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Bovine Acellular Dermal Matrix for Levator Lengthening in Thyroid-Related Upper-Eyelid Retraction

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Background: Eyelid retraction is the most common and often the first sign of thyroid eye disease (TED). Upper-eyelid retraction causes both functional and cosmetic problems. In order to correct the position of the upper eyelid, surgery is required. Many procedures have demonstrated good outcomes in mild and moderate cases; however, unpredictable results have been obtained in severe cases. Dryden introduced an upper-eyelid-lengthening procedure, which used scleral grafts, but outcomes were unsatisfactory. A new technique is introduced in this study as a reasonable alternative for TED-related severe upper-eyelid retraction correction.





Material/Methods: An innovative technique for levator lengthening using bovine acellular dermal matrix as a spacer graft is introduced for severe upper-eyelid retraction secondary to TED. Additionally, 2 modifications were introduced: the fibrous cords scattered on the surface of the levator aponeurosis were excised and the orbital fat pad anterior to the aponeurosis was dissected and sutured into the skin closure in a "skin-tarsus-fat-skin" fashion.

Results: The modified levator-lengthening surgery was performed on 32 eyelids in 26 patients consisting of 21 women and 5 men (mean age, 37.8 years; age range, 19–67 years). After corrective surgery, the average upper margin reflex distance was lowered from 7.7 ± 0.85 mm to 3.3 ± 0.43 mm. Eighteen cases (69%) had perfect results, while 6 cases (23%) had acceptable results.

Conclusions: A modified levator-lengthening procedure using bovine acellular dermal matrix as a spacer graft ameliorated both the symptoms and signs of severe upper-eyelid retraction secondary to TED. This procedure is a reasonable alternative for correction of TED-related severe upper-eyelid retraction.

MeSH Keywords: **Acellular Dermis • Eyelid Diseases • Graves Ophthalmopathy**

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Background

Thyroid eye disease (TED) is an autoimmune inflammatory disease that can occur in patients with Graves' hyperthyroidism or Hashimoto's thyroiditis. Eyelid retraction is the most common and often the first sign of TED onset. It is typically worse in downgaze and this is called lid lag. Upper-eyelid retraction has been suggested as one of the primary diagnostic criteria [1–3]. It increases the exposed areas of both the cornea and the conjunctiva, leading to such dry-eye symptoms as foreign-body sensation, photophobia, and tearing. Severe eyelid retraction can even cause lagophthalmos, corneal ulcer, and vision loss. Eyelid contour deformity also causes patients to have an aggressive appearance.

The etiology of TED-related eyelid retraction is likely first via excess activation of the sympathetic nervous system pathway. This is a reversible stage, as compared to the permanent fibrotic stage that occurs afterwards. Medicines such as artificial tears may relieve discomfort. Botulinum toxin A injection may have a temporary effect on retracted eyelids in the active phase. However, permanent correction of fibrosis eyelid retraction can only be obtained through surgery [4,5]. Various surgical techniques to correct upper-eyelid retraction have been described, including Müller's muscle excision, levator recession with or without adjustable sutures, levator marginal myotomy, levator lengthening with or without a spacer graft, and full-thickness blepharotomy [6–14]. However, many authors have not sorted their cases according to disease severity. Some procedures have obtained good outcomes in mild and moderate cases, but unpredictable results have been obtained in severe cases. Severe upper-eyelid retraction remains a therapeutic challenge. The reported corrective rate for severe TED-related upper-eyelid retraction after the first surgery is only approximately 65% [10]. There remains a paucity of literature that solely focuses on corrective surgeries for TED-related severe upper-eyelid retraction. In this study, we investigated the outcome of a modified levator-lengthening technique using bovine acellular dermal matrix (Haifu, ZH-Bio, Shandong, China) as a spacer graft.

Material and Methods

This study was conducted at the Department of Ophthalmology, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine between January 2014 and December 2015. Inclusion criteria were that patients required surgical correction of upper-eyelid retraction secondary to thyroid disease either because of ocular surface exposure or because of cosmetic deformity. The severity of upper-eyelid retraction was measured by the upper margin reflex distance (MRD). This was classified as severe if MRD was >7 mm, moderate if MRD was

5–7 mm, and mild if MRD was <5 mm [6]. Only severe cases were included in this study.

All patients were clinically and biochemically euthyroid for at least 6 months before surgery. Eyelid surgery was not performed until the patient had reached a quiescent stage (clinical activity score, CAS <3) for at least 6 months. An exception was made for patients with serious corneal ulcers, but such cases were excluded from this study. If orbital decompression and/or strabismus surgery were needed, these operations were performed at least 6 months before eyelid surgery. Exophthalmos was measured with a Hertel's exophthalmometer, and those with a variation of more than 2 mm between the eyes were excluded. Patients were excluded if their eye positions were abnormal or if they had a history of eyelid surgery/trauma before or during the follow-up period. Written informed consent was obtained from all patients. This study was approved by the Institutional Ethics Committee and all investigations were conducted in accordance with the Declaration of Helsinki on medical protocol and ethics.

Measurements

Patient demographics were collected at the first visit and ocular examinations were performed pre-operatively and 6 months post-operatively. Clinical signs, including eye discomfort, photophobia, tearing, lagophthalmos, and asymmetry, were recorded as present or absent pre-operatively. Post-operatively, they were recorded as resolved, partially improved, or without change. Patient satisfaction with the eyelid contour was also recorded as "yes" or "no". The height of the palpebral fissure (PH), upper MRD, and upper scleral show were measured with a millimeter ruler by a single doctor and recorded. Surgical complications were noted. For statistical analysis, SPSS V.19.0 for Windows (SPSS Inc., Chicago, Illinois, US) software was used. The paired-samples *t* test was used for mean comparisons of MRD and upper scleral show before and after the surgery.

Surgical techniques

This modified levator-lengthening technique was based on Dr. Dryden's procedure [9]. Both eyes were topically anesthetized with oxybuprocaine hydrochloride. A skin-marking pen was used to mark the upper eyelid at the site of the desired skin crease, approximately 6–8 mm from the eyelid margin. Next, 1.5 ml of lidocaine 2% was injected subcutaneously. After a few minutes, a skin incision was made along the marked line through the skin and orbicularis oculi muscle, and the muscle below the incision was removed. After the tarsal plate and orbital septum were exposed, the orbital septum was fully opened and the fat tissues were pulled upward to expose the levator aponeurosis. The upper eyelid was then turned over and the levator-Müller's muscle complex was hydrodissected from the

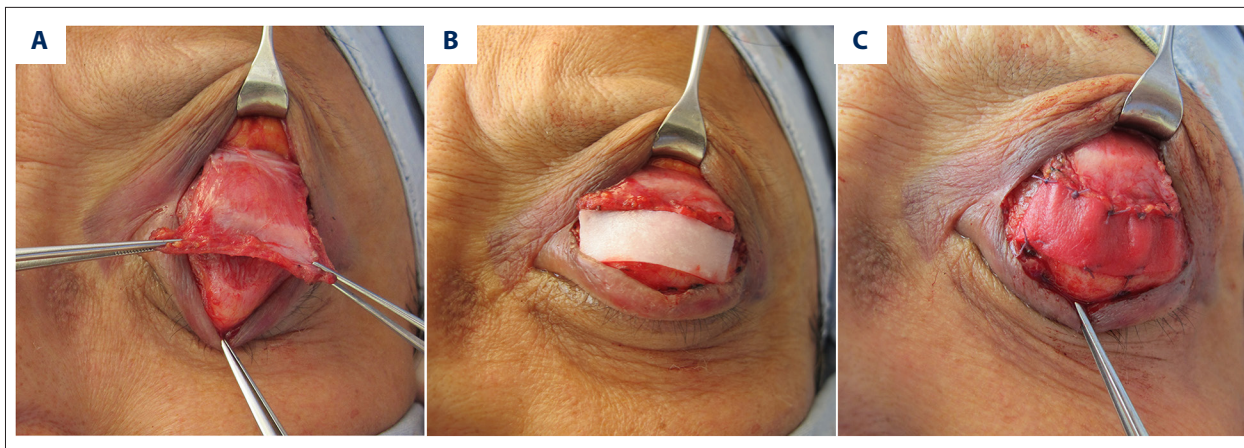


Figure 1. (A) The levator-Müller's muscle complex was dissected from the conjunctiva just above the superior tarsal plate and stripped upwards to the Whitnall's ligament. (B) The bovine acellular dermal matrix graft was cut into the vertical height at approximately twice the length of the eyelid retraction. (C) The graft was sutured to the superior border of the tarsus with 6-0 absorbable suture and to the inferior border of the levator aponeurosis.

underlying conjunctiva with lidocaine 2%. This complex was then dissected from the conjunctiva just above the superior tarsal plate and was stripped upwards from the conjunctiva up to Whitnall's ligament. The medial and lateral horns of the levator were identified and excised (Figure 1A). If there were a few fibrotic strands scattered on the surface of the levator aponeurosis, they were carefully stripped off. We left the conjunctiva intact to protect the cornea. The bovine acellular dermal matrix graft was cut into the vertical height at approximately twice the length of eyelid retraction. If the patient had lateral flare, the graft height was cut a few millimeters larger vertically on the lateral aspect than the medial aspect. After soaking the graft in normal saline for a few minutes, the graft was sutured to the superior border of the tarsus with 6-0 absorbable suture (coated Vicryl, polyglactin 910) and to the inferior border of the levator aponeurosis (Figure 1B, 1C). The height of the eyelid was set 2 mm lower than the desired height to compensate for postoperative eyelid ascent. The patient cooperated during the adjustment by opening and closing the eye or by sitting up, according to the surgeon's order, to establish an ideal eyelid contour. Next, the preaponeurotic fat was fully exposed and partly excised according to the eyelid contour. When the skin was closed by skin-tarsus-fat-skin sutures, a double-eyelid crease was created. It has been reported that suturing the fat to the upper edge of the tarsus before closing the skin can avoid creation of an unexpected crease. We believe the skin-tarsus-fat-skin method has the same effect. The sutures were removed after 7 days.

All the surgeries were conducted by a single surgeon, Dr. Zhou HF. The surgical correction of upper eyelid retraction was evaluated as good, acceptable, or unacceptable based on the system of Dr. Tucker and Dr. Mourits (Table 1) [11,12].

Table 1. Criteria for evaluation of upper eyelid lengthening surgery.

Good result:

- 1 The upper 1 to 2 mm of the cornea in the 12 o'clock position is covered by the eyelid.
- 2 The difference in lid aperture between the left and right side is less than 1 mm.
- 3 The patient is satisfied with the procedure.
- 4 The lid margin contour is smooth.
- 5 The lid crease is within 6-9mm from the lid margin.
- 6 The skin folds of the left and right eyelid are symmetrical.

Acceptable result:

- 1 The upper eyelid margin is within 1 mm of the limbus, or covers 2 to 3 mm of the cornea in the 12 o'clock position.
- 2 The difference in lid aperture between the left and right side is less than 2 mm.
- 3-6 As in a good result.

Unacceptable result:

One or more of the criteria above mentioned are not fulfilled.

Results

Modified levator-lengthening surgery using bovine acellular dermal matrix (Haifu) as a spacer graft was performed on 32 eyelids in 26 patients, including 21 women (mean age, 36.7 years; age range, 19-63 years) and 5 men (mean age, 46.8 years; range, 30-67 years).

The most common presenting symptom was asymmetry in 19 patients (73%), followed by eye discomfort in 18 patients (69%), photophobia in 14 patients (54%), and tearing in 8 patients (31%). In fact, fibrotic strands were found in 22 patients' levator aponeurosis (85%), which was typically worse near the

Table 2. Upper eyelid retraction related symptoms.

Preoperative symptoms	No. of patients	Postoperative symptoms	
		Resolved	Partial improvement
Asymmetry	19 (73%)	15 (79%)	4 (21%)
Eye discomfort	18 (69%)	15 (83%)	3 (17%)
Photophobia	14 (54%)	9 (64%)	5 (36%)
Tearing	8 (31%)	8 (100%)	0
Lagophthalmos	21 (81%)	13 (62%)	8 (38%)

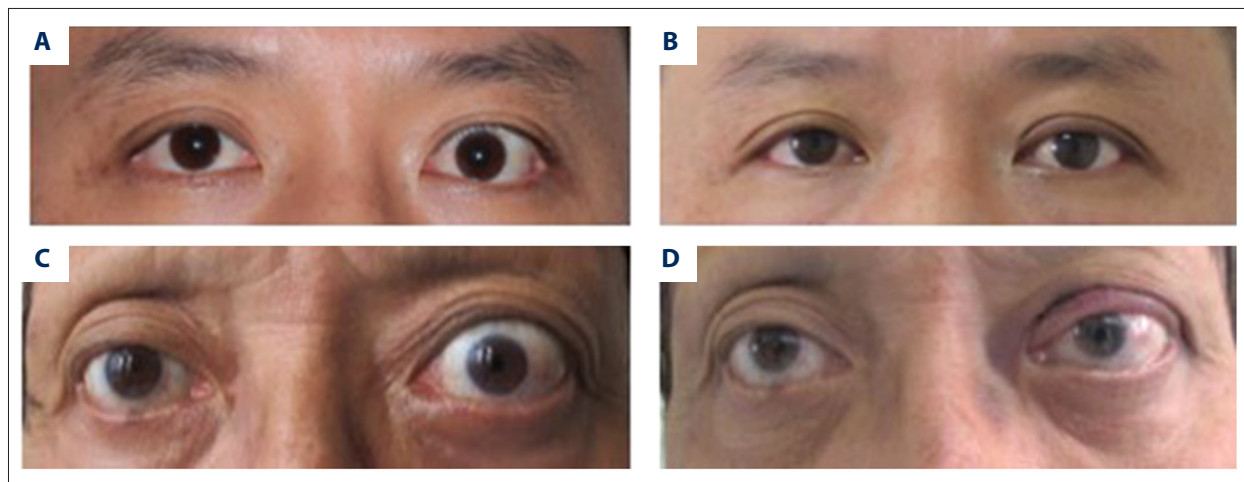


Figure 2. Pre- and post-operative photographs of levator-lengthening surgery with bovine acellular dermal matrix graft. (A) A 36-year-old patient with left upper-eyelid retraction due to thyroid eye disease. (B) Three months post-operatively, the result was categorized as “Good”. (C) Preoperative clinical photograph of a 67-year-old patient with left upper-eyelid retraction due to thyroid eye disease. (D) Three months post-operatively, the result was categorized as “Acceptable”.

Whitnall’s ligament. After surgery, the asymmetry was resolved in 15 patients (79%) and was improved in 4 patients (21%); eye discomfort was resolved in 15 patients (83%) and was improved in 3 patients (17%); photophobia was resolved in 9 patients (64%) and was improved in 5 patients (36%); and tearing was resolved in all 8 patients (100%).

Preoperative lagophthalmos was present in 25 eyes of 21 patients (81%); it was resolved in 17 eyes of 13 patients (62%) and was improved in 8 eyes of 8 patients (38%) after surgery (Table 2).

The average upper MRD was 7.7 ± 0.85 mm before surgery, and it was significantly lowered to 3.3 ± 0.43 mm at approximately 6 months after surgery ($p < 0.001$). The average scleral show was 3.4 ± 0.64 mm before surgery. After the procedure, all eyelids had no scleral show ($p < 0.001$).

According to the criteria in Table 1, 18 cases (69%) demonstrated good results, while 6 cases (23%) displayed acceptable results. There were 2 patients (8%) whose eyelid retraction

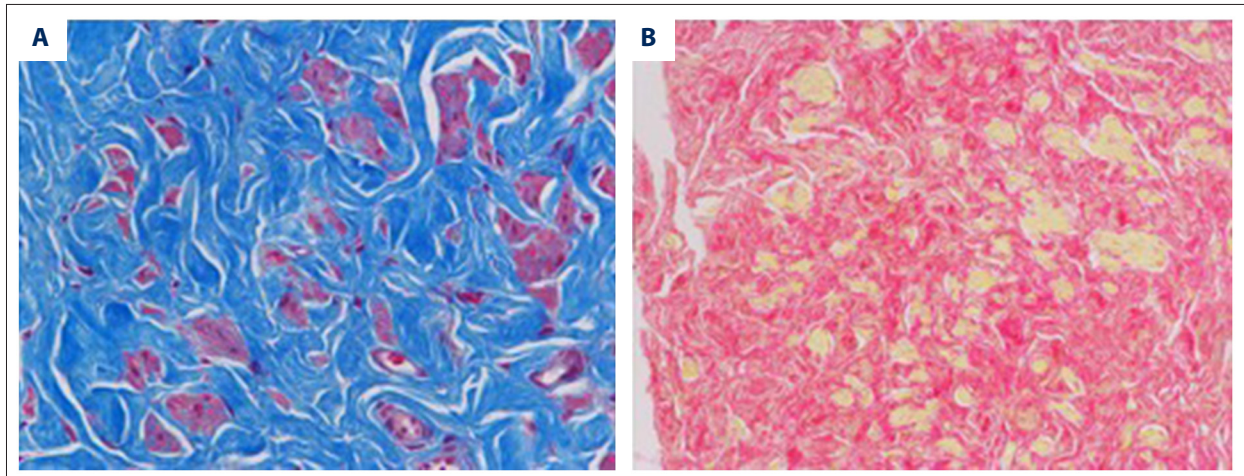
relapsed approximately 3 months after surgery (Figure 2). No other complications, such as infection or hematoma, occurred after surgery (Table 3).

Discussion

Eyelid retraction is the most common manifestation of thyroid eye disease. It causes both ocular discomfort and a staring appearance. Permanent correction is surgical. The first corrective surgery for upper-eyelid retraction was the transcutaneous levator aponeurosis and Mullers’ muscle recession procedure introduced by Moran in 1956 [15]. Several alternative surgical techniques were developed in the subsequent decades to give more favorable results. Although modified techniques have been developed, limitations such as undercorrection in severe cases remain. Two widely used techniques were graded full-thickness blepharotomy and transconjunctival eyelid lengthening. Recently, a prospective randomized interventional study performed on 47 eyelids reported that these 2 techniques were equally effective in the treatment of upper-eyelid retraction

Table 3. Outcome of upper eyelid lengthening surgery with Haiao graft.

MRD	Number	Result			
		Good	Acceptable	Total	Unacceptable
7–10 mm	26	18 (69%)	6 (23%)	24 (92%)	2 (8%)

**Figure 3.** Immunohistochemistry staining of the fibrotic strands scattered on the surface of the levator aponeurosis of patients. (A) Masson staining shows a large number of blue collagen fibers under the microscope, and there is infiltration of chronic inflammatory cells. (B) Sirius Red staining also shows a large number of pink collagen fibers (original magnification $\times 400$).

secondary to TED. Postoperative contour outcomes were considerably worse in patients with severe upper-eyelid retraction than mild or moderate patients, regardless of group [16]. In fact, surgeons commonly find that a repeatable and predictable surgical result for severe upper-eyelid retraction is difficult to attain and postoperative recurrences are difficult to avoid [6,17]. One possible reason may be that the full-thickness upper-eyelid fibrosis causes loss of elasticity, which then causes the upper eyelid to have an abnormal appearance. For surgery, it is difficult to calculate the amount of retraction and the postoperative height is difficult to predict. Moreover, fibrotic muscles lose their automatic adjustment function and the postoperative curvature of the eyelid is not smooth.

It has been suggested that the selection of a surgical method for the correction of upper-eyelid retraction should be primarily based on the amount of retraction in the primary gaze: a retraction of less than 2 mm should be treated with Mullerectomy, 2–4 mm of retraction should be treated with levator recession, and 5 mm or greater retraction should receive spacers [18].

The first upper-eyelid-lengthening procedure using a scleral graft was introduced by Dryden in 1977 [19]. He reported the outcome of this procedure when performed on 14 dysthyroid eyelid retraction patients in 1981; 66% of the patients

were corrected to within 1 mm of the desired position after the first operation. Therefore, the author recommended the sclera as “an excellent graft material for dysthyroid eyelid retraction” [9]. However, MP Mourits reported that only 50% of patients with TED-related upper-eyelid retraction showed acceptable results after the lid-lengthening procedure using sclera as a graft. Furthermore, complications occurred, such as medial overcorrection and eyelid margin deformity caused by lateral undercorrection. The author thus did not recommend sclera as a spacer graft in upper-eyelid lengthening [10].

Other types of grafts were tested in subsequent years, such as Mersilene mesh, conchal cartilage, and deep temporal fascia [20–22]. However, Mersilene mesh has a greater chance of postoperative wound infection or even mesh exposure in future eyelid surgery [23]. Autologous conchal cartilage and deep temporal fascia grafts can cause injury to the donor site and can increase the operative time. Acellular human dermal allografts have widely been used in oculoplastic surgeries, such as lower-eyelid lengthening, where they served as a scaffold for host cells to repopulate [24]. In the present study, bovine acellular dermal matrix was used as a new type of spacer graft in upper-lid lengthening. Favorable outcomes were obtained (69% good and 23% acceptable), which are better than those obtained in previous procedures. Compared with human dermal

allografts, bovine dermal matrix is abundant and is thus inexpensive. It also has a long shelf life and does not need to be refrigerated for preservation. When porcine dermal collagen was used to correct lower-eyelid retraction, it caused implant-related complications such as cyst formation, graft exposure, and transient inflammation [25]. These complications did not occur in our study. As the graft contains no cellular antigens, the risk of host rejection is very low.

Additionally, the following improvements have been made in Dryden's technique of upper-eyelid lengthening using spacer grafts. First, during the operation, some rigid fibrous cords scattered on the surface of the levator aponeurosis were observed, as in previous reports. It occurred in 85% of patients in our study and was typically worse near the Whitnall's ligament. This percentage was much higher than reported in previous studies [18] and was probably a characteristic of Chinese TED patients. Microscopic evaluation of these cords in tissue sections confirmed their fibrous nature (Figure 3) [26], suggesting that these irregularly distributed fibrous cords make the levator stiff and nonelastic; thus, the activity range of the eyelid is limited. These fibers should be removed as much as possible. Second, when we closed the skin to form the future eyelid crease, the fat pad was pulled out and the skin was closed using skin-tarsus-fat-skin sutures. This procedure can effectively avoid unpredictable upper-eyelid multi-layer creases. In a similar, previously reported procedure, the preaponeurotic fat was

fully exposed and fixed on the upper tarsal plate 1 mm superior to the planned eyelid crease before skin suturing. Hirohiko recommended this procedure for the prevention of an unexpectedly higher eyelid crease after upper-eyelid-lengthening surgery [27]. The one-step procedure can produce a smoother eyelid after surgery.

In this study, the bovine acellular dermal matrix acts as a resorbable scaffold that extends the levator aponeurosis to correct severe eyelid retraction and return the upper eyelid to a normal position. Among the 26 patients in this study, 92% obtained a good/acceptable result. Complaints about ocular discomfort and tearing were resolved, and signs of lagophthalmos were corrected. The procedure cured both functional and cosmetic problems. The probable disadvantage is that the procedure comprises multiple steps and requires relatively complicated manipulations. Only skilled surgeons should perform this technique.

Conclusions

A modified levator-lengthening procedure using bovine acellular dermal matrix as a spacer graft managed both the symptoms and the signs of severe upper-eyelid retraction secondary to TED. This procedure is a reasonable alternative to TED-related severe upper-eyelid contraction correction.

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