Corneal transplantation

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Corneal transplantation

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List of Abbreviations

AAC- Artificial Anterior Chamber

ALK- Anterior Lamellar Keratoplasty

EK- Endothelial Keratoplasty

DALK- Deep Anterior Lamellar Keratoplasty

DM- Descement Membrane

DMEK- Descement membrane endothelial Keratoplasty

DSEK- Descement Stripping endothelial Keratoplasty

DXEK- Descementorhexis and Endothelial Keratoplasty

PK- Penetrating Keratoplasty

PKL- Penetrating Lamellar Keratoplasty

SALK- Superficial Anterior Lamellar Keratoplasty

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SUMMARY

Titel: Corneal transplantation

Author: Meggy Grgic

Corneal transplantation, also known as corneal grafting or keratoplasty is a procedure during which dysfunctional cornea is removed from a patient's eye and replaced with healthy clear cornea from a donor.

Eduard Zirm performed the first successfully full-thickness corneal transplantation more than 100 years ago(1905). (6)

Nowadays the cornea is the most successfully transplanted tissue worldwide and one of the most frequent tissue graftings in the Western world.

This is especially possible because the cornea is quite suitable for tissue grafting due to its avascularity and the immunological privilege.

The indications for transplantation cover a wide range of diseases.

Most of them are obtained from the well-established cornea bank that is capable of preserving the excised donor tissue up to 4 weeks in culture medium.

Cadaveric donor tissue is used whereas the recovery of the donor eye tissue takes place within hours of death.

Surgical techniques and medical treatment of corneal grafts have changed within the last decades as well as our understanding about the immunological aspects of a corneal transplant has increased.

Today we have several surgical and medical options to get a prolonged graft survival, especially in eyes with a high risk for allograft rejection.

The success story of corneal transplantation began with the understanding of the immunological aspects and the introduction of topical and systemic immunosuppressive treatment.

Furthermore in order to cover undersupplied regionsthe need for donor corneas has initiated efforts to synthesize artificial corneas.

Key words: corneal transplantation, eye, graft

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In addition a big part of my recognition goes to his daughter Dra. Elena Barraquer Compte, with whom I first got into touch with Opthalmology. She was a big inspiration to me.

Last but not least, I would like to thank my family for the support they provided me with throughout my entire life, and especially now while writing my thesis.

1 THE CORNEA

“The importance of the cornea to the ocular structure and visual system is often overlooked because of the cornea’s unassuming transparent nature. The cornea lacks the neurobiological sophistication of the retina and the dynamic movement of the lens; yet, without its clarity, the eye would not be able to perform its necessary functions.

The complexity of structure and function necessary to maintain such elegant simplicity is the wonder that draws us to one of the most important components of our visual system.” (DelMonte D & Kim T, 2011)

1.1 Function

The cornea fulfills multiple different funtions.

It acts as a primary structural and infectious barrier of the eye. (13)

As a clear eye windowtogether with the overlying tear film, it also provides a proper anterior refractive surface for the eye, and is therefore the initial point of visual contact.

It allows images to go through, by acting as a powerful lens responsible for focusing the light that enters the eye on the retina. (12,13)

It accounts for more than 2/3 of the optical power of the eye, which cannot be changed physiologically. (2)

It provides approximately 70 percent to 80 percent of the eye's refractive power.(14)

1.1.1 Anatomy

The cornea is the transparent part of the eye that covers the front portion of the eye. It covers theiris (the colored part of the eye), the pupil (the opening at the center of the eye) and anterior chamber (the fluid-filled inside of the eye). (13)

The horizontal diameter of the cornea is 11.5 to 12.0 mm and about 1.0 mm larger than the vertical diameter, in the average adult. (23)

It increases in thickness toward the periphery and is approximately 0.5 mm thick at the center.

The shape of the cornea is aspheric, as the it is steeper centrally and flatter peripherally and it's general condition determine, to a large degree, the visual powers of the eye.

The intrinsic biomechanical structure and extrinsic environment of the cornea govern it's shape and curvature. (12,24)

The cornea is composed of cells and proteins (albumin is most abundant).
It neither contains blood vesselsnor lymph vessels which could modify the corneal transparency, prevent it from refracting light properly and perhaps adversely affect vision.
Therefore, since there are no nutrient-supplying blood vessels in the cornea, it receives nutrients via diffusion from the tear fluid through the outside surface and the aqueous humour through the inside surface. (13)

The cornea is one of the most heavily innervated and most sensitive tissues in the body. Unmyelinated nerve endings are present in the cornea. They are derived from the opthalmic branch of the trigeminal nerve and are sensitive to touch, temperature and

chemicals. (12,14)

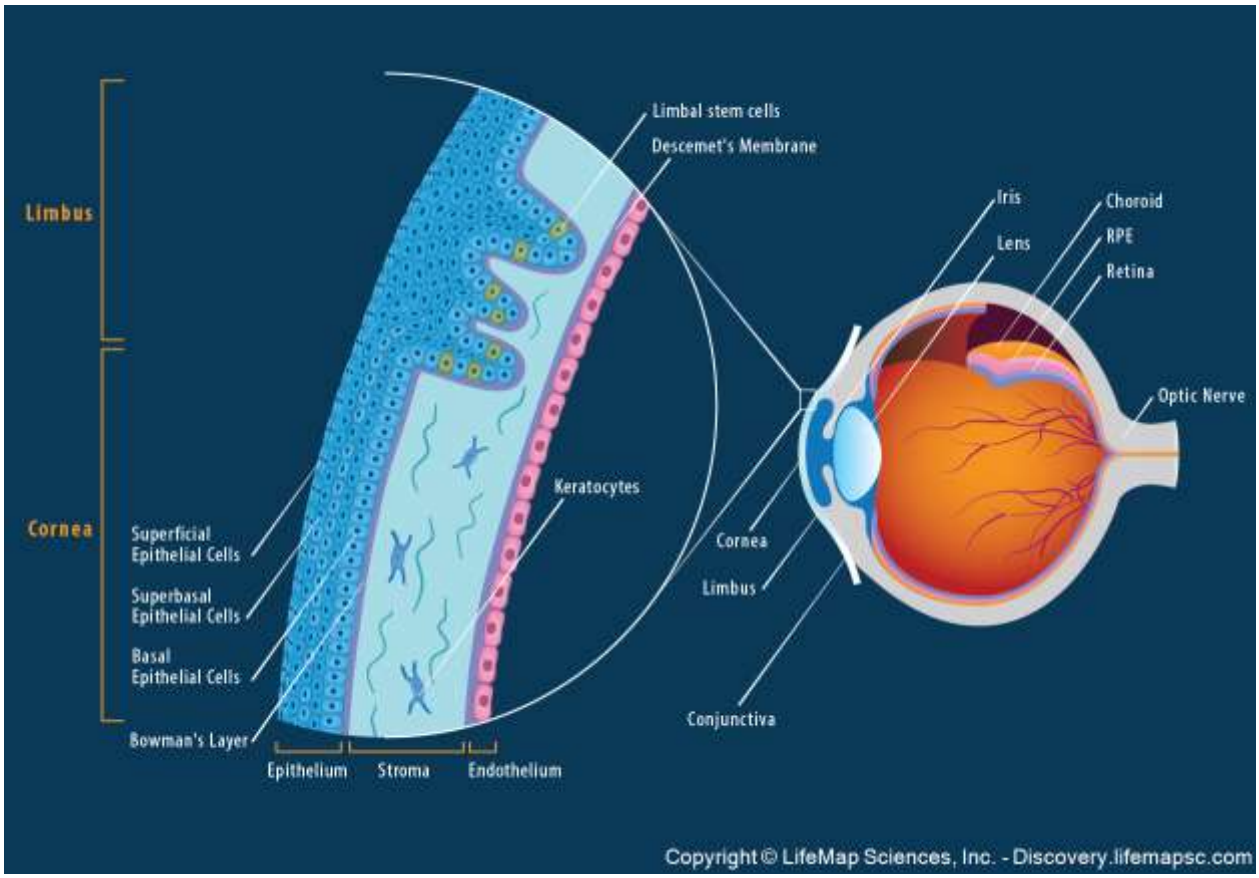

Figure 1. overview of anatomy of the eye and corneal layers (56)

1.1.2 Histology

The cornea is comprised of five layers (Figure 1) (14):

1) Epithelium
2) Bowman's layer
3) Stroma
4) Descemet's membrane
5) Endothelium

The epithelium accounts for approximately 10% oft the corneal thickness, the stroma and Bowman's layer for 88%, and the Descement's membrane and the endothelium for 1%. (2)

The first layer, the epithelium, is a layer of cells covering the cornea and acts as a protective barrier.

It is a part of the interface between the cornea with the tear film which is critical to the refractive power of the eye.(12)

It consists of about 5-6 cell layers, has a regular thickness of about 50µm and can be divided in 3 layers: the basal, middle and superficial layer. (2)

It quickly regenerates when the cornea is injured. But if the injury penetrates more deeply, it might leave a scar. (12)

The Bowman's layerlies just beneath the epithelium.

Histologically it is a homogenous, hyaline, acellular band.

The frontal part is smooth in comparison to the back part which is irregular and difficult to seperate from the corneal stroma. (14)

It consists of multiple collagen microfilaments and helps the cornea maintain its shape.

This layer is very tough and difficult to penetrate,and thus protects the cornea from injury. (2,12, 14)

If the Bowman's membrane is damaged however, scarring will normally occur. (2)

The third and thickest layer of the cornea is the stroma. (14)

It is composed collagen fibrils, very few cells and a groundsubstance which consists of glycoproteins and mucopolysaccharides (glycosaminoglycans). (2)

Theneatly compacted collagen fibrils that run parallel to each other and provide the eye with strength to withstand trauma.

This special formation gives the cornea its clarity. (13,2)

TheDescemet's membrane lies between the stroma and the endothelium.
It consists of modified collagen fibrils that are arranged in layers from which the endothelial cells are separated and serve are basal membrane.
The thickness increases (up to 10 µm)and shows a more homogenous posterior layer with age.
It serves as a barrier to infectious organisms while allowing water and nutrients to pass through. (2)

The endothelium is just underneath Descemet's and consists of a monolayer of about 500.000 hexagonal flattened cells. If damaged or disease, these cells will not regenerate.

Endothelial cell density and topography continue to change throughout life.
Sometimes it is called posterior epithelium because it is embyologically derived from the neural crest. (2)
It maintains hydration of corneal stroma, functional corneal thickness and transparency.
Principally the endothelium functions by actively pumping water from the stroma to the aqueous humor while simultaneously allowing the leakage of nutrients and solutes in the opposite direction, from the aqueous humor to the more superficial layers of the cornea. This passive bulk fluid movement requires no energy but is fueled by the energy-requiring processes of transporting ions to generate the osmotic gradient. The barrier

portion of the endothelium is unique in that it is permeable to some degree, permitting the ion flux necessary to establish the osmotic gradient. (2,12)

2 INDICATIONS

Corneal transplantations are done for several reasons:

1. OPTICAL: To improve the optical qualities of the cornea and thus improve visual acuity (eg, replacing a cornea that is scarred after a corneal ulcer, , is opaque because of deposits of nontransparent abnormal corneal stromal proteins as occurs in hereditary corneal stromal dystrophy, is clouded because of edema as occurs in Fuchs dystrophy or after cataract surgery, or has irregular astigmatism as occurs with keratoconus or a central leukoma is present)
2. REFRACTIVE: To change the curvature of the cornea
3. TECTONIC/RECONSTRUCTIVE: To reconstruct the cornea (eg, replacing a perforated or very thin cornea)
4. THERAPEUTIC: To treat a disorder unresponsive to medical management (eg, severe, uncontrolled fungal corneal ulcer, tumors, highly vascularized cornea) or to relieve intractable pain (eg, severe foreign body sensation due to recurrent ruptured bullae in bullous keratopathy)
5. COSMETIC: to improve the appearance of eyes (eg, amblyoplic eye (lazy eye)or opaque corneal scarring)

(2, 7, 6, 18, 19)

The most common indications are the following: (6,7,17-19)

- Bullous keratopathy:

  swelling of the cornea secondary to either traumatic or degenerative endothelium dysfunction

- Keratoconus:

  a degenerative disorder of the eye where the cornea progressively assumes an irregular conical shape
  rather than a regular curvature

- Repeat graft

- Stromal dystrophies:

  a group of hereditary dystrophies in which there is an accumulation of deposits throughout the anterior and middle stroma causing opacities in varying shapes

- Keratitis or postkeratitis:

  caused by viral, bacterial, fungal, or *Acanthamoeba* infection or perforation

- Herpetic eye disease:

  corneal scarring as a
  result of recurrent infection from the herpes simplex virus

- Corneal dystrophies :

  a group of diseases which are progressive, non-inflammatory, cornea opacifying and usually bilateral. Most of the dystrophies are genetically determined.

  (eg, Fuchs endothelial dystropie, which is especially prevelant in elderly people (7))

The geriatric population represents a distinct clinical group in the connection of corneal transplantation. Indications for surgery for older patients differ compared to younger ones as they are more likely to have had previous or coexisting ocular disease or surgery, and according to this the visual prognosis may be significantly worse. (7,19)

3 EYEBANK

An eye bank is a non-profit organization that obtains, medically evaluates and distributes eyes donated by caring individuals for use in corneal transplantation, research, and education. (14, 10)

3.1 Who can be a donor?

Almost everyone can be a universal donor. Due to the fact that the cornea is avascular (does not have blood vessels) the blood type of recipient and donor does not have to match.

Likewise race, sex and eye color are not considered or of ny relevance for

the outcome oft he surgery.

Clinical studies show that there is no connection between transparency of a transplant and age so that there is no age limit when chosing the suitable donor material. Furthermore the age neither has any influence on the loss of endothelial cells of the donor tissue during surgery nor postoperatively.

However donor tissue of newborns are not suitable for emmetropic recipients as they are thinner and steeper.

Because of the danger of disease transmission from donor to recipient, those suffering from infections or highly communicable systemic diseases such as HIV, hepatitis, syphilis, tuberculosis or have terminal sepsis are not qualified. If the cause of death is unclear this donor tissue should also not be used or perserved as long realise all the necessary test to exclude the presence of transmissive diseases. (2)

3.2 Corneal tissue retrieval

Corneal retrieval is done by enucleation and must be done by a trained and competent person.

Enucleation should be carried out as soon as possible, but no longer than 24 hours after death.

There should be a lawful consent beforehand and that at the time it should be evident that there is no known medical reason to suggest that the eyes should not be retrieved. Sterile, single-use instruments must be used and the eye should be irrigated with saline solution with additional antibiotics. (16,17)

After enucleation a stump of optic nerve at least 5 mm long must remain attached to the eye, which is then secured in a plastic eye stand. The eye stand and eye (cornea uppermost) are placed on top of a moist cotton wool ball or gauze swab and placed in a sterile pot (moist chamber). The eye must not be immersed in any liquid in the moist chamber. The moist chambers are then packed in an Human Tissue Transport box together with a plastic bag containing melting ice. At least 1 kg of ice is needed to keep the contents of the transport box below 5°C for up to 24 hours during transportation to the eye bank. The donor's eye sockets should be packed with cotton wool and lids closed over plastic eye caps to restore the original profile of the lids. The final cosmetic appearance is of critical importance as family or friends may wish to view the body. (13, 17)

3.3 Corneal tissue storage

If the donor tissue is enucleated within 6 hours post mortem is stored maximally 24hours at 4 °C it qualifies as fresh.

With increasing post mortem after tissue retrieval autolysis of the tissue and the pH change induce substantial degenerative change of the endothelium in the anterior segment.

Corneas may be stored for up to 2 weeks at 4°C in an appropriate hypothermic storage solution. Alternatively, the great majority of corneas are stored for up to 4 weeks in organ culture at 34°C. The corneal endothelium is examined by light microscopy a few days before use to ensure its suitability for transplantation in patients with corneal endothelial disease/deficiency. Organ-cultured corneas are delivered to hospitals in medium containing 5% dextran to reverse the stromal oedema that occurs during storage. Corneas with an inadequate endothelium may still be suitable for anterior lamellar grafts. These corneas may also be transferred to 70% ethanol and stored at room temperature for up to 12 months for use in glaucoma surgery.(2)

4 PROCEDURE

Despite its notable durability and elasticity, the cornea may experience some irreversible alterations causing diminution or loss of sight in the eye. Corneal transplant is usually indicated in those cases of congenital, degenerative, infectious, post-surgery or post-traumatic pathologies.

Generally any surgery of the cornea is called keratoplasty.

There are three main types of corneal transplantation techniques: (4)

- **Penetrating keratoplasty**– this is a full-thickness graft surgery when the whole of the cornea needs replacing.
- **Deep lamellarkeratoplasty** – this a partial thickness graft surgery replacing the front of the cornea to treat superficial damage to the cornea (damage to the surface only).
- **Endothelial lamellarkeratoplasty**– this is a partial thickness surgery graft replacing the back of the cornea used to treat conditions affecting only the innermost cornea or endothelium.

The increased availability of donor corneal tissue and the use of special storage media to maintain the donor tissue have allowed corneal transplantation to be done on an elective basis. Surgery is usually scheduled (pending the availability of tissue) 4-8 weeks in advance. Once acceptable tissue is received from the eyebank, the patient is notified and final arrangements are reviewed.

No special preparation for corneal transplant is needed. Some surgeons may request the patient have a complete physical examination before surgery.

The doctor will also discuss the risks and benefits of the various options and let the patient sign a consent.

Normally these surgeries are performed under general anaethesia. However in cases where this is not possible, local anaesthesia can be used instead.

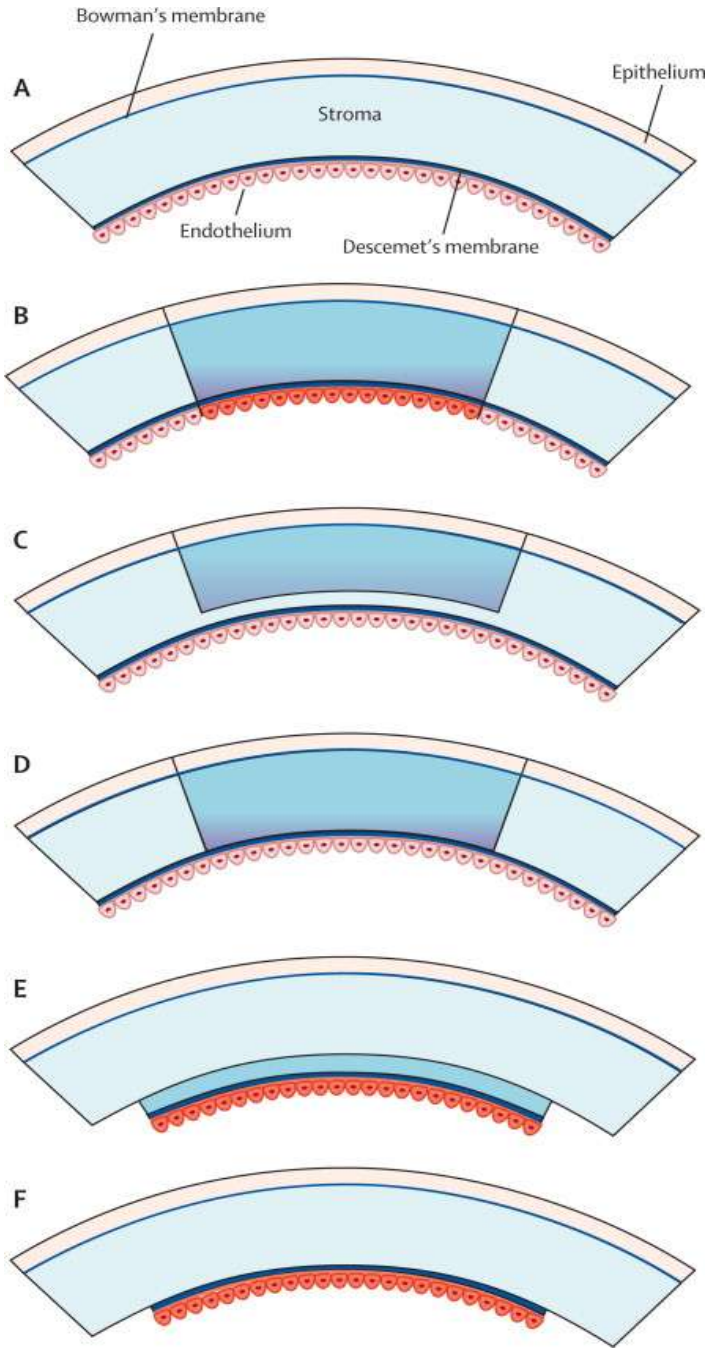

Table 4.

Different types of keratoplasties (corneal transplant)

(A) The cornea consists of five main layers: the superficial multilayered epithelial cell layer, Bowman's membrane, which is a condensation of the anterior stromal layer; the corneal stromal layer (making up the major thickness of the cornea) consisting largely of collagen with relatively low numbers of stromal keratocytes; Descemet's membrane; and most posteriorly, the endothelial cell monolayer that is responsible for deturgescing the stroma to maintain cornealtransparency. (B) Penetrating keratoplasty. (C) Anterior lamellar keratoplasty. (D) Deep lamellar endothelial keratoplasty. (E) Descemet's stripping automated endothelial keratoplasty. (F) Descemet's membrane endothelial keratoplasty.

(57)

4.1 Penetrating keratoplasty

The initial step in penetrating keratoplasty should be the preparation of the donor tissue. The use a corneal button 0.25-0.50mm larger than the diameter of the host corneal openning is recommneded as it can help reduce excessive postoperative corneal flattening, reduce the risk of secondary glaucoma and enhance wound closure.
The host cornea is trephined (trephine is a surgical circular cutting device), the anterior chamber is filled with viscoelastic and the the donor tissue is placed endothellial side down on the recipient's eye. The cornea is then sutured in place with either interrupted or continuous sutures. Interrupted sutures are preferred in vascularized, inflammed or thinned corneas as well as in pediatric cases.
Penetrating keratoplasty may be combined with cataract surgery, secondary intraocular lens implantation, glaucoma surgery and retinal surgery.
Prophylactic antibioticeyedrops and an eye patch are given. (10)
After the anaesthesia wears off the patients are usually allowed to home and return the next day fort he first postoperative examination.

The most common and vexing problem encountered after Penetrating Keratoplasty is the topographic changes induced by surface corneal sutures, high or irregular astigmatism or both can persist some times even years after all sutures have been removed. Surface corneal sutures in penetrating keratoplasty can threaten the vision and graft in other ways such as suture related infections which can lead to devastating wound dehiscence and even endophthalmitis. They also lead to vascularisation, which predisposes to graft rejection.

Penetrating keratoplasty (PK) has been considered the gold standard for treating corneal decompensation resulting from endothelial disease.[1] Recently, PK has been supplanted by endothelial keratoplasty (EK), which allows for selective replacement of the diseased endothelium.(4,8,5)

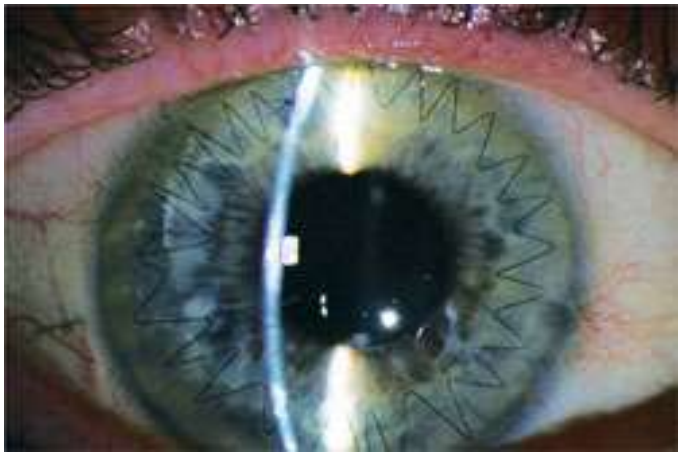

Table 4.1.Three months after transplantation, this detail of the zigzag penetrating keratoplasty shows an excellent graft-host interface. (58)

4.2 Lamellar keratoplasty

4.2.1 Anterior lamellar keratoplasty (ALK)

This procedure is indicated in corneal conditions where the endothelium is still functional, namely, keratoconus and other ectatic disorders, superficial corneal scars, and various corneal dystrophies. Because either superficial or deep, it involves removal of diseased corneal tissue, leaving behind healthy stroma, endothelium, and Descement membrane (DM). (3,20)

Stroma-to-stroma interfaces, as in superficial anterior lamellar keratoplasty (SALK), can degrade visual acuityover time, even if the microkeratomeor femtosecond laseris used to achieve a smooth initial resection. (26)

In deep anterior lamellar keratoplasty (DALK), Stroma-to-DM interfaces provide higher quality vision. (28,29)

Modern ALK procedures have several advantages over PK, even though there is not much difference between the two in terms of best corrected visual acuity, refractive error, immune graft rejection, and graft survival. In DALK where a DM plane is obtained, however, some report better visual results than PK.(35)Sutures can be removed earlier in lamellar procedures, and final visual recovery occurs sooner than with PK. Donor cornea requirements in lamellar procedures are.

As with all new procedures, ALK has a learning curve. Complications such as pupillary block from mismanagement of the air bubble or a fixed dilated pupil may occur when ALK is performed by inexperienced surgeons.Other complications include intraoperative perforation and loss of the anterior chamber forcing a conversion into a PK, incomplete or irregular deep lamellar dissection, interface neovascularization, and longer surgical times for beginners. (52)

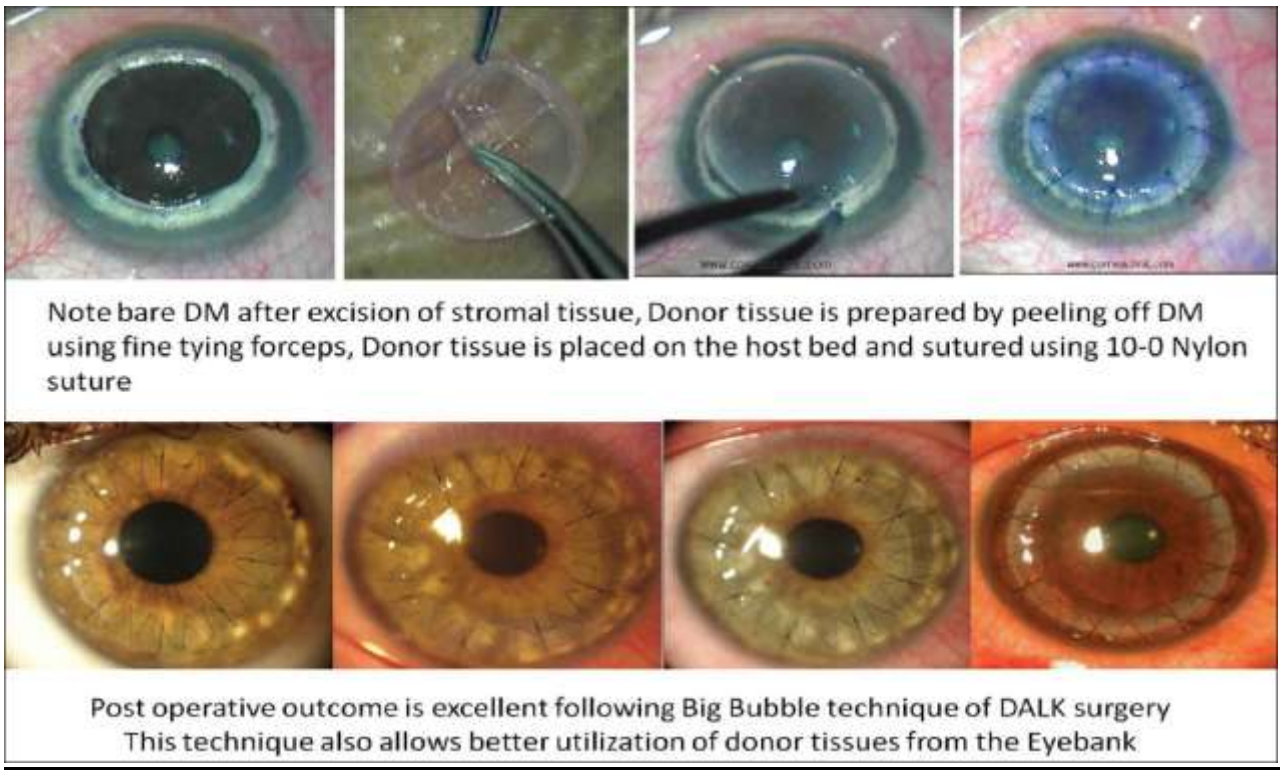

Figure 4.2. DALK Donor tissue prepared and placed into position and secured with 10-0 nylon sutures(59)

Superficial anterior lamellar keratoplasty (SALK) should be used when the anterior 30-50% of the cornea is affected with pathology and is to be replaced with a similar amount of donor tissue.

The main indications are superficial scars resulting from healed infections, including trachoma, trauma (post-laser or accidental), superficial corneal dystrophies and degenerations, or persistent epithelial defects. (36-38)

Some known surgical techniques for DALK are:

a. Direct Open Dissection

b. Dissection with Intrastromal Air Injection (36)

c. Dissection with Hydrodelamination (42)

d. Closed Dissection (41)

e. Dissection with Viscoelastics (40,41)

f. Dissection with Anwar's Big Bubble Technique (46)

g. Big Bubble Technique Combined with Zigzag Femtosecond Laser Incisions (30-32,34)

In the automated lamellar therapeutic keratoplasty a special microkeratome attached to a suitable suction corneal ring is used to excise an amount of stroma determined by the extent of diseased cornea. (23)Eyes with excessive corneal thinning are excluded. The donor cor- neoscleral button is mounted on an artificial anterior chamber (AAC). (53) Four 10-0 nylon cardinal sutures are used to secure the lamellar button, followed by a running 10-0 nylon suture. Finally, the four cardinal sutures are removed, and the running suture is tied. (53) This procedure is not popular because of the elaborate instrumentation required and the degree of attention to details that, if overlooked, may lead to significant complications. (54)

4.2.2 Posterior lamellar endothelial keratoplasty

Over the past decade endothelial keratoplasty has replaced penetrating keratoplasty as the preferred technique for treating endothelial disease beacause it allows for selective replacement of the diseased endothelium. (27,1)

In the DLEK technique, the preoperative corneal surface is left untouched in an attempt to preserve normal corneal topography. The corneal limbus is preserved to aid in the structural integrity of the globe, and to allow endothelial transfer in a relatively closed controlled system. The surgical steps are straightforward, but require specialized instrumentation. (1,43,44,46,47)
In comparison neither DLEK nor PK procedures became popular. This was primarily because required extensive manual lamellar dissections for both the posterior recipient corneal resection and for the creation of the donor lenticule.

This newest version of posterior lamellar keratoplasty has been termed Descements stripping automated endothelial keratoplasty (DSAEK). It is also known as DXEK (Descemetorhexis and endothelial keratoplasty). Primary advantages of DSAEK compared to other posterior graft procedures are the speed and degree of visual recovery. Vision usually recovers in one to three months.

For DSAEK the surgery basically is reduced to two steps. First the excision of the recipient Descemet’s membrane, ie, creating a Descemetorhexis, and second the implantation of a donor Descemet’s membrane into the anterior chamber and positioning of the tissue against the recipient posterior stroma. The performance of a Descemetorhexis is a quick and easy maneuver. For this proper donor tissue

preparation is essential, for this the donor cornea must have sufficiently large scleral rim to allow fixation with an artificial anterior chamber. Corneoscleral button of 16mm diameter is recommended. The posterior lamellar donor button should comprise endothelium, Descemet's membrane and 100-200 um of stromal tissue. The insertion of donor button in recipient eye is same as in posterior lamellar keratoplasty through a self-sealing tunnel incision.

The complications of high rates of primary graft failure (PGF) and donor tissue dislocation, however, remained significant problems in DSAEK surgery. (48)

In addition, the high cost of the microkeratome provided an economic obstacle.

DSAEK has been most commonly used for Fuchs endothelial dystrophy disease and pseudophakic bullous keratopathy. DSAEK has also been used for corneal edema from

post-surgical endothelial decompensation, genetic diseases such as irido-corneal-endothelial dystrophy, and congenital hereditary endothelial dystro-

phy.[161,174,246]

The two major complications following DSAEK surgery are graft dislocation and primary graft failure. Both are correlated with surgical technique and surgeon experience.

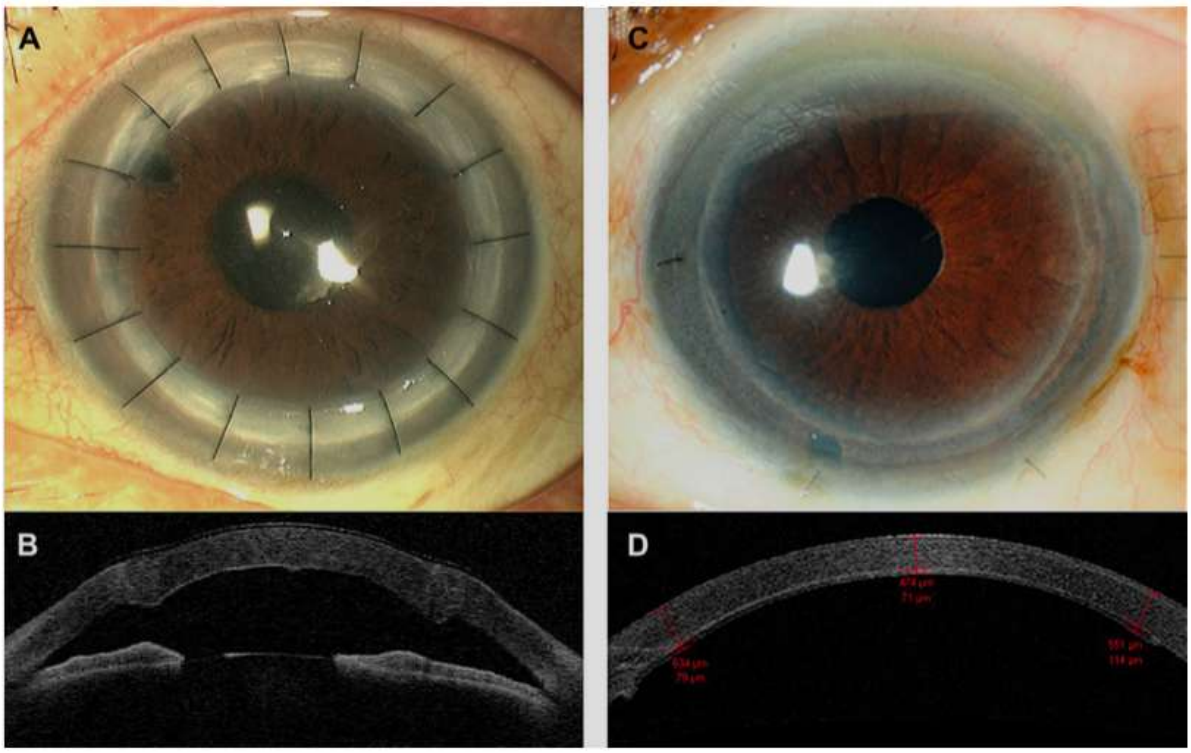

Fig. 1. Slit lamp image (*A*) and corresponding anterior segment optical coherence tomography image (*B*) of penetrating keratoplasty and corresponding images (*C, D*) of Descemet stripping endothelial keratoplasty demonstrating the tectonic and refractive advantage of DSEK over PK.

(60)

More recent modifications of EK have attempted to transplant only donor DM and have been named Descemet membrane endothelial keratoplasty (DMEK) by Melles. (51)

and Descemet membrane automated endothelial keratoplasty (DMAEK) by Price. (55)

In DMEK/DMAEK the donor graft just has the thin DM and endothelium in the center, with an outer rim of extra supporting tissue the thickness of a DSAEK graft. The biggest hurdle with DMEK is the preparation of the donor tissue. (49)Essentially, the endothelium and attached DM have to be peeled off the back of the donor cornea. The ultra-thin DMEK grafts are so fragile that sometimes the tissue tears while separating the layers and cannot be salvaged.

5 RISKS

Corneal grafting is complex surgery and there are many possible risks, which will vary between patients. Loss of vision is always a possibility. Some of the major risks include: (7, 8-11)

- Intraoperative bleeding:

  (1 in 200 people)

- Infection:

  Severe early post-operative infection is rare (1 in 500 people) but can lead to loss of sight or loss of the eye. Infections arising later are common (1 in 20) and often related to stitch problems. They are usually treatable with antibiotic eye drops.

- Corneal graft rejection

  occurs in up to 20% of low risk grafts and up to 80% of high risk grafts (replacement grafts after previous rejection, corneas with blood vessels or those that are inflamed at the time of surgery).

- Graft failure

  corneal clouding due to graft failure within the first year is only seen in 5% of routine penetrating keratoplasty cases but up to 20% of endothelial lamellar cases because of the increased tissue manipulation required. Lower risk of early graft failure is the main advantage of penetrating keratoplasty as compared to endothelial lamellarkeratoplasty.

- High astigmatism

  astigmatism occurs where the donor cornea resting on the patient's eye has a different curvature in one direction (axis) than another, andis normal after graft surgery. In about 10% of cases astigmatism surgery is required to permit useful spectacle vision and this is usually carried out between 15 – 24 months after the initial operation. Sometimes graft astigmatism can only be corrected with a contact lens.

- Interface opacity (cloudiness)

  the join between the patient's remaining tissue and the donor cornea heals by scarring, which creates an opacity across the vision in both types of lamellar graft. In most cases this is very mild, but in some case can significantly reduce vision or cause glare.

- Glaucoma

- Retinal detachment

- Cataract formation

Important signs to look out for after your operation, which could point to a postoperative complication, are:

Increasing pain, redness of the eye, light sensitivity and worsening of the vision

6 BIOGRAPHY

Meggy Grgić was born on June 23rd 1989, in Zagreb.

After attended Privatgymnasium St. Ursula in Salzburg she enrolled in the English Program at the Medical School of the University of Zagreb, where she is still a student.

In the future, Meggy hopes to practice Ophthalmology.

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