Review

Current approaches in the management of patients with keratoconus

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OPHTHALMOLOGY

Abstract

Keratoconus is a relatively frequent eye disease, especially in young patients, in which the cornea gradually thins and deforms in a cone shape. In the past, it could be treated only with glasses, rigid contact lenses or, for advanced cases, penetrating corneal transplant. Nowadays, corneal cross-linking, intracorneal ring segments implantation or deep anterior lamellar keratoplasty are available options of treatment, along with the above mentioned ones. Several studies focused on this disease and its management attempted to establish the applicability of these treatment methods in current practice. In the early stages, glasses or soft toric contact lenses are able to correct the astigmatism, but, as the disease progresses, rigid contact lenses are indicated. Corneal cross-linking is done in order to slow down or even stop the progression of the disease. Implanting intracorneal ring segments helps improve visual acuity in patients with low vision that cannot be corrected otherwise. Advanced stages need corneal transplant, either penetrating or anterior lamellar, depending on each patient's ocular characteristics. Thus, keratoconus treatment is individualized for every patient, according to the stage of the disease. Moreover, because of the new developed technology, keratoconus patients can benefit from efficient treatment, in much safer conditions.

Keywords: keratoconus, corneal cross-linking, intracorneal ring segments, deep anterior lamellar keratoplasty, penetrating keratoplasty

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Introduction

Keratoconus is a degenerative disease characterized as a progressive thinning of the cornea, which protrudes and takes on a cone shape. It is part of the corneal ectatic disorders, along with pellucid marginal degeneration and post-corneal refractive surgery keratectasia. The etiology is mostly genetic [1], but there are some risk factors, such as eye rubbing [2], which are also considered to play a role. Atopy seems to play a role, as well.

The condition is usually bilateral, with staging difference between eyes. Frequently, it arises in teenagers and young adults and progresses for a period of about 20 years, after which it tends to stabilize. The risk of progression is higher at younger ages [3].

There are four stages of keratoconus. The Amsler-Krumeich classification was commonly used until the development of modern technology; its main disadvantage was considering only the anterior surface of the cornea. Nowadays, corneal topography / tomography is an essential tool in diagnosing keratoconus; it can make an accurate characterization of both the anterior and posterior surfaces of the cornea and can help ophthalmologists discover subclinical forms (forme fruste keratoconus – FFKC). Based on topographic data, new keratoconus grading systems developed, for example the ABCD classification system [4].

Keratoconus treatment is in accordance with the stage of the disease. If in the past the only options of treatment were glasses, rigid contact lenses or penetrating keratoplasty, in the last years new methods were introduced: corneal cross-linking, intracorneal ring segments (ICRS) implantation and deep anterior lamellar keratoplasty (DALK) [5]. Further on, their applicability in current practice will be discussed.

Methods

Research of Wiley Online Library, ScienceDirect, PubMed, Springer Link and ResearchGate databases was performed, using keywords: keratoconus, contact lens, cross-linking, ICRS, deep anterior lamellar keratoplasty, penetrating keratoplasty, mushroom-type keratoplasty, corneal hydrops and associations between them as in the formula: (keratoconus) AND (CXL OR cross-linking) AND (ICRS OR intracorneal ring segments). The results were filtered in order to access articles published between 2010-2020, with full text or at least abstract availability. Finally, 25 articles, relevant for this review, have been selected.

Results and discussion

Keratoconus diagnosis is made based on the slit lamp examination (in moderate – advanced stages) (Figure 1) and corneal topography – mandatory for early and subclinical stages (Figure 2). Simpler investigations, such as auto-kerato-refractometry or Javal astigmometry, which reveal irregular and deformed images, can quickly suggest the presence of keratoconus. But with the help of the corneal topography and aberrometry, even subtle changes, which indicate a subclinical keratoconus, can be detected [6]. One major feature of the new systems of corneal topography and tomography is analyzing also the posterior surface of the cornea. This is extremely helpful because the first changes in keratoconus appear in the posterior surface of the cornea, which protrudes anteriorly before the anterior surface of the cornea protrudes anteriorly in a cone shape. Identifying subclinical and early stages of the disease is very important, especially in the preoperative evaluation for refractive surgery. A high number of the patients who present for refractive surgery might discover that they have an early stage of keratoconus and they are not eligible for corneal surgery, because the risk of iatrogenic keratectasia is high [7].

Once diagnosed, the management of keratoconus is different from patient to patient, depending on the stage of the disease. In the early stages, the astigmatism can be managed with glasses or contact lenses, but for more advanced cases ICRS implantation or even corneal transplant is required (Figure 3).

Glasses and contact lenses

Because of the corneal deformation, keratoconus induces an astigmatism which can be, in the early stages, corrected with glasses with cylindrical lenses or soft toric contact lenses. However, as the disease progresses, these won't help anymore, or will even worsen corrected visual acuity. This happens because the astigmatism becomes irregular, with higher-order optical aberrations.

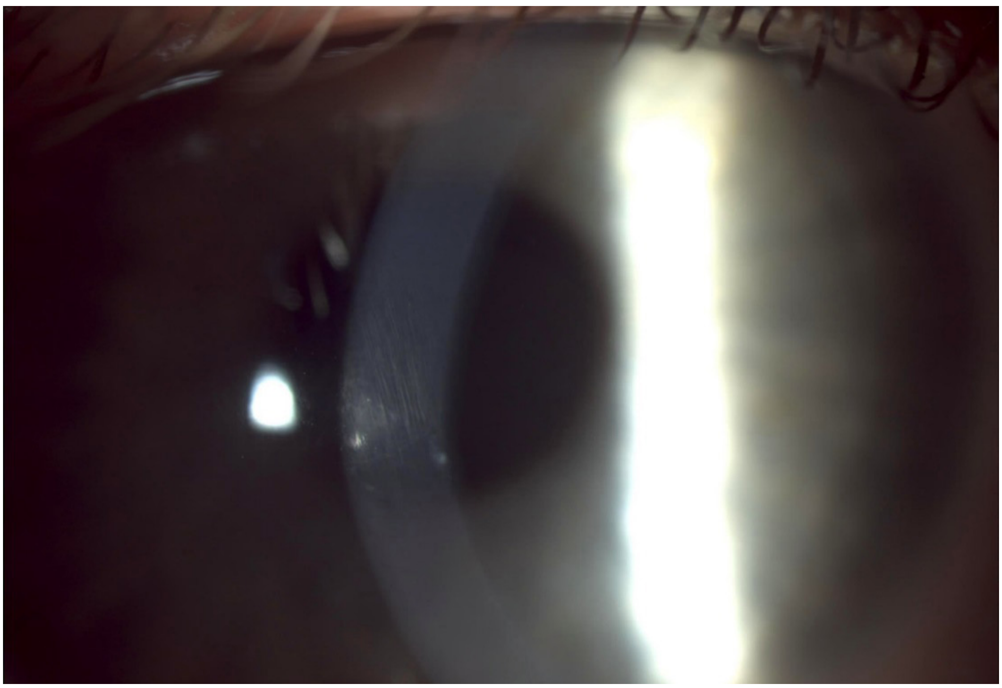

Figure 1. Slit lamp examination: cone-shaped cornea with Vogt striae (Photo courtesy of Dr. Ozana Moraru).

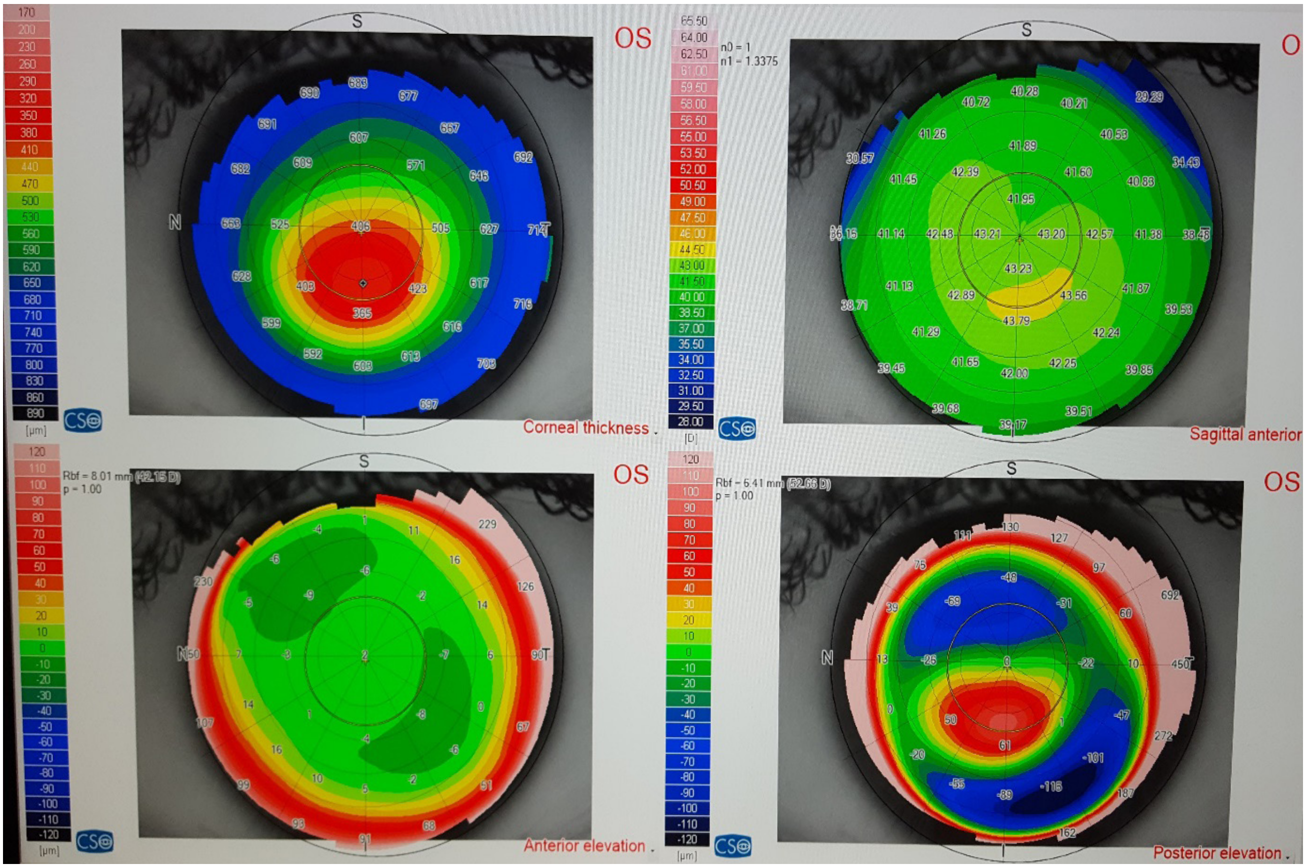

Figure 2. Corneal topography / tomography of an incipient keratoconus: no modifications seen on the anterior elevation map, while the posterior elevation map shows anterior protrusion of the posterior surface of the cornea, also depicted in the sagittal anterior map; paracentral inferior corneal thinning is shown in the corneal thickness map (Photo courtesy of Dr. Cristian Moraru).

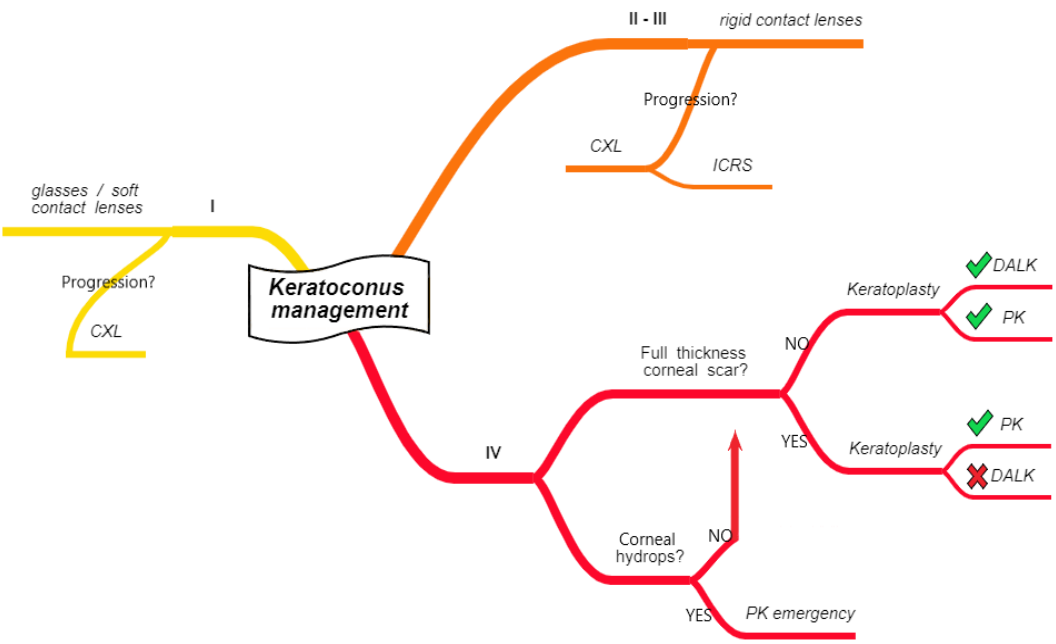

Figure 3. Keratoconus management.

In mild to moderate stages, rigid contact lenses are preferred. There are several varieties. Rigid gas permeable (RGP) lenses are small lenses which lie on the apex of the cone. In cases where there is RGP lens related discomfort or instability, piggyback contact lenses can help; this system consists of a soft contact lens with a RGP lens on top. But, there are also disadvantages such as losing the RGP lens or taking care of two lenses instead of one. Because of this, hybrid lenses have been developed; these have a rigid center and soft periphery and vault the apex. Scleral contact lenses represent the last and most modern option, when all other contact lenses are not suitable because of the corneal deformation; these lenses rest on the sclera and vault the cornea. Both the hybrid and the scleral lenses require to be filled with fluid before insertion [8].

All these lenses are customized to the patient's corneal aspect, based on the keratometry and corneal topography results. To assess the proper fit of the lens, fluorescein staining or anterior segment optical coherence tomography (AS-OCT) can be done [9]. Moreover, the patient is instructed how to take care of the contact lenses in order to prevent related complications, from which microbial keratitis is the most feared, leading to corneal ulcerations and even corneal perforations [10].

Corneal cross-linking

Keratoconus progression entails an increase in keratometry values and decreasing corneal pachymetry, with corneal deformation. A first step in trying to slow down or even stop the progression of keratoconus is by a procedure called corneal cross-linking. It strengthens the corneal structure by increasing the links between the collagen fibers within the stromal lamellae. Early intervention is indicated, especially in young patients, for early stabilization of the disease [11].

There are two main techniques of this procedure. The first described is the epi-off cross-linking which implies removing the first layer of the cornea, the epithelium, in order to facilitate the action of the riboflavin and the UV-A light. The epithelium removal is followed by 30 minutes of riboflavin application and another 30 minutes of UV-A light exposure. The procedure is done under topical anesthesia and after it, the patient needs to wear a therapeutic contact lens until re-epithelization. The treatment proved to reduce the keratometry values and, sometimes, to improve the visual acuity [12].

Although efficient, the epi-off technique has some disadvantages, varying from pain and slow visual rehabilitation to the risk of infection. As a consequence, a more modern epi-on technique developed, maintaining the corneal epithelium in place and making this procedure safer and less invasive. In this case, a higher concentration of riboflavin is used for better penetration of the epithelium. Also, the time of the procedure is halved, making it more comfortable for the patient. A recent study showed that the epi-on technique is similarly effective as the epi-off one [13]. Furthermore, most modern techniques are using supplemental oxygen to increase the efficacy of the procedure [14].

Intracorneal ring segments

When the disease reaches a more advanced stage and the patient's vision worsens, with glasses and rigid contact lenses being unable to help anymore, a way to improve the visual acuity and delay the corneal transplant is by implanting intracorneal ring segments (Figure 4). These are small polymethyl methacrylate (PMMA) segments which, implanted in the cornea, flatten it, reducing the irregular astigmatism and optical aberrations. One or two semicircular or one circular segment can be implanted, depending on the patient's preoperative measurements, including visual acuity, keratometry and corneal topography and aberrometry. A minimum pachymetry of 380-400 microns is, however, needed for a safe placement of the ICRS.

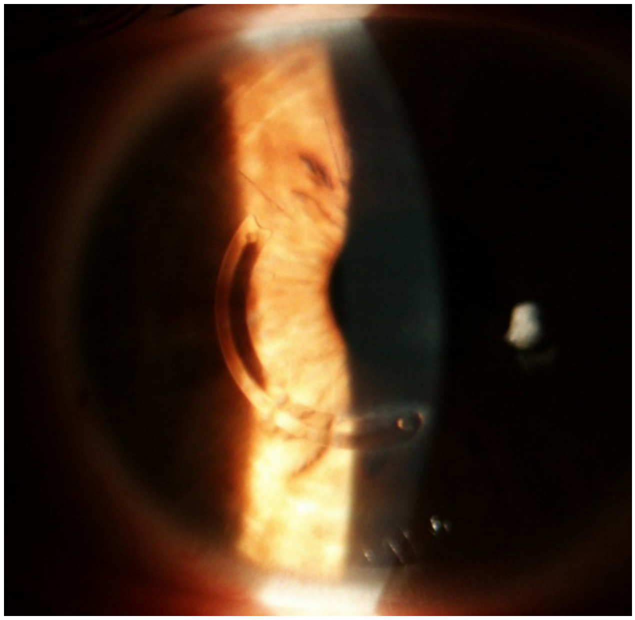

Figure 4. ICRS - postoperative aspect (Photo courtesy of Dr. Cristian Moraru).

The surgery, which is done under topical anesthesia, involves creating a corneal tunnel through which the ICRS is implanted. This tunnel can be made manually or with the femtosecond laser. In the manual technique, an incision is first made in the cornea, at a certain depth, followed by the tunnel creation with a circular dissector which advances through a rotating movement. With the help of the femtosecond laser, the stromal tunnel creation becomes highly precise, being done at the specified depth and based on the ICRS characteristics and patient's preoperative measurements [15].

Recently, progress has been made regarding the material from which ICRS are made. Because implanting synthetic ICRS can develop some complications, for example segment extrusion or migration, a new method evolved, using donor stromal rings. Corneal allogenic intrastromal ring segments (CAIRS) have showed better tolerability compared to synthetic ones, but further studies are needed to establish the long-term outcomes [16].

Corneal transplant

Advanced stages of keratoconus, with a very low visual acuity due to severe deformation of the cornea and presence of corneal scarring, require corneal transplant. During the surgery, the patient's altered cornea is replaced with a donor corneal graft. Depending on the location of the scar within the corneal layers, the surgeon may choose between a penetrating keratoplasty or a lamellar one; each of them can be performed either in a manual approach or, more recently, with the help of the femtosecond laser [17].

Penetrating keratoplasty (PK) is done when all layers of the cornea are affected. In the manual manner, the patient's cornea is first cut using a vacuum trephine at a certain diameter. Afterwards, the cut is completed with the curved scissors. The corneal graft, previously cut with a vacuum punch at a bit larger diameter (0,25 or 0,5 mm larger than the recipient cut), is then put in place and sutured with 16 interrupted sutures, with or without an additional continuous running suture. The femtosecond laser can make smooth and precise cuts of the patient's cornea and also of the donor corneal graft, previously prepared on the artificial anterior chamber system. Moreover, the femtolaser allows for different designs and shapes of the cut, both in recipient and donor cornea (e.g. ”mushroom” or ”top-hat”), according to the surgeon's preference for every case. In keratoconus, ”mushroom” type is preferable, due to two advantages: it preserves more of the recipient's healthy endothelium (the stem of the mushroom being of smaller diameter) and, at the same time, it allows for a lower postoperative astigmatism, due to the ”hat” of the mushroom, which has larger diameter (see later). The surgery is done under local anesthesia and can be performed even on an outpatient basis. It helps restore patient's visual function [18].

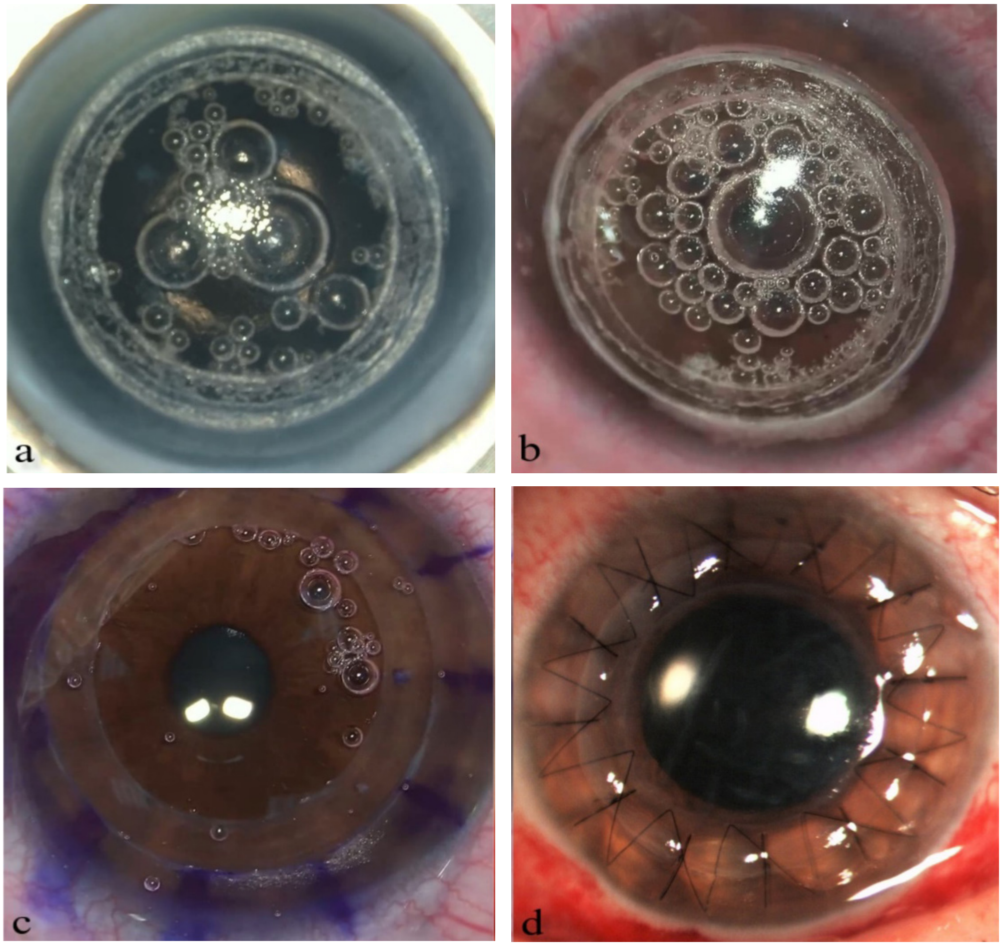

Figure 5. Femtolaser mushroom-type keratoplasty: **(a)** cutting of the graft cornea, placed on the artificial anterior chamber; cutting **(b)** and removal **(c)** of the patient's cornea; **(d)** first postoperative day (Photos courtesy of Dr. Cristian Moraru).

Because it is an open-sky procedure, PK can have some serious intraoperative complications, from choroidal effusion up to expulsive hemorrhage. After the surgery, close follow-ups, especially in the first few weeks, are necessary to prevent postoperative complications. These can include delayed epithelization, increased intraocular pressure (IOP), graft rejection, primary graft failure and infection. Another complication is the postoperative suture-induced astigmatism; when the sutures will be withdrawn, the diopters will stabilize. In penetrating keratoplasties, this happens within approximately one year after the surgery, or even later.

A particular form of penetrating keratoplasty which can be performed in keratoconus patients is *the mushroom technique*. If in classic penetrating keratoplasty, the cornea is cut straight, in mushroom technique, the anterior part of the cornea is cut at a large diameter, while the posterior part is cut at a smaller one. This technique can also be done manually (bi-lamellar keratoplasty) or with the femtosecond laser, when the cornea is cut as a whole in a mushroom design (Figure 5). The advantage of mushroom technique is that it preserves more of the patient's endothelium, which plays an important role in graft survival [19]. In comparison with the manual technique, the femtosecond laser offers more precision in cutting both patient's and graft corneas, with better apposition of the host-graft junction; moreover, with the femtolaser technique there is no interface between the cornea layers, allowing for a clear visual axis and a better visual acuity than in the manual one.

When only the anterior layers of the cornea are affected, the surgeon may opt for a lamellar keratoplasty, in this case *deep anterior lamellar keratoplasty (DALK)*. This technique consists of removal and transplantation of only the anterior layers of the cornea, leaving the patient's healthy Descemet membrane and endothelium in place (Figure 6). The patient's cornea is partially cut with a vacuum trephine, resulting a circular groove. A radial tunnel is made in the cornea, at the base of this groove, through which air is injected in order to dissect the stroma from the Descemet membrane; this is called the big-bubble technique. Further on, the anterior and posterior stroma are very carefully cut and removed, paying attention not to puncture the Descemet membrane. The corneal graft, previously punched to the same diameter and from which the Descemet membrane and endothelium were removed, is then put on the recipient bed [20].

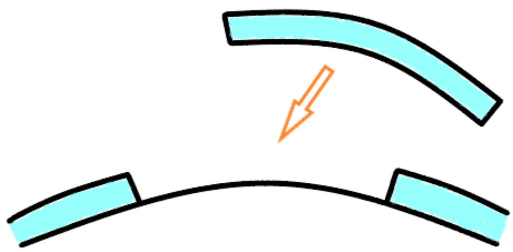

Figure 6. DALK.

In this technique, the femtosecond laser assists by making the circular groove at a precise depth in the cornea, under the OCT guidance. Also, it creates with high accuracy the tunnel through which the big-bubble will be achieved [21]. Intraoperative OCT (iOCT) is another important tool which can help in lamellar keratoplasties. In DALK, iOCT can be used at the begining of the surgery, during the creation of the big-bubble, to check the dissection of the stroma from the Descemet membrane (Figure 7) and also at the end of the surgery, to check the complete attachment of the graft lamella to the patient's Descemet membrane and endothelium [22].

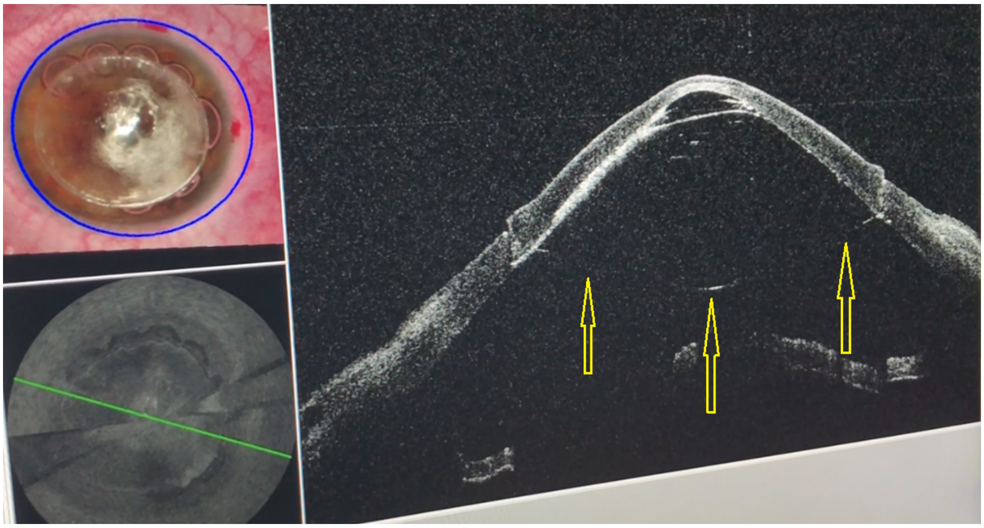

Figure 7. Intraoperative OCT - yellow arrows: the air bubble between the stroma and the Descemet membrane (Photo courtesy of Dr. Cristian Moraru).

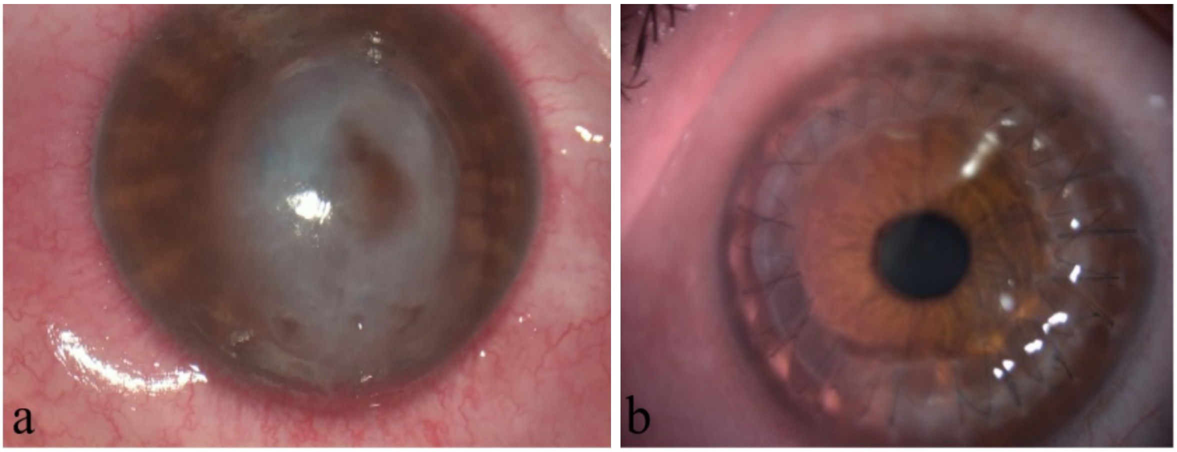

Figure 8. Severe corneal hydrops - beginning **(a)** and end **(b)** of a PK procedure (Photos courtesy of Dr. Ozana Moraru).

Although DALK is a more complex procedure, compared to PK and requires an experienced surgeon, it has major advantages. Leaving the endothelium in place not only reduces the risk of graft rejection, but also the intraoperative complications associated with an open-sky procedure are diminished. Moreover, the recovery is faster; in DALK, the visual rehabilitation can occur in about six months postoperatively because the sutures' removal can start quicker [23].

Even for advanced cases of keratoconus, attempts are made to postpone an actual corneal transplant. Bowman layer transplantation involves implantation of an isolated donor Bowman layer graft into a stromal pocket made in the patient's cornea. It is not a widely used procedure, but, so far, it seems to stabilize the cornea from further progression of this disease [24].

Management of corneal hydrops

Corneal hydrops (Figure 8a) is a complication which can appear in ectatic disorders like keratoconus. It is caused by a tear in the Descemet membrane, through which the aqueous humor gets in the cornea, leading to corneal edema. In most cases, it can resolve spontaneously, but, for rapid recovery or for those cases that cannot resolve by themselves, treatment is necessary.

Medical options include topical antibiotics, cycloplegics, hyperosmotic eyedrops and IOP-lowering medication. Surgical treatment is needed especially when Descemet membrane detachment is present; air injection in the anterior chamber is done in order to reattach it. Venting incisions can also be made to drain the intrastromal fluid. Surgical management of corneal hydrops can also be aided by preoperative AS-OCT [25] or by iOCT.

Conclusion

Keratoconus management has evolved over time. Today, the treatment is individualized for every patient, according to the stage of the disease and anatomical ocular characteristics of each of them. The new technology developed in ophthalmology has allowed early diagnosis for keratoconus patients and, also, efficient treatment, both optical and surgical (advanced contact lenses, ICRS, CAIRS), in much safer conditions (femtolaser in ICRS and in corneal transplants).

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References

1. Burdon KP, Vincent AL. Insights into keratoconus from a genetic perspective. Vol. 96, Clinical and Experimental Optometry. John Wiley & Sons, Ltd; 2013. p. 146–54.
2. Magalhaes OA, Fujihara FMF, de Brittes EBN, Tavares RN. Keratoconus Development Risk Factors: A Contralateral Eye Study. Journal of EuCornea. 2020;7:1–3.
3. Millodot M, Ortenberg I, Lahav-Yacouel K, Behrman S. Effect of ageing on keratoconic corneas. J Optom. 2016;9:72–77.
4. Belin MW, Duncan JK. Keratoconus: The ABCD Grading System. Klin Monbl Augenheilkd. 2016;233:701–707.
5. Andreanos KD, Hashemi K, Petrelli M, Droutsas K, Georgalas I, Kymionis GD. Keratoconus Treatment

Algorithm. Ophthalmol Ther. 2017;6:245–262.

6. Xu Z, Li W, Jiang J, Zhuang X, Chen W, Peng M, et al. Characteristic of entire corneal topography and tomography for the detection of sub-clinical keratoconus with Zernike polynomials using Pentacam. Sci Rep. 2017;7: 16486.
7. Al-Amri AM. Prevalence of Keratoconus in a Refractive Surgery Population. J Ophthalmol. 2018;2018:5983530.
8. Rathi VM, Mandathara PS, Dumpati S. Contact lens in keratoconus. Indian J Ophthalmol. 2013;61:410–415.
9. Downie LE, Lindsay RG. Contact lens management of keratoconus. Clin Exp Optom. 2015;98:299–311.
10. Alipour F, Khaheshi S, Soleimanzadeh M, Heidarzadeh S, Heydarzadeh S. Contact Lens-related Complications: A Review. J Ophthalmic Vis Res. 2017;12:193–204.
11. Barbisan PRT, Pinto RDP, Gusmão CC, de Castro RS, Arieta CEL. Corneal Collagen Cross-Linking in Young Patients for Progressive Keratoconus. Cornea. 2020;39:186-191.
12. Ayvaz A, Brekelmans J, Berendschot T, Dickman MM, Visser N, Nuijts RMMA, et al. Five years outcomes after corneal cross-linking for keratoconus. Journal of EuCornea. 2020;6:9–12.
13. Madeira C, Vasques A, Beato J, Godinho G, Torrão L, Falcão M, et al. Transepithelial accelerated versus conventional corneal collagen crosslinking in patients with keratoconus: a comparative study. Clin Ophthalmol. 2019;13:445–452.
14. Hill J, Liu C, Deardorff P, Tavakol B, Eddington W, Thompson V, et al. Optimization of Oxygen Dynamics, UV-A Delivery, and Drug Formulation for Accelerated Epi-On Corneal Crosslinking. Curr Eye Res. 2020;45:450–458.
15. Sakellaris D, Balidis M, Gorou O, Szentmary N, Alexoudis A, Grieshaber MC, et al. Intracorneal Ring Segment Implantation in the Management of Keratoconus: An Evidence-Based Approach. Ophthalmol Ther. 2019;8(Suppl 1):5–14.
16. Jacob S, Patel SR, Agarwal A, Ramalingam A, Saijimol AI, Raj JM. Corneal Allogenic Intrastromal Ring Segments (CAIRS) Combined With Corneal Cross-linking for Keratoconus. J Refract Surg. 2018;34:296–303.
17. Arnalich-Montiel F, Alió del Barrio JL, Alió JL. Corneal surgery in keratoconus: which type, which technique, which outcomes? Eye Vis (Lond). 2016;3:2.
18. Kamiya K, Takahashi M, Igarashi A, Shoji N. Visual Performance in Eyes Undergoing Femtosecond Laser-Assisted Keratoplasty for Advanced Keratoconus. Sci Rep. 2019;9:6442.
19. Busin M, Madi S, Scorcia V, Santorum P, Nahum Y. A Two-Piece Microkeratome-Assisted Mushroom Keratoplasty Improves the Outcomes and Survival of Grafts Performed in Eyes with Diseased Stroma and Healthy Endothelium (An American Ophthalmological Society Thesis). Trans Am Ophthalmol Soc. 2015;113:T1.
20. Nanavaty MA, Vijjan KS, Yvon C. Deep anterior lamellar keratoplasty: A surgeon's guide. J Curr Ophthalmol. 2018;30:297–310.
21. Liu YC, Wittwer VV, Yusoff NZM, Lwin CN, Seah XY, Mehta JS, et al. Intraoperative Optical Coherence Tomography–Guided Femtosecond Laser–Assisted Deep Anterior Lamellar Keratoplasty. Cornea. 2019;38:648–653.
22. Steven P, Le Blanc C, Lankenau E, Krug M, Oelckers S, Heindl LM, et al. Optimising deep anterior lamellar keratoplasty (DALK) using intraoperative online optical coherence tomography (iOCT). Br J Ophthalmol. 2014;98:900–904.
23. Reinhart WJ, Musch DC, Jacobs DS, Lee WB, Kaufman SC, Shtein RM. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty: a report by the American Academy of Ophthalmology. Ophthalmology. 2011;118:209–218.
24. Dragnea DC, Birbal RS, Ham L, Dapena I, Oellerich S, van Dijk K, et al. Bowman layer transplantation in the treatment of keratoconus. Eye Vis (Lond). 2018;5:24.
25. Vajpayee RB, Maharana PK, Kaweri L, Sharma N, Jhanji V. Intrastromal fluid drainage with air tamponade: Anterior segment optical coherence tomography guided technique for the management of acute corneal hydrops. Br J Ophthalmol. 2013;97:834–836.