led to greater prominence of lamellar keratoplasty surgery in recent years, with studies...
Corneal surgery has evolved exponentially over the past few years. We propose that the evolution of corneal surgical techniques will occur on three fronts: biological, technological and intellectual innovation. As we have discussed in this article, some of the most advanced surgical techniques (e.g., DMEK) are the product of intellectual ingenuity, without the need for expensive equipment. Wavefront technology, on the other hand, has required the perfecting of numerous aspects of technology. We anticipate that, in the future, corneal regeneration at different levels will become routine, with any number of approaches such as bioengineered scaffolds, ex vivo augmentation of stem cells or pharmacologic endothelial cell regeneration. In refractive surgery, we predict that ‘one-step’ lasers will offer what is currently possible with two separate instruments, and that we will continue to see innovations in presbyopic corrections. Finally, there is no limit to what the human mind can devise. Whether by designing innovative surgical approaches, or by developing new technology, we can guarantee that the cornea, merely 0.5 mm in thickness, will continue its journey of being prodded, diagnosed, spliced, regenerated and cured.

**Five-year view**

Corneal surgery has evolved exponentially over the past few years. We propose that the evolution of corneal surgical techniques will occur on three fronts: biological, technological and intellectual innovation. As we have discussed in this article, some of the most advanced surgical techniques (e.g., DMEK) are the product of intellectual ingenuity, without the need for expensive equipment. Wavefront technology, on the other hand, has required the perfecting of numerous aspects of technology. We anticipate that, in the future, corneal regeneration at different levels will become routine, with any number of approaches such as bioengineered scaffolds, ex vivo augmentation of stem cells or pharmacologic endothelial cell regeneration. In refractive surgery, we predict that ‘one-step’ lasers will offer what is currently possible with two separate instruments, and that we will continue to see innovations in presbyopic corrections. Finally, there is no limit to what the human mind can devise. Whether by designing innovative surgical approaches, or by developing new technology, we can guarantee that the cornea, merely 0.5 mm in thickness, will continue its journey of being prodded, diagnosed, spliced, regenerated and cured.

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**Key issues**

- Laser-assisted in situ keratomileusis (LASIK) is the most commonly performed refractive surgery due to its fast recovery and minimal postoperative discomfort.
- Photorefractive keratectomy is the preferred refractive procedure for those not suitable for LASIK owing to refractive (e.g., large correction) or lifestyle (e.g., high risk for flap dislocation) restrictions.
- Laser subepithelial keratomileusis/epi-LASIK is theoretically a good alternative refractive procedure but has fallen out of favor given its lack of advantages over LASIK or photorefractive keratectomy clinically.
- Collagen crosslinking employs riboflavin and UVA light, and is effective in delaying the progression of corneal ectasia such as keratoconus.
- Intracorneal ring segments are now used in corneal ectatic conditions such as keratoconus, often in combination with collagen crosslinking, to improve best corrected visual acuity.
- Phototherapeutic keratectomy is effective in treating a wide variety of anterior corneal lesions to produce a smooth corneal surface.
- Lamellar keratoplasty, rather than penetrating keratoplasty, is now the surgery of choice for many corneal conditions.
- Deep anterior lamellar keratoplasty, a lamellar keratoplasty where only layers anterior to Descemet’s membrane are replaced with donor tissue, is used in conditions where the diseased cornea is at or anterior to the deep stroma.
- Endothelial keratoplasties, including Descemet stripping and endothelial keratoplasty, replace the diseased Descemet’s membrane and endothelium with healthy donor posterior lamella and are used to treat endothelial failure.
- Boston Keratoprosthesis, osteo–odonto keratoprosthesis and biointegrable keratoprostheses (AlphaCor™ and Pintucci keratoprosthesis) are artificial corneal substitutes currently available, while tissue-engineered corneas are still being developed.
- It is likely that there will be wider uses for femtosecond lasers in corneal surgery in the near future.

**References**


Modern corneal & refractive procedures

Review

Chuo, Yeung & Rocha


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Review

Modern corneal & refractive procedures


1. Which of the following statements about the use of the femtosecond (FS) laser vs mechanical microkeratome in corneal procedures is most accurate?

- A. The FS laser reduces the risk for transient light-sensitivity syndrome
- B. The FS laser can increase the risk for dry eyes
- C. The FS laser can improve flap adhesion and flap strength
- D. The FS laser generally cuts thicker flaps

2. What should you consider in recommending keratectomy to patients?

- A. Tearing and photophobia are normal immediately following phototherapeutic keratectomy (PTK)
- B. PTK is best suited to full-thickness corneal lesions
- C. Laser treatment in PTK should be performed until all opacities are removed
- D. Masking or modulating agents should never be used to guide treatment in PTK

3. Which 2 elements are most significant for corneal collagen crosslinking?

- A. Thiamine (vitamin B1) and UV-B
- B. Folate (vitamin B9) and a combination of antibiotics
- C. Vitamin B12 and corticosteroids
- D. Riboflavin (vitamin B2) and UV-A

4. Which of the following statements about the Boston Keratoprosthesis is most accurate?

- A. It is now first-line therapy for patients needing corneal grafts
- B. Postoperative treatment includes a regimen of antibiotic and steroid drops for life
- C. Tonometry is still helpful to measure intraocular pressure after surgery
- D. The graft retention rate is approximately 30% at 8 months