

## Fat or fillers: The dilemma in eyelid surgery

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### Abstract

The aging of the periocular region has always aroused great interest. A fresh, young, and attractive sight determined an ever-greater attention to surgical and non-surgical techniques to obtain this result. In particular, the change in the concept of a young look, considered then "full", led to the increasing use of surgical (fat grafting) or medical (hyaluronic acid) filling techniques. Eyelid rejuvenation became increasingly popular in the field of cosmetic treatments, with a focus on achieving a youthful and refreshed appearance. Among the various techniques available, the choice between using fat grafting or fillers presented a clinical dilemma. In particular, what surgery considered of fundamental importance was a long-lasting result over time. On the other hand, aesthetic medicine

considered it fundamental not to have to resort to invasive treatments. But what was the reality? Was there one path better than the other, and above all, was there a better path for patients? The minireview aims to explore the physiopathology, diagnosis, treatment options, prognosis, and future studies regarding this dilemma. We analyzed the literature produced in the last 20 years comparing the two techniques. Current literature reveals advancements in biomaterials, stem cell research and tissue engineering held promise for further enhancing the field of eyelid rejuvenation. The choice between fat grafting and fillers in eyelid cosmetic treatments presented a clinical dilemma. Understanding physiopathology, accurately diagnosing eyelid aging, exploring treatment options, assessing prognosis, and conducting future studies were essential for providing optimal care to patients seeking eyelid rejuvenation.

**Key Words:** Stem cells; Adipose stem cell; Ocular therapy; Oculoplastics; Regenerative

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**Core Tip:** Rejuvenation of the periocular area is an area of interest when attempting to seem younger, which is why non-surgical (hyaluronic acid fillers) and surgical (fat grafting) methods are often considered. The decision between invasive and non-invasive therapies presents a therapeutic challenge for practitioners due to changing views about youthfulness. Fat grafting and fillers have been used over the last 20 years. The physiopathology, diagnosis, prognosis, and future approaches in eyelid rejuvenation are fundamental issues when addressing options for patients. Advances in tissue engineering, biomaterials, and stem cell research provide exciting options for further increasing outcomes in eyelid rejuvenation, which may play a useful role for effective patient care in modern-day eyelid surgery.

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## INTRODUCTION

The face is an extremely fascinating region from an aesthetic point of view (it represents our “business card” to the world). For this reason, scientific attention is always very high towards this region of the body. Thanks to numerous anatomical and radiological studies as well as careful observation of the changes that occur over time, knowledge of facial aging has seen a significant improvement in recent years[1-3].

Studies on cadavers by Rohrich and Pessa[4], have shown that there are different compartments of adipose tissue in the face, both superficial and deep, each one behaving and aging differently depending on the surrounding structures. They have found that deep fat pads give shape and contour to the overlying skin and are the ones determining the anterior projection that can be seen in young faces. Among the signs of aging, a descent of those deep fat compartments plays a prominent role, and it can be seen especially in eyebrows, eyelids, and cheeks. On the other hand, skin wrinkles tend to form between different superficial fat pads and become more evident when one of them loses volume[4,5].

If at the basis of the study of aging there is a constantly increasing literature based on anatomy, there is also a literature made up of evidence and subjective perception of these dynamics. The attractiveness of a face, and specifically of the gaze, is an extremely personal concept and difficult to judge objectively. Multiple works have attempted to objectively analyze the attractiveness of the face and other works have in turn confirmed how this aspect has foundations rooted in neuroscience which justify our constant search for rejuvenation[6-8].

Aging is a process involving a variety of factors, ranging from altered skin quality (atrophy) to volume loss, which inevitably leads to tissue ptosis. These modifications are not only determined by the passing of time but could also be associated with external elements such as ultraviolet radiation, chemicals, trauma, and smoking. With one of these actors at play, cellular oxidative stress increases, thus worsening tissue damage[9,10].

Clinically, the first signs of aging are epidermal thinning and loss of skin elasticity, with the appearance of fine lines in the periocular region. Dyschromia may arise later as a consequence of skin laxity, together with deeper wrinkles caused by a gravitational effect on loose tissues. The result in the upper eyelid region is a sunken superior sulcus, while in the lower eyelid, infraorbital hollows become evident and exacerbated by midface descent[10,11].

Therefore, a combination of volume loss and gravitational pull on soft tissues, together with repeated contractions of mimic musculature, is the key to understanding the changes seen in older faces. Last but not least, facial bone structures also go through a remodeling phase. It mainly consists of posterior movement of maxillary bones, movement of the inferior-lateral orbital border, and tightening of mandibular bones[3,12]. These modifications, causing a reduced space in the central part of the face, affect the soft tissues which in turn bend over themselves[13]. Such an aspect has also been described in the past by Pessa *et al*[14] as the “concertina effect”.

Diagnosis of eyelid aging is mostly based on clinical assessment, taking into consideration both the changes the different anatomical structures in the periocular region go through and the degree of facial volume loss they lead to. Some of these changes are illustrated in [Table 1](#).

The search for a rejuvenated face, and in particular a younger and more attractive eye, is certainly one of the cornerstones of surgery and aesthetic medicine[2,15]. The periocular region, contrary to the past, is today considered as a single unit with regard to aging. We can no longer think about the aging of a single anatomical structure (bone, adipose tissue, muscle, *etc.*) but about the aging of the entire oculo-palpebral unit. Corrective aesthetic treatments must therefore also consider this.

A second but equally important aspect, which differs from the past, is the concept of “young sight”. In the past, the classic approach to periocular rejuvenation was the removal of excess tissues (such as fat bags) or descended ones (such as the skin). Today a young gaze, by definition, is not only characterized by the absence of excess skin but also by the absence of grooves resulting from the removal of deep tissues. For this reason, blepharoplasty, which today represents one of the most performed surgical interventions in the world, has gone from subtractive to repositioning and additive [16,17]. However, surgery is no longer the only option nowadays. Aesthetic medicine is also frequently used to complete the process of rejuvenation[16].

Surgical approach for periocular rejuvenation remains the most used technique today. However, more and more attention is being paid to the solutions offered by aesthetic medicine. Non-surgical treatments are now increasingly used to treat the first signs of aging[16]. The most used and studied techniques so far are those based on lasers (fractional or ablative, with different possible sources)[18,19], dermal fillers and other injectables [hyaluronic acid (HA), poly lactic acid, polymethylmethacrylate, *etc.*][20,21], polydioxanone threads[22], and platelet rich plasma injections[23].

At the basis of the concept of addition blepharoplasty, well described by Tonnard *et al*[17], is the search to fill those furrows and depressions resulting from the removal of sagging or excess tissue. From the beginning, to achieve this objective, surgery has used adipose tissue as a natural filler[24].

Fat grafting utilizes autologous fat harvested from the patient’s own body. Among the most frequent donor sites are the abdomen, the medial aspect of thighs and knees, the trochanteric regions and hips. The standard procedure described by Coleman uses a 3-mm blunt cannula connected to a syringe and fat is aspirated manually by withdrawing the plunger [25]. Then, there are several methods to process fat. The most commonly used is centrifugation which separates the harvested adipose tissue into three components. The most superficial is oily and only contains destroyed adipocytes while the deepest contains blood mixed with local anesthetics. The intermediate level is comprised of purified fat (the so-called macrofat) which can also be washed and/or filtered[26]. After these steps the final product is injected in the desired area of treatment to achieve volume augmentation. It is a safe and long-lasting procedure, even though an unpredictable reabsorption rate (from 20% to 80%) has always been a limitation[27,28].

Microfat and nanofat, on the other hand, have a reduced reabsorption rate than macrofat. They are typically harvested through cannulas with smaller diameters (around 0.7-1.0 mm) and processed with a series of emulsifiers and strainers [29]. Microfat contains sparse non-viable adipocytes and normal cellular architecture while nanofat is devoid of differentiated fat cells but has a higher concentration of stem cells[30].

In general, the added benefit of using fat is that it enables the transfer of adipose-derived stem cells (ASCs) to a receiving site that does not simply need augmentation but also regeneration. ASCs possess the ability to differentiate into mesenchymal or endothelial cells and secrete cytokines that stimulate tissue repair[31].

Even so, aesthetic medicine has also started proposing a series of molecules that could mimic the role of adipose tissue for additive purposes, in particular HA[32]. This approach has widely spread because these treatments don’t require surgery but can be carried out in a medical office. HA fillers seem to have immediate volumizing effects and can improve skin appearance by enabling tissue rehydration as well. HA usually lasts between 8 months to 10 months, with the effect slowly reducing over time, though it has been detected up to 36 months by ultrasound scan[33,34]. However, the question one may ask is whether they are comparable to fat grafting in terms of long-term results, effectiveness, potential complications, and patient satisfaction. In this review, we have analyzed the literature to try to understand what the current point of view is concerning periocular rejuvenation.

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## LITERATURE REVIEW

We conducted a search of the literature published between January 1, 2003, to January 1, 2023, using MEDLINE (PubMed). The database was first searched using the keywords “eyelid rejuvenation, blepharoplasty, eyelid AND fat grafting, filler, HA, aesthetic medicine”. The inclusion criteria evidenced only studies in English and those referring to humans and with an abstract, thus reducing the count to 768 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. The research of articles was performed using PubMed (<https://pubmed.ncbi.nlm.nih.gov>), ResearchGate database (<https://www.researchgate.net>), and Reference Citation Analysis (RCA, <https://www.referencecitationanalysis.com>). The quality of each article was evaluated using the American Society of Plastic Surgeons guidelines for therapeutic studies[35]. Considering that the literature currently available on this topic is in the majority of cases made up of reviews, the use of this type of articles has not been excluded in our mini-review. Each study was independently assessed by at least two reviewers (Miotti G and Zeppieri M), and rating decisions were based on the consensus of the reviewing authors.

Seven hundred and sixty-eight records were retrieved, of which three duplicate records were excluded. 35 records were not in English language while the authors could not access full-length text for 577 records. Another 108 records were out of scope of this paper. A total of 53 papers were included in this review. This number included 8 studies that were not

**Table 1 Anatomical changes in the periocular region can lead to a “sunken eyeball” appearance**

Periocular region	Anatomical changes
Skin	Thinning of eyelids, reduction of collagen deposition, distortion of elastin fibers, increased laxity
Subcutaneous tissue	Descent of facial fat pads, atrophy of subcutaneous tissue, and subsequent volume loss
Muscle	Hypertrophy of orbicularis oculi muscle (can accentuate wrinkles) and hyperlaxity of orbito-malar ligament
Bone	Receding of superior and inferior orbital rims

in the original search group of 768 manuscripts but they were rather obtained by citation searching of relevant studies (Figure 1).

The aging process in the face, especially in the periorbital area, is characterized by volume loss due to redistribution and atrophy of facial fat[36]. There are many studies carried out with different techniques, including imaging, which have led to the knowledge of these dynamics. Various works have highlighted how aging is not only a process affecting soft tissues but also involves deeper structures such as bone[1].

Regarding the upper eyelid region, skin deflation and reduced elasticity as well as gravitational effects lead to several changes including brow ptosis, dermatochalasis, unmasking of the medial fat pad, and exposure of the superior orbital rim[37]. As for the lower eyelid region, changes such as the weakening of the orbital septum and pseudoherniation of fat pads can be associated with the appearance of eyelid shadows and bags. The inferior orbital rim can also become more evident with the descent of the malar and sub-orbicularis oculi (SOOF) fat pad. Moreover, both superior and inferior orbital rims tend to recede with age, thus exacerbating the typical hollowed look of older individuals[1,12].

## SURGICAL TECHNIQUES FOR EYELID SURGERY

Surgical techniques for periorbital rejuvenation have been performed to remove excess skin or adipose tissue, to correct ptosis, or to achieve a tightening of the eyelid. However, they cannot be used alone to treat sunken eyes if tissue atrophy and volume loss are present[38,39].

One of the most frequently used approaches for restoring volume is fat grafting. It allows not only correction of contour deformities but also rejuvenation, thanks to the regenerative effects of ASCs. These cells have a paracrine activity, secreting cytokines and growth factors (such as vascular endothelial growth factor, hepatocyte growth factor, and transforming growth factor) that influence cell differentiation. They stimulate wound healing and have been associated with extracellular matrix remodeling, immunoregulation, and increased angiogenesis. The aim is to reduce inflammation and local tissue fibrosis[29,40,41].

Moreover, fat grafting has been performed both in reconstructive settings (*e.g.*, thyroid-associated orbitopathy and anophthalmic sockets) and cosmetic ones. A meta-analysis collecting more than 4000 cases has shown that it is a procedure with a high satisfaction rate (90.9%) and low complication rate. Major improvements have been seen after treating orbital fat prolapse, eyelid skin transparency, and tear-trough depression[42]. Boureaux *et al*[26], in their systematic review collecting data from more than 1000 patients, have demonstrated how lipofilling can achieve satisfactory and sustainable results. Furthermore, it is worth mentioning that in comparison to surgery is a minimally invasive method with lower post-operative pain and fewer complications[43]. Among these, the most common are ecchymosis or edema, over- or under-correction, contour irregularities, and harvest site abnormal scarring, erythema, or hyperpigmentation. The most severe, though rare, are vision loss or stroke due to vascular embolization. To prevent them attention must be paid during both fat harvesting, processing, and infiltration. To increase adipose-tissue viability large-diameter harvesting cannulas and gentle aspiration are recommended. Besides, during fat processing, any debris left after liposuction should be removed to prevent an inflammatory response. To reduce the asymmetric distribution of the graft, small volumes should be injected, always following a fanning pattern. Most importantly, to avoid the risk of vascular damage and subsequent higher risk of embolization, blunt cannulas should be used while the injection should be slow and retrograde (during withdrawal of the cannula)[44,45].

Regarding the upper eyelid, authors suggest placing fat along the inferior margin of the supraorbital rim at the preseptal space, descending to the palpebral crease, filling especially the atrophic lateral fat compartment. Injection should be parallel to the supraorbital rim. As for the lower eyelid, fat should also be deposited under the orbicularis oculi muscle/pre-periosteal plane, anterior to the infraorbital rim and perpendicular to it. In this case, the target is to obtain a smooth cheek-eyelid transition. Subcutaneous plane should be avoided in order to reduce the risk of contour irregularities[45,46].

Compared to HA fillers, fat grafting has some advantages: It allows both volumetric restoration and rejuvenation thanks to the properties of ASCs. It integrates with facial tissues unlike fillers giving the face a more natural appearance when in movement. Furthermore, it can produce long-lasting results, also avoiding the so-called Tyndall effect which is a bluish discoloration in the tear trough and infraorbital area created by subcutaneous filler injection[38]. On the other hand, HA filler injection is a widely recognized, rapid, non-surgical technique with relatively long-lasting results and no associated donor site morbidity. Table 2 summarizes some studies on eyelid surgical techniques.

Table 2 Summary of studies on eyelid surgery

Technique	Type of study	Number of cases	Region treated	Comparison/follow-up	Outcome	Rate complications	Results	Type of fat	Conclusions	Ref.
Fat graft	Original article	1047	Upper eyelid; eyebrow	Median follow-up 3 months	Volume enhancement, exophthalmos and ptosis correction	26 out of 1047	See rate of complications	Microfat	Discussion on “ugly” results trying to minimize complications and unsatisfaction	Benslimane <i>et al</i> [45], 2021
	Original article	98	Perioral, periocular, chin, malar region, temporal fossa	Average 6 months follow-up	Volume enhancement, rhytids reduction, skin quality	0.039	Volume restoration was evaluated by 2 senior authors rated the results independently as good in 62 patients (63%) and excellent in 36 patients (37%)	Superficial enhanced fluid fat injection	The fat administered by SEFFI is easily harvested <i>via</i> small side-port cannulae, yielding micro fat that is rich in viable adipocytes and stem cells. Both volumes of fat (0.5 mL and 0.8 mL) were effective for treating age-related lipoatrophy, reducing facial rhytids, and improving skin quality	Bernardini <i>et al</i> [78], 2015
	Original article-retrospective	200	Periocular area	6 month-1 yr follow-up	Volume and contour	< 2%	Nearly all patients had improvement in periocular contour, but variable loss of volume was observed by 1 yr. Patients who presented initially with scleral show often had noticeable improvement. At 1 yr, only 3 patients experienced contour irregularities comprising soft bulges, similar to fat hernias. Two patients showed fat accumulation after substantial weight gain later than 1 yr postoperatively	Properly diluted fat	Preparation and periocular delivery of PDF by the described techniques yield good contour with a low risk of visible masses occurrence	Pelle-Ceravolo <i>et al</i> [79], 2020
	Original article	31	Upper periorbital area	Average total follow-up period was 15.33 months ( $\pm$ 4.821 months; range 12-28 months)	The primary result was the quantitative volume difference in the superior sulcus region before and after grafting. This was evaluated through three-dimensional VECTRA® imaging. The secondary results included the aesthetic	Bruises 12 (38.7%); edema 6 (19.4%); infection 0; palpable granules 0; asymmetry 2 (6.5%); ptosis 0	The median preoperative pretarsal space and upper lid area ratio was 1.010 ( $\pm$ 0.150). The median postoperative pretarsal space and upper lid area ratio at 1 year was 0.159 ( $\pm$ 0.031) ( $n = 62$ ; $P < 0.0001$ ), indicating a significantly reduced sunken appearance. The	SVF gel	SVF gel is safe and effective for the treatment of a mild-to-moderate sunken superior sulcus and is associated with satisfactory clinical outcomes and short recovery times	Ding <i>et al</i> [72], 2023

				quantitative evaluation results (upper lid area and pretarsal space ratio), GAIS score, and complications		average GAIS score was 2.174 ( $\pm$ 0.391). All patients were satisfied with their surgical outcomes. The reoperation rate was 12.9%			
Original article	99	Periorbital	5 groups based on follow-up length	Volume enhancement, aesthetic rating	-	Independent evaluators correlation, $k = 0.316$	Enriched centrifugated fat	Autologous periorbital lipotransfer remains a valid and effective technique for periorbital rejuvenation and demonstrates long-term potential effectiveness	Yeh <i>et al</i> [66], 2011
Clinical trial	96	Tear trough	Hyaluronic vs Lipofilling	Aesthetic	-	Tear trough grade improvement in both groups. One year after treatment, while patients treated with HA start having a regression of correction, all patients of group treated with lipofilling keep a stable result  In patients with grades 1, 2, and 3 deformities, lipofilling resulted in significantly greater grade improvement, compared with HA filling	Centrifugated fat	Both HA and lipofilling are effective treatments for tear-trough depression, though lipofilling provided a higher grade of improvement of the deformity as well as prolonged effects	Pascali <i>et al</i> [65], 2017
Editor's invited commentary	-						Centrifugated fat	Graft should be placed under orbicularis oculi muscle; subcutaneous plane should be avoided to reduce risk of irregularities	Marten <i>et al</i> [46], 2018
Meta-analysis	> 4000							FG is a procedure with high satisfaction rate (90.9%) and low complication rate	Yang <i>et al</i> [42], 2021
Review	> 1000							FG is easy to perform and achieved satisfactory and sustainable results with few complications. However, a wide disparity exists in fat harvesting, purification, and re-injection techniques	Boureaux <i>et al</i> [26], 2016
Review	-							FG in comparison to major surgery is a minimally invasive method with lower	Çetinkaya <i>et al</i> [43], 2013

Hyaluronic Acid	Original article	147	Periorbital hollows	Long-term follow-up (at least 5 yr)	Volume enhancement; omplications	17 patients had malar edema; 46 blue-gray dyschromia; 45 contour irregularity/orbital ridge	See rate of complications; no statistically significant difference in the mean volumes injected by severity grading of each measured complication	post-operative pain and fewer complications  The vast majority of cases of malar edema, blue-gray dyschromia, and contour irregularities are mild and do not require intervention. Injection should be pre-periosteal, deep to the orbicularis oculi muscle, to avoid compression to lymphatic structures as well as decrease the risk of Tyndall effect	Mustak <i>et al</i> [59], 2018
	Original article prospective single blind	600	Tear trough by means of cannula or needle	Average follow-up time was 12 months ± 1 months	Hirmand's classification improvement	Tyndall effect, a blue-gray dyschromia, and contour irregularities are the most frequently reported complications with injection into this site, being referred in up to 30.5% of cases. With respect to the results here presented, post-injection complications encountered with needle use occurred in 5.1% of cases, compared to cannula use in 11.0% of cases, and they are usually transient and self-limited within hours (swelling, bruising, redness and pain)	Improvement mostly seen in younger patients under 50 yr old and improvement duration up to 1 yr	HA injection of the tear trough is most effective in patients between 30 and 40 years of age, while its benefits extend to up to 50 years old; afterward, it should no longer be the treatment of choice. This confirms that correction of tear trough with hyaluronic acid injections may provide an option to achieve immediate and durable results for up to one year after the injection	Diaspro <i>et al</i> [56], 2022
	Original article retrospective	101	Infraorbital hollows	Mean follow-up 12 months	FACE-Q with eyes and decision survey	Adverse effects include bruising [in 10 (10%), contour irregularities 2 (2%), swelling 3 (3%), and Tyndall effect 1 (1%)]	Overall mean (SD) patient satisfaction (based on FACE-Q scores) was 71.1% (27.3) and 65.6% (31.3), respectively. (eyes and decision survey)		Hall <i>et al</i> [55], 2018
	Original article retrospective	45	Tear trough inferior to lateral orbital thickening	Yes	Improvement in tear trough grade (classified according to Hirman)	-	The improvement was I grade 29 patients and II grades in 16 patients. The improvement lasted (10.8 ± 2.3) months. No severe adverse events were noted	See results	Wollina <i>et al</i> [52], 2021
	Clinical trial	151	Preperiosteal tear trough	Follow-up (1 month)	Treatment safety	At the first visit post-treatment on 151 patients: Swelling in 22 patients (mild 10, moderate 2, missing data 10); Bruising in 17 patients (mild 9, moderate 2, severe 1, missing data 5);	Most patients (97%) described marked or moderate satisfaction with the treatment; see complications	Effective use of semi-cross-linked HA gel in tear-trough rejuvenation. It has excellent patient tolerability and satisfaction and minimal complications	Berguiga <i>et al</i> [49], 2017

					<p>Redness in 32 patients (mild 12, moderate 3, severe 1, missing data 16); Pain in 1 patient (mild); Blue discoloration in 4 patients (moderate 2, missing data 2); Other (itching, hollow) in 1 patient (1 missing data)</p> <p>At follow-up 1 month (visit 2) on 112 patients; Swelling in 13 patients (mild 4, moderate 2, severe 1, missing data 6); Bruising in 12 patients (7 mild, moderate 1, missing data 4); Redness in 7 patients (mild 3, missing data 4); Blue discoloration in 1 patient (1 missing data); Other (itching, hollow) in 2</p>			
Observational study	150	Tear trough	Follow-up immediate, 1 wk, 1, 3, 6, and 12 months)	Treatment efficacy	<p>Immediately after injection: 12/150 patients (8.0%) had swelling, redness in 6/150 patients (4.0%), pain in 3/150 patients (2.0%), bruising in 3/150 patients (2.0%)</p> <p>After 1 wk post-treatment: 7/147 patients had swelling (4.7%), bruising in 2/147 patients (1.4%)</p>	<p>Approximately 90% at all time points rated their results as “very” or “exceptionally” improved. Adverse events were short term and included swelling, redness, pain, and bruising. No adverse events seen after the 1-wk visit. No Tyndall effect was noted throughout the study and no filler required removal</p>	<p>For tear-trough deformity treatment, simplified, quantifiable HA injection technique in 3 areas (medial, central and lateral infraorbital) with predictable and satisfactory outcome and low complication rate</p>	Hussain <i>et al</i> [50], 2019
Comment	-						<p>Hyaluronic acid functions as an osmole, attracting and capturing large amounts of water. It is also known to act as an antioxidant, and by stretching tissue, it indirectly stimulates neocollagenogenesis</p>	Sisti <i>et al</i> [48], 2019
Systematic review	-						<p>Patient satisfaction after the procedure is high (85%-90%) and with a duration of effect between 8-12 months</p>	Trinh <i>et al</i> [47], 2022



Review	-	Hyaluronic acid fillers are minimally invasive and suitable for periorbital area, also because they can be easily dissolved with hyaluronidase. Low-viscosity HA is safe for tear-trough region	Montes <i>et al</i> [63], 2021
Review	-	Hyaluronic acid has the most evidence to support its efficacy in periorbital area, with good safety profile. Most adverse events are mild and transient	Mandal <i>et al</i> [32], 2021
Review	-	Vascular compromise is rare but could happen especially in the glabellar area, probably due to the presence of small vessels and a lack of good collateral circulation	Lee <i>et al</i> [61], 2017

PDF: Properly diluted fat; GAIS: Global aesthetic improvement scale; FG: Fat graft; HA: Hyaluronic acid; SVF: Stromal vascular fraction; SEFFI: Superficial enhanced fluid fat injection.

## REVIEW OF STUDIES ON EYELID SURGERY

A recent systematic review analyzing the treatment of tear trough deformity with fillers has found that patient satisfaction after the procedure is high (85%-90%) and with a duration of effect between 8 to 12 months[47]. Besides, Sisti *et al*[48] have stated that volumizing effects partially persist after a year due to neo-collagenogenesis, angiogenesis, and proliferation of adipocytes in the area.

Berguiga *et al*[49], in their prospective multicenter study collecting 151 patients, have assessed the results of HA injections to tear-trough area, glabella, and crow's feet. At 1 month they have found objective improvement for all patients and no major complications.

Similar results have been seen by Hussain *et al*[50] who have recorded high efficacy, predictable and satisfactory outcomes at 12 months of follow-up, with low complication rates. They have proposed a simplified, quantifiable, and reproducible approach called "the tick technique". It consists of injecting a precise quantity of HA, depending on the degree of volume loss, in three different zones forming a tick sign (central, medial, and lateral infraorbital area). The plane of treatment is deep on the periosteum and under the orbicularis oculi muscle[50].

A correct choice of product, as well as an appropriate injection technique, are essential factors to a good result. A high level of cross-linking is associated with long-lasting fillers, as is larger particle size, however, it also increases water reabsorption and subsequent edema. That's why fillers with low hygroscopic behavior are preferred[51].

Wollina and Goldman[52] chose a HA filler with high viscosity and cohesivity to be placed above the periosteum to treat tear-trough deformity and the palpebro-malar groove. They selected a single injection point inferior to the lateral orbital thickening so as to avoid Tyndall effect and vascular danger zones. Moreover, Vadera *et al*[53] conducted a study comparing the standard injection technique for the correction of hollow tear-trough area, a medial approach using low G Prime (G') filler, to a lateral injection technique with high G' filler. The latter led to a lower complication rate with a

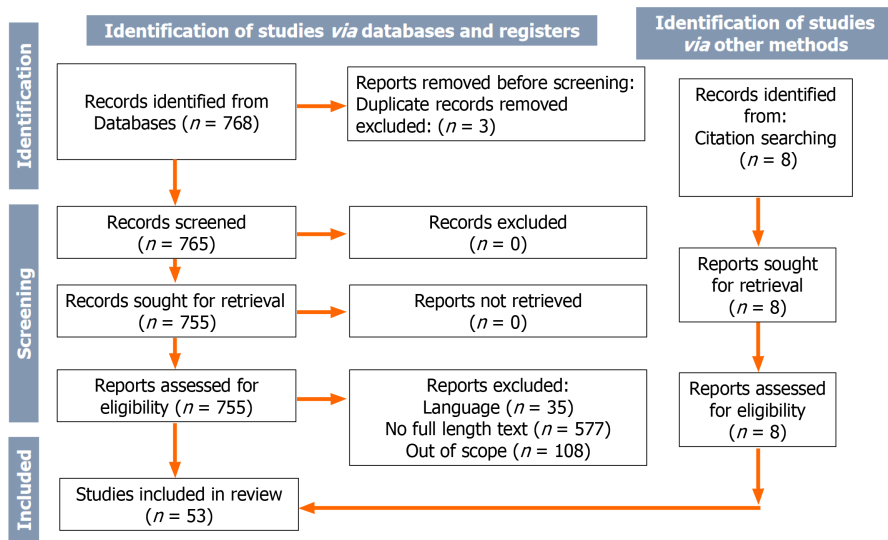


Figure 1 Search criteria for study.

reduced risk of developing Tyndall effect. Besides, a smaller volume of high G' filler was needed and it had more longevity. This method was similar to the one described by Wollina but it was performed with three injection points rather than a single one[53].

Shah-Desai and Joganathan[54] offered their contribution on treatment of infraorbital dark circles and sunken eyes as well, especially in patients with thin eyelid skin. They experienced good aesthetic results, long-lasting effect (up to 36 months) and low complication rate. The technique they developed consisted of placing small subdermal boluses of HA along the upper third of the tear-trough region[54]. Volumizing HA filler was also injected in the infraorbital region of 101 patients by Hall *et al*[55] with acceptable safety profile and satisfactory outcomes.

On another note, an inverse correlation between age and success of the procedure was found by Diaspro *et al*[56], who conducted a clinical trial on 600 patients undergoing HA injection for correction of tear-trough deformity. Improvements were mostly seen in younger patients under 50 years old with a duration of result up to 1 year.

Regarding treatment of deflated upper eyelids, Romeo and *at* proposed a classification based on the ratio between pre-tarsal and pre-septal skin show, also considering volume deficiency and possible skin excess. Five hundred patients underwent HA filling, sometimes as an adjuvant to blepharoplasty. The correct above-mentioned ratio was achieved in all cases, the results were long-lasting and the complication rate was only 0.4%[57]. Natural and stable results were also recorded by Spada in a more recent article focusing on treatment of the same region with HA[58].

Particular attention must be paid to the plane of injection. It should be pre-periosteal, deep to the orbicularis oculi muscle, to avoid compression to lymphatic structures as well as decrease the risk of the Tyndall effect[59]. Injections should be slow to avoid overcorrection. It is advisable initially to perform under-correction considering that injected HA will undergo a process of consolidation, drying, and then rehydration in the following month. Care must also be taken to avoid unnecessary movements of the needle or cannula to minimize the risk of vascular damage[60].

Treatment with HA fillers is safe and well-tolerated. Low rates of complications have been described, mostly bruising or redness, contour irregularities, and over/under-correction. Vascular compromise is rare but could happen especially in the glabellar area, probably due to the presence of small vessels and a lack of good collateral circulation[61]. Advantages include, other than the absence of a donor site, the ability to be performed in the office, the possibility for the HA filler to be molded with massage, minimal risk of infection, and the potential for complete reversibility using hyaluronidase[62].

Other than HA fillers or fat grafting, complimentary treatments to surgery include neurotoxins, biostimulant agents, and skin rejuvenation procedures, such as chemical peels and laser resurfacing. Among biostimulant agents, the most commonly used are calcium hydroxyapatite and poly-L-lactic acid (PLLA). The former has more consistency than HA fillers and minimal hydrophilic properties. The latter promotes fibroblast activity, thus stimulating collagen production and achieving a gradual soft tissue augmentation[61,63]. However, PLLA can cause chronic inflammation, leading to fibrosis, which can compromise subsequent treatments. This can also happen with calcium hydroxyapatite or with permanent fillers (silicone, polymethylmethacrylate). In these cases, lipofilling is not recommended due to impaired graft survival and uneven graft take, which can still occur if HA filler has been previously injected or even if it has been dissolved with hyaluronidase (due to residual phlogosis). Besides, other factors can jeopardize the outcome of such procedures: Smoking history, previous radiofrequency or ultrasonic treatments to the face for aesthetic purposes, and immunological or dermatological disorders. So accurate patient selection is of paramount importance[38].

## FUTURE PERSPECTIVES IN EYELID SURGERY

In the past several years, there has been an increasing demand for enhanced aesthetic outcomes with procedures that can offer quicker operative and postoperative wound-healing times, preferably with fewer complications and fewer

discomfort with anesthesia. Non-invasive aesthetic procedures have become relatively popular in providing effective and safe alternatives[64].

Pascali *et al*[65] published an article comparing the treatment of tear-trough depression with HA filler and fat grafting. Both achieved satisfactory results, though lipofilling provided a higher grade of improvement of the deformity as well as prolonged effects with no patients requiring another treatment within the 6-month study period.

Yeh *et al*[66] have also stated the superiority of fat grafting in terms of longevity (up to three years), however, the rate of injection site reactions has been higher compared to HA, with post-operative edema lasting over two weeks.

Future studies should focus more on comparative effectiveness research, evaluating the long-term outcomes and safety profiles of fat grafting *vs* fillers, to help surgeons make an easier choice between apparently similar alternatives.

Additionally, advancements in stem cell research and tissue engineering hold promise for further enhancing the field of eyelid rejuvenation. For example, a recent article by Sun *et al*[67] has proposed the use of combined stromal vascular fraction (SVF)-gel and nanofat for the treatment of tear-trough depression. The authors have remarked on the different properties shown by these two fat derivatives, which are mostly related to the process of their preparation. SVF gel is obtained through centrifugation of filtered lipoaspirate. It has high elasticity and viscosity, is more difficult to spread, and appears to have a high-volume retention rate (around 80%). These features make it more resistant to shear forces so a good product both for lifting and volume purposes. Moreover, it is richer in ASCs and growth factors which are the key elements in rejuvenation[68,69]. On the other hand, nanofat is produced through mechanical emulsification and subsequent filtration. What such a process achieves is a product with a low number of SVF cells and a high concentration of fragmented adipocytes. It is believed that the latter can elicit a moderate inflammatory response able to stimulate ECM remodeling and fibroblast proliferation[70,71]. Sun *et al*[67] have tried injecting SVF-gel in the SOOF plane to gain volume and at the same time nanofat in the superficial layer of orbicularis oculi muscle/subcutaneous space to improve skin texture and treat dark circles. Even though the patient sample is small, satisfactory results were reached with no major complications and an effective correction of tear-trough deformity. To evaluate changes at a 12-month follow-up visit, they used photogrammetric techniques, whose use will probably spread in the future, also considering the development of artificial intelligence (AI) and the fact that they could be useful during surgical planning. The possibility to obtain a 3D rendition of a patient's face from a simple photo can help identify, for example, the areas where more volume is needed (hollows, grooves) and how are the results after treatment. Such tools may help surgeons understand the degree of volume loss they need to treat.

Ding *et al*[72] used SVF-gel for augmentation of sunken upper periorbital area in patients with mild-to-moderate defect. Since complications can occur with the traditional fat grafting method, such as nodules or liponecrosis, SVF was chosen based on its more stable survival rate. The results were satisfactory with patients experiencing short recovery times. Post-operative assessments were also made using three-dimensional imaging software.

In their preliminary work, Yao *et al*[73] also reported that patients treated with SVF-gel experienced a low re-intervention rate and were mostly satisfied with the results (77.3%). Small-caliber cannulas were used for injection, thus lowering damage-induced inflammation. Moreover, due to its reduced re-absorption rate, overcorrection was not necessary and prolonged augmentation effect was registered. SVF-gel has also been used successfully to treat tear-trough depression and infraorbital hollows, with a high retention rate[74,75].

Regarding microfat grafting, several studies showed its advantages in comparison with the traditional approach, such as increased concentration of stem cells and higher safety in periocular region, also thanks to the possibility of superficial injection with syringe needles (in contrast with the traditional plane of injection)[76,77]. Bernardini *et al*[78] developed a new technique for the preparation of microfat, which they called superficial enhanced fluid fat injection (SEFFI), overcoming the necessity of fat manipulation after harvesting. Usually, collagenase digestion or manual centrifugation were needed after fat harvest to obtain microfat, though at the expense of adipocyte viability. With SEFFI, however, the authors used 0.5-0.8 mm side-port cannulae to directly collect microfat, which was then mixed with platelet-rich plasma (PRP) increasing its fluidity and so allowing easier injection in the superficial orbicularis muscle plane. The aim was to minimize the risk of visible lumps and delivering growth factors closer to the skin. SEFFI microfat was able to promote not only skin regeneration, similar to nanofat due to their elevated concentration of ASCs, but also volume restoration thanks to the higher rate of viable adipocytes[78].

Pelle-Ceravolo *et al*[79] have also developed a method, called "Properly Diluted Fat" (PDF), to increase fluidity of adipose tissue, harvested with unconventional cannulas, to reduce risk of contour irregularities. After fat harvesting and centrifugation, it was diluted with saline and infranatant fluid and injected in the periocular area in a submuscular plane. Good results were registered at 6-month and 1-year follow-up, even though variable volume loss was detected.

Microfat was also used by Lin *et al*[80] for the treatment of sunken upper eyelids with promising results. They underlined the potential reduced complication rate and introduced a new device, the MAFT (microautologous fat grafting)-gun, to accurately deliver fat particles with definite volumes in order to increase graft survival rate.

As already previously mentioned, various other techniques and materials find space today in the field of aesthetic treatments[16].

PRP has been proposed by Aust *et al*[23] in order to rejuvenate the skin of the lower eyelid region and treat actinic elastosis. Despite the small number of patients treated, 20, the increase in elasticity of the skin treated with this method appears significant.

Other authors have published their experiences with other injectable substances. Mani *et al*[21] presented their experience with PMMA in 289 patients. They demonstrated how PMMA subdermal injection is a safe technique to correct infraorbital rhytids with natural effects.

Amore *et al*[22] have recently presented the promising results obtained from the treatment of 120 patients with Sodium deoxycholate in a multi-center observational prospective study.

A review conducted by Urdiales-Gálvez *et al*[81] has found a combination of laser treatment and HA filler injection for skin rejuvenation to be both safe and effective. The timing between these procedures (performed during the same day) does not appear to be strictly relevant, though they have stressed the importance of two elements. The first one is the sequence of treatment, with non-ablative laser applied prior to HA injection, while the second one concerns the wavelength of the laser, which determines the depth of its action.

In the field of plastic surgery, a relevant issue is also how to objectively measure results. Evaluating aesthetic outcomes has usually relied on subjective perspectives from both patients and surgeons. Although there is general consensus on what is considered universal standards of beauty, various factors affect people's beliefs on the matter (society, culture, age, and ethnicity). AI may also be able to help provide objective analysis. Pattern recognition models, along with 3D surface image technology, can be used to interpret facial characteristics and movements to assess patient satisfaction. Facial emotion recognition systems are in development as well. However, AI predictions and data interpretations should be evaluated carefully and critically. Further research on this new field will be important to understand its potential role in both aesthetic medicine and surgery[82,83].

Regarding long-term outcomes, the current literature reports a lack of consistent data. Mustak *et al*[59] achieved a minimum follow-up period of 5 years in their sample: HA gel filling of the periorbital hollows has been shown to be well tolerated. Malar edema, orbital rim fullness, and blue-gray dyschromia continue to be the predominant adverse effects, but the majority of cases are only mildly affected with adverse effects occurring late, sometimes years after the injection. Among fat grafting studies included in our reviewing process Ding *et al*[72] showed longer follow up time (average total follow-up period was 15.33 months with 12-28 months range): Bruises and oedema were predominant complications. Further studies with standardized investigated outcomes and median follow-up times longer than 48 months are needed.

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## CONCLUSION

The choice between fat grafting and fillers in periorbital cosmetic treatment remains a clinical dilemma. Both procedures have shown comparable effectiveness, long-term results, and safety profiles, with low complication rates. There are perks and disadvantages related to each technique, but in the end, what seems to drive the decision is the examination of the patient. What emerges is that knowledge of the pathophysiology of aging and anatomy are fundamental in choosing the most appropriate treatment, which in the case of mild or moderate signs can be medical, otherwise surgical. The limitations that emerge from this review are the few works that compare medical and surgical treatments. This causes further research to be necessary. Deepening eyelid aging knowledge, exploring treatment options, assessing prognosis, and conducting future comparative studies (especially considering long-term outcomes) are essential for providing optimal care to patients seeking eyelid rejuvenation.

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## FOOTNOTES

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