Posterior lamella substitutes in full-thickness eyelid reconstruction: a narrative review

Yongwei Guo[1]^, Tao Gao[1]^, Ming Lin[2]^, Wanlin Fan[3]^, Alexander C. Rokohl[3]^, Vinodh Kakkassery[4]^, Ludwig M. Heindl[3,5]^, Juan Ye[1]^

[1]Eye Center, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany; [4]Department of Ophthalmology, University of Lübeck, Lübeck, Germany; [5]Center for Integrated Oncology (CIO) Aachen-Cologne-Bonn-Duesseldorf, Cologne, Germany

Contributions: (I) Conception and design: Y Guo, T Gao, LM Heindl, J Ye; (II) Administrative support: T Gao, J Ye; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Juan Ye, MD, PhD. Eye Center, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China. Email: yejuan@zju.edu.cn.

Background and Objective: Severe full-thickness eyelid defects seriously endanger the health and beauty of the ocular surface. It is the most challenging field of oculoplastic and reconstructive surgery to reconstruct eyelid's natural appearance and function, in which the posterior eyelid lamella plays an essential role. Without enough substitute support in eyelids suffered sizeable posterior lamella defects, various complications may occur, e.g., entropion, ectropion, incomplete eyelid closure, corneal irritation, keratitis, corneal ulcers, and even vision loss, leading to failure of eyelid reconstruction. This manuscript aimed to summarize recent advances in posterior eyelid lamella substitutes and summarize the types, advantages, and disadvantages of the present posterior lamella substitutes in full-thickness eyelid reconstruction.

Methods: A literature search was conducted in the PubMed database to identify relevant publications using the search algorithm "eyelid reconstruction". The full-text publication reports about posterior substitutes from January 2016 to April 2021 in English were selected and reviewed. We also screened relevant research missed in this search algorithm from the reference lists of specific full-text papers.

Key Content and Findings: A variety of autologous or allogeneic tissues have been reported as promising techniques for replacing the posterior eyelid lamella in full-thickness and more than 50% length eyelid defects, e.g., the auricular cartilage, hard palate mucosa, buccal mucosa, nasal septum, and periosteal flaps, among others. However, various disadvantages have to be considered, i.e., limited sources, surgical complexity, increased complications, poor mechanical properties, inflammatory immune response, and the spread of potential infectious diseases. Besides, it provides a novel perspective for posterior lamella reconstruction to develop new biomaterials with excellent biocompatibility and more physiological properties, as well as tissue-engineered tarsal and conjunctival tissues with appropriate structure, biomechanical properties, and specific secretory function similar to the human tarsus.

Conclusions: In summary, our findings suggest that autologous and allogeneic tarsal substitutes are practical reconstructive technique in current condition, but in the future, in-depth study of new biomaterials and tissue engineering may provide a novel perspective for the research of tarsal substitutes in oculoplastic and reconstructive surgery.

Keywords: Eyelid reconstruction; posterior lamella; tarsus; substitute; tissue engineering

^ ORCID: Yongwei Guo, 0000-0001-9195-0770; Tao Gao, 0000-0001-5684-0015; Ming Lin, 0000-0001-6467-4643; Wanlin Fan, 0000-0001-7143-6707; Alexander C. Rokohl, 0000-0002-0224-3597; Vinodh Kakkassery, 0000-0001-6212-8964; Ludwig M. Heindl, 0000-0002-4413-6132; Juan Ye, 0000-0002-1948-2500.

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Introduction

The eyelid is one of the most delicate facial structures and a crucial aesthetic focus on the face (1). It is divided into anterior and posterior lamellae by the grey line. The anterior lamella includes the eyelid skin, subcutaneous tissue, and orbicularis oculi muscle, while the posterior consists of the tarsal plate and conjunctiva (2,3). The intact eyelid structure and function are responsible for the stable ocular structure and visual function and necessary for the composition of eye expression.

Eyelid defects are secondary to tumor resection, trauma, and congenital disabilities, among others (1,4,5). Based on tissue depth, eyelid defects are divided into anterior layer defect, posterior layer defect, and full-thickness defect (involving both the anterior and posterior layers). Severe full-thickness eyelid defects significantly endanger the eyes' health and facial beauty. The purpose of reconstructing eyelid defects is to maximize or reconstruct their function and natural appearance. The posterior layer, especially the tarsal plate, is the key to restoring the defective eyelid's structural integrity and intact function (1). Without enough tarsal substitute support for the eyelid with sizeable posterior lamella defects, various complications may be introduced, e.g., entropion, ectropion, incomplete eyelid closure, corneal irritation, keratitis, corneal ulcers, and even vision loss, leading to failure of eyelid reconstruction (1,4,5). However, it lacks a uniform substitute to reconstruct the posterior lamella. Therefore, there is a need for a review to summarize various posterior lamella substitutes, which would be beneficial to the clinical practice for comprehensive analysis and different reconstruction plans based on the location, depth, and scope of eyelid defects (4,5).

Up to date, it remains the most challenging field in oculoplastic and reconstructive surgery to repair severe full-thickness eyelid defects, especially the reconstruction of the tarsus. That is partly due to the fact that various autologous and allogeneic posterior lamella substitutes have advantages and disadvantages, while new materials and tissue engineering are still in the early stages of research. Therefore, this narrative review aims to summarize recent advances in posterior eyelid lamella substitutes and the types, advantages, as well as disadvantages of the present posterior lamella reconstruction technique to disclose the future research directions. This review allows clinicians to gain a comprehensive understanding of substitute options for reconstructing the posterior lamella, continuously verify their clinical effectiveness, and improve and innovate these options in clinical practice by conducting clinical trials or basic research. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-80/rc).

Methods

This study conducted a literature search in the PubMed database to identify relevant publications using the search algorithm "eyelid reconstruction". The full-text publication reports from January 2016 to April 2021 in English were selected and reviewed. We also screened relevant research missed in this search algorithm from the reference lists of specific full-text papers. *Table 1* presents more detailed search summary.

Discussion

Anterior lamella reconstruction and local flap for posterior lamella reconstruction

The anterior and posterior lamellae should be repaired when reconstructing full-thickness eyelid defects (6). It can be sutured directly for the minor full-thickness eyelid defects involving less than 25% of the eyelid width. A lateral canthotomy and cantholysis may be required for defects between 25% and 50% of the eyelid width. That facilitates the medial movement of the remnant lateral tarsoconjunctival flap. Furthermore, a periosteal flap may be created to stabilize the posterior lamella with the pedicle to the lateral orbital rim (6).

It is the traditional surgical procedure for severe full-thickness eyelid defects to make full use of the tarsoconjunctival flap and musculocutaneous flap near the defect area. The tarsal reconstruction procedures commonly involve harvesting and transplanting free tarsal graft (7) or sliding and rotating the tarsal plate and conjunctiva of

Table 1 The search strategy summary

Items	Specification
Date of search	April 30th, 2021
Databases and other sources searched	PubMed
Search terms used	"eyelid reconstruction"
Timeframe	January 2016 to April 2021
Inclusion and exclusion criteria	English full-text publication reports
Selection process	YG conducted the selection

the eyelid to the defect area (6). Among them, medium-sized defects involving 33% to 66% or up to 75% of the whole eyelid may be repaired by a Tenzel semicircular musculocutaneous rotation procedure or Cutler-Beard flap combined with a free tarsal graft (8,9). Even up to 100% of the lower eyelid, extensive defects may be reconstructed by a Hughes tarsoconjunctival flap combined with a local musculocutaneous flap or midface lift (6,10).

The periosteal flap is a robust and reproducible reconstructive alternative for the posterior lamella. It is a dense band of fibrous connective tissue serving as the native tarsal plate to restore the structural integrity of lateral full-thickness lower eyelid defects when the lateral tarsal plate is missing. Perry and Allen (11) described a one-stage periosteal strip procedure to reconstruct 50–70% full-thickness lower eyelid defects as an alternative to a Hughes flap. They adopted the periosteal strip to stabilize the posterior lamella laterally, transposed the lateral remaining posterior lamella medially for central and medial defects, and made a musculocutaneous advancement flap to repair the anterior lamella. After an average follow-up of 5.6 months, 11 patients (29%) presented postoperative sequelae, but only two (5%) required additional treatment. Therefore, this procedure seems to avoid many complications in the Hughes procedure and is comparable to other techniques for reconstructing subtotal, full-thickness lower eyelid defects. Scott *et al.* (12) performed a periosteal flap combined with a Tenzel flap to reconstruct a lateral full-thickness defect involving approximately 50% of the lower eyelid. The defect involved the lateral canthus with an absence of the lateral canthal tendon and tarsal plate. At 1-year follow-up, the patient did not report any functional or cosmetic concerns, and the lower eyelid was close to the eyeball. In the future, more cases and extended follow-up periods are still needed for both techniques.

Furthermore, various modifications to the traditional procedures have been reported with satisfactory results. For Hughes flap connection sites, Kaufman *et al.* (13) reported a case report of Hughes tarsoconjunctival flap with modified flap connections utilizing cicatrix and remaining viable tissue to reconstruct a full width, full-thickness cicatricial lower eyelid defect after blastomycosis. They exposed the lateral orbital rim, created a periosteal flap, and sutured it to the temporal edge of the tarsoconjunctival flap. Concerning the medial anchor point of the Hughes flap, they fashioned the subcutaneous scar tissue to a flap with firm adherence to the underlying periosteum. Although the satisfactory cosmetic outcome was achieved at a follow-up of 3.5 months postoperatively, more cases and extended follow-up periods are still needed for future research. Regarding lamellar combinations, Fang *et al.* (14) described a modified surgical procedure in a total of 15 patients with extensive full-thickness lower eyelid defects in functioning eyes. They combined the tarsoconjunctival flap, orbicularis musculocutaneous advancement flap, and paranasal-island flap to correct large to giant lower eyelid defects. No significant complications were observed. Moreover, an alternative technique using myotarsal (MT) flap is reported in 163 patients to reconstruct minor to subtotal full-thickness lower eyelid defects up to 8 mm in height (15). The flap comprises a 3-mm tarsal strip with the levator and Müller muscles attached without a conjunctiva lining. The modified MT flap involved a quilted full-thickness skin graft, which is shown to be safe, versatile, and effective with satisfactory aesthetic and functional results for reconstructing the lower eyelid. Concerning lamellar rotation or slide patterns, Li (16) reported a lamellar rotation surgery in three cases for repairing upper eyelid defects, which rotated the inferior lateral tarsus superiorly to reconstruct the posterior lamella of the upper eyelid. Further studies with larger sample sizes and comparative design are required for further validation of this procedure.

Custer and Neimkin (17) performed a sliding tarsal flap in 32 patients with an average marginal defects width of 11.3 mm (range, 7–19 mm) to repair marginal lower eyelid defects. They found minimal contour abnormalities in nine patients, while noticeable notch in three who did not desired revision.

Autologous tissue graft

Reconstruction of total eyelid defects poses a considerable challenge, requiring precise lamellar reconstruction to achieve proper eyelid function and aesthetics. However, most of the above local flaps are more suitable for minor to medium-sized full-thickness eyelid defects with a certain amount of remnants of the posterior layer. Furthermore, they may cause numerous postoperative complications, e.g., scar contraction of the transplanted area, pyogenic granuloma, eyelid margin cyst, as well as eyelid entropion and ectropion requiring reoperations in severe cases. In addition, conventional local flap reconstruction techniques often require multiple surgeries, blocking the visual axis for varying periods before achieving the final result. Above all, the local flaps mentioned above might not meet the repair requirements sufficiently for more significant full-thickness eyelid defects. Therefore, to restore the structure and function of the eyelid and minimize the possible complications, it is the priority to seek suitable tarsoconjunctival substitutes, which is also the keynote and difficulty of eyelid reconstruction surgery.

Contralateral tarsoconjunctival graft

The contralateral tarsus is one of the most commonly used posterior lamella substitutes (18). The tarsus with a height of at least 4 mm should be left at the donor site to avoid destabilizing the eyelid (19,20). Compared with the modified Hughes procedure, the potential disadvantage of a free tarsal graft is the absence of upward traction on the reconstructed eyelid. In contrast, the advantage of free tarsal graft is the minimal visual axis occlusion and single surgical step avoiding adjustment of the final lower eyelid margin position at a second stage, i.e., graft division. Additionally, combined with an overlying free skin graft, it can be used in patients without adequate musculocutaneous flaps or vascularized orbicularis flaps and eliminate any deformity or asymmetry resulting from adjacent tissue flaps.

Bortz and Al-Shweiki (21) reconstructed lower eyelid defects in four patients, including the eyelid margin with a free tarsal autograft from the contralateral upper eyelid and an overlying free post-auricular skin graft. Two developed lateral ectropion or dehiscence, requiring a secondary revision, within 2 to 3 weeks postoperatively. Compared with modified Hughes flaps, this technique yielded the same functional and aesthetic effects, and all patients were pleased with this procedure. Therefore, the authors proposed that vascular support may be unnecessary for reconstructing the anterior or posterior lamella. However, it still needs further validation by recruiting more patients and following up extended period. As for the reconstruction of sizeable upper eyelid defects, Yazici *et al.* (22) reported a bilobed flap combined with a tarsoconjunctival graft from the contralateral upper eyelid. That was demonstrated to be a good alternative for the single-stage procedure for sizeable upper eyelid defects.

Furthermore, the bilamellar full-thickness autograft has been investigated to repair sizeable full-thickness eyelid defects. It may offer a more cost-effective and less time-consuming alternative surgical approach with a high likelihood for optimal cosmesis postoperatively (23-25). Reed *et al.* (23) evaluated the possibility of a bilamellar full-thickness autograft to repair full-thickness eyelid defects with varying sizes in the upper and lower eyelids of a Yorkshire/Yorkshire crossed swine model. After the postoperative monitoring period, clinically viable and vascular ingrowth were found in 27/28 grafts. Similarly, Tenland *et al.* (26) harvested free bilamellar autografts from the contralateral or opposing eyelid to reconstruct 10 significant eyelid defects resulting from tumor excision. All grafts survived and did not develop tissue necrosis. In consideration of the excellent functional and cosmetic results, they concluded that free bilamellar eyelid grafts appear to be an excellent alternative to the tarsoconjunctival flap procedure for repairing either upper or lower eyelid defects. That is particularly suitable for patients who had compelling reasons to avoid visual axis occlusion or a second surgical procedure at a later date to divide the tarsoconjunctival flap.

However, free tarsoconjuntival grafts have their limitations. On the one hand, concurrent eyelid pathologies and previous surgery may limit contralateral tarsus availability. On the other hand, the tarsus size restricts the resectable graft without destroying the function and aesthetic of the donor site. The superior tarsal plate is an average of 11 mm in height and 28–30 mm in length. Yoon and McCulley's study (27) has shown that it is safe to preserve 4 mm adjacent tarsus to the eyelid margin and remove at most 17 mm in length and 6 to 7 mm in height. Thus, it would be enough to reconstruct full-thickness upper eyelid defects not involving the medial or lateral canthus and leaving certain tarsus for the graft's attaching on both sides of the defect. Whereas, regarding defects involving the medial or lateral canthus, the orbital rim periosteal flaps might be utilized to stabilize the margin and graft by attaching the tarsoconjunctival graft (28).

Hard palatal graft

The anatomical structure and biomechanics of hard palatal mucoperiosteum (HPM) are similar to the tarsoconjunctiva with dense collagen fiber structure and density (1,29-31). HPM can simultaneously replace the tarsal plate and palpebral conjunctiva. It has several advantages, e.g., moderate hardness, smooth surface, small glands, excellent stability and resistance to deformation, rich blood supply, concealed incisions, no risk of rejection, and readily acquired adequate sizes (1,32). Wang *et al.* (33) reconstructed serious full-thickness lower eyelid defects in 34 patients by a novel "three-layer structure" tissue combining palmaris longus tendon with superiorly-based nasolabial skin flap and palatal mucosal graft. Their results showed that the three-layer structure is an effective procedure with satisfactory long-term results for reconstructing giant full-thickness defects in the lower eyelid with a mean follow-up period of 15 months (range, 6–24 months). Furthermore, in combination with frontal axial pattern flap, hard palatal mucosa transplant has been reported to reconstruct midfacial defects in four patients after the excision of giant basal cell carcinoma involving both the eyelid and nose (34). All the patients preserved well functional and cosmetic results despite the small sample size.

After repairing the posterior lamella of the eyelid, HPM also performs as a stent well attaching to the eyeball surface and conforming to the eyeball curvature, which are apparent advantages among various tarsal substitutes, e.g., ear cartilage graft (1). However, applying the HPM to repair upper eyelid defects is controversial because the stratum corneum of the HPM may cause friction against the cornea (29).

Previous studies showed that keratinization consists of stratum corneum, parakeratosis, and non-keratinization in the stratified squamous epithelium of HPM graft. Its degree might be determined by the defect location, blood supply, and time after implantation. Yue *et al.* (29) conducted a pilot study to evaluate the HPM graft's function and outcome in seven patients with lateral or medial full-thickness upper eyelid defects occupied approximately 50% of the length. They used this graft to reconstruct the posterior lamella, a transposition flap to reconstruct the anterior lamella, a bandage contact lens to protect the corneal, and a Frost suture to help close the eye and resist shrinkage if needed. Despite an average shrinkage rate of 16.3%±7.1%, they found that all grafts incorporated smoothly with the normal tarsoconjunctiva. The high shrinkage percentage decreases the opportunity for the graft to rub the central cornea. All patients were satisfied with the overall outcome with normal physiological blink and relatively normal physiological eyelid appearance. Regarding complications, eyelashes loss occurred in 100% of the seven patients, abnormal curvature of the eyelid 28.5%, mild lagophthalmos 14.3%, trichiasis 14.3%, and slight corneal epithelium exfoliation 42.8%. The authors found that the stratum corneum was not apparent in the graft surface, mainly comprised of stratified squamous epithelium with a narrow adjacent area between the HPM and cornea. Therefore, they proposed that HPM is safe and feasible for reconstructing the lateral or medial upper eyelid defects involving the canthus, even though further verifications are still needed in the future.

Additionally, Lee *et al.* (19) described a single sitting surgical technique to reconstruct the total eyelid defects in eight patients. They made a composite posterior lamella graft from a free contralateral tarsoconjunctival graft and hard palatal graft and combined it with an upper eyelid preseptal musculocutaneous advancement flap. The tarsoconjunctival graft directly contacts the cornea as a like-for-like substitute to reduce ocular surface complications. To reform a natural contour to the eyelid and reach good eyelid-globe apposition, they thinned the tough hard palatal graft and added two additional bending points along with the tarsal plate at the tarsus-HPM junction. This seems to be an excellent "best of both worlds" solution except the need for three surgical sites and enough anterior lamella allowing an advancement flap.

Buccal mucosal graft

The lower lip and cheek were also the candidate site of the buccal mucosal graft to replace the posterior lamella of the upper eyelid (35,36). Yamashita *et al.* (37) recommended the cheek mucosa to reconstruct posterior lamella rather than HPM. The HPM is too thick to process, and it takes a long time to epithelialize. Sakata *et al.* (38) reported a case reconstructing the entire upper eyelid after resecting a Merkel cell carcinoma. The technique consists of a buccal mucosal graft and reverse Hughes flap as the posterior layer and a radial forearm flap as the anterior layer. To reconstruct functions of wide- and full-thickness total upper eyelid defects, Iwanaga *et al.* (39) combined full thickness of the buccal mucosa with a composite radial forearm-splitting palmaris longus tendon flap in two cases. Results showed no tumor recurrence and keratalgia occurred, and the eyelid opening and closing functions were maintained. Baltu (40) described a gingivoalveolar mucosal graft to repair 13 posterior lamellar defects of the lower eyelid that ranged from 10×8 to 20×10 mm. In the graft, the gingival mucosal part supports the marginal area with stable and tight structures, and the alveolar part is located at the conjunctival side without irritating the cornea. The current studies demonstrated that this graft might be a reliable and easily accessible alternative for posterior lamellar reconstruction of eyelid defects, even though the hardness, toughness, and long-term absorbability must still be verified.

Auricular cartilage

The conchal cartilage has been recommended to reconstruct the posterior lamella due to its simplicity for harvest and use, avoiding multi-staged procedures (41-45). However, previous studies have reported undesirable results, e.g., displacement, detachment, warping, down-gaze disturbance, and surface irregularity of the cartilage graft. Hence, reoperations may be required in some conditions. Yamashita *et al.* (37) designed a lower lid switch flap to reconstruct the full-thickness entire upper eyelid in three patients. After switching the flap, they repaired the lower eyelid donor site with a sandwich-like three-layered structure: cheek mucosa, conchal cartilage, and a reverse superficial temporal artery flap, which is similar to Yamamoto *et al.*'s (46) eyelid reconstruction technique using oral mucosa and ear cartilage strips as sandwich grafting. Ito *et al.*'s (47) study proposed a single-stage, more straightforward, less invasive reconstruction procedure in four patients. Their research reconstructed full-thickness defects with an advanced flap using excess upper eyelid skin and ear cartilage after the upper eyelid tumor excision. All patients got good functional and aesthetic results.

Auricular cartilage has been published widely as an available substitute of defected tarsus to restore stability of the lower eyelid (42). Fodor *et al.* (48) reported a novel "all-in-one" sandwich technique to reconstruct a full-thickness defect of the lower eyelid after removing a basal cell carcinoma. They placed a sandwich ear cartilage graft into a paramedian forehead flap and rotated it into the defect site, which helps maintain the eyelid's vertical dimension. The study showed favorable results with sufficient soft tissues for the lower eyelid reconstruction. Zhai *et al.* (49) recommended a new technique using a combination of π-shaped auricular cartilage and a local flap to restore the horizontal and vertical lower eyelid stability, maintaining the lower eyelid in a normal position. To fulfill the principle of "replace with like", Barin and Cinal (50) developed a two-stage technique to reconstruct full-thickness lower lid defects in six cases, in which they harvested a chondrocutaneous graft from the ear and placed it under an orbicularis oculi musculocutaneous flap in the upper eyelid. After three weeks, they created the lower eyelid defect and transposed the flap to the defect site. The composite graft technique showed low donor morbidity and good outcomes.

Nasal chondromucosal graft

The nasal chondromucosal graft has been reported to reconstruct the posterior lamella of eyelids due to mucosal covering, good eyelid stability, and esthetic outcome in the late postoperative period (42,51-55). Keçeci *et al.* (51) used a septal chondromucosal graft with a nasojugal angular artery-based axial flap to repair full-thickness eyelid defects in eight patients. That was shown a safe and straightforward procedure for both upper and lower eyelid full-thickness defect reconstruction, with inconspicuous scar concealed in the nasojugal area and without septal perforation or hemorrhage complications in the nose.

A Texier procedure is indicated for one-step reconstruction of the lower eyelid with full-thickness defects of less than 50% (56). It typically involved an upper lid musculocutaneous flap and a chondromucosal alar graft. Bejinariu *et al.* (57) performed a nasal chondral-mucosal graft from alar (Texier procedure), triangular, or septal nasal cartilages to reconstruct a series of lower eyelids with a tissue loss of more than half. Cristofari *et al.* (56) evaluated its feasibility for lower eyelid defects between 50% and 75% and those longer than 75% with a chondromucosal nasal septal graft. They did not find lower eyelid retraction or ectropion after the Texier procedure. Therefore, they proposed that the Texier procedure may be performed as a first-line treatment to repair most full-thickness defects of the lower eyelid, even subtotal defects. Although septal cartilage can be harvested with attached mucosal tissue, the complicated harvesting method and significant thickness to work with are doubtful (37).

Concerning the potential complications, Suga *et al.* (58) retrospectively compared chondromucosal grafts from the nasal septum and ear cartilage grafts to repair the lower eyelid's posterior layer in a case series. No difference was found in operative time, blood loss, or length of hospital stay between cases in both procedures. However, they found different postoperative complication rates at the donor site. Among eight patients with the nasal septum graft, one suffered from perforation of the nasal septum and one nasal bleeding, while no donor site complications were in the ear cartilage group. Therefore, the surgeon should be familiar with the nasal septum anatomy and care more when making a nasal septal graft.

Other autologous grafts

In addition to the commonly used autologous tissue graft, some autologous tissues have been reported for posterior lamella substitute, e.g., the lateral periorbital superficial musculoaponeurotic system (SMAS), dorsal dermal dermis, and rib cartilage, among others. Eisendle *et al.* (59) proposed a single-stage modified Tenzel flap for more significant and full-thickness lateral lower eyelid defects in a case report. They used the lateral periorbital SMAS for the posterior layer reconstruction and a lateral cheek rotational flap for the anterior layer reconstruction to avoid the more complex two-stage Hughes tarsoconjunctival flap procedure. The autologous dorsal dermal dermis has also been proposed as posterior lamellar substitutes with well functional and esthetic results (60). This graft is available in large quantities and seems reliable, simple, fast, achievable in one operative time, etc. (60). Kurnik *et al.* (61) reported the first case of autologous rib cartilage grafting and fat grafting for lower eyelid reconstruction in a patient with ablepharon macrostomia syndrome, and satisfying effects were achieved. However, their long-term efficacy still needs to be investigated further.

Allogeneic tissue graft

Allografts are promising posterior lamella substitutes due to reduced surgical time and no donor site sequelae. However, a series of disadvantages are apparent, e.g., the economic cost, availability, risk of rejection, potential disease transmission, etc. Among them, the unpredictable resorption rate is of importance due to its negative influence on graft effectiveness over time (62). In contrast, autologous grafts possess the merit of minimal resorption, are free of transmitted diseases, and have no risk of graft rejection even though it may bring about the risk of donor site morbidity.

Allogeneic sclera graft

Scleral segments are cost-efficient and associated with a low risk of pathogen transmission in addition to their wide availability, strength, flexibility, and ease of storage (63). Sabater-Cruz *et al.* (63) reviewed 874 scleral patches eye indications in a Spanish region over 6 years from 2013 to 2018. The scleral patch's most frequent indication over the 6 years was glaucoma surgery in 77.5%, eyelid reconstruction in 5.2%, and corneal or scleral ulcer in 5%. During the study period, a statistically significant increasing trend surpassing a linear slope was found in eyelid reconstruction. However, no reasons were suggested for this tremendous increase. Scleral patches were well-known for eyelid reconstruction, especially spacer graft in eyelid retraction, despite no evidence about its superiority to others, e.g., HPM, cartilage, etc. According to the authors' experience, the absorption and subsequent eyelid retraction and entropion are the most significant obstacles to the long-term efficacy of scleral patches, and further research into the mechanisms and prevention strategies is needed in the future.

Allogeneic acellular dermal allograft (ADA)

Over the last two decades, ADA has become popular for a tarsal substitute to reconstruct the sizeable full-thickness eyelid defects where eyelid donor tissue is either unavailable or insufficient to cover the whole extent of the defect (64-68). It presents various advantages for tarsal substitutes, e.g., adequate to cover, eliminated donor site-related morbidity, excellent and stable structural support, simple maneuverability, multiple sizes, satisfactory biocompatibility and tissue integration, reduced operating time, and good cosmesis (64). In contrast, several potential disadvantages include theoretical risk of infectious disease transmission, allergic or toxic reactions, as well as resorption and contraction tendency over time (64). Vahdani *et al.* (64) retrospectively reviewed ADA for reconstructing the posterior lamella in 10 patients. These patients suffered from sizeable full-thickness eyelid defects due to tumor, trauma, burn, and necrosis, respectively. Seven patients presented excellent anatomical, cosmetic, and functional results. In contrast, reoperation was indicated for postoperative upper lid retraction, upper lid entropion, and lower fornix reconstruction in three patients despite acceptable initial results. Eah and Sa (69) reconstructed significant full-thickness upper eyelid defects (≥70%) in six patients with sebaceous carcinomas. They combined a reverse Hughes flap with an acellular dermal matrix sandwich graft (AlloDerm) as a tarsal substitute covered by a skin-orbicularis muscle flap superior to the defect. After a median follow-up of 40 months (range, 6–62 months), the study showed satisfactory functional and cosmetic outcomes with no complications occurred.

Additionally, other allografts involved Achilles tendon (70), irradiated aorta (71), and allogeneic irradiated tarsus (71). However, they were reported in small sample sizes and presented similar complications. Moreover, their sources are limited, thus restricting clinical applications.

Heterogenic tissue graft

Custer and Maamari (72) retrospected 13 cases with porcine acellular dermal matrix sandwich graft between the skin and conjunctival flaps. The lower eyelid defects followed a Mohs surgery during 2013 and 2018. No infection and graft failure was found. Apart from minimal irregularities in two cases, excellent marginal contours were shown in the rest (84.6%). Besides, marginal conjunctive overgrowth was in one case, and symptomatic trichiasis in two (15.4%). They proposed that the acellular dermal matrix sandwich graft is an effective technique for repairing marginal eyelid defects when sufficient conjunctiva and skin are remained to develop the necessary flaps. Although mild, relatively uncommon complications occurred, the complications are similar to those in other reconstructive procedures. This single-stage, tissue-sparing procedure preserves the feasibility of future tarsoconjunctival flaps or lateral canthal procedures, should the need arise.

Biomaterial transplant

Although autologous and allogeneic tarsal substitutes have shown promising application prospects, various disadvantages have to be considered. They include limited sources, surgical complexity, increased complications, poor mechanical properties, inflammatory immune response, and the spread of potential infectious diseases. Therefore, the in-depth study of new biomaterials and tissue engineering may provide a new perspective for the research of tarsal substitutes due to more flexible biomaterial structures and tissue engineering design (1,2,73).

A few studies have reported biomaterials of tarsal substitutes for reconstructing the defects of eyelids. Using gel freezing technology, Sun *et al.* (73) fabricated a novel three-dimensional large-pore chitosan hydrogel scaffold material. The scaffold mimicked the biomechanical characteristics of human tarsal tissue. They found that the scaffold facilitated the fibroblasts from mouse and human eyelids to attach, grow, and proliferate *in vitro*. Zhou *et al.* (74) implanted a poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) scaffold into the eyelid defects in rats to investigate its feasibility as a tarsal substitute. They observed the acute and chronic inflammatory reaction, scaffolds biodegradation, and fibrous capsule formation at the implantation site by histological staining. The results showed that at postoperative week four, the scaffolds presented a mixed reaction of acute and chronic inflammatory responses with high-density inflammatory cells infiltration. The percentages of neutrophils, macrophages, lymphocytes, and fibroblasts were almost identical in the first two weeks after surgery. However, a significant decrease was demonstrated from the 4th to the 8th week in the number of neutrophils representing the acute inflammatory response. At the same time, the proportion of lymphocytes and fibroblasts representing chronic inflammation and tissue repair increased slightly, macrophages decreased somewhat, and foreign body giant cells (FBGCs) gradually increased within 1–8 weeks.

Recently, Gao *et al.* (75) made a toughening modification of polypropylene fumarate material to meet tarsus's mechanical performance and fabricated porous scaffolds for further study. They studied its cytotoxicity to human dermal fibroblasts (HDFs) and the degradation characteristics of polypropylene fumarate scaffolds *in vitro*. Then they implanted the scaffolds into rabbit tarsal defects and evaluated their biocompatibility and degradation behavior by histological methods. The study found that the repair effect and biocompatibility are satisfactory, and tissue responses (fibroblast growth and fibrous capsule formation) are mild. T raditional 3D porous scaffolds directly repairing the tarsus may cause corneal irritation, conjunctival mucus-like secretions, and even blindness, as well as scar deformity of the eyelid. To eliminate these disadvantages, Xu *et al.* (2) designed a dual-phase scaffold to simulate the complete posterior layer structure of the eyelid, i.e., the tarsus and the conjunctiva. The scaffold comprised collagen/chitosan sponge and polypropylene fumarate and repaired tarsoconjunctival defects in a rabbit model. The scaffold facilitated the re-epithelialization of the functional regenerated conjunctiva. They also fabricated a new branched polyethylene elastomer porous scaffold to repair rabbit tarsal defects (3). It was confirmed *in vitro* that the scaffold has no apparent cytotoxicity to NIH3T3 fibroblasts and human vascular endothelial cells. Analyzed by histology and real-time fluorescent quantitative polymerase chain reaction, the subcutaneous implant model showed satisfactory biocompatibility, mild inflammation, moderate collagen deposition, and rapid fibrovascularization.

Tissue engineering technology

The eyelid is mainly supported by the tarsus, composed of fibroblasts, meibomian glands, and the surrounding extracellular matrix (type I, type III collagen, proteoglycan) (73). Its thin composite tissue is conducive to exchanging nutrients and metabolites between cells and tissues, making it easier to nourish new tissues in the scaffold. Therefore, the tarsus is a promising tissue to be substituted by alternative materials through tissue engineering.

Tissue engineering is a hot spot in current medical research and has become a priority development scientific field in many countries and regions. Seed cells, scaffold materials, and biological factors are three primary keys in constructing tissue engineering tarsus. Based on the tarsal biomechanics research, it is the scientific direction to apply tissue engineering technology to construct the artificial tarsus. However, as mentioned above, the present tarsal regenerative studies remain in the early experimental stage. They aim to simulate the natural tarsus' fatigue resistance, mechanical strength, hydrophilicity and hydrophobicity, as well as biocompatibility at the histological level. Few studies have systematically studied the fundamental theories involving the regulation mechanism of tarsal tissue repair by scaffold materials (1).

Summary

In conclusion, at present, for full-thickness eyelid defects with a length of more than 50%, clinicians are gradually exploring the application of autologous or allogeneic tissues as a substitute for the posterior lamella to repair and strengthen eyelids' stability (1). The ideal substitute should be easy to obtain, biocompatible, and most importantly, similar in thickness and toughness to normal tarsal (1,2). Several substitutes have been reported with different specialties, e.g., the auricular cartilage, hard palate mucosa, buccal mucosa, nasal septum, and periosteal flaps. In addition, tissue engineering provides a novel perspective for posterior lamella reconstruction and may be a promising field for tarsal regenerative medicine in the future. As for the limitations of this study, we strived to include as much research as possible in eyelid reconstruction, but several studies were published as case reports without enough follow-up or sample sizes. Besides, the study only reviewed papers published in English from January 2016 to April 2021, hence the restrictions on the publication date and language of literature may result in selection bias. Thus, more studies with increased sample size and extended follow-up period are necessary for specific reconstruction techniques in the future. As for tissue engineering techniques, it remains an essential direction for basic research to develop more physiological, non-rejective, and excellently biocompatible biomaterials with appropriate structure, biomechanical properties, and specific secretory function similar to the human tarsus.

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