REVIEW PAPER

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The use of stem cells and keratoprosthesis – special surgery types for corneal disorders (a narrative review)

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ABSTRACT

Corneal disease and damage can arise from various causes, including infections, corneal dystrophies, trauma and improper contact lens use. These factors can lead to corneal blindness which greatly decreases the patient's quality of life. Although corneal transplantation is a viable treatment option for many patients, the risk of rejection after corneal transplantation remains a concern. Severe corneal damage requires special methods of treatment, which are still sought after. This narrative review aims to summarize the use of stem cells and keratoprosthesis in the treatment of corneal diseases. Stem cell therapy, particularly limbal stem cell transplantation, shows promise in corneal regenerative therapy, especially the treatment of limbal stem cell deficiency. Additionally, induced pluripotent stem cells have been successfully used in cornea transplantation, offering a novel approach to restoring vision in patients with corneal diseases. Keratoprosthesis, such as the Boston keratoprosthesis and osteo-odonto-keratoprosthesis, provides an alternative for patients who cannot undergo traditional corneal transplantation. Artificial prostheses are also an alternative to corneal transplantation in cases of extensive trauma or in the absence of donor tissue. Continued research and development in stem cell therapy and keratoprosthesis hold the potential to improve the outcomes, accessibility of corneal disease treatment and reducing the global burden of corneal blindness.

Introduction

The cornea is a translucent structure located at the anterior pole of the eyeball and is made up of 5 layers, which include the epithelium, the Bowman's layer, the stroma, the Descemet's membrane, and the endothelium [1,2]. Some also distinguish the Dua layer, which is located in front of

the Descemet's membrane, and is characterized by high tensile strength [3]. Corneal disease and damage, which leads to reduced corneal transparency, can be attributed to several underlying causes. One of the primary factors is keratitis, caused by bacterial, viral, or fungal infections that directly affect the cornea. These infections can weaken the cornea and lead to inflammation, scarring, and vision impairment [4]. Secondly, corneal dystrophies, which are genetic disorders, can cause gradual deterioration of the cornea over time. These conditions result in the accumulation of abnormal proteins, affecting corneal transparency and function [5]. Additionally, external factors like trauma, such as injuries from accidents or foreign objects entering the eye, can cause corneal damage, leading to vision problems [6]. Lastly, prolonged and improper use of contact lenses without adequate hygiene and care can increase the risk of corneal infections and damage [7].

A complete loss of corneal translucency leads to corneal blindness, which can be treated only surgically by replacing the patient's cornea with donor tissue [8,9]. Corneal transplantation, also called keratoplasty, is the most widely and successfully performed allogeneic transplantation globally. For over 100 years, the technique has developed from total corneal replacement to grafting specific corneal layers. The changes were brought about by the improvement of technology, surgical techniques, and knowledge [10].

Indications for keratoplasty include corneal perforations, eye injuries, keratoconus and corneal scarring, among others. When qualifying a patient for the procedure, risk factors for graft failure should be considered. History of graft rejection, glaucoma, infection, and mismatched graft size increase the risk of failure. Keratoprosthesis is indicated for patients with a high risk of corneal graft rejection, patients with predisposition to endothelial failure, and patients with corneal stem cell deficiency [11–13].

This narrative review aims to summarize current knowledge on the use of two special techniques in corneal treatment: stem cells transplantation and keratoprosthesis. In the work presented here, we describe both methods and present the possibility of combining them to allow keratoprosthesis for patients in whom this was not possible, due to damage to the ocular surface. This review also presents the latest research from 2023 on keratolimbal allograft (KLAL), the aforementioned preparatory procedure for keratoprosthesis.

Keratoprosthesis

Keratoprosthesis is a type of surgery, which involves implanting an artificial optical system into the eye with corneal blindness. It is an alternative form of treatment indicated for patients, who are not candidates for traditional penetrating keratoplasty due to bilateral corneal blindness because of, for example, multiple failed grafts, herpetic keratitis, silicon oil-filled eyes, mucous membrane pemphigoid, Steven Johnson's Syndrome (SJS), or severe chemical injuries [14]. Keratoplasty, however, carries the risk of complications, such as secondary infections, increased intraocular pressure, graft dehiscence, and consequently graft rejection [15]. Regardless of the cause of corneal blindness, risk factors for corneal graft rejection include: neovascularization, previous graft rejection, high intraocular pressure, long operating time, and older age of the patient [11,16,17].

The originator of keratoprosthesis was the French ophthalmologist Guillaume Pellier de Quengsy, who first mentioned it in 1789 in his publication Précis au cours d'operations sur la chirurgie des yeux – accuracy during eye surgery [18]. However, the idea had to wait many years until the discovery of antibiotics, steroids, and transparent, non-toxic plastics [19].

Currently, the commonly used keratoprostheses include the Boston keratoprosthesis type I (B-KPro type I) and the osteo-odonto-keratoprosthesis (OOKP). Novel prostheses are still being developed, and include the Boston keratoprosthesis type II (B-KPro type II), KeraKlear ®, Micro Cornea ®, Lucia keratoprosthesis, and Alphacor [20]. Current research in the field of keratoprosthesis is focused on improving surgical techniques and finding new materials to increase bioavailability, mechanical properties, and accessibility for people of low socioeconomic status. The B-KPro type I, B-KPro type II, and OOKP will be reviewed in detail in this part of the review.

Boston keratoprosthesis

B-KPro type I was developed by Dohlman in 1974. Originally, the entire prosthesis was made of polymethylmethacrylate, but now its components are also made of titanium. The prosthesis takes the form of a buckled collar, constructed of an anterior plate that contains an optic stem, a corneal allograft button, and a fenestrated posterior plate with a titanium ring protecting it [21,22]. The B-KPro type I is recommended for patients with an adequate eye surface area and intact eye protection apparatus [17]. The B-KPro type II differs from B-KPro type I in that it has an additional anterior cylinder protruding through the surgically closed eyelids. It is used in severe ocular surface disorders such as mucous membrane pemhigoid and Stevens-Johnson syndrome (SJS) [23]. A 2015 systematic review indicated that in two studies conducted in the United States, 88% and 87%, respectively, of the indications for keratoprosthesis were implantation after failed keratoplasty. In contrast, primary implantation of the prosthesis was chosen for severe chemical or thermal damage to the ocular surface (7–30.4%, depending on the study), SJS (2.5–100%, depending on the study) and aniridia (1–100%, depending on the study) [24]. The B-KPro type I can be used for patients after prior rejection of a corneal transplant; however, Kang et al. [25] postulated its efficacy as the primary treatment of corneal blindness for patients with a high rejection risk. The results of a matched case control study that included 56 eyes revealed, that the chance of maintaining a 20/200 visual acuity over 5 years was significantly higher for patients with primary B-KPro type I implantation (without performing prior keratoplasty) than for patients with secondary B-KPro type I implantation (after prior graft rejection). Moreover, the primary use of B-KPro type I was shown to ensure a higher probability of maintaining the best corrected postoperative visual acuity after 5 years (79%, compared to 49% of patients with secondary keratoprosthesis implantation) [25]. A metaanalysis comparing B-KPro implantation with repeat PKP analyzing the postoperative visual acuity achieved showed a 42% probability of achieving BVCA ≥ 20/200 after 2 years with repeat PKP. In comparison, B-KPro showed an 80% probability of a similar result after 2 years [26]. In contrast, a meta-analysis analyzing the long-term results of B-KPro based on 407 papers indicated visual acuity >6/60 at 2 years after implantation achieved in 45–77% of cases. Of note, hemifacial virus-associated keratopathy contributes to prosthesis failure and higher complication rates, making it inappropriate to use them in patients with this condition [27].

Because the proper structure of the eyeball is essential for implanting B-KPro, some patients, for example after severe burns, or extensive lacerations caused by mechanical trauma, may not qualify for the keratoprosthesis. To attain a steady eye surface before B-KPro insertion, patients may undergo stem cell treatment (KLAL or conjunctival limbal autograft). Pretreatment of the eye surface with stem cells can allow for future B-KPro implantation in the cases of patients with severe damage to the ocular surface [28].

Before implantation, the prosthesis has to be properly sterilized. Currently, B-KPro is sterilized before being sent to the hospital using ethylene oxide and then is attached to the fresh corneal tissue. A recent study revealed the beneficial effect of using an electron beam (E-beam) during sterilization, which could allow B-KPro to be stored for up to 2 years at room temperature. E-beam sterilization increases the tensile strength of the cornea improving its mechanical properties and stabilization without detrimental effects on the tissue and its optical properties [29].

With B-KPro implantation, there is a risk of certain postoperative complications, which include the formation of a retroprosthetic membrane, corneal fusion, and glaucoma [29–32]. Some of the most common complications include retroprotic membrane, which affects 12–67% of eyes after B-KPro implantation; infectious keratitis and aniridia have been identified as predisposing factors, while chemical trauma has a protective effect. In contrast, the most difficult complication to treat is glaucoma [24]. Uncontrolled glaucoma in its most advanced form can lead to permanent and irreversible blindness [33–35]. Preventive implantation of the Ahmed glaucoma valve has shown promising results in ameliorating glaucoma consequences [36]. Another method of preventing glaucomatous damage to the eye after B-KPro implantation is a transdermal postoperative endoscopic cyclophotocoagulation, after which about two-thirds of the patients

can achieve normal intraocular pressure. A Canadian study showed that cyclophotocoagulation helped control postoperative glaucoma in 61% of patients but did not reduce the need for medication in the process. In patients with contraindications to endoscopic cyclophotocoagulation, immunosuppressive treatment can be implemented [37–39].

Osteo-odonto keratoprosthesis

An OOKP is a complex structure prepared with the use of the patient's tissues – the root of a tooth along with part of the alveolar bone used as the scaffolding for an artificial lens, and a fragment of the patient's buccal mucosa, used as a shielding element and to improve integration with the eye structures. OOKP was first developed by Strampelli and later modified by Falcinelli [11,40]. This prosthesis type is designed for patients with significant damage to the eye surface, mainly caused by extensive burns, mechanical injuries, or severe dry eye syndrome [17]. OOKP has a very high survival rate of more than 80% over a 20-year follow-up period, thus providing the best long-term outcomes for patients with severe ocular surface damage [41]. The need to use the patient's tooth is a limitation to performing such a procedure in edentulous patients [42]. An alternative may be to use a fragment of the tibial cortex [43]. The demand promotes the search for material that could replace the patient's tissues [44,45]. A study assessed the efficacy of using a high-strength hydrogel with nanocrystalline hydroxyapatite coated with microspheres of lactic and glycolic acid copolymer using agarose and poly-glycol-ethylene diacrylate polymer, which showed high mechanical strength and the potential to replace dentinal tissue. In addition, based on low levels of interleukin-6, this material proved to be non-inflammatory. The hydrogel polymer composite can be used in the future as an alternative for the dentinal part of the OOKP [42].

Stem cells

Human stem cells are undifferentiated cells that can be found throughout the body. They have the potential to specialize into any cell in an organism (multilineage differentiation) and are capable of self-renewal. Stem cells can be found in both embryonic and adult tissues. They can be classified into:

- totipotent cells, which can differentiate into each cell of the body,
- pluripotent cells, which can differentiate into every tissue except extraembryonic structures,
- multipotent cells, which can specialize within a germ cell layer (endoderm, mesoderm, ectoderm),
- monopotent cells, which can form cells of a specific lineage within the tissue [46–48].

The possible medical use of pluripotent cells has been unsatisfactory in the past, as pluripotent cell therapy risks genomic instability, rejection, or teratoma formation. Monopotent stem cells, such as mesenchymal stem cells (MSCs), or hematopoietic stem/progenitor cells obtained from postnatal tissues, have thus far proved to be safe in regenerative therapy [49–51]. Stem cell transplantation is also of interest to ophthalmologists, who search for its application in the treatment of corneal diseases.

The cornea, like other tissues of the body, requires stem cell proliferation for maintaining transparency and homeostasis. Stem cells of the cornea are located in the corneoscleral limbus. Within the limbus, there are two populations of corneal stem cells – limbal epithelial stem cells (LESCs) and corneal stromal stem cells [52–54]. The loss of limbal stem cells leads to limbal stem cell deficiency (LSCD). As a result, the corneal epithelium is unable to maintain its normal homeostasis. This manifests as conjunctivalization of the cornea and/or other symptoms of epithelial dysfunction, such as ocular surface inflammation, scarring, or neovascularization. LSCD can be classified as acquired (cornea injury, pterygium, infections, drug-induced, allergic, and more) and hereditary (congenital aniridia, dyskeratosis congenita, and more) [55,56].

The ultimate treatment for high-stage LSCD is surgical and can include limbal stem cell transplantation. For unilateral LSCD, an autologous LESCs transplantation from the healthy eye can be performed as a keratolimbal allograft (KLAL), conjunctival limbal allograft (CLAL), autologous simple limbal epithelial transplantation, or an ex vivo-cultivated LESCs autograft. For bilateral

LSCD, KLAL, CLAL, and ex vivo-cultivated LESCs allografts can be performed [57]. A procedure for cultivating LESCs ex vivo has been described by Jurkunas et al., to standardize the manufacturing process [58]. As of May 2024, this team has carried out a clinical trial concerning LSCD treatment with cultivated autologous limbal epithelial cell transplantation, though no results have been posted yet (clinical trial NCT number at *clinicaltrials.gov*: NCT02592330). Patients with unilateral LSCD undergo limbal biopsy in the healthy eye; the stem cells are cultivated into a graft and transplanted into the diseased eye. The trial enrolled 17 patients, but no results have yet been published [59].

A novel therapy using stem cells for cornea regenerative therapy has also been developed in Japan, where in 2019 the first cornea transplant using induced pluripotent stem cells has been performed. A donor's skin cells have been harvested and reprogrammed to differentiate into corneal cells, with a good effect on vision for the patient [60].

Other stem cells with potential for use in ophthalmology are MSCs which were proven to promote graft survival. MSCs exert immunomodulatory action by inhibiting the activation of antigen-presenting cells and dendritic cells, which leads to allograft tolerance [61,62]. Further application of MSCs is researched, with promising results of in vitro and in vivo studies on murine models, that used bone marrow MSCs, adipose tissue MSCs, and human umbilical cord MSCs for promoting corneal epithelium regeneration [63–66].

Keratolimbal allograft

To perform the keratoplasty and keratoprosthesis procedures, a stable ocular surface is needed. To provide it in patients with LSCD, the first-line treatment is to perform the KLAL procedure. KLAL and keratoplasty can be performed either as a single-stage procedure or as a sequential procedure. In the case of a sequential procedure, KLAL is the first stage and aims to restore a translucent, stable corneal surface devoid of vessels. The performance of KLAL does not always provide the expected clarity and acceptable vision, and the end result depends on a subsequent corneal transplantation or keratoprosthesis implantation [67]. If KLAL does not provide adequate visual rehabilitation, a keratoplasty or keratoprosthesis procedure is performed. Keratoplasty is chosen for patients in whom immunosuppression cannot be used or an allograft stem cell transplant is not available [28,67,68].

A retrospective study by F. Karimian et al. published in 2023 described an "en bloc procedure", which involves simultaneous KLAL and penetrating keratoplasty (PKP) from tissues taken from a single donor and placed in a single piece. Nine patients with bilateral total LSCD were included in the study. The combined procedure provided a lower antigenic load for the patient, while the sequential surgeries helped reduce inflammation in the recipient, which is a major risk factor of rejection of the transplanted tissues. Among the study group, surgical success was achieved in eight patients, who underwent a follow-up period of 6.5 years. Three patients developed persistent epithelial defects. For two, conservative treatment was sufficient, and for one patient, a secondary PKP was necessary due to corneal graft failure [67]. Another study by the aforementioned scientist compared 108 eyes in patients with mustard gas-induced keratopathy. KLAL alone was performed in 62 eyes, KLAL combined with lamellar keratoplasty (KLAL-LKP) in 40 eyes, and KLAL combined with PKP (KLAL-PKP) in 6 eyes. The Kaplan-Meier analysis in the KLAL-LKP group showed a 90% survival rate, while the KLAL alone group showed a 75% survival rate [69].

A retrospective analysis by Zongyuan Li et al. in 2022 described 49 eyes, 24 of which underwent KLAL alone and 25 KLAL in combination with deep anterior lamellar keratoplasty (KLAL-DALK). All eyes included in the study showed preoperative severe or complete LSCD. In patients with satisfactory corneal translucency, KLAL alone was performed, while if deep scarring or insufficient corneal clarity was present, the surgeon decided to perform KLAL-DALK. Final follow-up showed success or partial success in 35 eyes, defined as resolution of LSCD symptoms and restoration of a transparent, avascular, stable corneal surface. In the KLAL-only group, improvement was achieved in 16 eyes (66.67%), and in the KLAL-DALK group, 19 (76%). At one-year follow-up, improvement was seen in

39 eyes, 19 in the KLAL-only group (79.17%) and 20 in the KLAL-DALK group (80%). Complications occurred in 17 of 49 eyes and mainly included corneal ulceration, glaucoma and corneal perforation. Choosing the DALK procedure over PKP preserves the host corneal endothelium, thereby eliminating the possibility of endothelial immune graft rejction [68]. The results of this study were contrasted with a meta-analysis on post-KLAL outcomes presenting similar results [68,70].

Krysik K. et al., along with a Polish team of researchers, published two articles on KLAL. One on KLAL as preparation for PKP, the other on KLAL as preparation for keratoprosthesis implantation [28,71]. 43 eyes with complete LSCD and severe ocular surface abnormalities were included in the first study as a pre-PKP procedure. 40 patients underwent KLAL and PKP, and three patients underwent KLAL only. In 17 eyes (39%), KLAL had to be repeated in order to obtain suitable conditions for PKP. The PKP procedure was performed 9–12 months after KLAL, and graft failure requiring a repeat PKP procedure was described in 14 eyes (32%) [71].

A study describing the preparation of the eye for Boston KPro type 1 keratoprosthesis implantation compared the performance of conjunctival limbal autograft (CLAU) with KLAL in patients with complete LSCD. The study included 69 preparatory procedures performed. Although the main purpose of performing CLAU and KLAL is to prepare the ocular surface, visual acuity improved from light perception to hand movement in three eyes (16%) in the CLAU group and in eight eyes (15%) in the KLAL group. In contrast, in two eyes (12%) from the CLAU group and in two eyes (4%) from the KLAL group, visual acuity improved from hand movements to finger counting. Repetition of KLAL was necessary in seven eyes, with one eye requiring this procedure three times [28].

Boston KPro type 1 implantation can be another line of treatment when keratoplasty fails. Seven eyes prepared for Boston KPro type 1 implantation after a failed keratoplasty procedure performed after a previous KLAL were included in the study. After implantation of the keratoprosthesis, visual acuity improved in all eyes from the range of hand motion to 20/400. Only one case with a primary diagnosis of aniridia required a second implantation of the prosthesis, though it is worth noting that the patient abruptly discontinued immunosuppressive treatment which resulted in KLAL rejection. In the remaining 3 patients with a primary diagnosis of aniridia, a satisfactory therapeutic outcome was achieved [72].

Patients with aniridia are characterized by LSCD in both eyes and present a therapeutic challenge. Current treatment includes lens surface moisture-enhancing therapy with bandage and tarsoraphy, contact lenses, and PKP, which, however, is characterized by the risk of failure associated with LSCD recurrence. Alternative management including KeraKlear artificial cornea implantation performed in two patients was characterized by maintenance of a stable ocular surface 3 years after surgery [73].

A 2018 systematic review reviewed the available publications on the effects of KLAL in patients with LSCD due to chemical damage. Only 6 papers presenting a total of 36 eyes met the criteria. For 30 eyes, the studies presented criteria for the success of the KLAL procedure; 19 of the 30 eyes (63.33%) met the criteria. In 11 cases, KLAL-PKP was performed, in 15 PKP was performed after the KLAL procedure, and in 5 cases it was not described whether PKP was performed at the same time or at a later time. In addition, one eye underwent a lamellar keratoplasty. Rejection of PKP was reported in 12 of 32 cases (37.5%) while 8 eyes required a repeat procedure. Five of the six publications analyzed postoperative visual acuity The BVCA effect of ≥20/200 was achieved in 20 of 29 eyes (69%) with a median follow-up of 42 months [74].

The 2021 systematic review set as its goal the identification of best acceptable practices for the surgical treatment of LSCD. The review included 17 papers describing the KLAL procedure, CLAU, KLAL-CLAU combination, cultivated limbal epithelial transplantation (CLET) and simple limbal epithelial transplantation (SLET). They showed no significant difference between any of the aforementioned procedures in terms of achieving a stable surface (the results are in the range of 47.4–89%, and averaged at 75.84% of the anatomical success achieved in the described works). In contrast, KLAL had a better functional success rate in terms of visual acuity gain after KLAL surgery. In our publication we presented, the success rate, defined as achieving a stable corneal surface, ranged from 61–79%, and averaged 71.67% [75].

KLAL as a procedure performed prior to PKP and keratoprosthesis is broadly discussed in a review article by Atallah et al. in 2016 [76]. More recent studies suggest that KLAL can substantially reduce, or even eliminate, the risk of endothelial graft rejection when compared to PKP, as it is performed above the Descemet's membrane [68]. KLAL also requires less time to treat the postoperative inflammation Performing the second phase of sequential treatments too quickly can result in graft rejection [28]. However, in the situation of an unsuccessful KLAL-PKP procedure, Boston KPro type 1 can be implanted with satisfactory results [73]. Current research emphasizes the role of possible visual acuity improvement after the KLAL procedure alone, and even better visual acuity improvement when a keratoplasty or keratoprosthesis procedure is performed in the next stage [28,72,73].

Conclusions

Stem cell therapies show promise in addressing the challenges associated with corneal transplantations and improving outcomes for patients with limbal stem deficiency. Keratoprosthesis provides an alternative treatment option for patients with corneal blindness who are not suitable candidates for traditional corneal transplantation, offering the potential to restore vision and improve quality of life. Further research and advancements in stem cell-based approaches and keratoprostheses hold the potential to reduce the global burden of corneal blindness and enhance vision restoration.

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Authors` contributions
Conceptualization: M.D., D.K. and E.S.; Literature review: M.D., E.S., P.S. and R.T.; Writing – Abstract: M.D. and E.S.; Writing – Introduction: M.D. and R.T.; Writing – Stem cells: E.S. and P.S.; Writing – Keratoprosthesis: R.T. and M.D.; Writing – Boston keratoprosthesis: M.D. and P.S.; Writing – Osteo-odonto-keratoprosthesis: R.T.; Writing KLAL: M.D. and E.S. Writing – Conclusions: M.D. and P.S.; Editing and reviewing D.K.

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