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Aesthetic Surgery Journal 2014 34: 985 originally published online 15 July 2014
DOI: 10.1177/1090820X14542649

Aesthetic Surgery Journal
2014, Vol. 34(7) 985–994

DOI:10.1177/1090820X14542649
www.aestheticsurgeryjournal.com
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David J. Gerth, MD; Bethany King, MD; Lesley Rabach, MD; Robert A. Glasgold, MD; and Mark J. Glasgold, MD

Abstract

Background: Some practitioners have criticized the unpredictable retention associated with autologous fat transfer. Potential causes of variations in predictability include intrinsic (patient-related) or extrinsic factors, such as harvesting, processing, and graft-delivery technique.

Objectives: The authors sought to determine the long-term retention of autologous fat graft processed with a closed-membrane filtration system, to compare this retention with centrifuge-processed fat, and to analyze factors that affect graft retention.

Methods: This was a prospective analysis of 26 female patients (representing 52 hemi-midfaces) who underwent autologous fat transfer to the midface via the closed-membrane filtration system. The Vectra 3D camera and software were employed for all photography, which was then analyzed to compare immediate preoperative images with long-term follow-up images (obtained at least 10 months postprocedure). The authors compared the findings with data from their previous study of centrifuge-processed fat grafts (historical controls).

Results: Mean values were as follows: age, 55 years; follow-up period, 17 months; amount of autologous fat injected, 8.88 mL; absolute volume augmentation measured at the last postoperative visit, 3.71 mL; and retention, 41.2%. Results of Welch's *t* test, in which the membrane-filtration data were compared with the previous centrifuge data (31.8% long-term retention), showed a significant difference ($P = .03$). Retention in this study was significantly higher in patients younger than 55 years (53.0% vs 31% for older patients; $P = .001$) and lower in patients who underwent rhytidectomy (23.8% vs 47.6% for nonrhytidectomy patients; $P < .001$).

Conclusions: Autologous fat processed by closed-membrane filtration had a significantly higher long-term retention rate than did centrifuged-processed fat injected by the same surgeons.

Level of Evidence: 3

Keywords

autologous fat grafting, fat injection, closed-membrane filtration, centrifugation, minimally invasive cosmetic surgery

Accepted for publication February 21, 2014.

Volume augmentation as part of complete facial rejuvenation continues to increase in popularity, and autologous fat grafting has become more frequently used for this purpose. Critics of the technique emphasize the unpredictable nature of long-term results. Major variables that can be examined in trying to improve reliability include both intrinsic (patient-related) and extrinsic factors, such as harvesting and injection techniques, and processing methods. An ideal processing method should remove unwanted materials (free fatty acids, blood products, and tumescence solution) that may affect engraftment and retention. The gold standard for fat-graft processing has long been centrifugation.[1] To our knowledge, our previously published findings represent the

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only long-term study in humans to date. In that study, the senior authors (R.A.G. and M.J.G.) found that long-term volume retention (>1 year) of centrifuge-processed fat grafts averaged nearly 32%.[2]

Puregraft (Cytori Therapeutics, San Diego, California) is a closed-membrane filtration system for processing harvested fat. Tumescent fluid, free fatty acids, blood cells, and other debris are washed and filtered from the harvested adipose tissue, leaving highly purified fat. This closed-system design decreases the risk of graft contamination and eliminates the trauma of centrifugation, while potentially producing a graft with less unwanted content than the centrifugation process. In the present study, we examined the long-term retention of fat grafts processed with Puregraft and compared the results with those of our previous study of centrifuged fat. We also examined certain intrinsic factors of the study cohort and their effect on long-term retention.

METHODS

The setting of this retrospective study was private practice, and all procedures were performed by the senior authors (R.A.G. and M.J.G.). Patients underwent autologous fat transfer between November 2010 and November 2012, with fat processed by the Puregraft membrane-filtration system. All patients provided informed consent. Approval from an institutional review board was not obtained because this was strictly a retrospective review in a private practice. The device used (Puregraft) has been approved for clinical use.

Twenty-six female patients, representing 52 hemimidfaces, were included in the study. Only 1 patient was identified as a smoker. All patients had fat grafted to the inferior orbital rim and anterior cheek. Other inclusion criteria were the availability of pre- and postoperative 3-dimensional (3D) clinical photographs captured with the Vectra 3D system (Canfield Scientific, Fairfield, New Jersey) and a minimum follow-up of 10 months. Patients who underwent concomitant aesthetic procedures (eg, rhytidectomy), excluding liposuction in nearby areas, were included. Exclusion criteria were liposuction in adjacent or overlapping regions, subsequent facial surgery during the follow-up period, and volume changes detected in unoperated areas of the face, which would indicate a change in body weight.

Standard harvesting and injecting techniques, described previously,[3] were employed. Briefly, the donor site was infiltrated with 0.5% lidocaine and 1:200 000 epinephrine for recipients of local anesthesia only, or with 0.25% lidocaine plus 1:400 000 epinephrine for those who had conscious sedation. Site of harvest was typically the abdomen or thigh. After the skin was prepared with Betadine (Purdue Products L.P., Stamford, Connecticut) solution, a stab incision was made with an 18-gauge Nokor needle (Becton Dickinson, Franklin Lakes, New Jersey).

A liposuction cannula (usually a 3-mm keel type) was introduced into the stab wound, and 15 mL of negative pressure was applied to the attached Toomey syringe and secured with a Johnnie Lok (Tulip Medical, San Diego, California). Multiple passes were made with the cannula until the desired amount of fat was harvested. After being injected into the port on the Puregraft processing bag, the collected fat was mixed with saline so that the adipose content was preserved in the bag, while the aqueous and oil layer was separated from it. Next, the adipose content was withdrawn from the bag through a Luer-Lok port. A 20-gauge needle was employed to create an entry site in the skin for fat grafting. An injecting cannula (Tulip Medical) assisted in the transfer of processed fat from a 1-mL syringe into the subcutaneous plane (cheek) or suborbicularis plane (inferior orbital rim). For each case, the following information was documented in the medical record: harvested volume, harvest site, postprocessing volume, volume injected into each site, and total volume injected.

Concurrent rhytidectomies were performed with a deep-plane technique after the fat grafting procedure. Transconjunctival blepharoplasties were performed before fat grafting.

Once the appropriate follow-up 3D photographs were obtained, image analysis was performed with Vectra 3D Mirror software (Canfield Scientific), as described in our earlier study (Figure 1).[2] To ensure the longest possible follow-up, patients were contacted and asked to return for 3D photography just prior to the planned image analysis. Data collected during the study included follow-up time, concurrent procedures, total volume injected, and volume present at latest follow-up, from which the percentage of retained volume was calculated. Volume changes were calculated in milliliters and reported as a percentage of the total volume injected into the measured region.

Statistical analysis was performed with SPSS 22.0 (SPSS, Inc, an IBM Company, Chicago, Illinois), and Welch's *t* test was applied to determine long-term retention by processing method, age, and concurrent surgery. Analysis of variance (ANOVA) was employed to compare mean retention by follow-up time, which was grouped by duration: <1 month, 1 to 3 months, 3 to 6 months, 6 to 9 months, 9 to 12 months, 12 to 18 months, 18 to 24 months, and >24 months.

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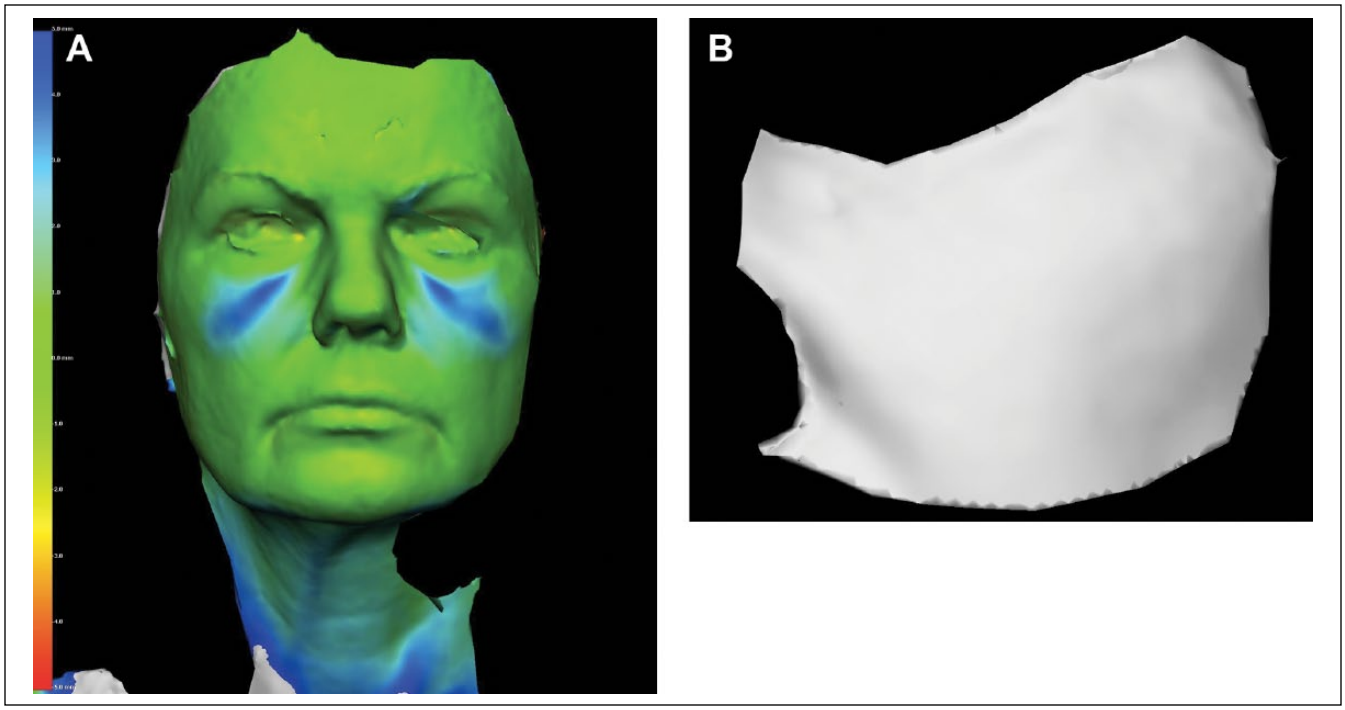

Figure 1. (A) Once postoperative 3-dimensional (3D) images are registered to the preoperative baseline image, a topographic map of volume differences is produced. Green hues represent no volumetric change, blue hues represent positive volume change, and red hues (not present here) represent negative volume change. (B) A 3D object is created from the selected treatment area (in this case, the left infraorbital and cheek region). Its volume is then calculated with the Vectra 3D Mirror software (Canfield Scientific, Fairfield, New Jersey).

RESULTS

Characteristics and descriptive data for the 26 patients (52 hemi-midface regions) are shown in Table 1. Their mean age was 55 years (SD, 11 years), mean follow-up time was 17 months (SD, 6.8), and mean amount of fat injected into each measured region was 8.88 mL (SD, 3.78). For 10 (38%) of the 26 patients, a different amount was injected into each side. Overall, the mean absolute volume of augmentation was 3.71 mL (SD, 2.64), and the mean percentage of retention was 41.2% (SD, 24.4%). The mean difference between sides, per patient, was 12.3% (SD, 12%). To date, there has been only 1 (3.8%) case of donor-site hematoma. No surgical-site infections have been recorded. Four (15.3%) patients underwent fat-transfer touchup procedures. Two representative cases are provided to illustrate our technique and results (Figures 2 and 3).

We examined our previous data[2] to determine the difference in long-term retention between processing with Puregraft and the gold standard of centrifugation (Table 2). The mean retention for patients treated with centrifuged fat was nearly 32%. The data for the 2 processes were compared by Welch's *t* test, which yielded a *P* value of .03.

We were able to identify patient factors that were associated with long-term retention in our membrane-filtration cohort, including age at time of surgery and rhytidectomy as a concurrent procedure (Tables 3 and 4). For patients younger than 55 years (n = 12), the mean retention rate was 53.0%. For patients older than 55 years (n = 14), the mean retention rate was 31.1% ($P = .001$). Interestingly, age < 55 years in the centrifuge cohort did not correlate significantly with greater long-term retention (data not shown). The mean retention rate was 47.6% for patients who did not undergo concurrent rhytidectomy (n = 19) and 23.8% for those who did (n = 7) ($P < .0001$). Although patients with a higher injection volume (> 8 mL) and higher processing yield (> 33%) had greater long-term volume retention, the difference in retention between these patients and those with lower volume/yield was not statistically significant (data not shown).

Because many patients had 3D photographs taken throughout the postoperative period, we were able to calculate retention based on follow-up time. Within 1 month of surgery, the mean retention rate was 69.7%. A nadir was reached at the 6- to 9-month time point (34.7%). Mean retention increased in the subsequent time points to 47.1% at > 24 months. However, none of the differences were statistically significant by ANOVA ($P = .06$).

Table 1. Patient Characteristics and Related Study Data

Patient No.	Age at Surgery, y	Rhytidectomy, +/–	Processed Volume, mL (% Yield)	Final Follow-up, mo	Midface Injected Volume, mL[a]	Retention, mL (%)[a]
1	70	+	25 (28.7)	15	9	2.7 (30.5)
					7	2.1 (30.1)
2	51	–	21 (26.3)	36	8	2.7 (34.3)
					8	2.7 (33.2)
3	44	–	50.7 (42.3)	13	13	7.2 (55.7)
					13	9.6 (74.2)
4	62	+	29 (36.3)	21	7.5	3.0 (39.5)
					7.5	2.4 (31.3)
5	69	–	16.6 (27.7)	17	7.3	0.4 (5.5)
					7.3	3.0 (75.6)
6	64	–	16 (22.9)	25	4	2.3 (57.5)
					4	3.0 (75.6)
7	50	–	30 (42.9)	23	4.7	3.1 (66.8)
					4.7	3.8 (81.2)
8	68	–	17 (20)	15	6	1.3 (22.3)
					6	1.1 (19.0)
9	69	+	5.6 (14)	25	2.3	0.5 (21.6)
					2.3	0.4 (18.7)
10	55	–	45 (33.3)	12	12.2	4.5 (37.3)
					16	5.2 (32.4)
11	67	–	30 (30)	26	7.25	1.8 (25.8)
					7.25	3.0 (41.7)
12	39	–	35 (35)	14	10	8.0 (79.9)
					10.5	8.7 (83.1)
13	49	–	12 (25.5)	26	4.6	4.4 (95.0)
					5.6	3.4 (61.3)
14	56	–	24 (40)	18	11.3	3.6 (32.3)
					11.3	3.6 (31.6)
15	40	–	26 (34.7)	24	10.75	5.9 (54.5)
					10.75	6.2 (57.4)
16	54	–	33 (35)	12	11.5	4.0 (34.8)
					11.5	5.7 (50.0)
17	47	–	47 (38.3)	27	15	6.5 (43.0)
					16.1	8.2 (50.7)
18	60	–	12 (13.3)	10	5.5	2.3 (41.2)
					5.5	2.4 (43.0)

(continued)

Table 1. (continued)

Patient No.	Age at Surgery, y	Rhytidectomy, +/–	Processed Volume, mL (% Yield)	Final Follow-up, mo	Midface Injected Volume, mL[a]	Retention, mL (%)[a]
19	42	–	30 (25.8)	12	9.7	1.6 (16.5)
					6.5	0.07 (1.1)
20	59	+	43 (53.8)	11	16	3.1 (19.1)
					16	1.6 (10.2)
21	34	–	26 (32.5)	10	9.3	7.8 (84.1)
					8.7	3.1 (35.4)
22	49	+	29 (36.3)	13.9	7	0.3 (5.0)
					4.5	0.4 (9.3)
23	66	+	37 (46.3)	10	13	5.7 (44.3)
					18	7.8 (43.4)
24	60	+	26 (37.1)	16	6	0.8 (12.9)
					6	1.0 (17.1)
25	66	–	17 (30.9)	13	8.5	4.1 (47.9)
					8.5	2.2 (25.8)
26	34	–	33 (47.1)	13	10	7.1 (70.6)
					10	9.6 (95.9)
Mean (SD) values	55 (11)	NA	32.9 (9.6)	17 (6.8)	8.88 (3.78)	3.71 (2.64)[b]

Abbreviations: NA, not applicable; SD, standard deviation.
[a]Data highlighted in gray pertain to the right side of each patient's face.
[b]Mean (SD) retention percentage = 41.2% (24.4%).

DISCUSSION

To date, the primary criticism of autologous fat transfer for facial rejuvenation has been the unpredictability of long-term retention. Varying predictability can result from 2 types of factors: intrinsic patient-related (host) factors, which are uncontrollable, and extrinsic factors such as harvesting, processing, and graft-delivery technique, which are controllable.

An ideal technique for processing autologous fat should maximize the number of viable graft cells by minimizing tissue trauma; remove useless components, such as tumescent solution; remove free lipids and blood cells, which could be detrimental to long-term graft viability; and prevent loss of growth factors and graft-favoring cytokines. The Puregraft filtration system is a proprietary closed-membrane filtration system that was originally designed to prepare fat for isolation of the stromal vascular fraction, which contains adipose-derived mesenchymal stem cells (MSC). The technology it employs has yet to be publicly disclosed, although its mechanism is known to work by principles similar to a dialysis unit.

Anecdotally, the senior authors had harvested 80 mL of fat and processed 40 mL with Puregraft and 40 mL by centrifugation. Puregraft processing yielded 3.5 mL of injectable fat, whereas centrifugation yielded 17 mL. This 17 mL was then placed through Puregraft and yielded 3.5 mL. This demonstrated the potential for Puregraft to produce a more viable grafting material, which could lead to greater volume retention. The manufacturer's literature on Puregraft suggests that this difference is due to more thorough removal of free fatty acids and nonviable blood contaminants.[4] Zhu et al[4] compared the Puregraft filtration system with 3 groups: centrifugation, gravity separation, and no manipulation (control). Viable graft content (as determined by stimulated lipolysis) was highest in the Puregraft groups. With relative lipolysis activity set at "1" for the control group, the average relative stimulated lipolysis of the PG850 group (Puregraft 850-mL processing unit) was >1.5 times that of the controls. Average relative stimulated lipolysis of the Puregraft

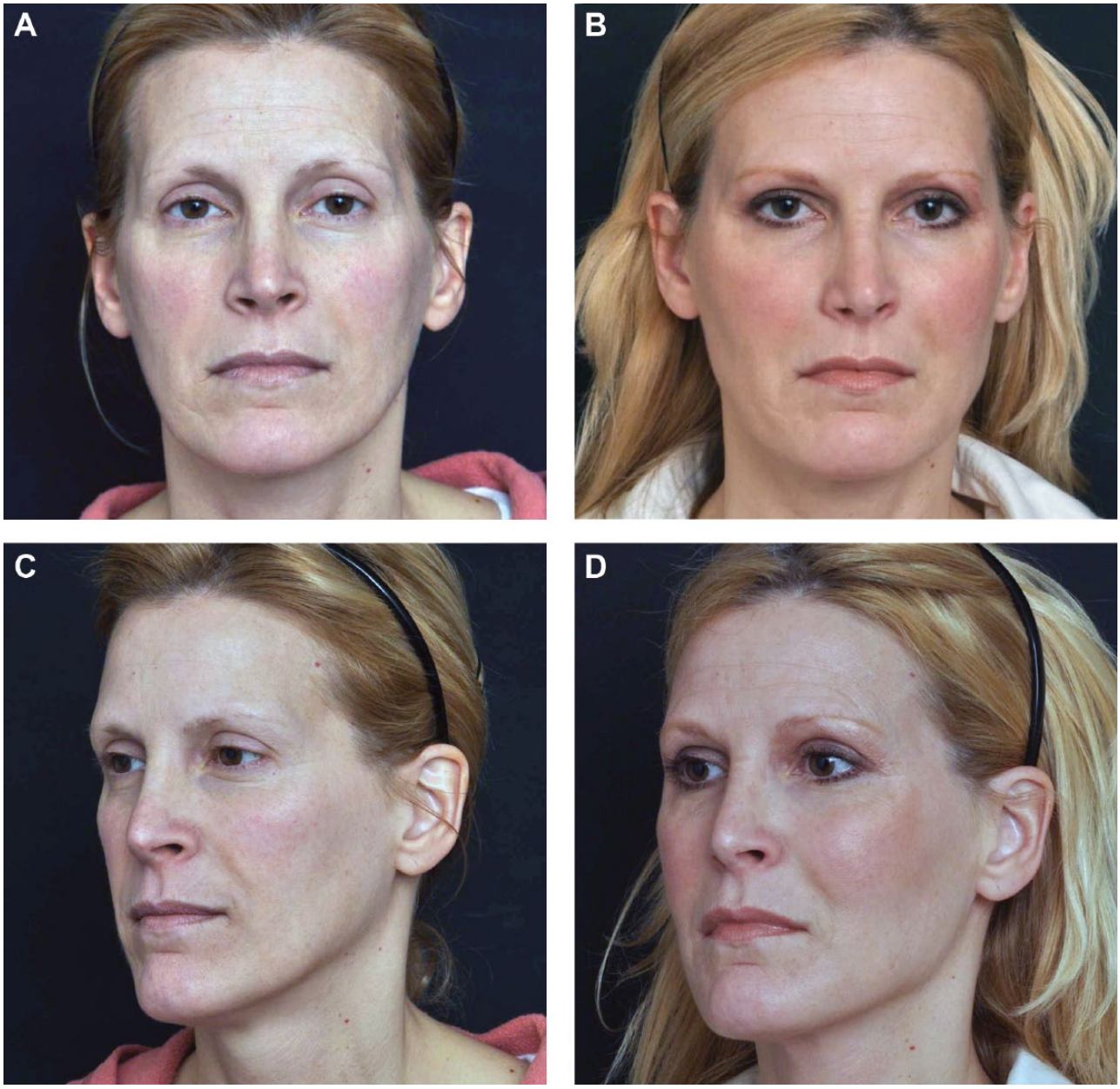

Figure 2. (A, C) This 44-year-old woman (patient 3) complained of a "tired" look and facial aging. She underwent autologous fat grafting to bilateral superior orbital rims, inferior orbital rims, cheeks, perioral region, and mandible. She also had alar base narrowing at the time of surgery. (B, D) Postoperative images obtained at 13 months. Only the inferior orbital rim and cheek regions were included in the volumetric analysis.

250 group (250 mL) was approximately 1.5 times that of controls. Conversely, the relative activity of centrifuged fat was slightly less than that of controls. The remaining aqueous content was similar by volume among the centrifugation, gravity separation, and control groups. Free lipid, white blood cell (WBC), and red blood cell (RBC) content was significantly lower in Puregraft-processed fat. Growth factor and cytokine profiles were similar for centrifuged and Puregraft-processed fat. Because most growth factors are contained within intracellular stores, the authors postulated that graft viability is a more valid indicator of overall growth factor content than free growth factor and cytokine concentrations. These data suggest that processing with the closed-membrane filtration system is less traumatic than centrifugation and that centrifugation is less able to clear free lipid, WBC, and RBC content from the fat graft.

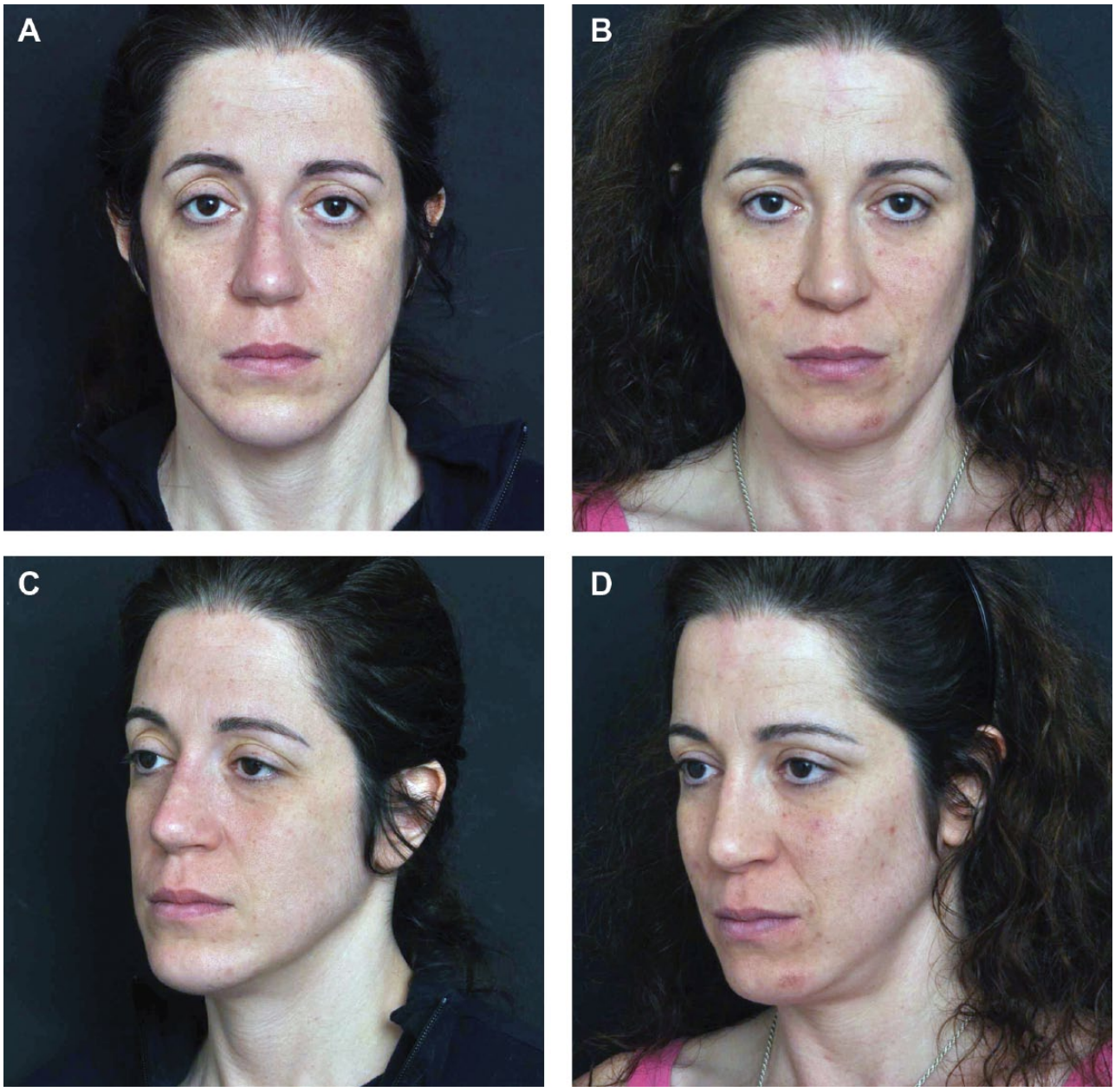

Figure 3. (A, C) This 40-year-old woman (patient 15) complained of facial aging. She underwent autologous fat transfer to the bilateral superior orbital rims, inferior orbital rims, cheeks, and lower perioral region. (B, D) Postoperative images obtained at 24 months. Only the inferior orbital rim and cheek regions were included in the volumetric analysis.

Some authors have examined other filtration techniques and found no significant differences among the methods. Smith et al[5] compared centrifugation, washing with saline, washing with lactated Ringer's solution, and centrifugation plus washing. Filtration was not performed in any of the 4 groups. The XTT (sodium 3-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis (4-methoxy-6-nitro) benzene sulfonic acid hydrate assay was performed to determine viability after harvest, and no significant differences were noted. The grafts were then injected into murine muscle and were weighed at 12 weeks; however, no significant difference in mass was observed.[5] Minn et al,[6] also via XTT assay, tested the viability of grafts prepared by centrifugation, metal sieve concentration, and cotton gauze concentration. Again, retention rates did not differ significantly among the 3 groups, as determined by graft harvest from murine muscle at 12 weeks. A more clinically relevant study was performed by Botti et al,[7] in which subjective (patient questionnaire) as

Table 2. Comparison of Data for Puregraft and Centrifuge-Processed Grafts[a]

Technique	No. of Cases	Age, Mean (SD), y	Follow-up, Mean (SD), mo	Retention, Mean (SD), %	*P* Value (Welch's *t* Test)
Centrifuge (historical controls)	66	54 (8)	16 (2.3)	31.8 (20.3)	.03
Puregraft	52	55 (11)	17 (6.8)	41.2 (24.4)	

Abbreviation: SD, standard deviation.
[a]Data from Meier et al.[2]

Table 3. Comparison of Long-Term Retention by Age Group

Age Group	Hemi-Midface Cases, n	Mean Follow-up, mo	Retention, Mean (SD), %	*P* Value (Welch's *t* Test)
<55 y	24	18	53.0 (27.8)	.001
>55 y	28	17	31.1 (15.4)	

Table 4. Comparison of Long-Term Retention in Patients With and Without Concurrent Rhytidectomy.

Rhytidectomy	Hemi-Midface Cases, n	Mean Age, y	Mean Follow-up, mo	Retention, Mean (SD), %	*P* Value (Welch's *t* Test)
Without rhytidectomy	38	52	18	47.6 (24.7)	<.0001
With rhytidectomy	14	62	16	23.8 (12.9)	

well as objective methods (review of preoperative and postoperative photographs) were used to compare mean 12-month retention rates in a split-face paradigm of fat processed by centrifuge vs fat filtered through a metal strainer and washed in saline. Results showed no significant difference between the 2 techniques.

Findings of the present study showed a mean retention rate of 41.2% for fat processed with Puregraft. This is significantly better than the 31.8% retention noted in our study of centrifuged fat.[2] The increased retention is consistent with an in vitro study[4] and our hypothesis that purer fat grafts with less contamination lead to increased retention of graft volume.

We also examined intrinsic factors relating to long-term retention. We were able to demonstrate that older age (> 55 years) negatively affects retention rates. The exact mechanism of autologous fat engraftment has yet to be elucidated, but the presence of growth factors, cytokines, and viable MSC likely play pivotal roles in the process. Investigation of MSC has shown that they elicit immunomodulatory,[8-13] antimicrobial,[14] proliferative,[15,16] and angiogenic effects,[15,17,18] all of which are important for wound healing and engraftment of adipose tissue. However, MSC function is age dependent, and old MSC take longer to replicate[19-21] and are slower to differentiate.[22,23] These findings support our data wherein older patients experienced poorer graft retention, suggesting that this may relate to decreased stem cell function. Although we also found a significantly lower retention rate among patients who underwent rhytidectomy concurrently, this cohort comprised only 7 patients, and of these, all were significantly older than most patients in the study. To further elucidate the relationship between concurrent rhytidectomy and autologous fat retention, a larger sample size with age-matched controls should be analyzed.

Other limitations of this study include using a historical control group rather than randomly allocating patients to each study arm. The size of our historical control group was slightly larger than the Puregraft study group (33 vs 26, respectively). However, the mean age and mean follow-up period were similar for the 2 study populations. Another shortcoming is the lack of data on body mass index throughout the study. Several patients were excluded from the study due to volume changes in untreated areas, thought to result from body weight changes. However, some changes in body weight might have been small enough to obscure a significant volume change outside the treatment area yet large enough to have affected measurements within the treatment area. Other intrinsic factors that can transiently affect volume measurements include fluid retention, timing of menstrual cycle, oral contraceptives, menopausal status, and hormone replacement therapy. Emmerson et al[24] have shown that estrogen positively affects wound healing, and therefore, menopausal status may in part account for the decreased volume retention in older patients. Future research could potentially include these variables to help stratify the cohort and improve our understanding of the relationship between intrinsic factors and graft retention. We did observe a "rebound" effect for volume retention, with the lowest being in the 6- to 9-month range and increasing thereafter. However, the differences were not significant ($P = .06$). A larger sample size and multiple time points for all patients may demonstrate a true rebound trend. Further investigation into MSC

function and cytokine levels at different time points of engraftment with age-matched controls may shed some light on the mechanism of this phenomenon. Other areas of interest include processing yield and volume injected, as well as their impact on long-term retention. Although our findings were not statistically significant, retention was greater when the processing yield was higher. This may indicate that those grafts possessed superior viability. Clearly, a larger sample size is needed to ascertain whether this is effect is real.

Larger volume (> 8 mL) was associated with a higher mean percentage retention in the Puregraft cohort, but this difference was not statistically significant. In our previous study (centrifuged fat),[2] the mean volume of injected fat was 10.1 mL, but overall retention was significantly lower than in the present study (Puregraft-processed fat). The effect of injection volume on retention remains unclear, and further investigation is warranted.

Our data collection technique also contains inherent limitations. The Vectra 3D camera system contains multiple cameras that are placed at different angles on the patient's face. The acquired images are reconstructed as a 3D "mask" of the patient's face. Once a reference image is chosen and registered (with several landmarks or surface areas on the mask deemed to be static from one image to the next), volume changes in subsequent images can be measured. As in any imaging study, this is an *indirect* measure of volume change. In animal studies, the fat graft is excised and weighed to determine retention.[4,5] Since this is not feasible in human studies, image-based measures are employed. Magnetic resonance imaging (MRI) is an alternative imaging method to 3D photography that has been used for volumetric measurements in several studies.[25-27] Unfortunately, MRI is expensive, time-consuming, and not easily accessible, especially in the outpatient setting.

Vectra 3D software is a relatively inexpensive, accessible option. However, the accuracy of the software's measurements is user dependent. If the follow-up image is not properly registered to the baseline (preoperative) image, errors in volume measurement can be introduced. An improper registration usually can be detected from unilateral volume changes in bony areas, such as the nose or forehead. This would indicate a tilt to one side or the other, which would falsely augment the volume change on one side of the face and falsely decrease it on the other side. Improper registration also can be detected when volume changes are noted throughout the vertical length of the face. For example, the distance color map may show that the forehead has lost volume, whereas the chin has gained volume, or vice versa. Recognizing these patterns is crucial to obtaining proper registration and thus reliable volume measurements. In most of this study's cases, we detected differences in retention between the sides of the face (see Results). This cannot be explained by errors in measurement, because these differences were consistent for several images and time points. More likely causes of these differences are local variations in edema and graft resorption.

To our knowledge, there has been no study of the accuracy of Vectra 3D software vs more direct measures. Regardless, the Vectra 3D system provided a very effective means of capturing data on volume retention in our study population. Future studies should compare the various imaging modalities with direct measurement (eg weighing grafted fat).

CONCLUSIONS

Autologous fat grafting is widely employed to increase facial volume. It is inert and readily available, and donor-site morbidity is low. Long-term retention is achievable, as evidenced by our results, but remains somewhat unpredictable. It appears that the closed-membrane filtration system improves overall retention. However, in the effort to improve predictability, further studies are needed to investigate intrinsic factors that may affect engraftment.

Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding

The authors received no financial support for the research, authorship, and publication of this article.

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