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New Findings in Prominent Lower Eyelid Fat Pads Possibly Contributing to Their Etiology: Two Prospective Studies

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Background: Little is known about the actual composition of prominent orbital fat pads. It was incidentally noted that hyaluronidase injections in prominent lower eyelid fat pads attenuated them, suggesting prevalence of hyaluronic acid (HA), and raising questions regarding their etiology. This led to 2 institutional review board studies: The first quantified HA concentration in orbital fat pads and assessed possible correlation between HA levels and degree of lower eyelid puffiness. The second determined if regular hyaluronidase injections in prominent lower eyelid fat pads impacted their size to uncover a possible role of intrinsic HA and its hydrophilic properties in their etiology.

Methods: Lower eyelid orbital fat harvested from 20 filler-naive blepharoplasty patients underwent enzyme linked immunosorbent assay for HA quantification. A separate group of 14 filler-naive patients requesting nonsurgical treatment of lower eyelid puffiness were treated with a series of hyaluronidase injections.

Results: HA levels in prominent eyelid orbital fat pads averaged 39.3 μg/mg of the dry weight, higher than reported in other solid human tissues. Orbital fat HA levels correlated with the degree of clinical puffiness. Hyaluronidase attenuated lower eyelid puffiness in 78.6% of patients. The extent and duration of improvement varied between responders but increased with repetitive injections.

Conclusions: Prominent orbital fat pads have a higher HA concentration than reported in other solid human tissues. HA hydrophilic properties likely contribute to fat pad edema manifesting as puffiness. Attenuation of prominent lower eyelid fat pads following hyaluronidase injections further implicates intrinsic HA in the etiology of prominent eyelid fat pads. *(Plast Reconstr Surg Glob Open 2024; 12:e6340; doi: 10.1097/GOX.0000000000006340; Published online 22 November 2024.)*

INTRODUCTION

Changes along the lower eyelids manifesting as dermatochalasis, puffiness, and deepening tear trough are concerning to many, particularly with advancing age. Decreased skin elasticity and weakened connective tissue are compounded by orbital septum attenuation resulting in orbital fat pad pseudoherniation.[1–4] These changes are exaggerated by infraorbital skeletal resorption leading to orbital rim and tear trough prominence.[5,6] Lower blepharoplasty is a multifarious procedure with intrinsic challenges. It necessitates addressing protruding fat pads, blending the eyelid-cheek junction, tightening lateral canthal laxity, and managing dermatochalasis.[7–9]

In 1988, de la Plaza and Arroyo[10] introduced the concept of fat preservation to prevent postsurgical orbital skeletalization. The importance of orbital fullness was furthered by Hamra,[11] who described resetting the orbital septum over the orbital rim to create a youthful convexity along the eyelid-cheek junction. Despite meticulous orbital fat repositioning without fat resection, there may be attenuation of repositioned fat leading to orbital hollowness.[5] Blepharoplasty is predicated on the principle that orbital fat pads protrude secondary to pseudoherniation

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but does not consider fat pad size fluctuations secondary to varying edematous states.

There is a paucity of literature characterizing the composition of prominent orbital fat pads. It was incidentally noted that hyaluronidase injections along bulging lower eyelids of a filler-naive patient attenuated the puffiness. A 56-year-old woman new to our practice reported bulging lower eyelids following an isolated session of facial injectables performed months earlier. She reported filler placement along the lower eyelids, and was treated with 3 weekly sessions of hyaluronidase along the fat pads and overlying soft tissue. At her initial treatment, 150 units of hyaluronidase were injected along each lower eyelid, flooding the soft tissues. At her subsequent 2 sessions, there appeared much less lower eyelid fullness, but the fat pads appeared more well-defined. Each fat pad was injected with 25 units of hyaluronidase (75 units per eyelid). At her 2-week follow-up, the lower eyelid puffiness and fat pad prominence had significantly decreased. Afterward, her medical records became available and verified no history of fillers, only onabotulinumtoxin A. Similar findings were subsequently observed in another filler-naive patient in our practice following 1 session of hyaluronidase (Fig. 1). This response to hyaluronidase suggested prevalence of hyaluronic acid (HA) in prominent orbital fat pads, raising questions as to their etiology.

HA is a vital extracellular matrix component of all vertebral tissues and body fluids.[12,13] It consists of a repeating disaccharide polymer of β-D-glucuronate and N-acetyl-β-D-glucosamine molecules synthesized in the plasma membrane by hyaluron synthases (HAS-1, - 2, and -3).[14] HA has a high turnover rate with a half-life from less than 24 hours to several days depending on the tissue.[13] The biological roles of HA are dictated by its molecular weight which ranges from 5 to 20,000 kDa,[15,16] most commonly1000–8000 kDa.[12] These high molecular weight HA (HMWHA) polymers are anti-inflammatory scavengers of damaging free radicals.[12] When HA degradation exceeds HA formation, there is an increase in low molecular weight HA (LMWHA) polymers which are proinflammatory, leading to tissue fibrosis.[16,17] LMWHA polymers induce fibrosis in many tissues, including aging ovarian stroma,[18] lung,[19] and systemic adipose tissue.[14]

Takeaways

Question: Could an increase in hyaluronic acid levels in lower eyelid fat pads be a factor in increased fat pad prominence?

Findings: We have found significant amounts of hyaluronic acid in prominent lower eyelid orbital fat pads, higher than reported in other solid human tissues. High levels of hyaluronic acid may contribute to fat pad edema resulting in lower eyelid puffiness. We have also found that hyaluronidase injections temporarily attenuate lower eyelid puffiness to varying degrees.

Meaning: An increase in hyaluronic acid levels in lower eyelid fat pads is a possible contributing factor to lower eyelid fat pad prominence and lower eyelid puffiness.

Hyaluronidase has been legally marketed in the United States since 1948[20] and is used extensively off-label to dissolve undesirable injected HA.[21,22] Multiple articles demonstrate its safety and efficacy in dissolving injected HA, highlighting lack of negative sequelae on native HA,[23–25] but there is a paucity of literature on its aesthetic use in filler-naive patients. There is 1 case report of hyaluronidase to treat Graves disease–associated periorbital myxedema.[26] Another article reports short-term improvement in idiopathic malar mounds following hyaluronidase injections in 6 patients.[27] These findings were briefly referenced in a review article addressing idiopathic malar edema.[28] An extensive literature review did not reveal publications regarding HA levels in orbital fat pads and potential effects of hyaluronidase. The goals of this study were to measure HA levels in prominent lower eyelid fat pads and to study their response to hyaluronidase, more specifically to Hylenex human recombinant hyaluronidase (HHRH; Halozyme Therapeutics, Inc.).[29]

In humans, there are 6 hyaluronidase enzymes: HYAL-1,2,3,4; HYALP1; and PH-20.[30] HHRH is the purified preparation of human hyaluronidase PH-20.[29] It is produced by genetically engineered Chinese hamster ovary cells containing DNA plasmid encoding PH-20.[29] HHRH modifies connective tissue permeability by splitting the bond between the HA acetylglucosamine and glucuronic acid moieties.[29]

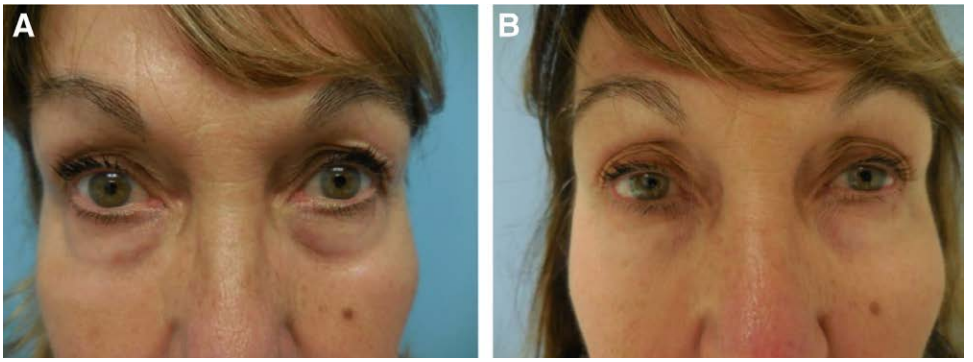


Fig. 1. Patient shown before (A) and 3 weeks after (B) 1 session of hyaluronidase injection along bilateral lower eyelid fat pads.

Degrading extracellular matrix HA temporarily decreases cellular adhesions, allowing improved dispersion of fluids. HHRH was Food and Drug Administration-approved in 2005 as a dispersant to enhance diffusion, absorption and bioavailability of injected drugs and to facilitate subcutaneous fluid infusion.[20,31,32]

HHRH is antigenic, and repeat injections may stimulate neutralizing antibodies due to trace Chinese hamster ovary proteins.[20] Urticaria or angioedema occur in less than 0.1% of patients, and anaphylactic-like reactions are rarer.[20] Exact mechanisms of hyaluronidase elimination remain unknown; it has a serum half-life of 2.1 ± 0.2 minutes in mammalian blood and is inactivated by the kidneys and liver.[33] Following dermal HHRH injections, the dermal barrier restoration rate is inversely dose-related at 24 hours and complete at 48 hours regardless of dose.[29]

METHODS

Two prospective clinical trials approved through the Western institutional review board were performed. One (No. 20203105; approved October 7, 2020) measured the HA in eyelid fat pads of patients who underwent lower blepharoplasty where some orbital fat required removal. The second (No. 20204240; approved April 29, 2021) evaluated potential effect of hyaluronidase in attenuating prominent fat pads and lower eyelid fullness. Exclusion criteria for both groups included history of blepharoplasty, thyroid disease, hypertension, diabetes, kidney disease, glaucoma, nicotine use, autoimmune disease, diagnosed idiopathic edema, soft-tissue filler injections in the upper two-thirds of the face, and use of bimatoprost-containing or prostaglandin-derived eye drops or serums. In the hyaluronidase group, no facial fillers or neuromodulators were permitted during the study.

Written informed consents were obtained from all participants, and the ethical principles of human research were followed throughout the study. All blepharoplasty procedures and hyaluronidase injections were performed by the first author.

Surgical Patients

Twenty patients, 5 men and 15 women (49–73 years) underwent a bilateral transconjunctival blepharoplasty under general anesthesia as an isolated procedure or with upper blepharoplasty and/or rhytidectomy (December 1, 2021 to October 10, 2023). One woman was eliminated due to previously undiagnosed hypothyroidism, permitting samples from 38 eyes.

During surgery, the conjunctiva along each lower eyelid was infiltrated with 1.5 mL of 1% lidocaine + 1:100,000 epinephrine. Dissection was performed using a coated needle tip electrocautery with precautions to limit tissue damage. Samples were harvested from the three fat pads and placed in sterile Falcon 6-well cell culture dishes (Becton, Dickinson and Company). These were packed on ice in Styrofoam coolers, and transferred to Avocet Polymer Technologies, Inc. (Avocet, Chicago, IL) laboratories for assay of adipose tissue hyaluronan content.

Hyaluronan Quantikine Immunoassay kits from R&D Systems, Inc. (Minneapolis, MN) were used by Avocet's chemists for quantifying adipose hyaluronan content normalized to wet and dry weight of the tissue. The R&D Systems published protocol was used.[34] These kits measure greater than 35 kDa hyaluronan. The HA calibration curve was derived from serial dilution of hyaluronan provided with the kit. Calibration for tissue HA was performed using engineered hyaluronan-collagen gels over the expected range of HA content. The HA contents determined by multiple biopsies from each gel were reproducible to within ±10%.

The HA contents were measured using the following enzyme linked immunosorbent assay (ELISA) protocol: Harvested tissues were stored at −20 °C until time of assay. The fat pad biopsies were thawed, bisected and processed in a Baker Sterilgard II hood (The Baker Company). Each biopsy was assayed in duplicate, and the average corrected optical density was evaluated to determine the concentration of HA in each biopsy. This was then multiplied by the total volume of sample used to obtain the amount of HA in micrograms. To normalize the HA content values for the differing weights of each sample, ratios of wet and dry weight were calculated in micrograms per milligram. All assays were reported in duplicate.

Nonsurgical Patients

Fourteen female patients (34–72 years) requesting nonsurgical treatment of lower eyelid bulging were treated with hyaluronidase injections along bilateral lower eyelids (May 3, 2021 to October 16, 2023). All patients were treated with HHRH.

Typically, fat pad pseudoherniation is assessed by applying gentle pressure along the globe to elicit fat pad protrusion. However, if the fullness is due to edema of the fat pads or overlying soft tissues, and not pseudoherniation, pressure on the globe will increase eyelid fullness mimicking pseudoherniation. As such, we used a simple examination relying on orbicularis oculi muscle (OOM) contraction to better decipher the periorbital fullness seen above the orbital rim: eyelid squint test (EST).

Eyelid Squint Test

While upright with head in Frankfort horizontal position, the subject is asked to look straight and squint. The following observations are made:

- If the fullness disappears, its etiology is posterior to the OOM and secondary to fat pad pseudoherniation, fat pad edema, or both.
- If the fullness partially improves, its etiology is due to processes both anterior and posterior to the OOM, or significant fat pad enlargement.
- If the fullness persists unchanged, its etiology is anterior to the OOM and due to soft tissue edema, not fat pad prominence. If the fullness worsens, it is due to a prominent pretarsal OOM. Both of these groups were excluded.

Injection Technique

The patient was seated with head elevated 45 degrees and instructed to look upward so as to localize the 3 fat

Fig. 2. Hylauronidase injection technique.

pads. All injections consisted of 75 units of undiluted HHRH per eyelid (25 per fat pad) and performed using a BD 0.5 mL insulin syringe with a fixed 31 Gauge × 5/16″ needle (Becton, Dickinson and Company) directed away from the globe toward the orbital floor while standing at the patient vertex (Fig. 2).

If the EST demonstrated only fat pad prominence, a single-needle insertion (4–6 mm in depth) was used to deliver 25 units of HHRH into each fat pad, for a total of three injections (75 units HHRH) per lower eyelid. If the EST demonstrated both fat pad prominence and subcutaneous fullness, identical technique and dosage were used but delivery continued while withdrawing the needle to deposit HHRH into each fat pad and overlying tissues. After the initial injection session, subjects were evaluated at 24 hours and every 2 weeks for 1 month to ascertain safety. There were no limiting adverse events. At 1 month, all subjects were enrolled for 4 additional identical weekly injections. Subjects were followed up monthly after their last injection for 3 months to evaluate safety and extent and duration of efficacy. The total study period was 5 months. At each visit, patients were asked to report adverse effects, and quantify percentage and duration of improvement in eyelid bulging from baseline. The primary investigator rated improvement independently based on photographs at each visit. Four patients were randomly selected to undergo lower eyelid volume analysis using the Canfield Vectra H1 camera (Canfield Scientific) to further assess correlation between clinical findings with patient and physician assessments.

RESULTS

Surgical Patients

The ELISA analysis of 38 eyes documented significant amounts of HA in orbital fat pads, higher than reported in other solid human tissues. The HA amount averaged 39 μg/mg (range: 10.6–127 μg/mg) of fat pad dry weight and 16.5 μg/mg (range: 6.5–31.3 μg/mg) of wet weight. (**See table, Supplemental Digital Content 1,** which displays the average amount of HA in each lower eyelid fat pad expressed in wet weight ratio [μg/mg]. **http://links.lww.com/PRSGO/D655**.) (**See table, Supplemental Digital Content 2**, which displays the average amount of HA in each lower eyelid fat pad expressed in dry weight ratio [μg/mg]. **http://links.lww.com/PRSGO/D656**.) As seen in all other human tissues, we found considerable variation in HA amount between patients and between fat pads in each patient.

We quantified the clinical degree of puffiness in each patient using their preoperative photographs and assessed each fat pad on a scale of 0 to 3, with 0 = minimal, 1 = mild, 2 = moderate, and 3 = severe (Table 1). Overall, the

Table 1. Clinical Lower Eyelid Puffiness Scale (0–3)

Case	Patient ID	RLL	RLC	RLM	LLM	LLC	LLL
1	60FME	3	3	3	3	3	3
2	70FW	2	3	3	3	3	2
3	65MW	3	3	3	3	3	2
4	59FW	2	2	2	2	2	2
5	73FW	2	2	2	2	0	1
6	57FW	2	3	3	3	3	2
7	62FW	2	2	2	2	2	2
8	49MW	3	3	3	3	3	3
9	63FW	3	3	3	3	3	3
10	66MW	2	2	2	2	2	1
11	55FW	3	3	3	3	3	3
12	54FW	1	2	2	1	2	0
13	59FW	2	2	2	1	2	1
14	61FW	1	2	0	0	1	1
15	68MW	3	3	2	3	3	1
16	54MW	3	3	2	2	3	3
17	52FW	2	2	1	1	2	0
18	55FW	3	1	2	3	2	3
19	71FW	3	2	3	2	2	3

Code: 0, flat; 1, mild puffiness; 2, moderate puffiness; 3, severe puffiness.
Fat pad location: LLC, left lower central; LLL, left lower lateral; LLM, left lower medial; RLC, right lower central; RLL, right lower lateral; RLM, right lower medial.

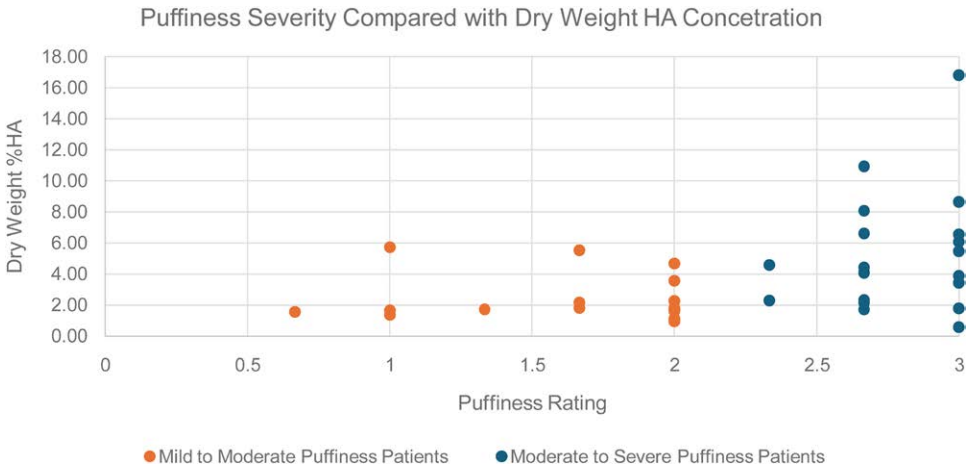


Fig. 3. Puffiness severity relative to dry weight HA concentration expressed per eye (N=38). Puffiness rating is the puffiness average score for the 3 fat pads in each lower eyelid. Dry weight % HA is the average % HA in the 3 fat pads of each lower eyelid.

Moderate to severe puffiness patients (rating > 2)			
Patient ID	**Puffiness Rating**	**HA % in Dry Weight**	**Average HA concentration of moderate to severe puffiness is 4.97%**
60FW	3.0	12.73%	
49MW	3.0	1.16%	
63FW	3.0	4.98%	
55FW	3.0	6.00%	
65MW	2.83	2.77%	
70FW	2.67	5.66%	
57FW	2.67	1.95%	
54MW	2.67	8.78%	
68MW	2.5	2.30%	
71FW	2.5	4.50%	
55FW	2.33	3.84%	
Mild to moderate puffiness patients (rating ≤ 2)			
Patient ID	**Puffiness Rating**	**HA % in Dry Weight**	**Average HA concentration of mild to moderate puffiness is 2.33%**
62FW	2.0	1.70%	
59FW	2.0	1.04%	
66MW	1.83	2.21%	
59FW	1.67	1.73%	
73FW	1.5	3.16%	
54FW	1.33	1.73%	
52FW	1.33	5.62%	
61FW	0.83	1.45%	

Fig. 4. Puffiness severity compared with HA concentration.

clinical degree of puffiness correlated with fat pad HA content, with mild-to-moderate puffiness having lower fat pad HA levels (2.33%) than moderate-to-severe puffiness (4.97%) (Figs. 3-4). There was no correlation between fat pad HA levels and patient age.

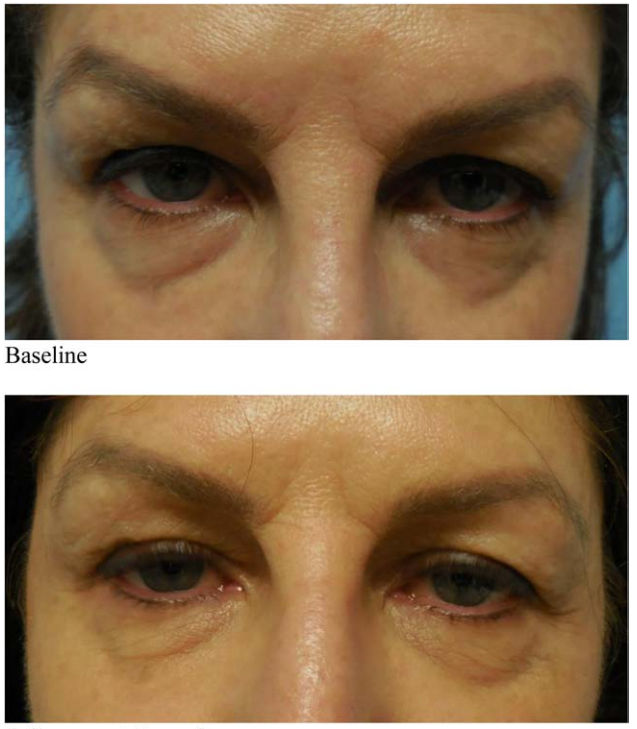
We measured HA levels using fat pad wet and dry weight. We included both for proper comparison to reported HA contents of other tissues because historically, investigators used wet tissue weight[12,35–43] (Tables 2, 3). Table 2 lists HA levels of all tissues reported in the

Table 2. Reported HA Concentration in Human Fluids and Solid Tissues[12,35–43]

Human Fluids/Tissues	Dry/Wet Sample	HA Concentration Range
Fluids		
Knee synovial fluid	Wet	1450–3120 μg/mL
Tears	Wet	0–840 μg/mL
Lymph fluid	Wet	0.2–50 μg/mL
Aqueous humor	Wet	1.0–1.2 μg/mL
Human milk	Wet	0.2–0.8 μg/mL
Urine	Wet	0.1–0.3 μg/mL
Blood serum	Wet	0.01–0.1 μg/mL
Solid tissues		
Articular cartilage	Wet	0.5–2.5 μg/mg
Skin	Undefined	0.4–0.5 μg/mg
Vitreous humor	Wet	0.1–0.4 μg/mg

Table 3. Measured HA Concentration in Lower Eyelid Prominent Fat Pads

Surgical Patients, N = 38	Dry/Wet Sample	Range of HA Concentration per Fat Pad, N = 109 (μg/mg)	Average HA Concentration per Fat Pad, N = 109 (μg/mg)
Lower eyelid fat pads	Dry	2.61–217.9	39.26
Lower eyelid fat pads	Wet	1.26–65.81	16.43


Baseline

Follow up at 5 months

Fig. 5. Before and after HHRH, case 1.

literature. We were unable to find any publications of HA levels in any human adipose tissue.

We believe tissue dry weight provides more accurate measurements of HA levels because HA is hydrophilic and water saturation may affect wet weight results. Our wet weight HA concentrations correlated with eyelid puffiness levels, but less so than dry weight measurements.

Nonsurgical Patients

Based on EST, 12 of 14 patients demonstrated puffiness secondary to enlarged fat pads and edema of overlying soft tissues, and 2 demonstrated puffiness secondary to enlarged fat pads alone. All 14 patients completed the study, and all reported some improvement in lower eyelid puffiness. However, based on physician assessment using 2-dimensional patient photographs, 11 of 14 patients demonstrated improvement. At the final follow-up, the median degree of improvement in lower eyelid puffiness was 60% per patient self-assessment and 40% per physician assessment. (**See table, Supplemental Digital Content 3**, which displays the hyaluronidase patients clinical degree of improvement from baseline. A, Patient self-assessment of improvement expressed as percentage [%] of improvement from baseline. B, Physician assessment of improvement based on clinical photograph comparisons expressed as percentage [%] of improvement from baseline. C, Canfield Vectra Camera decrease in volume [puffiness] from baseline measured as cubic centimeter in right [R] and left [L] eyes. **http://links.lww.com/PRSGO/D657**.) Examples of HHRH results are shown (Figs. 5-6).

Following injections, all HHRH patients experienced mild edema lasting 30 to 180 minutes. One patient reported slight bruising after 2 sessions. There were no visual changes, extraocular muscle movement abnormalities, or other adverse events. The onset, extent, and duration of improvement varied between responders. Patients whose puffiness was secondary to both enlarged fat pads and subcutaneous edema detected improvement within the first 24–48 hours following the initial treatment; the majority of their initial improvement was in the soft-tissue edema. Patients whose puffiness was due to enlarged fat pads alone did not see improvement until the second or third injection session.

Fig. 6. Before and after HHRH, case 3.

In all responders, the degree of improvement increased with subsequent injections, suggesting a cumulative effect. The earliest response rate in fat pads was in the lateral, then central, then medial, with the medial remaining the most resistant. The degree of improvement reported by patients was highest at the last injection session, and began decreasing to varying degrees over the three subsequent visits.

To further evaluate the accuracy of patient and physician assessments of improvement, we randomly chose 4 patients to undergo lower eyelid volume measurements using the Canfield Vectra H1 camera (Fig. 7). There was significant correlation between the physician assessment of improvement and Vectra H1 volume reduction analysis (R^2 = 0.934 and P = 0. 065). The patient's self- assessment of improvement also correlated with Vectra H1 measurements (R^2 = 0.865 and P = 0.134), but to a slightly lesser extent (**Supplemental Digital Content 3, http://links.lww.com/PRSGO/D657**).

DISCUSSION

Lower eyelid aging is secondary to multiple mechanisms that weaken the supporting components of the eyelid.[1–4] Additionally, many endure malar puffiness and festoons from edema of tissues along the eyelid, tear trough, eyelid-cheek junction, and malar region.[44,45] These conditions are challenging to treat, and surgery is often marginally ameliorative.[28,46,47] Our understanding of these anatomical changes at the cellular level is limited. The composition of the orbital fat pads is not completely understood, but anatomical studies have confirmed they are discrete compartments separated from posterior orbital fat.[48]

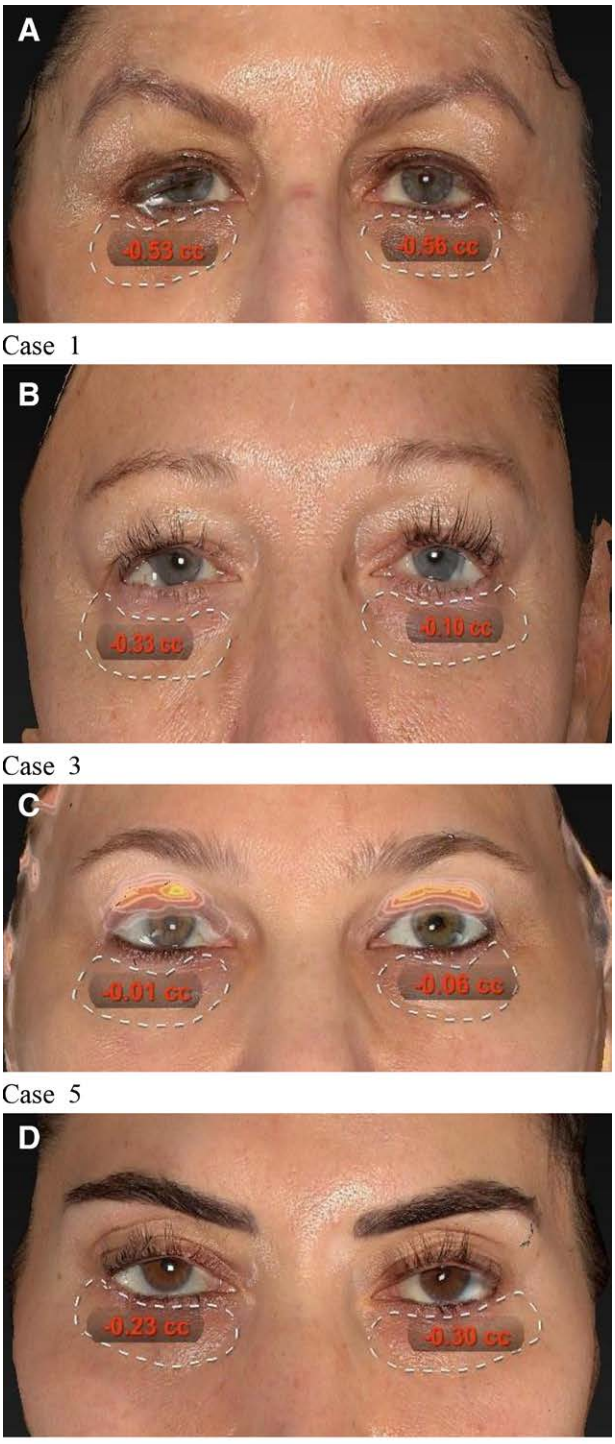


Fig. 7. Vectra lower eyelid decreased volume measurements following HHRH treatment. A, Case 1. B, Case 3. C, Case 5. D, Case 6.

There is heightened interest in orbital fat as a potential source of autologous stem cells.[49] Orbital fat pads are apparent at 14 weeks of gestation[50] and have different embryological origins.[51] Most systemic adipose tissue derives from mesoderm, whereas head and neck adipose tissue derives primarily from neural crest cells.[51] Orbital fat

is unique because it originates from both mesoderm and neural crest cells.[49,51] The white medial fat pads originate from neural crest cells, whereas the yellow central and lateral fat pads originate from mesoderm.[49,51] The richer yellow color is due to higher carotenoid concentrations.[52] Orbital adipocytes are approximately 50% smaller in cell diameter with higher concentrations of connective tissue and blood vessels relative to systemic adipocytes.[53] Medial fat pads are more finely lobulated and more fibrous in comparison to central and lateral fat pads.[52] Their more fibrous nature may explain why medial fat pads were the most resistant to HHRH injections in our study.

Protruding orbital fat pads are attributed to a weakened orbital septum. However, there is clinical evidence that prominent lower eyelid fat pads demonstrate actual enlargement.[54] Using magnetic resonance imaging studies, Darcy et al[54] illustrated that orbital fat expands with age. They concluded that fat expansion is the primary age-associated contributor to lower eyelid prominence, not fat pseudoherniation caused by a weakened orbital septum.[54] Darcy et al hypothesized this fat expansion was secondary to chronic fluid accumulation or adipocyte hyperplasia/hypertrophy.[54] Additionally, Lee et al[55] reported that total orbital fat volume, not just fat volume anterior to the inferior orbital rim, increased significantly in people after their 40s compared with their 20s, providing further evidence that orbital fat and fat pads expand with age.

There are young people who develop prominent lower eyelid fat pads before age-related orbital septal weakness could be implicated. Baek and Jang[56] observed lower eyelid bulging without orbital septum flaccidity in 3 patients (14–42 years) who underwent surgery for unilateral or bilateral lower eyelid prominent fat pads. They reported these as orbital fat hyperplasia.[56] Furthermore, some patients present with severely prominent eyelid fat pads that exceed normal orbital dimensions, implicating more than a weak orbital septum.[57]

There is paucity of literature addressing cellular changes seen in prominent orbital fat pads to explain their increased volume. Our findings of high HA levels in orbital fat pads and their response to HHRH, coupled with the findings of Darcy et al and Lee et al, raise the possibility of a primary role of HA and edema in eyelid fat pad prominence. It is possible that with age, fat pad HA levels increase or the protective HMWHA polymers break down into proinflammatory LMWHA polymers.[16,17] The latter may explain why there was not a completely linear correlation between HA levels and extent of eyelid puffiness in some of our patients. The ELISA methods do not differentiate between HMWHA and LMWHA polymers. Both increased HA levels or presence of inflammatory LMWHA would potentially lead to greater fat pad edema. If there is increased HA concentration in fat pads, the source of this increase is unclear.

There remains limited knowledge of the anatomy and function of the eye lymphatics[58] and debate regarding the number and configuration of orbital veins due to their variability.[59–61] This further complicates understanding intrinsic dynamics explaining tendency towards edema and fluctuating fat pad size. Unexpectedly, the volume of orbital fat and orbital fat pads is affected by prostaglandin F2-alpha (PGF2α) eye drops used to decrease intraocular pressure.[62–65] Filippopoulos et al[62] documented significant fat atrophy, enophthalmos and loss of lower eyelid fullness in glaucoma patients treated with topical PGF2α. These effects were partially reversible after discontinuing the eye drops[62] and not observed when sustained-release PGF2α drugs are injected into the eye,[66] indicating a topical effect on orbital fat. Histopathologic evaluation of periorbital fat following topical PGF2α demonstrated smaller adipocytes and increased adipocyte density.[64] These findings further emphasize our limited understanding of the physiology of aging orbital fat pads.

CONCLUSIONS

We have found significant amounts of HA in prominent lower eyelid orbital fat pads, higher than reported in other solid human tissues. We have also found that hyaluronidase injections temporarily attenuate lower eyelid puffiness to varying degrees, implicating HA as a possible progenitor to edema and increased lower eyelid fat pad size. Possibly, orbital fat prominence may be due to a cascade of events starting with enlargement of the fat pads due to presence of increased HA or LMWHA, leading to partial fat pad pseudoherniation due to volume limitations of the bony orbit. Over time, pseudoherniation is exaggerated by orbital septum weakness coupled with resorption of the infraorbital and mid-cheek skeleton. Genetics and lifestyle determine the rate and sequence of these changes.

The limitations of our studies are that they reflect a single practice experience, include a small number of subjects, and lack sufficient gender and ethnic variability. Furthermore, we did not have control groups for either of our studies. We did not have fat biopsies from nonprominent orbital fat pads to compare the HA content, and we did not have a nonsurgical group undergoing an injection series using a placebo such as normal saline. The only way to know for certain that prominent fat pads contain higher levels of HA than nonprominent fat pads is to measure the HA levels in nonprominent lower eyelid fat pads. Executing such a study carries its own ethical and procurement limitations. Furthermore, our institutional review board studies were focused on studying the HA content in lower eyelid fat pads; we did not measure the HA levels of adipose tissue in other parts of the face or elsewhere for comparison. Finally, although the Canfield Vectra H1 assessment helped to further confirm our findings, it is a less reliable method for volumetric assessment than magnetic resonance imaging or computed tomography scan evaluations. We believe our findings warrant further investigation of the role of HA in eyelid fat pad prominence and possible potential effect of hyaluronidase on eyelid puffiness.

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DISCLOSURES

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