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ORIGINAL ARTICLE
Cosmetic

Autologous Fat Transfer for Facial Rejuvenation: A Systematic Review on Technique, Efficacy, and Satisfaction

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Background: Parallel to the steady decline in surgical aesthetic procedures to the face, dermal fillers seem to have gained a more prominent place in facial rejuvenation over the last couple of years. As a dermal, facial filler, autologous fat transfer (AFT) seems to have real potential because of the biocompatibility of adipose tissue besides being a procedure with few and primarily minor complications. This systematic review aims to evaluate the available evidence regarding the safety and effectiveness of AFT for facial rejuvenation.

Method: A systematic review after the Preferred-Reporting-Items-for-Systematic-Reviews-and-Meta-Analysis (PRISMA) statement was conducted. MEDLINE, Embase, and Cochrane Library were searched up to December 2016, with no language restrictions imposed. Case series, cohort studies, and randomized controlled trials (RCTs) reporting on relevant outcomes were included.

Results: Eighteen clinical articles were included, reporting on 3,073 patients in total over a mean follow-up period of 13.9 months. Meta-analysis showed an overall complication rate of 6% (95% CI 3.0–14.0), with hematoma/ecchymosis (5%), fat necrosis/oil cysts (2%), and irregular fat distribution and scars (both 2%) being among the most reported. No major complications were reported, and the overall patient satisfaction rate was 81%.

Conclusion: Although the evidence in this systematic review is still limited and plagued by heterogeneity between studies, AFT seems to be a promising method in facial rejuvenation with fewer complications than other fillers and high patient satisfaction rates. Further large-cohort, preferably multicenter, RCTs should substantiate these results through quantifiable volumetric assessment tools and validated patient questionnaires, while adhering to predetermined nomenclature in terms of complications. *(Plast Reconstr Surg Glob Open 2017;5:e1606; doi: 10.1097/GOX.0000000000001606; Published online 22 December 2017.)*

INTRODUCTION

For ages, the face has been considered the most prominent feature of the human being, and the motivation to alter its appearance for cosmetic purposes is as old as the work of Sushruta.[1] Over the past decades, fueled by western media adjusting to the growing older population, there has been an increasing demand for minimally invasive cosmetic procedures that enhance or maintain the youthful-looking appearance of the face.[2] The 17% decrease of facial surgical cosmetic procedures since 2000[3,4] combined with the 6.5% increase of hyaluronic acid, globally in 2015,[5] further illustrates the growing demand for dermal fillers. The ideal filler opposes many of the aspects that menace the aging face (sagging, skin-atrophy), while at the same time being predictable, adjustable to facial anatomy and especially biocompatible.[6] None of the numerous soft-tissue augmen-

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Received for publication September 12, 2017; accepted October 24, 2017.

DOI: 10.1097/GOX.0000000000001606

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

Supplemental digital content is available for this article. Clickable URL citations appear in the text.

tation products currently approved by the FDA, both temporary fillers and permanent fillers adhere perfectly to these qualities, and complications range from minor (bruising) to severe (embolisms, blindness).[7,8] As a result, it was not long before autologous fat transfer (AFT) or lipofilling found its way as a potentially superior facial filler with numerous studies reporting on the promising results besides minimal side effects.[9–11] Numerous reviews and articles describing the authors preferred method for facial AFT currently exist,[12–26] but they generally lack a comprehensive study design. Furthermore, the abundance of anatomical facial zones further complicates pooling of data, with most authors describing its appliance to 1 or 2 facial regions.[10] Therefore, the aim of this systematic review was to determine the rejuvenating properties of AFT to the whole face in terms of volume enhancement and patient/surgeon satisfaction and objectify these terms by determining technique, complications, volume retention, and specific patient/surgeon satisfaction rates.

METHODS

A systematic review of literature reporting on technique, efficacy, and patient/surgeon satisfaction rates regarding AFT for facial rejuvenation was conducted according to the preferred-reporting-items-for-systematic-reviews-and-meta-analysis (PRISMA) statement.[27] Medline (Ovid), Embase.com, and Cochrane Library (Wiley) were searched from inception (by JG and TK) up to December 11, 2016. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "facial" and "rejuvenation" or "aging" or "wrinkles" and "Autologous-Fat-Transfer." The full search strategy can be found in the supplementary information (see Appendix, Supplemental Digital Content 1, which displays the search strategy for Pubmed, ***http://links.lww.com/PRSGO/A628***). Studies that were considered relevant based on the titles were stored using Endnote (Clarivate Analytics),[28] with no restriction on language, study design, or publication media. Bibliographies of relevant articles were manually searched for relevant or missed references.

Eligibility Criteria

Original randomized controlled trials (RCTs) and cohort studies on facial rejuvenation with the use of AFT with or without supplementation, which reported on efficacy (ie, volume enhancement, improving skin trophicity, and decreasing wrinkles), technique, and patient/surgeon satisfaction, were included. Studies reporting on AFT for facial rejuvenation in conjunction with/or following other surgical procedures or injectables were excluded. However, studies combining AFT with laser-resurfacing techniques or studies that included combinations of treatment (ie, AFT + surgical procedures) but clearly reported on AFT-specific complications were included. Duplicate articles, case reports, or case series with a sample size <10 and articles with a mean follow-up period <6 months were excluded.

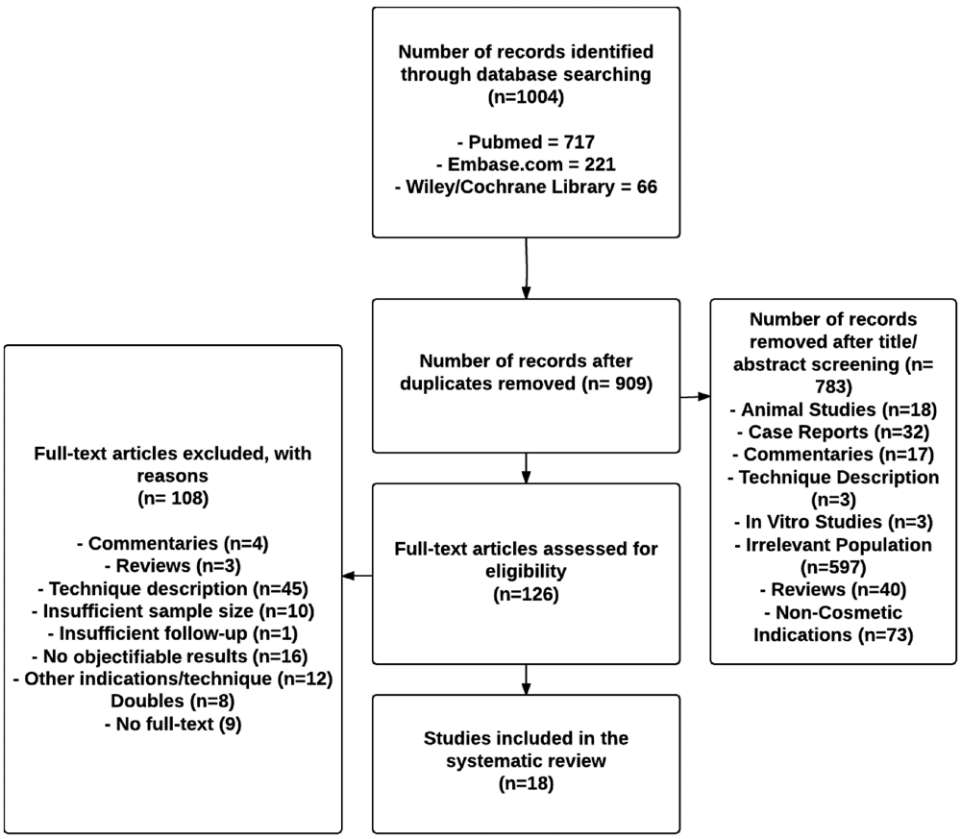

Fig. 1. Flow diagram illustrating systematic inclusion of studies for systematic review.

Table 1. Baseline: Characteristics of Included Studies

Reference	Year	Country	Study Design	No. Patients	Female Patients (%)	Exclusion Criteria	Age (y): Mean/ Median (SD/ Range)	Reported Outcomes	Follow-Up (mo): Mean/ Median (SD/ Range)	Level of Evidence (OCEBM[37])	ROBINS-I
Gormley and Eremia[38]	1990	United States	Retrospective cohort study	18	18 (100)	NR	Range: 35–70	FTG, VA	12 (actual)	III	Moderate
Eremia et al.[39]	2000	United States	Retrospective cohort study	116	115 (99.1)	Less than 2 AFG treatments Less than 12 months follow-up	57 (range: 34–72)	FTG, complications, satisfaction	Range: 9–14	III	Moderate
Dasiou-Plakida[40]	2004	Greece	Retrospective cohort study	1,720	NR	NR	NR	FTG, VA	Range: 12–24	III	Moderate
Botti et al.[35]	2010	Italy, Romania	Prospective double-blind cohort study	25 (BI*)	21 (84)	Chemotherapy Radiotherapy Chronic steroid use Connective tissue disease Chronic blood abnormalities Systemic metabolic disorders History of obesity Body dysmorphic disorder Anticoagulant treatment Assymetric facial features	46.3 (range: 21–72)	FTG, satisfaction	6 (actual)	III	/
Xie et al.[41]	2010	China, United States	Retrospective cohort study	83	64 (77.1)	Absence of clear indication (ie, temporal, cheek, periocular hollowing, lean or aging face, facial asymmetry)	53.16 (range: 18–55)	FTG, complications, satisfaction	32 (mean)	III	Moderate
Monreal[42]	2011	Spain	Retrospective cohort study	18	NR	NR	NR	FTG, complications	12 (actual)	III	Serious
Ransom et al.[43]	2011	United States	Retrospective cohort study	17	17 (100)	Incomplete photographical documentation	61 (range: 49–74)	FTG, complications	7 (mean)	III	Moderate
Tsai and Liao[44]	2011	Taiwan	Retrospective cohort study	209	NR	Satisfaction with NLF History of previous aesthetic facial surgery Previous use of fillers	46.7 (range: 35–61)	FTG, complications, satisfaction	24 (actual)	III	Moderate
Li et al.[45]	2012	China	Retrospective cohort study	38	38 (100)	NR	29.5 (SD: 6.8)	FTG, complications, VA, satisfaction	6 (actual)	III	Moderate
Rusciani Scorza et al.[46]	2012	Italy	Retrospective cohort study	215	215 (100)	Current anticoagulant treatment Pregnancy Previous use of fillers Bacterial/fungal/viral skin infection Systemic disease (diabetes, coagulation disorders, connective tissue disease) Aberrant laboratory values: (CBC, liver/kidney function, electrolytes, coagulation profile, serology for Hepatitis and HIV) Cardiac disease Male sex Age: <45, >70	55.5 (SD: 2.1)	FTG, complications, satisfaction	12 (actual)	III	Moderate

(*Continued*)

Table 1. (*Continued*)

Reference	Year	Country	Study Design	No. Patients	Female Patients (%)	Exclusion Criteria	Age (y): Mean/Median (SD/Range)	Reported Outcomes	Follow-Up (mo): Mean/Median (SD/Range)	Level of Evidence (OCEBM[37])	ROBINS-I
Zeltzer et al.[47]	2012	Belgium	Retrospective cohort study	250	222 (89)	NR	53 (range: 35–71)	FTG, complications	14 (mean); range: 1–36	III	Moderate
Keyhan et al.[36]	2013	Iran	Double-blind prospective clinical trial	25 (BI*)	17 (68)	Previous or additional surgical procedures Compromising systemic conditions (platelet dysfunction, thrombocytopenia) Hemoglobin <10 g/dl Infection History of local or systemic corticosteroid consumption Addiction Dramatic weight gain/loss in previous month	45 (range: 24–69)	FTG, complications, VA, satisfaction	12 (actual)	II	/
Asilian et al.[48]	2014	Iran	Prospective comparative cohort study	32	NR	Severe photoaging Coagulopathy disorder Severe systemic disease Infection Previous fat or gel injection at nasolabial fold	NR	FTG, satisfaction	12 (actual)	III	/
Le et al.[49]	2014	United States	Retrospective cohort study	70	65 (93)	Prior eyelid surgery	53	FTG, complications	10 (actual)	III	Moderate
Bernardini et al.[50]	2015	Italy	Retrospective cohort study	98	92 (94)	NR	51 (range: 27–74)	FTG, complications, VA	6 (mean)	III	Moderate
Schendel[51]	2015	United States	Prospective cohort study	10	10 (100)	Insufficient 3D scan Large weight fluctuations Additional facial surgery	51.6 (SD: 9.57; range: 36–71)	FTG, VA	12.6 (mean)	III	Moderate
Ibrahiem et al.[52]	2016	Egypt	Retrospective cohort study	(66/104 for facial AFG)	NR	NR	34	FTG, complications, satisfaction	39 (range: 12–133)	III	Serious
Tepavcevic et al.[9]	2016	Serbia	Prospective cohort study	63	56 (88.9)	Preexisting psychiatric disorder Antidepressive therapy during last month	50.0 (SD: 9.6; range: 29–68)	FTG, satisfaction	6 (actual)	III	Serious

*Study designs in which the face was divided through the horizontal axis, and both sides were used for different treatment methods (ie, different preparation, with or without supplementation, etc).
BI, bilateral injection; FTG, fat grafting technique; NLF, nasolabial fold; NR, not reported; VA, volumetric assessment.

Study Selection

Articles were screened for relevancy by 2 independent reviewers (JG, TK). When considered eligible by both reviewers, the full-text article was retrieved for possible inclusion. Discrepancies between the 2 reviewers were discussed and when a solution was not found, a third reviewer (JH) was consulted. When a study could not be retrieved, the authors were contacted to request a copy of the original article.

Outcome Measures

We included the following outcomes:

1. facial rejuvenating properties (ie, volume enhancement, improving skin trophicity, decreasing wrinkles) objectified in numerical (ie, percentile) or ordinal scale
2. complications
3. patient/surgeon satisfaction.

Data Extraction

Data were extracted by 1 researcher (JG) using standardized tables developed for this purpose and checked by a second reviewer (TK). Extracted data included the following: country, publication year, study design, number of subjects, AFT technique, complication rate and management, volumetric measurements, and satisfaction rates. Included studies were evaluated with respect to the following factors: inclusion/exclusion criteria, patient selection (ie, consecutive versus nonconsecutive recruitment), and use of objective outcomes. Included studies were assigned a level of evidence (OCEBM, 2011) by 2 independent reviewers (JG, TK). The principal summary measures are rates or actual numbers with percentages given between parentheses, besides means over follow-up periods.

Assessment of Risk of Bias

Observational studies and clinical trials without detailed randomization protocols were considered studies with high risk of bias. The Cochrane Risk of Bias for Randomized Clinical Trials[29] and Risk-Of-Bias-In-Non-randomized-Studies-of-Interventions (ROBINS-I)[30] were used for quantifying the risk of bias across RCTs and non-RCTs respectively.

Data Synthesis

In accordance with the Cochrane Handbook for Meta-analyses, in the studies that compared 2 methods, only the data from the group treated with AFT was used.[31]

Statistical Analysis

R statistical software was used for analyzing the data.[32] The pooled proportion of complications was estimated by both a fixed and random-effects model. The amount of heterogeneity between the studies was tested with Cochrane's Q and quantified with I^2. A random-effects model was used if Q was significant, a fixed effects model otherwise.[33,34]

RESULTS

There was a high interrater agreement, in selecting relevant articles based on the abstract screening, of 0.88. After screening (Fig. 1), a total of 18—English written—articles were included. The risk of bias across the cohort studies (Table 1) was considered moderate in 80%. The risk of bias of the 3 comparative studies is illustrated in Figure 2. Extracted data are summarized in Tables 1–5. The included studies were published between 1990 and 2016, with 13 retrospective and 2 prospective cohort designs next to 3 trials. There were 17 level-III studies and 1 level-II study involving a total of 3,073 patients. Two studies[35,36] studied the same set of patients by applying different methods of preparation or supplementation respectively using 2 different sides of the face (split over a vertical axis). The mean follow-up period was 13.9 months (range: 9–133).

Fat Grafting Technique

All articles described, to some extent, the methods of preparing and grafting the adipose tissue (Table 2).[9,35,36,38–52] Eleven out of 14 studies used a local form of anesthesia,[9,36,38–42,44–46,48,49,51,52] and 3 authors preferred general anesthesia.[35,47,50] The abdomen was the primary donor site in most studies with fat from the thigh and flank area used in cases of insufficient supply. The infiltration cannula size was poorly reported, with 3 studies[35,40,46] reporting using 1-, 2-, or 3-mm cannulas, respectively, and the infiltration solution varied widely among studies. Ten studies[9,35,40,41,45–50] (additionally) used some form of local anesthetic in combination with different solutions of epinephrine and saline before harvesting by way of manual aspiration in 16 of

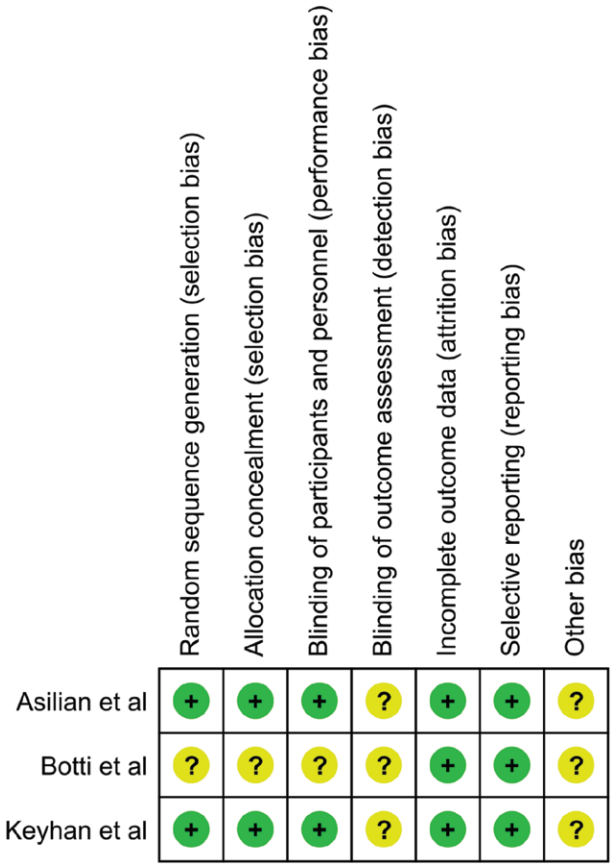

Fig. 2. Risk of bias in studies with a comparative study design.

Table 2. Fat Grafting Technique: Overview of the Form of Anesthesia, Donor Site, Infiltration Solution, Harvesting, Preparation, and Injection Technique Used

Reference	Year	Patient #	Anesthesia	Donor Site	Infiltration Cannula	Infiltration Solution	Harvesting Method	Harvesting Cannula + Syringe
Gormley and Eremia[38]	1990	18	Local anesthesia	Abdomen	NR	Lidocaine 1% (skin) + NaCl (cold) (subcutaneous)	MA	14-gauge + 10-ml LLS
Eremia et al.[39]	2000	116	NR	Abdomen, thighs, flanks	NR	NaCl (cold)	MA	14 gauge + 20–30 ml LLS
Dasiou-Plakida[40]	2004	1,720	Local anesthesia (+diazepam when indicated)	Abdomen, thighs, knees, gluteus region, trochanteric region, flanks	2 mm	Lidocaine 0.1% + epinephrine $1:10^5$ + NaBic 20 milliequivalent/liter	MA	2–3 mm/blunt + 20-ml LLS
Botti et al.[35]	2010	25 (right) 25 (left)	General anesthesia (analgesic sedation)	Abdomen, knees, thighs	3 mm (Klein)	NaCl +0.25% mepivacaine + epinephrine $1:5\times10^5$	MA	2 mm/blunt/2 h + 10-ml LLS
Xie et al.[41]	2010	83	Local anesthesia	Abdomen, thighs	NR	Lidocaine 0.08% + epinephrine $1:5\times10^5$	MA	2.5 mm/2 h + 60-ml LLS
Monreal[42]	2011	18	Local anesthesia	Abdomen, thighs	NR	NR	MA	3 mm/multiple-h + 10-ml syringe (NS)
Ransom et al.[43]	2011	17	NR	NR	Coleman (NS)	Coleman (NS)	MA	Coleman cannula NS + 10-ml LLS
Tsai and Liao[44]	2011	209	Local anesthesia	NR (patients preference)	Coleman (NS)	Coleman (NS)	MA	NR
Li et al.[45]	2012	26 12	Local anesthesia	Abdomen, thighs	NR	Lidocaine 0.08% + epinephrine $1:5\times10^5$	MA	2.5 mm/2 h
Rusciani Scorza et al.[46]	2012	215	Local anesthesia	Abdomen, trochanteric region, thighs, knees	1 mm	NaCl 500 ml + 25 ml lidocaine 1% + epinephrine 0.5 ml + triamcinolone acetonide 40 mg/ml + NaBic 2 ml	MA	2 mm/blunt + 10-ml LLS
Zeltzer et al.[47]	2012	250	General anesthesia/local anesthesia (NS)	Abdomen, flanks, thighs, knees	NR	Modified Klein (800 mg lidocaine + epinephrine $1/1\times10^6$)	MA/LD†	2–3 mm/blunt/10 h + 10-ml LLS
Keyhan et al.[36]	2013	25 25	NR	Knees, abdomen	Coleman (NS)	CS	MA	3 mm/2 h
Asilian et al.[48]	2014	16 16	Local anesthesia	Flanks	NR	Lidocaine 0.05% + epinephrine $1:10^6$ in LRS	MA	2 mm/blunt/3 h + 10-ml LLS
Le et al.[49]	2014	70	Local anesthesia	Knees, thighs	NR	Lidocaine 1% + epinephrine $1:1\times10^5$ + NaCl	NR	14 gauge/blunt
Bernardini et al.[50]	2015	98	General anesthesia (analgesic sedation)	Suprapubic, trochanteric region, knees	NR	LRS (500 ml) + lidocaine (500 mg) + NaBic 5 milliequivalent + epinephrine 0.5%	MA	2 mm/multiple-h
Schendel[51]	2015	10	NR	NR	NR	NR	LD	3 mm/2 h
Ibrahiem et al.[52]	2016	66	Local anesthesia (general anesthesia when indicated)	Abdomen, thighs	BLI	LRS (500 ml) + lignocaine 2% 20 ml + epinephrine 0.5 ml $1:2\times10^5$	MA	2.1 mm/blunt + 60-ml LLS
Tepavcevic et al.[9]	2016	63	Local anesthesia	Abdomen, trochanteric region	NR	Lidocaine 0.5-ml + epinephrine $1:2\times10^5$	MA	3 mm/3 h + 10-ml LLS

Addition of supplementation, the number of sessions, and the injected volume are subsequently given.
*Sedimentation (the process of settling down of heavy solids in a mixture of a liquid and insoluble solid) and decantation (the removal of the clear layer of the liquid without disturbing the settled solids) are used interchangeably because it both describes the process of letting the lipoaspirate settle to remove the desired layer. In the table, decantation is used.
†Manual aspiration was used when the desired volume of fat was <10 ml, and a liposuction device was used when this exceeded 10 ml.
AFT, autologous fat transfer; BLI, blunt lamis infiltrator; CC, Coleman cannula; CS, Coleman's solution; DFA, dermo-fascial attachment; FF, freezing of fat; h, number of cannula holes; LD, liposuction device; LLS, Luer lock syringe; LO, lateral opening; LRS, lactate Ringer solution; MA, manual aspiration; *n*, sample size; NaBic, sodium bicarbonate; NaCl, sodium chloride; NLF, nasolabial fold; NR, not reported; NS, not specified; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; SMAS, superficial muscular aponeurotic system; SVF, stromal vascular fraction.

Preparation	Supplementation	Injection Cannula	Injection Technique	Injection Planes	No. Sessions (*n*)	Postoperative Care	Other
NaCl washing + decantation (NS)	NR	14 gauge	NR	Intradermal	NR	NR	Overcorrection (NS)
NaCl washing + decantation* (NS)	NR	14 gauge (16 gauge glabella region)	Retrograde (+ fat-molding for lips)	Subcutaneous	2 (3 in 52/116)	Systemic antibiotics (6 d postoperative)	Overcorrection (NS)
Decantation (x2) + centrifugation: 2,000 rpm/2 min	NR	21–23 gauge	Retrograde/ fanning	Subcutaneous, intradermal	Multiple (NS)	NR	FF (−30°C/ 24 mo)
Centrifugation: 3,000 rpm/3 min Sterile filtering + NaCl washing	NR	1–2 mm/ blunt/LO	Retrograde/ fanning	Multiple (NS)	NR	Steristrips injection site, systemic antibiotics, cold/ compressing dressings donor site/injection site	NR
Intra-syringe NaCl washing + centrifugation: 1,000 rpm/2 min	NR	2–3 mm/ blunt	Retrograde/ fanning	Subcutaneous, sub-SMAS	1–3 (NS)	Compressing dressings (1 wk), facial inactivity instructions	Overcorrection (20–30%)
Decantation: 20 min	NR	1.2–1.4 mm/ blunt	Retrograde	Subcutaneous, SMAS	NR	NR	NR
Decantation: 10 min + centrifugation 3,000 rpm/3 min	NR	17 gauge	NS	NR	NR	Gentle cleansing + Aquaphor ointment for 1 week, avoidance of sunexposure	AFT + Laser (CO2) resurfacing
Centrifugation (NS)	NR	NS (3-ml syringe)	NR	NLF (NS)	NR	Massage contra-indicated, facial activity	Dissection of NLF–DFA
Centrifugation: 1,000 rpm/3 min	SVF None	1.5/3 mm	Retrograde/ fanning	Subcutaneous, sub-SMAS	1	Compressing dressings, facial inactivity instructions	Overcorrection (20–30%)
10–12 cycles of intra-syringe washing	NR	17 gauge/ blunt (+Ratchet Gun)	Retrograde/ 0.1 ml/cm^3 (through Ratchet Gun)	Subcutaneous, above SMAS	2	Steristrips injection site, antibiotics cream	NR
Washing (NS)	NR	23 gauge/ sharp	Retrograde	Intradermal	1 (218), 2 (32)	NR	NR
Centrifugation: 3,000 rpm/3 min	PRP PRF	Variable	Retrograde	Multiple (NS)	1	NR	NR
Centrifugation: 3,400 rpm/1 min Sterile filtering + NaCl washing	NR	1–1.5 mm/ blunt/LO	Retrograde/ fanning	Subcutaneous	-	Steristrips injection site, systemic antibiotics, cold/ compressing dressings donor site, massage contra-indicated	NR
Washing (NS)	NR	0.9–1.2 mm/ blunt	Fanning	Orbicularis muscle/ malar fatpad	1 (54), 2 (15), 3 (1)	NR	NR
Centrifugation: 2,000 rpm/1 min	PRP	20–23 gauge/ sharp	NR	Subcutaneous, muscle	NR	NR	NR
Centrifugation + washing (multiple. sessions, NS)	SVF	CC (NS)	NR	NS (surgeons discretion)	1	NR	NR
Decantation (30 min)	NR	NR	NR	NR	3–4 (NS)	Warm/compressing dressings, massage of injection site, local anesthesia antibiotics	FF (−18 °C)
Centrifugation: 3,000 rpm/3 min	NR	NR	NR	NR	1	NR	NR

Table 3. Complications: Overview of Complications and Management

Study	Year	Patient #	Complications (%)	Management
Eremia et al.[39]	2000	116	Infection NR Hematoma/ecchymosis 3.3% Scars 0.9% Temporary asymmetry 0.9%	Scars were revised during a subsequent treatment session
Xie et al.[41]	2010	83	Scars NR Irregular fat distribution NR	NR
Monreal[42]	2011	18	Irregular fat distribution NR	—
Ransom et al.[43]	2011	17	Infection NR Hematoma/ecchymosis NR Scars NR Complete fat resorption (5.9%)	Hyaluronic acid filler
Tsai and Liao[44]	2011	209	Donor site Infection NR Edema NR Hematoma/ecchymosis NR Irregular fat distribution NR Scars NR Implant site Infection NR Edema NR Hematoma/ecchymosis NR Irregular fat distribution NR Scars NR	NR
Li et al.[45]	2012	38	Scars NR	NR
Rusciani Scorza et al.[46]	2012	215	Donor site Bleeding 1.9% Hematoma/ecchymosis 0.5% Hyperpigmented access points 2.3% Pain 5.1% Implant site Hematoma/ecchymosis 7.4% Fat necrosis/oil cysts 1% Irregular fat distribution 4.6%	NR
Zeltzer et al.[47]	2012	250	Edema 9% Fat necrosis/oil cysts NR Infection NR Fat emboli NR Hematoma/ecchymosis 38%	NR
Keyhan et al.[36]	2013	25	Edema NR Hematoma/ecchymosis NR (Severe) pain NR	NR
Le et al.[49]	2014	70	Edema 7.0% Infection NR Hematoma/ecchymosis NR Seroma NR	Steroid injections (4/5 patients)
Bernardini et al.[50]	2015	98	Fat necrosis/oil cysts 3.1% Irregular fat distribution 1.0%	Aspiration or surgical removal NR
Ibrahiem et al.[52]	2016	66	Infection 6% Hematoma/ecchymosis 4.5% (infra-orbital, $n = 2$; nasolabial fold, $n = 1$) Fat necrosis/oil cysts 4.5% (all inner-infra-orbital/upper nasolabial fold)	NS Conservative treatment with hot compresses and local heparin crème Fine needle aspiration

NR, not reported. NS, not specified.

the 18 reporting studies. Harvesting was done by 2–3 mm cannulas, mostly blunt with 2–3 holes and attached to 10–60 ml Luer lock syringes. Preparation of the adipose tissue was done solely by centrifugation in 5 studies[9,36,44,45,50] ranging from 1,000 to 3,000 rpm over 1–3 minutes spans, with the studies of Asilian et al.[48] and Botti et al.[35] comparing centrifugation and washing between groups. Furthermore, 6 studies[38–41,43,51] used combinations of preparations in a none-comparative study design. Stromal vascular fraction (SVF), platelet-rich fibrin (PRF), and platelet-rich plasma (PRP) were used to supplement the fat in 4 studies, 2 by comparative design.[36,45] The injection cannula sizes ranged from 1 to 3 mm (14–23 gauge) and were mostly blunt with 2 studies reporting using lateral openings[35,48] and 1 study using a ratchet gun for precise fat distribution.[46] For the injections, most studies described a retrograde injection technique. The primary site of injection was the subcutaneous space with additional injections most often performed above or just beneath the superficial muscular aponeurotic system (SMAS). The number of AFT sessions was reported in 11 studies[9,36,39–41,45–47,49,51,52] and varied from 1 to 4 with an mean interval of 4.25 months.[39–41,47,49,52] Postoperative management varied greatly among the 9 reporting studies[35,39,41,43–46,48,52] and was even contradictory with Ibrahiem et al.[52] recommending massage, as opposed to other studies.

Complications

Meta-analysis was performed over the 12 reporting studies.[36,39,41–47,49,50,52] To determine the amount of heterogeneity between studies, Cochran's Q was calculated (101.45, $P < 0.0001$) and quantified with I^2 ($tau^2 = 2.0747$; H = 3.81 [2.98, 4.87]; I^2 = 93.1% [88.7%, 95.8%]). According to the Cochrane's Handbook for Systematic Reviews of Interventions[53]—in the case of between-trial heterogeneity—the random-effects meta-analysis weights the studies relatively more equally and is therefore used in the following description. The overall complication rate was 6% (95% CI: 3.0–14.0) after a mean follow-up of 15.8 months in 1,205 patients (see Tables, Supplemental Digital Content 2, which displays different data charts including overall complications and infections, ***http://links.lww.com/PRSGO/A629***). Hematoma/ecchymosis most reported (5%, 95% CI: 2.0–15.0), followed by fat necrosis/oil cysts (2%, 95% CI: 1.0–5.0), irregular fat distribution and scars (both 2%, 95% CI: 1.0–4.0). Infections were reported in 1% (95% CI: 0.0–4.0) of 728 patients in 6 studies.

Volume Retention

Objective measurements of the volumetric result are imperative to demonstrate the efficacy of AFT. However, the face consists of multiple anatomical units greatly varying in important features like density causing great heterogeneity in comparing results. Five studies[36,38,40,45,51] were included in the volumetric analysis (Table 4). The methods of determining volume retention varied greatly between studies. Supplements added to the fat graft were reported in 3 studies. As great heterogeneity between studies in regard to injection site and volumetric assessment exists, no pooling of data could be achieved, and volume retention varied greatly from 13% to 68% over a mean of 12.2 months.

Patient/Surgeon Satisfaction

A total of 9 studies[9,35,36,39,41,44,46,48,52] reported on patient and/or surgeon satisfaction either on a visual analog scale (VAS) or a 2-4 point Likert scale (Table 5). Meta-analysis for patient satisfaction was performed after conversion to a dichotomous scale (see Tables, Supplemental Digital Content 3, which displays patient satisfaction results, ***http://links.lww.com/PRSGO/A630***). To account for between-trial heterogeneity (Cochran's Q: 35.26-6<0.0001/ I^2: $tau^2 = 0.4391$; H = 2.42 [1.72, 3.41]; I^2 = 83.0% [66.3%, 91.4%]), the random-effect model was used for reporting patient satisfaction. Furthermore, overall scores were used only postoperatively, and when satisfaction rates were compared between study groups,[48] a mean over the total cohort was calculated. The satisfaction rate over a total cohort of 630 patients in 6 studies[36,41,44,46,48,52] was 81% (95% CI: 70.0–89.0). It should be noted that Asilian et al.[48] compared 2 groups of patients according to preparation method (centrifugation vs filtering/washing), and both groups were included in the analysis. Surgeons reported a good cosmetic outcome in 89%, and the overall postoperative mean VAS score among 88 patients in 2 reporting studies[9,35] was 79.5.

DISCUSSION

This study was performed to obtain a comprehensive overview of the available evidence on the outcomes of AFT in facial rejuvenation with objective outcome measures and a clear description of the technique applied. The first remarkable issue is the small number of studies to evaluate AFT in rejuvenation of the face. Although AFT is used widely all over the world, the number of well-designed studies is limited.

As is the case in AFT for other indications—such as the breast—the techniques used for harvesting, preparation, and reinjection of the fat varied greatly among authors. The most important aim in this continuing search for the golden standard in AFT is improving the volume retention, which is believed to be influenced by almost all the AFT aspects. Whether shear stress of the adipocytes caused by cannula size (either during harvesting or injection) or high osmolality of the infiltration solution plays a role remains a matter of debate. Both have been shown to vary greatly in this systematic review but have also been shown to matter significantly to the long-term volume retention.[54] Two recently published in vitro studies[55,56] shed some light on this interesting topic with Hivernaud et al.[56] reporting on—among others—adipose tissue resorption variances between different combinations of harvesting (ie, manual, power-assisted, or water-assisted lipoaspiration) and preparation (ie, decantation, centrifugation, or filtration). They found that both in the in vitro and in the murine models, greater efficiency (in terms of retaining tissue volume) was achieved with manual aspiration, soft centrifugation (400 g for 1 min), and washing steps. Although the majority of studies in this systematic review used manual aspiration, the centrifugation settings and times were considerably higher. Secondly, Streit et al.[55] further studied the differences in morphology between fat samples obtained through decantation, centrifugation, and membrane-based tissue filtration and found the highest numbers of adipose-derived stem cells in the upper fraction of centrifuged lipoaspirates but the maximal concentration of adipose fraction after membrane-based tissue filtration. In conclusion, both studies seem to suggest superiority of manual aspiration and centrifugation and/or washing procedures—in line with both the British and German clinical guidelines[57,58]—but longer follow-up for the former, and affirmation in clinical practice for the latter study is necessary to make conclusive statements. As was stated in the recent systematic review of Shim et al.,[59] the same can be said for harvest location, because multiple studies have shown a great varying degree in adipocyte number, volume, and morphology and also adipocyte-derived stem cells depending on where the fat is harvested.

Complications after dermal fillers are usually divided into early and late events and again into minor and major.[8] One of the advantages of AFT over other facial fillers in both early and late events is the absence of hypersensitivity reactions and granuloma formation, respectively. Furthermore, when comparing AFT with the use of hyaluronic acid (HA) fillers, major complications such as necrosis and blindness—which have both been described

Table 4. Injected Volume Per Facial Region and Retention

Study	No. Patients	Auxiliary Method	Methods of Measuring	Injected Volume: Periorbital (Mean, SD, Range)	Injected Volume: NLF (Mean, SD, Range)	Injected Volume: Forehead (Mean, SD, Range)	Injected Volume: Lips (Mean, SD, Range)	Injected Volume: Chin (Mean, SD, Range)
Gormley and Eremia[38]	18	NR	Optical profilometric technique	NR	Mean: 2.5 ml	NR	NR	NR
Eremia et al.[39]	116	NR	NR	NR	Mean: 2.2 ml (range: 1.5–2.5 ml)	NR	Mean: 3.7 ml (range: 1–2.5 ml)	NR
Dasiou-Plakida[40]	1,720	NR	Pre/postoperative photograph estimation	NR	NR	NR	NR	NR
Botti et al.[35]	25 (right) 25 (left)	NR	NR	Range: 1.5–4 ml	Range: 2–3 ml	Range: 2–4 ml	Range: 3–5 ml	Range: 2–4 ml
Xie et al.[41]	83	NR	NR	Mean: 1.2 ml	NR	Mean: 16.5 ml	NR	Mean: 2.0 ml
Li et al.[45]	26 12	SVF None	Pre/postoperative CT + photograph comparison	NR	NR	NR	NR	NR
Rusciani Scorza et al.[46]	215	NR	NR	NS	NS	NS	NS	NR
Keyhan et al.[36]	25 25	PRP PRF	Pre/postoperative photograph analysis in mm	NR	NR	NR	NR	NR
Le et al.[49]	70	NR	NR	0–2 ml	NS	NR	NR	NR
Bernardini et al.[50]	98	NR	NR	Mean: 3.7 ml	NR	NR	Mean: 4.9 ml	Mean: 3.5 ml
Schendel[51]	10	SVF	Pre/postoperative photograph comparison; 3dMD system + Vultus software	NS	NR	NS	NS	NS
Ibrahiem et al.[52]	66	NR	NR	NR	NR	NR	NR	NR
Tepavcevic et al.[9]	63	NR	NR	Mean: 4.0 ml	Mean: 4.0 ml	Mean: 4.0 ml	NR	Mean: 4.0 ml

Overview of the auxiliary method, the method of measuring volume retention, the mean total injected volume, the volume gain, and the percentage of gain relative to the injected volume.
NLF, nasolabial fold; NR, not reported; NS, not specified; PRF, platelet-rich fibrin; PRP, platelet-rich plasma.

after HA injection[60–63]—were not reported. The most reported complication after AFT for facial rejuvenation—hematoma/ecchymosis—was reported in 5% (95% CI: 2.0–15.0) of the total cohort, which is in line with that reported in studies using other dermal fillers.[64] Late onset complications such as fat necrosis (2.0%, n = 629) have been reported but are among the other complications[10,11] minimal.

As stated before, the long-term volume retention is crucial in defining AFT as a biocompatible permanent filler in general and in verifying its superiority over other fillers. Three studies[40,45,51] reported an overall volume retention ranging from 40% to 68% over a follow-up of 6 to 12 months without specifying the injected locations. The remaining studies[36,38] while specifying the locations (nasolabial/marionette fold and cheek/malar, respectively) reported much lower volume retentions, ranging from 13% to 19% over a follow-up of 12 months indicating the importance of the location in regard to the long-term retention of the reinjected fat. However, because of the great heterogeneity among studies—especially when it comes to the different injected facial zones—no definitive conclusion could be made with regard to overall volume retention after AFT for facial rejuvenation. Supplements were used in 2 studies that reported on volume retention[36,51]; however the injected facial zones, the method of measuring volume retention, and the supplements used (PrP/PrF vs SVF) all varied, so no beneficial effect could be reported. Therefore, the aim of further studies should be toward facial location-specific volumetric assessment using objectifiable tools like 3D imaging (such as the VECTRA XT 3D imaging system), CT, or MRI.

The patient and surgeon satisfaction rates in the included studies were considered acceptable and in line with other publications and a recently published study on quality of life after minimally invasive facial cosmetic procedures.[65] However, only standard visual analog scales, and also Likert scales, were used without the inclusion of validated questionnaires like the FACE-Q.[66] Also satisfaction scores per facial zone are only reported in 1 study[35] on VAS, ranging from 6 in the lips to 9 in the eyelids and malar region. Therefore, further studies should focus on incorporating the FACE-Q into the study design and report per facial zone.

Injected Volume: Mandible (Mean, SD, Range)	Injected Volume: Cheek (Mean, SD, Range)	Injected Volume: Malar (Mean, SD, Range)	Injected Volume: Marionette Fold (Mean, SD, Range)	Injected Volume: Glabella (Mean, SD, Range)	Total Injected Volume (Mean, SD, Range)	Volume Gain Relative to Graft Volume (%)	Follow-up mo (Mean, Range, Actual)
NR	NR	NR	Mean: 1.0 ml	NR	Mean: 3.5 ml	19.4	12 (actual)
NR	NR	NR	Mean: 1.3 ml (range: 1–1.5 ml)	Mean: 1.4 ml (range: 1–2 ml)	Mean: 8.9 ml (range: 5.5–10 ml)	NR	Range: 9–14
NR	NR	NR	NR	NR	Range: 3–105 ml	40–60	Range: 12–24
Range: 4–6 ml	Range: 5–7 ml	Range: 3–4 ml	Range: 3–5 ml	NR	Range: 25.5–42 ml	NR	6 (actual)
Mean: 11.0 ml	Mean: 20.0 ml	Mean: 7.5 ml	NR	NR	Mean: 58.2 ml	NR	Mean: 32
NR	NR	NR	NR	NR	Mean: 17.5 ml (SD: 7.3) Mean: 16.2 ml (SD: 6.3)	64.8 46.4	6 (actual)
NS	NS	NS	NS	NR	Mean: 13.25 ml (SD: 3.12)	NR	12 (actual)
NR	Mean: 7.0 ml Mean: 7.0 ml	Mean: 8.0 ml Mean: 8.0 ml	NR	NR	Mean: 15.0 ml Mean: 15.0 ml	18 13	12 (actual)
NR	NS	NS	NS	NS	5–42 ml	NR	10 (actual)
NR	NR	Mean: 7.0 ml	NR	Mean: 3.0 ml	Mean: 71.4 ml	NR	Mean: 6 (range: 4–12)
NR	NS	NS	NR	NS	Mean: 18.4 ml (SD: 15.34)	68	Mean: 12.6
NR	NR	NR	NR	NR	Mean: 7.0 ml	NR	Mean: 39 (range: 12–133)
Mean: 5.5 ml	Mean: 4.5 ml	Mean: 4.5 ml	NR	Mean: 4.0 ml	Mean: 34.5 ml	NR	6 (actual)

Limitations

This systematic review has several limitations. Only low-level evidence studies (OCEBM III) and mainly retrospective studies without a control group were found. The 3 studies that used a comparative study design failed to report on some important aspects like allocation concealment and blinding, as is illustrated in Figure 2. The use of validated measurement tools to assess patient-reported outcomes is lacking, and objectifiable data on volume retention are generally absent. Heterogeneity between studies in reported outcomes and nomenclature regarding specific facial zones and complications makes it difficult to draw conclusions. This was partly resolved by combining similar terms under 1 common nominator (eg, bruising and ecchymosis), but this may have introduced some bias. More important is the fact that several studies neglected to specify the complications and only sufficed with the annotation that there were none. These studies[67,68] were therefore excluded, and this adds further to a possible reporting bias. Finally, the very definition of a complication of AFT in facial rejuvenation is a complicated matter and a clear consensus whether, for example, postoperative pain qualifies as a complication or part of the normal postoperative course is still lacking. A strong example thereof is the 38% rate of hematoma in the study of Zeltzer et al.,[47] which deviates significantly from the reported rate in the rest of the studies, and while the authors tried to correct this by using a random-effect model, the reader should be cautious in interpreting these results. Therefore, on a methodological basis, the focus for further studies should be, first, to define complications and, second, to adhere to this definition when reporting on complications. In reporting on patient/surgeon satisfaction, the authors took certain liberties in translating Likert scales to dichotomous (satisfied vs dissatisfied) data by categorizing "moderately satisfied"—in a 3-point Likert scale—under "satisfied," because the patients might answered differently when presented with an actual dichotomous question. This should be kept in mind when interpreting these results.

The aim of this study was to complement the broad database of descriptive reviews and expert opinions on the subject of AFT for facial rejuvenation with the addition of a more comprehensive, systematically reviewed overview of the recent literature, including meta-analysis of complications and satisfaction. The authors believe this systematic review accomplishes that by the inclusion of structured tables on im-

Table 5. Patient/Surgeon Satisfaction

Study	Year	No. Patients	Follow-up, mo (Mean/SD/Range)	Patient Satisfaction: Three-point Scale (Satisfied/Moderately Satisfied/Dissatisfied)	Surgeon Satisfaction: Measurement	Surgeon Satisfaction: Three-point Scale (Good/Neutral/Poor)
Eremia et al.[39]	2000	116	Range: 9–14	NR	PPoCc/TS	Nasolabial fold (n = 85/116) Good: 14.1%/neutral: 21.2%/poor: 58.8% Glabella (n = 26/116) Good: 0%/neutral: 0%/poor: 100% Lips (n = 27/116) Good: 0%/neutral: 0%/poor: 100%
Xie et al.[41]	2010	83	32 (mean)	Satisfied: 83.13%/moderately satisfied: 14.46%/dissatisfied: 2.4%	PPoCc/IS	Good: 86.74%/neutral: 12.04%/poor: 1.2%
Tsai and Liao[44]	2011	209	24 (actual)	Satisfied: 66.7%/dissatisfied: 33.3%	NR	NR
Rusciani Scorza et al.[46]	2012	215	12 (actual)	Satisfied: 85.6%/moderately satisfied: 0%/dissatisfied: 14.4%	PPoPc/TS + ID	Good: 88.8%/neutral: 0%/poor: 11.2%
Keyhan et al.[36]	2013	25 25	12 (actual)	Satisfied: 96%/moderately satisfied: 0%/dissatisfied: 4%	NR	NR
Asilian et al.[48]	2014	16 16	12 (actual)	Satisfied: 12.5%/moderately satisfied: 62.5%/dissatisfied: 25% Satisfied: 6.25%/moderately satisfied: 56.25%/dissatisfied: 37.5%	NR	NR
Ibrahiem et al.[52]	2016	66	39 (range: 12–133)	Satisfied: 91.0%/moderately satisfied: 0%/dissatisfied: 9.0%	PPoCc/TS	Good: 91.35%/neutral: 0%/poor: 8.65%

Study	Year	No. Patients	Follow-up, mo (Mean/SD/Range)	Patients Satisfaction: VAS Evaluation 1–10 Score (SD)	Surgeons Satisfaction: Measurement	Surgeons Satisfaction: VAS Evaluation 1–10 Score (SD)
Botti et al.[35]	2010	25 (right/AFG + centrifugation) 25 (left/AFG + saline washing)	6 (actual)	Postoperative score: temporal, 6.7 (1.5); eyelids, 9.1 (1.3); malar, 8.7 (1.3); tear through, 8.5 (1.5); cheek, 7.0 (2.2); nasolabial fold, 7.9 (2.0); lips, 6.7 (2.0); mandible, 7.6 (1.8); marionette fold, 7.6 (2.1); chin, 7.2 (1.7); global, 7.6 (1.9) Postoperative score: temporal, 6.2 (1.4); eyelids, 8.8 (1.2); malar, 8.9 (1.2); tear through, 8.5 (1.5); cheek, 7.2 (2.0); nasolabial fold, 7.6 (2.1); lips, 6.1 (2.0); mandible, 7.4 (1.7); marionette fold, 7.9 (2.0); chin, 7.4 (1.8); global, 7.5 (1.9)	PPoPc/IS + nurse + MA	Postoperative score: temporal, 6.3 (2.1); eyelids, 9.0 (1.0); malar, 9.0 (1.0); tear through, 8.7 (1.2); cheek, 6.7 (0.6); nasolabial fold, 6.7 (0.6); lips, 6.3 (1.5); mandible, 8.7 (1.2); marionette fold, 7.7 (2.1); chin, 7.0 (1.0); global, 8.0 (1.0) Postoperative score: temporal, 6.0 (2.0); eyelids, 8.7 (1.2); malar, 9.3 (1.2); tear through, 8.7 (1.2); cheek, 7.0 (1.0); nasolabial fold, 6.7 (0.6); lips, 6.3 (1.5); mandible, 7.7 (1.5); marionette fold, 7.7 (2.0); chin, 7.0 (1.0); global, 7.7 (0.6)
Tepavcevic et al.[9]	2016	63	6 (actual)	Preoperative score: 4.6 (SD: 1.3) Postoperative score: 8.3 (SD: 1.3)	NR	NR

AFG, autologous fat grafting; ID, independent dermatologist; IS, independent surgeon; MA, make-up artist; NR, not reported; PPoCc, pre/postoperative clinical comparison; PPoPc, pre/postoperative photograph comparison; TS, treating surgeon(s).

portant outcomes and also the exclusion of case series and case reports and studies with insufficient follow-up periods.

CONCLUSIONS

This systematic review provides an updated overview of the important outcomes of AFT for facial rejuvenation. Although the evidence in this review is still limited and plagued by the same heterogeneity that is often found in reporting on AFT for other indications, still, this technique is regarded as a promising method in facial rejuvenation. Although AFT has a number of obvious advantages over other dermal fillers in terms of biocompatibility, such as the absence of hypersensitivity reactions and the risks of granuloma formation, other complications such as fat necrosis have to be taken into account. Furthermore, the great variation in reported volume retentions in this systematic review suggests further studies are needed to clarify the facial-unit-specific, long-term preservation of the achieved volume before AFT can rightfully be called a true permanent filler. However, in achieving these goals, proper research should evaluate whether AFT is the superior biocompatible next-generation facial filler.

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ACKNOWLEDGMENT

The authors would like to thank Mr. Quinten de Bakker, from the medical library, VieCuri Medical Center, Venlo, the Netherlands for his widespread assistance in the search process.

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