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Facial Surgery

Review Article

Supplementation of Facial Fat Grafting to Increase Volume Retention: A Systematic Review

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Jan Aart M. Schipper, MD; Linda Vriend, MD; Aartje J. Tuin, MD, DMD, PhD; Pieter U. Dijkstra, PT, MT, PhD; Rutger H. Schepers, MD, DMD, MSc, PhD; Berend van der Lei, MD, PhD; Johan Jansma, MD, DMD, MSc, PhD, FEBOMFS; and Martin C. Harmsen, PhD

Abstract

Background: For decades, facial fat grafting has been used in clinical practice for volume restoration. The main challenge of this technique is variable volume retention. The addition of supplements to augment fat grafts and increase volume retention has been reported in recent years.

Objectives: The aim of this systematic review was to investigate which supplements increase volume retention in facial fat grafting as assessed by volumetric outcomes and patient satisfaction.

Methods: Embase, Medline, Ovid, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar were searched up to November 30, 2020. Only studies assessing volume after facial fat grafting with supplementation in human subjects were included. Outcomes of interest were volume or patient satisfaction. The quality of the studies was assessed with the Effective Public Health Practice Project tool.

Results: After duplicates were removed 3724 studies were screened by title and abstract. After reading 95 full-text articles, 27 studies were eligible and included for comparison. Supplementation comprised of platelet-rich plasma, platelet-rich fibrin, adipose tissue–derived stromal cells or bone marrow–derived stromal cells, cellular or tissue stromal vascular fraction, or nanofat. In 13 out of 22 studies the supplemented group showed improved volumetric retention and 5 out of 16 studies showed greater satisfaction. The scientific quality of the studies was rated as weak for 20 of 27 studies, moderate for 6 of 27 studies, and strong for 1 study.

Conclusions: It remains unclear if additives contribute to facial fat graft retention and there is a need to standardize methodology.

Level of Evidence: 4

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Dr Schipper is a medical doctor and Dr Harmsen is a professor of cardiovascular regenerative medicine, Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. Dr Tuin is an oral and maxillofacial surgeon in training and Drs Schepers and Jansma are oral and maxillofacial surgeons, Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. Dr Vriend is a medical doctor and Dr van der Lei is a professor, Department of Plastic and Reconstructive Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. Dr Dijkstra is a professor, Department of Rehabilitation Medicine, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Corresponding Author:
Dr Martin C. Harmsen, Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Hanzeplein 1-EA11, 9713 GZ Groningen, the Netherlands.
E-mail: m.c.harmsen@umcg.nl

Fat grafting has been performed in clinical practice since the end of the 19th century.[1] It has been used to restore volume loss due to trauma, aging, congenital defects, or for aesthetic reasons, predominantly in the face, breasts, and buttock. Facial fat grafting can be performed easily, safely, and with minimum donor-site morbidity and complications.[2] However, not all transplanted tissue is retained at the acceptor site. Long-term volume retention rates vary widely between 25% and 80%.[3-5] Additionally, multiple surgical procedures are often required to obtain the desired volume.

Lipografting is a form of tissue transplantation, albeit of fragmented adipose tissue. These fragments consist of multiple large lipid-laden adipocytes that are structurally supported by connective tissue and perfused with a highly developed microvasculature. Adipocytes are about 4-fold less numerous than stromal vascular cells, yet comprise about 90% of the total volume of fat.[6] Upon transplantation (ie, fat grafting), the survival and regeneration of adipocytes are pivotal to retaining the grafted volume.[7] Ischemia may cause apoptotic loss of adipocytes, and thus suppression of apoptosis in fat grafts might improve graft volume retention. For graft survival, it is essential to form a rapid connection between local vasculature and capillaries that literally stick out from the tissue clumps in the fat graft. Thus angiogenic stimulation by fat graft supplements is warranted. Any adipocytes lost from ischemic insult require replenishment through proliferation of preadipocytes (adipose tissue–derived stromal cells [ASCs]) and their differentiation and maturation into adipocytes, which would be supported by promitogenic factors in supplements. Finally, metabolic maintenance is important because adipocyte volume, ie, the storage of the high-energy triglycerides, varies with the body's metabolic demand. Weight loss is associated with loss of adipocyte volume and consequently with reduced graft volume.[8] Although repeated fat grafting does build up sufficient volume, this is an undesirable burden for the patient. Therefore, supplements that augment suppression of apoptosis, stimulate proliferation, and enhance angiogenesis are desired. In clinical applications, the cellular fate of grafted fat is usually not assessed, yet this does not preclude investigation of the influence of supplements on graft volume.

To increase graft retention, supplementation with several autologous components has been investigated. Blood-derived products, eg, platelet-rich plasma (PRP) and platelet-rich fibrin (PRF),[9,10] are a source of concentrated platelets, growth factors, and cytokines which could induce better graft retention by promoting angiogenesis and reducing apoptosis.[11] Adipose tissue–derived components, eg, ASCs, cellular and tissue stromal vascular fraction (cSVF, tSVF),[12,13] and nano- and microfat,[14-16] have shown proangiogenic action through paracrine factors which could induce better graft vascularization, reduce apoptosis, and increase proliferation.[17,18] Furthermore, enzymatic cell-assisted lipografting made addition of cSVF or cultured ASC to fat grafting popular.[4, 19-20] However, because cell-assisted lipografting requires enzymatic digestion of SVF and the use of animal-derived enzymes such as collagenase it is restricted by legislation in many countries,[21] and hence new nonenzymatic, fast, intraoperative, mechanical dissociation procedures have been developed to produce tSVF.[22,23] PRP or PRF are also easily obtained by centrifugation of blood with or without anticoagulant.[24] These supplementations are believed to improve retention through either increased survival of the grafted cells by reducing/preventing cell apoptosis, or by restoring hypertrophy or increasing vascularization at the injection site.

Currently, the number of clinical studies investigating supplemented fat grafting is increasing rapidly, and multiple new supplementation therapies are being developed.[25] These developments warrant systematic evaluation of the clinical available evidence. The current systematic reviews on fat graft supplementation are heterogeneous because they include human and animal studies for various indications.[26,27] The aim of this systematic review was therefore to investigate the efficacy of human facial fat grafting based on quantitative volumetric outcome measures and patient satisfaction assessments.

METHODS

Protocol and Registration

This manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[28] The study was registered in Prospero (register code: CRD42020179975).

Search Strategy and Information Sources

A systematic literature search was conducted in the electronic medical databases Embase (Elsevier, Amsterdam, the Netherlands), MEDLINE (National Library of Medicine, Bethesda, MD), Ovid (Wolters Kluwer, Alphen aan den Rijn, the Netherlands), Web of Science Core Collection (Clarivate Analytics, London, UK), Cochrane Central Register of Controlled Trials (CENTER; London, UK), and Google Scholar (Google, Mountain View, CA) from inception to November 30, 2020. Search strategy was based on the PICO (population, intervention, comparison, outcome) framework and combined terms related to fat graft transplantation (ie, lipofilling, fat transplantation, adipose tissue transplantation, adipose tissue grafting, volume retention) plus a supplementation therapy (ie, PRP, ASCs, SVF, nanofat, microfat).[29] In databases where a thesaurus was available (Embase and MEDLINE), papers were searched by thesaurus terms and by title and/or abstract.

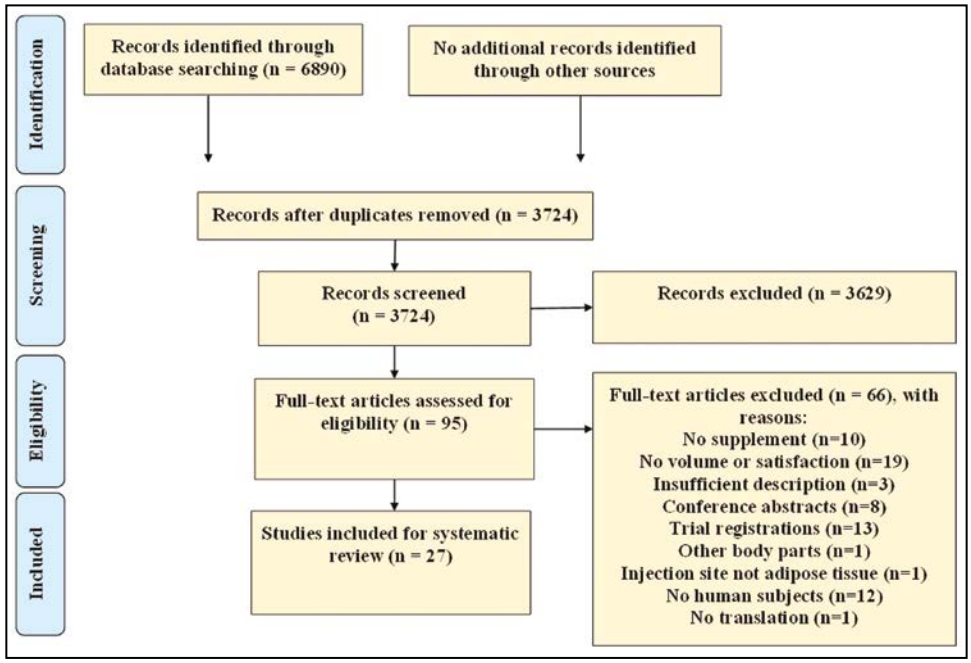

Figure 1. Flow diagram of study selection.

The searches were adapted corresponding to each database (Supplemental Table 1, available online at www.aestheticsurgeryjournal.com, and Figure 1). Reference lists of included studies were analyzed to identify relevant studies missed in the searches.

Eligibility Criteria

Studies were included if they clinically evaluated the effects of fat grafting in combination with a supplement, for instance the addition of PRP, ASCs, or SVF, on volume restoration in the face or patient satisfaction. Only studies injecting in the adipose tissue plane in the face were included. Studies were excluded when no volumetric outcome was reported, as were studies reporting on other body parts than the face only. If studies described multiple body parts and data of the face were separately described, the study was included. (Systematic) reviews, case studies, conference abstracts, letters to the editor, and animal and in vitro studies were also excluded. No publication date restriction was applied.

Study Selection and Data Collection Process

Two reviewers (J.S., L.V.) independently assessed titles, abstracts, and full texts. Disagreement between reviewers was discussed until consensus was reached. In the case of persistent disagreement, a senior author (M.H.) gave a binding verdict.

Data Extraction

All data were extracted by the same 2 reviewers and consisted of 5 categories: study characteristics, treatment characteristics, complications, volumetric assessment of fat graft (retention), and patient satisfaction.

Complications were categorized as minor (erythema, mild edema, hematoma, local pain at incision site, and oily cyst) and major complications (infection, tissue loss, skin necrosis, fibrosis, severe edema, pain spreading beyond injection site, cellulitis, fat embolus, and embolus causing blindness). For supplemented fat grafting therapy, data outcomes of interest were time between harvesting and injection, injected volumes, supplement dosing, cell yield or PRP concentration, isolation procedures, repeated treatments, and characterization of supplementation therapy. For volumetric outcomes, data from objective and subjective volume measurement tools and follow-up points were extracted. When studies reported fat graft resorption as an outcome measure, retention was calculated as inverse resorption (100% – x%). For each volume retention reported, a fold-change was calculated (% supplemented fat divided by % fat). A difference was reported when there was a statistically significant difference ($P < 0.05$).

Risk of Bias in Individual Studies

The 2 reviewers independently assessed risk of bias with the Effective Public Health Practice Project tool (EPHPP).[30] This tool enables quality assessment of different types of

study design. Studies were given an overall final rating as strong, moderate, or weak based on ratings of study design, selection bias, confounders, data blinding, data collection, and dropouts. According to the EPHPP tool, "strong studies" had no weak rating, "moderate studies" had 1 weak rating and "weak studies" had 2 or more weak ratings.

RESULTS

Study Selection

In total, 3724 studies were identified. After title and abstract screening, 95 studies remained for full-text assessment of eligibility criteria (Figure 1). A total of 27 studies were included; 68 studies were excluded for the following reasons: 10 studies were excluded because the fat graft was not supplemented;[23,31-39] 19 studies were excluded because fat graft retention was not assessed by volumetric or patient satisfaction measurements;[40-59] 3 studies were excluded because the study methods or intervention were not evaluable due to insufficient description;[60-62] 8 studies were excluded because these were conference abstracts;[63-69] 13 studies were excluded because these concerned trial registrations;[70-82] 1 study was excluded because the supplementation therapy was not carried out in the face, but in other body parts;[83] in 1 study the injection site was not adipose tissue but product was injected within the muscles of the face (facial muscular plane);[84] 12 studies were excluded because they did not describe human subjects or clinical results;[85-95] no translation of 1 study was available (Russian).[96]

Study Characteristics

The studies included were published between 2008 and 2020 (Table 1). Follow up ranged from 6 to 60 months and a total of 1117 participants were described in the studies (range, 6 to 236 per study). The mean age of the participants ranged between 6 and 61.5 years old and 73% of all patients were female (range, 33%-100%). Five studies had a female sex bias due to the inclusion of female participants only.[97-101] Eight studies reported mean BMI, which ranged from 17 to 32 kg/m^2. Indications for supplemented fat grafting were with underlying pathology (48%) or cosmetic (without underlying pathology) with (19%) or without facelift (33%). Indications with underlying pathology were craniofacial deformity (31%), scars (23%), (hemi)facial lipoatrophy (15%), Parry-Romberg syndrome (15%), or a combination of these indications (15%). The majority (13/27) of the studies supplemented fat grafts with PRP/PRF. Three studies reported multiple supplements.[102-104] Studies were categorized by type of supplement (PRP, SVF, and cellular components) for analysis of supplement characteristics, volumetric, and patient satisfaction outcomes (Supplemental Table 2, available online at www.aestheticsurgeryjournal.com, and Tables 2, 3).

Study Design and Quality

Study designs included randomized controlled trials (n = 6),[67,99,101,105-107] controlled trials (n = 6),[4,19,108-111] cohort studies (2 groups with pre- and posttreatment evaluation, n = 6),[34,103,104,108,112,113] cohort studies (1 group with pre- and posttreatment evaluation, n = 8)[98,100,114-119] and a retrospective study (n = 1)[45] (Table 4). Confounding factors were not controlled for in 8 studies.[42,44,108,110,114,116-118] The reliability and validity of outcome measurements were weak in 12 studies.[4,19,44,67,105,108,110,113-116,119] Four studies reported dropouts and reported the number of participants who completed the follow up.[101,105,107,118] Based on the EPHPP guidelines, 20 studies had an overall final rating of weak, 6 studies were rated as moderate, and only 1 study was rated as strong (4%).[106] Data pooling and meta-analysis was not possible due to heterogeneity across studies in terms of clinical features, eg, population characteristics, indications, supplementation strategies, and additional interventions (facelift, additional injections), and methodologic characteristics, eg, assessment tools, study design, and follow up.

Characteristics of Supplementation Strategies

The mean injected total volume ranged from 6.8 to 100 mL. The volume-to-volume ratio of PRP-to-fat ranged from 1:2 to 1:9. In SVF-supplemented therapies, 2 out of 14 studies reported the ratio of supplementation. Repeated supplemented fat graft injections were performed in 11 studies and concerned merely supplementation with SVF and cellular components.[19,34,108-113,115,117,118] A minority of studies reported supplement concentrations: platelet concentration in PRP or PRF was 0.8×10^9 to 3.6×10^9/mL (mean [standard deviation], 2.6 [1.3] $\times 10^9$/mL), and the number of nucleated cells in cSVF or tSVF was 0.3×10^5 to 100×10^5 cells.[112,107,109] Some studies reported a concentration range of fat-supplemented therapy and the single addition of bone marrow–derived stromal cells (BMSCs) ranged from 3 to 86×10^8 at a volume ratio of 2:1 of BMSC:fat graft.[113] Most studies performed intraoperative isolation procedures of the supplementation therapy. Two studies cultured ASCs for 14 days[109] and 14 to 28 days[34] before supplementing fat grafts but the volume ratio was not reported.[34,109] Only 4 studies reported the lag time between preparation of supplements to administration to the patient or the time (range) to prepare the supplements.[106,108-110] Three studies described the characterization of supplements; nanofat plus PRF, ASCs, cSVF.[19,106,109] The shared joint analyzed markers included expression of mesenchymal cell markers (CD73, CD90, and CD105) albeit that these are not restricted to mesenchyme, integrin β1 (CD29), and the absence of leukocyte markers (CD45).

Table 1. Study Characteristics

Author (year)	Design	Follow up (months)	Indication	Pathology[a]	Injection site	Total (n)	Age[b] (years)	Female (n)	BMI (kg/m^2)	Comorbidities	Intervention (fat +)	Intervention (n)	Control	Control (n)	Minor complications	Major complications
Bashir et al 2019	C2G	6	UP	Hemifacial atrophy, craniofacial microsomia, posttraumatic and postinfective deformity	NR	37	24.9 [8.1]	28	NR	NR	cASC	16	Fat	21	"Most patients"	Both in control and intervention group: 6% cellulitis
Bernardini et al 2015	C1G	12	C + FL		Brows, upper sulcus, inferior orbit hollow, tear trough, perioral area, malar and zygomatic areas, lips, chin, temporal fossa	98	51	92	NR	NR	PRP	98	—	—	4%	3% of patients oil cyst, 1 case requiring surgical removal
Castro-Govea et al 2018	C1G	18	UP	Craniosynostosis	Forehead	12	6	8	NR	NR	cSVF	12	—	—	0	0
Cervelli et al 2009	RC	18	UP	Scars, Parry-Romberg, hemifacial atrophy, mandibular cyst	Zygomatic region, cheek, buccal rim, upper and lower eyelid, temporal area, orbital area	25	NR	NR	NR	Diabetes, hypertension, nasal polypus, neurologic disease, arteriopathy, cardiologic disease, dislipidemy, trauma	PRP	19	Fat	10	0	0
Chang et al 2013	CCT	18	UP	Hemifacial atrophy	NR	20	27.5	12	NR	—	cSVF	10	Fat	10	0	0
Fontdevila et al 2014	RCT	12	UP	HIV lipoatrophy	Cheeks	49	46.3 [7.4]	16	24.3 [3.2]	Diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, fibrates/statin/antidepressant/anxiolytic/antidiabetic drug use	PRP	20	Fat	29	0	0
Gennai et al 2017	C1G	6	C + FL		Periocular, perioral area	65	49.7	58	NR	NR	PRP	65	—	—	0	0
Gentile et al 2014	C2G	12	UP	Burns, posttraumatic scars	NR	20	NR	10	NR	NR	cSVFPRP	1010	Fat	10	0	0
Gentile et al 2020	C2G	60	C		Zygomatic/cheek region, lower orbital area, nasolabial fold, lips	63	42.1[d]	63	27 (21-33.16)	—	tSVF	33	Fat	30	Intervention group: 9%; control group: 13%	0
Gu et al 2018	C1G	6	UP	Scars	NR	20 (25 scars)	38.3	14	NR	—	tSVF	25	—	—	NR	NR
Hesamirostami et al 2019	C1G	30	C		Forehead	56	40.2	52	NR	NR	PRP	56	—	—	0	0
Jianhui et al 2014	C2G	12	UP	Parry-Romberg	NR	36	24.3 [6.6][d]	25	NR	NR	Intraoperative BMSC	10	Fat	26	0	0

Table 1. Continued

Author (year)	Design	Follow up (months)	Indication	Pathology[a]	Injection site	Total (n)	Age[b] (years)	Female (n)	BMI (kg/m^2)	Comorbidities	Intervention (fat +)	Intervention (n)	Control	Control (n)	Minor complications	Major complications
Keyhan et al 2013	RCT[c]	12	C		Cheek, cheekbone area	25	45	17	NR	—	PRP	25[c]	Fat/PRF	25[c]	0	0
Koh et al 2012	CCT	15	UP	Parry-Romberg	NR	10	28	5	NR	—	cASC	5	Fat	5	0	0
Lee et al 2012	C1G[c]	11	C + FL		Malar eminence, infraorbital region, nasolabial fold	9	43.3	6	NR	NR	cSVF	9[c]	Fat	9[c]	0	0
Li et al 2013	C2G	6	NRG		Temporal, cheek, facial asymmetry	38	29.4 [6.6][d]	38	NR	NR	cSVF	26	Fat	12	"Most patients"	0
Ozer et al 2019	C1G	9	C		NR	14	44.9 [11.9]	14	NR	NR	PRP	14	—	—	0	0
Sasaki et al 2015	C2G	12	C + FL		Midface	236	61.5[d]	227	22.2 (16.9-32.3)[d]	—	PRP cSVF cSVF/PRP	106 929	Fat	92	"All patients"	0
Sasaki et al 2019	RCT[c]	12	C + FL		Midface	10	54.4	10	22.4 (20.5-24.6)	—	PRP	10[c]	Fat/saline	10[c]	"All patients"	0
Schendel et al 2015	C1G	17	C		Temples, malar areas, forehead/glabella, eyelid area, lips, chin	10	51.6 [9.6]	10	NR	NR	cSVF	10	—	—	0	0
Sterodimas et al 2011	CCT	18	UP	Several congenital or acquired facial tissue defects	NR	20	45.1[d]	10	21.6[d]	Smoking, hypertension, diabetes, COPD	cSVF	10	Fat	10	"Most patients"	Control group: 10% infection
Tanikawa et al 2013	RCT	6	UP	Craniofacial microsomia	NR	14	15.4 [5.6][d]	9	<25	NR	cSVF	7	Fat	7	"All patients"	0
Tenna 2017	CCT	6	UP	Acne scars	Cheeks	30	NR	NR	NR	—	Fat/PRP/laser	15	Fat/PRP	15	NR	NR
Wei et al 2017	CCT	24	C		Tempora, geisoma, frontal part, palpebra sup inf, lacrimal groove, zygoma, cheeks, nasolabial groove, chin, marionette lines, submaxilla	139	28.5	NR	NR	NR	Nanofat/PRF	62	Fat	77	0	0
Willemsen et al 2018	RCT	12	C		Temporal, midface, nasolabial fold, marionette lines, prejowling, chin	25	52.1 [6.8]	32	(20-25)	NR	PRP	13	Fat/saline	12	0	0
Yin et al 2020	RCT	50	C		Forehead, temporal, cheek/zygomatic, nasolabial fold	50	35.4 [8.2][d]	50	21.4 [1.9][d]	—	cSVF	25	Fat	25	0	0

Table 1. Continued

Author (year)	Design	Follow up (months)	Indication	Pathology[a]	Injection site	Total (n)	Age[b] (years)	Female (n)	BMI (kg/m^2)	Comorbidities	Intervention (fat +)	Intervention (n)	Control	Control (n)	Minor complications	Major complications
Yoshimura et al 2008	CCT	13	UP	Parry-Romberg and lupus lipoatrophy	NR	6	42.5 [8.0][d]	4	NR	NR	cSVF	3	Fat	3	"All patients"	Control group: 33% necrotized tissue requiring surgical removal

Where indicated, values are mean [standard deviation] or mean (range); NR, not reported; COPD, chronic obstructive pulmonary disease. Study design: RCT, randomized controlled trial; CCT, controlled clinical trial; Cohort 2G, cohort study (2 groups, pre- + postoperative); Cohort 1G, cohort study (1 group pre- + postoperative); Retrospective, retrospective study. Indication: UP, underlying pathology, meaning with underlying disease, trauma, or congenital volume loss; C, cosmetic, meaning with no underlying pathology or facial disease, such as fat grafting for facial rejuvenation; C + FL, cosmetic with concomitant facelift. Enrichments, PRP, platelet-rich plasma; PRF, platelet-rich fibrin; cSVF, cellular stromal vascular fraction; tSVF, tissue stromal vascular fraction; cASC, cultured adipose-derived stromal cell; BMSC, bone marrow–derived stromal cell. [a]In the cosmetic group, there is no pathology present (ie, facial rejuvenation). [b]When decimals are reported, these are rounded to 1 decimal place. [c]Split-face design: in the studies using a split-face design: the patients themselves serve as both intervention group (one half of the face) and control group (the other half of the face). [d]When data are presented per group, the pooled value is calculated. —, not present in the study reported (eg, no control group was present or no complications occurred in the study).

Influence of Supplementation Therapies on Fat Graft Retention

Twenty studies assessed volume retention of supplemented fat grafts after 3 to 36 months, of which 3 studies reported multiple supplementation groups (PRP/cSVF, PRP/cSVF/PRP + cSVF, PRP/tSVF).[102-104] Volume was measured by computed tomography (CT), MRI, 3-dimensional (3D) surface imaging, ultrasound, visual 2D photograph assessment, numeric rating scale (NRS), or Likert scale. Seven studies used 3D surface imaging to assess fat graft retention. Volume measurement methods were often not validated and details of volumetric measurements were often not described, or described too briefly to allow for reproduction of studies.

Out of the 9 studies in which the graft was supplemented with PRP, 2 showed a difference between groups.[103,120] One study showed a 30% increase of volume compared to the control, ie, conventional fat grafting.[103] The other study showed a difference of 5% less retention in the PRP group compared to the control group, in which PRF was used as a control.[120] In 4 out of 9 PRP studies there was no difference between groups.[99,101,105,111] In the other 3 studies no statistical tests were performed or could not be performed due to the absence of controls.[45,104,114]

The 2 studies investigating supplementation of culture-expanded ASCs both showed a difference when compared with the conventional fat graft.[34,109] The volume retention varied from 1.5-fold higher[109] to 3-fold higher.[34] Seven out of 9 studies with cSVF as supplement showed a statistically significant increased volume compared with the conventional fat graft (1.2- to 1.9-fold).[97,103,104,106-108,119] Two studies showed no increased volume. One study without a control group reported a retention of 68%.[100] In 1 study no difference between groups was found. Only 6 patients were included in that study and surgeons assessed volume visually from 2D photographs.[4]

One study investigating tSVF supplementation showed improved outcomes.[112] A 2-fold increase in volume in the supplemented group was found, but the measurement methods on MRI were not described.[112] The only study describing PRP and cSVF mixed as a supplement showed significantly increased volume retention (70%).[103] However, the mix of PRP and cSVF did not result in additional volume increase compared with cSVF (73%) or PRP (69%) alone.

Influence of Supplementation Therapies on Patient Satisfaction

Patient satisfaction or patient-reported outcome measures (PROMs) are considered the key outcome measurement of facial aesthetic procedures.[121] Validated and reliable outcome measures, eg, the FACE-Q questionnaire, are readily available.[122,123] Sixteen studies assessed patient satisfaction with the FACE-Q, the Patient and Observer Assessment Scale (POSAS), the Global Aesthetic Improvement Scale (GAIS), a visual analog scale (VAS), the Likert scale, or an NRS. The FACE-Q, GAIS, and POSAS are the only validated outcome measures and were used in 4 studies only.

To evaluate the differences in patient satisfaction between procedures in a controlled trial, the satisfaction for both the intervention and the control group should be evaluated and statistically tested for differences. Nine studies performed these "between-group" comparisons,

Table 2. Volume Outcomes

Author (year)	Outcome assessment	Follow up (months)	Intervention % retention	Control % retention	Fold change	Difference in retention[b] (intervention compared with control)
PRP/PRF						
Bernardini et al 2015	VA of volume	6	Good result (63%), excellent result (37%)	—		–
Cervelli et al 2009	VA of volume	18	65%	26%	2.5	—
Fontdevila et al 2014	CT	12	NR	NR		−0.3 mL (−1.1 to −0.5 mL)[a] (NS)
Gentile et al 2014	MRI	12	69%	39%	1.8	-
Keyhan et al 2013	Linear measurements of photographs	12	82% (PRP)	87% (PRF)	ND	5% ↑ (PRF) ($P < 0.05$)
Sasaki et al 2015	3D SI	12	69% [40%]	38% [13%]	1.8	31% ↑ ($P < 0.01$)
Sasaki et al 2019	3D SI	12	24% [10%]	21% [1%]	1.1	3% ↑ NS
Tenna et al	US	12	0.7 cm improvement	0.6 cm improvement	1.1	0.1 cm ↑ NS
Willemsen et al 2018	VA of nasolabial fold	12	NR	NR	ND	NS
ASCs						
Bashir et al 2019	US	6	95% [4%]	31% [13%]	3.1	64% ↑ ($P < 0.001$)
Koh et al 2012	3D SI	6	79%	53%	1.5	26% ↑ ($P = 0.002$)
cSVF						
Chang et al 2013	CT	6	68% [2%]	59% [1%]	1.2	10% ↑ ($P < 0.001$)
Gentile et al 2014	MRI	12	63%	39%	1.6	24% ↑ ($P < 0.0001$)
Lee et al 2012	NRS (1-10)	3	Malar eminence 7 (6-8) Infraorbital region 7 (6-9) Nasolabial fold 8 (7-9)[c]	Malar eminence 6 (5-7) Infraorbital region 6 (5-6) Nasolabial fold 6 (5-8)[c]	Malar 1.2 Infraorbital 1.2l Nasolabial 1.3	Malar eminence 1 ↑ ($P = 0.015$) Infraorbital region 1 ↑ ($P = 0.010$) Nasolabial fold 2 ↑ ($P = 0.017$)
Li et al 2013	CT	6	65% [10%]	46% [9%]	1.4	18% ↑ ($P < 0.01$)
Sasaki et al 2015	3D SI	12	73% [50%]	38% [13%]	1.9	35% ↑ ($P < 0.01$)
Schendel et al 2015	3D SI	12	68%	—	ND	—
Tanikawa et al 2013	CT	6	88% [13%]	54% [20%]	1.6	34% ↑ ($P = 0.002$)
Yin et al 2020	3D SI (handheld)	6	78% [12%]	56% [10%]	1.4	21% ↑ ($P < 0.001$)
Yoshimura et al 2008	LS (1-4)	12	NR	NR	ND	NS

Table 2. Continued

Author (year)	Outcome assessment	Follow up (months)	Intervention % retention	Control % retention	Fold change	Difference in retention[b] (intervention compared with control)
tSVF						
Gentile et al 2020	MRI	36	61% [5%]	31% [5%]	2	30% ↑ ($P < 0.0001$)
PRP + cSVF						
Sasaki et al 2015	3D SI	12	70% [35%]	38% [13%]	1.8	31% ↑ ($P < 0.01$)

Where indicated, values are mean [standard deviation] or (range). —, no test was performed, or no quantification was described; NR, not reported; NS, not significant. Outcome assessment: NRS, numeric rating scale; US, ultrasound; CT, computed tomography; LS, Likert scale; VA, visual assessment; SI, surface imaging. Supplements: PRP, platelet-rich plasma; PRF, platelet-rich fibrin; cSVF, cellular stromal vascular fraction; tSVF, tissue stromal vascular fraction; ASC, adipose-derived stromal cell; BMSC, bone marrow–derived stromal cell. [a]Fontdevila et al described no separate intervention or control volume. Only a difference between groups with a range was described. [b]Difference is described in absolute percentage points; however, for the readibility of this table we have used the percentage sign %. Differences are based on the original (not rounded) data, which means rounding errors can be present. [c]Lee et al described surgeon-rated volume consistency based on a numeric rating scale. [d]Gu et al described the thickness using the POSAS questionnaire. The specific question about thickness is extracted.

Table 3. Patient Satisfaction Outcomes

Author (publication year)	Outcome assessment	Follow up (months)	Comparison[a]	Comparison with preoperative photographs	Satisfaction intervention	Satisfaction control	Difference in satisfaction (intervention compared with control or postoperative compared with preoperative)
PRP/PRF							
Gennai et al 2017	LS (1-4)	6	Within-group outcome	Yes	Fair to good effect (2.6)	—	—
Gentile et al 2014	LS (1-6)	12	Within-group outcome	Yes	nr	—	—
Hesamirostami et al 2019	GAIS	12 (6-30)	Within-group outcome	Yes	Moderate to excellent improvement, 7% poor improvement.	—	—
Ozer et al 2019	FACE-Q	9	Within-group change	—	Improved from 28.4 [23.3] to 90.3 [17.5]	—	61.9 ↑ ($P < 0.001$)
Tenna et al 2017	FACE-Q	6	Between-group outcome	No	84%[b]	81%[b]	NS
Willemsen et al 2018	VAS (1-10)	6	Between-group outcome	No	NR	NR	NS
ASCs/BMSCs							
Bashir et al 2019	LS (1-5)	6	Between-group outcome	Yes	4.3 [0.7]	2.5 [0.5]	1.8 ↑ NSR
Jianhui et al	LS (1-3)	NR	Between-group outcome	No	NR	NR	—
Koh et al 2012	VAS (1-5)	NR	Between-group outcome	No	4.5	3.1	1.4 ↑ NSR
cSVF							

Table 3. Continued

Author (publication year)	Outcome assessment	Follow up (months)	Comparison	Comparison with preoperative photographs	Satisfaction intervention	Satisfaction control	Difference in satisfaction (intervention compared with control or postoperative compared with preoperative)
Castro-Govea et al 2018	LS of parents (1-5)	18	Within-group outcome	No	67% of the parents were satisfied and 33% were slightly satisfied	—	—
Lee et al 2012	NRS (1-10)	3	Between-group outcome	Yes	Malar eminence 7 (6-8) Infraorbital fold 8 (7-9) Nasolabial fold 8 (7-9)[a]	Malar eminence 6 (5-8) Infraorbital fold 6 (5-7) Nasolabial fold 7 (5-8)[a]	Malar eminence 1 ↑ ($P = 0.008$) Infraorbital fold 2 ↑ ($P = 0.010$) Nasolabial fold 1 ↑ ($P = 0.011$)
Sterodimas et al 2011	LS (1-5)	18	Between-group outcome	No	4.0 [b]	4.0 [b]	0 NS
Yin et al 2020	LS (1-5)	6	NR	No	—	—	—
tSVF							
Gentile et al 2020	LS (1-6)	NR	Between-group outcome	No	91% fully satisfied and 9% not fully satisfied	37% fully satisfied and 63% not fully satisfied	($P = 0.031$)
Gu et al 2018	POSAS	12	Within-group change	Yes	Preoperative 28.8 [1.0] vs postoperative 12.2 [0.8]	—	16.6 ↓ ($P < 0.001$)[d]
Wei et al 2017	nr	24	Between group outcome	No	90%	70%	20% ↑ ($P < 0.01$)

Where indicated, values are mean [standard deviation] or (range). NR, not reported; NS, not significant; NSR, no significance reported, no statistical test was performed/reported; —, no quantification, no intervention or control group present or no statistical test reported. Outcome assessment: NRS, numeric rating scale, with a higher number meaning a better score; LS, Likert scale, each number represents an outcome, such as unsatisfactory-slightly satisfactory, satisfactory; VAS, visual analog scale; FACE-Q, a validated questionnaire using a combination of Likert scales and visual analog scales; POSAS, a validated questionnaire specifically designed for scars (the overall patient-reported POSAS score is reported in this table; a lower score means a greater satisfaction); GAIS, Global Aesthetic Improvement Scale is a Likert scale, 0-4. Supplements: PRP, platelet-rich plasma; PRF, platelet-rich fibrin; cSVF, cellular stromal vascular fraction; tSVF, tissue stromal vascular fraction; ASC, adipose-derived stromal cell; BMSC, bone marrow–derived stromal cell. [a]Overall patient satisfaction was noted from the patient satisfaction scores. [b]Data were manually calculated from the tables in the article. [c]Within-group outcome means that no comparison to baseline or comparison to a control group was made. Participants were asked to evaluate the outcome after surgery without evaluating the preoperative situation. [d]A lower score of the POSAS questionnaire means a greater satisfaction.

but only 6 of these 9 studies performed statistical testing. Patient satisfaction assessment was sometimes performed together (or in the same room) with the operating surgeon,[116] which may have induced interviewer bias and social desirability bias. Other studies omitted to describe the conditions under which measurements were performed and how results were obtained.[102,104,112] Follow up was sometimes not reported or ranged considerably within studies (3-30 months).[109,112,113,118]

Overall, patients reported high satisfaction rates after both conventional and supplemented facial fat grafting. Statistical tests were performed in 8 out of 16 studies.[98,101,102,110-112,117,119] Six of these 8 studies statistically tested for differences between the intervention and control group, of which 3 reported improved satisfaction in the intervention group.[101,102,110-112,117,119] Two PRP studies showed no significant improvement, of which the study of Tenna et al compared PRP with or without laser.[101,111] One cSVF study showed significant improvement and 1 cSVF showed no significant improvement.[110,119] Two tSVF studies showed significant improvement.[102,112]

Complications

Minor complications occurred in 9 out of 27 studies. Three out of these 9 studies also reported major complications occurring in the acceptor site. Major complications were reported in the groups supplemented with ASCs and PRP and were also reported in the control groups (conventional fat grafting). Overall, bruising and swelling were the most common minor complications reported. Of the studies that

Table 4. Quality of the Included Studies Based on the Effective Public Health Practice Project Tool

Reference	Selection bias	Study Design	Confounders	Blinding	Data Collection	Dropouts	Global rating
Bashir et al 2019	0	0	–	0	+	–	–
Bernardini et al 2015	–	0	–	0	–	–	–
Castro-Govea et al 2018	–	0	–	0	–	–	–
Cervelli et al 2009	–	0	–	–	–	–	–
Chang et al 2013	–	+	–	0	–	–	–
Fontdevila et al 2014	0	+	+	+	–	+	0
Gennai et al 2017	–	0	–	–	–	NA	–
Gentile et al 2014	–	0	+	0	0	–	–
Gentile et al 2020	–	0	–	–	0	–	–
Gu et al 2018	–	0	–	–	+	–	–
Hesamirostami et al 2019	0	0	–	–	+	+	–
Jianhui et al 2014	–	0	–	–	–	–	–
Keyhan et al 2013	–	+	+	0	–	–	–
Koh et al 2012	–	+	+	0	+	–	–
Lee et al 2012	–	0	+	0	–	–	–
Li et al 2013	–	0	+	0	0	NA	0
Ozer et al 2019	–	0	+	0	+	NA	0
Sasaki et al 2015	–	0	–	–	0	–	–
Sasaki et al 2019	–	+	+	0	0	–	–
Schendel et al 2015	–	0	+	0	0	+	0
Sterodimas et al 2011	–	+	0	0	–	–	–
Tanikawa et al 2013	0	+	+	0	0	0	+
Tenna et al 2017	–	+	–	0	+	–	–
Wei et al 2017	–	+	–	0	–	–	–
Willemsen et al 2018	–	+	+	0	+	0	0
Yin et al 2020	–	+	+	+	0	+	0
Yoshimura et al 2008	–	+	+	0	–	–	–
Totals							
Weak, n (%)	23 (85%)	0 (0%)	13 (48%)	7 (26%)	12 (44%)	18 (67%)	20 (74%)
Moderate, n (%)	4 (15%)	15 (56%)	1 (4%)	18 (67%)	8 (30%)	2 (7%)	6 (22%)
Strong, n (%)	0 (0%)	12 (44%)	13 (48%)	2 (7%)	7 (26%)	4 (15%)	1 (4%)

The totals at the bottom represent the distribution of how weak, moderate and strong each criterion is. Ref, reference, +, strong, 0, moderate, –, weak.

reported major complications Bernardini et al reported 3 cases of oily cysts that required surgical removal.[114] Bashir et al reported 2 cases of cellulitis: 1 in the intervention and 1 in the control group.[34] Yoshimura et al reported a case of necrotized tissue in the control group that was surgically removed.[4]

DISCUSSION

Our study systematically reviewed the current literature to assess the efficacy of supplemented clinical facial fat grafting on volume retention. Our main results are that: (1) few studies include volumetric data or patient satisfaction; (2) these studies are heterogeneous with respect to (a) age, (b) injection frequency, (c) injection volume, (d) type of supplement, (e) mixing ratio of fat and supplement, (f) imaging, (g) concomitant interventions, (h) follow-up time, (i) outcome parameters, and (j) use of controls; and therefore (3) the low number of studies and their high heterogeneity did not allow for a proper meta-analysis.

The results showed that of all supplements, culture-derived ASCs were most effective at retaining injected fat volume, whereas addition of PRP, or mixtures of PRP and cSVF did not affect volume retention. Some of our reviewed papers assessed complications and found virtually none, irrespective of supplements. This corroborates previous studies that show fat grafting to be safe.[2,124]

A major shortcoming in virtually all analyzed papers is the near lack of properly described standardized procedures, and the reporting of interassay and intraassay variation. This causes several of the studies to be subjective rather than objective and unfortunately reduces the value of the outcomes.

Volume retention is the goal of facial fat grafting but is also a highly challenging parameter to measure and monitor. Several studies used validated imaging methods, including CT and MRI scanning or 3D surface imaging. It was surprising to note that none of the papers disclosed the unbiased reliability, ie, inter- and intrameasurement variation, as well as inter- and intraobserver variation. This reduces the value of the measurements as these are prone to subjective bias.

With regard to the use of validated inquiries to measure patient satisfaction and outcome, the FACE-Q, GAIS, and POSAS have been available for several years.[121-123] Unfortunately, no more than a quarter of the papers report utilizing these instruments. Again, comparisons with these instruments were not reported, but we included these in our results. In general, statistical testing of outcomes was neglected in more than half of the studies. We consider this a major flaw that reduces the value of potentially relevant clinical trials to a minimum. Journal editorial boards and peer-review processes should continue to improve their standards for statistics.

Our quest was to find published papers that reported the benefit of supplemented fat grafting on volume retention. However, we could neither corroborate nor dispute these findings based on our current systematic literature analyses on supplemented clinical facial fat grafting. This study focused on supplemented fat grafting in the facial area, which might be a strength or a limitation. A systematic review on fat graft supplementation in other body parts would be interesting because it may elucidate whether supplementation therapies are effective and the influence of body location on fat graft viability. One Russian study was excluded because no translation was available in the medical library. However, it is doubtful whether inclusion of this

Table 5. Recommendations for the Study Design of New Trials

Recommendations for new studies	
Quality of the study	1. Controlled design (comparison with standard treatment or placebo) 2. Randomized 3. Minimal follow-up duration of 12 months 4. Following CONSORT[a] statement for reporting 5. Statistically testing for differences between groups
Standardization of the procedure	1. Standardized harvesting, processing and injection technique 2. Standardized injection volume and volume-to-volume ratio of supplement-to-fat graft 3. No concomitant procedures (eg, facelift) that can influence volume or satisfaction outcomes 4. Single injections, no repeated procedures
Measurement of volume retention	1. Clear definition of how retention is measured, based on injected volume or based on first volume measurement after surgery 2. Using valid imaging modalities (without ionizing radiation) 3. Using a reliable method of volume measurement, by either reporting reliability or using a validated method of volume measurement
Measurement of patient satisfaction	1. Using a validated PROM[b] 2. Measuring change of PROM, including a preoperative (baseline) measurement 3. Statistically testing for difference of PROM between intervention and control group 4. Observer/surgeon should not be present when PROM is recorded, to exclude interviewer/social desirability bias

[a]Consolidated Standards of Reporting Trials. [b]Patient-reported outcome measures.

study would have changed the general message of this systematic review. Future studies should focus on conducting well-designed randomized controlled clinical trials to be able to establish a higher level of evidence and to minimize inter- and intrastudy variation. Volume outcome measurement should be performed with valid imaging modalities and reliable volume measurement methods. Inter- and intrameasurement variation should be measured and reported. Imaging modalities based on ionizing radiation, such as CT, for follow up should be avoided. Validated patient-reported outcome questionnaires should be used and recorded both pre- and postoperatively to minimize potential recall bias. Procedures for harvesting and processing should be standardized.[12,125,126] No concomitant procedures such as a facelift or blepharoplasty should be performed during these studies because these influence volume outcome and patient satisfaction. We have established a summary of recommendations for the design of future trials in Table 5.

CONCLUSIONS

Despite multiple studies showing improved volume retention and increased patient satisfaction, no clinical superiority of supplementations could be objectified. Future well-designed clinical trials may elucidate whether supplementation therapies enhance fat graft retention and may increase patient satisfaction.

Supplemental Material

This article contains supplemental material located online at www.aestheticsurgeryjournal.com.

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