Systematic review of "filling" procedures for lip augmentation regarding types of material, outcomes and complications

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Systematic review of "filling" procedures for lip augmentation regarding types of material, outcomes and complications

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ABSTRACT

Background: The ideal lip augmentation technique provides the longest period of efficacy, lowest complication rate, and best aesthetic results. A myriad of techniques have been described for lip augmentation, but the optimal approach has not yet been established. This systematic review with meta-regression will focus on the various filling procedures for lip augmentation (FPLA), with the goal of determining the optimal approach.

Methods: A systematic search for all English, French, Spanish, German, Italian, Portuguese and Dutch language studies involving FPLA was performed using these databases: Elsevier Science Direct, PubMed, Highwire Press, Springer Standard Collection, SAGE, DOAJ, Sweetswise, Free E-Journals, Ovid Lippincott Williams & Wilkins, Willey Online Library Journals, and Cochrane Plus. The reference section of every study selected through this database search was subsequently examined to identify additional relevant studies.

Results: The database search yielded 29 studies. Nine more studies were retrieved from the reference sections of these 29 studies. The level of evidence ratings of these 38 studies were as follows: level Ib, four studies; level IIb, four studies; level IIIb, one study; and level IV, 29 studies. Ten studies were prospective.

Conclusions: This systematic review sought to highlight all the quality data currently available regarding FPLA. Because of the considerable diversity of procedures, no definitive comparisons or conclusions were possible. Additional prospective studies and clinical trials are required to more conclusively determine the most appropriate approach for this procedure.

Level of evidence: IV.

1. Introduction

The best filler material for facial soft tissue augmentation remains to be determined. A myriad of natural and synthetic compounds have been used, but none is clearly superior to the rest. The ideal filler material achieves the best aesthetic long-term results and has the lowest complication rate and lowest cost.

Determining the optimal filler material is especially difficult for lip augmentation surgery. Not only has the best filler material not been established, the best aesthetic result has also not been agreed upon. The words 'youthful', 'pouty', and 'voluptuous' are commonly used to define the ideal result of a lip augmentation procedure. Essentially, this is accomplished by enlarging the lip, but it is not a simple matter. Reports of unnatural (and sometimes disastrous) appearances caused by lip augmentation frequently appear in the media (Browning, 2012; Parsons, 2012; 20minutes.es 2012). Voluminous lips are not appealing if the upper incisors are camouflaged behind the lips while speaking or laughing, or if the lip movements are affected, or there are noticeable nodules, or the natural vermilion grooves are obliterated.

The attractiveness of the lip generally parallels the attractiveness of the teeth visible while speaking or smiling, and studies typically correlate the smile line with the position of the upper lip

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during a smile. A smile makes a face appear more attractive (Doherty et al., 2003), and approximately 75%–100% of the maxillary anterior teeth should be exposed for the smile to be most appealing (Passia et al., 2011). The human brain has specific areas and circuits (afferent fibers from the fusiform area [Brodmann Area (BA)37] to the medial orbitofrontal cortex BA14, BA32) to perceive smiles and feel pleasure (Shahin and Tootell, 2012; Tsukiura and Cabeza, 2008). Furthermore, an enlarged lip is not beautiful if its shape is not attractive; however, the ideal shape has not been established. Although general rules have been established, the attractiveness of specific shapes has not yet been investigated. Thus, even though lip augmentation techniques using fillers are being analyzed in this systematic review, the results will be taken very cautiously, since in virtually no study are the results analyzed when smiling or speaking, and the change in the shape is not analyzed in any of them.

Nevertheless, dermal fillers are a thriving business, and the overall dermal filler market in the United States (US) has expanded at a compound annual rate of 20.2%, reaching $782,645,560 in total sales (Surgery.org, 2012). The market in the rest of the world has similarly increased by 20%, reaching $1.5 billion in global sales (Miinews.com, 2010). Factors contributing to this expanding market demand likely include the aging population, expanding media exposure and consumer awareness, new and improved filler technologies, and expanding social acceptance. Injection of hyaluronate fillers is the second most common nonsurgical procedure in the USA with a total of 1.5 million injections performed annually (Surgery.org, 2012).

With the above considerations in mind, we designed the current study to systematically review all the heretofore-published quality studies regarding filling procedures for lip augmentation (FPLA). The review included studies evaluating fillers or grafts. The goal was to evaluate good quality data regarding the various FPLA techniques to determine the optimal approach.

2. Materials and methods

2.1. Literature search

A systematic literature search shown as a QUOROM-flow diagram in Fig. 1 (Moher et al., 1999) was conducted with the assistance of the Unika Library Service from the University of Navarre (Clínica Universitaria de Navarra, Pamplona, Spain) and the assistance of LIMO Library Service from the Catholic University of Leuven (Leuven, Belgium). These services allowed us to access the Elsevier Science Direct Complete, PubMed Central, Highwire Press, Springer Standard Collection, SAGE Premier 2011, DOAJ Directory of Open Access Journals, Sweetswise, Free E-Journals, Ovid Lippincott Williams & Wilkins total Access Collection, Willey Online Library Journals, and Cochrane Plus databases. The following heading sequence was used: {'Lip' OR 'Mouth' OR 'Perioral' or 'Nasolabial} AND {['filler'] OR [('graft' AND ('dermal' OR 'fat' OR 'adipose' OR 'tendon' OR 'muscular')] OR [('hyaluronan' OR 'hyaluronic acid' OR 'Hylan' OR 'Hylaform' OR 'Revanesse' OR 'Hyaluderm' OR 'Juvederm' OR 'Teosyal' OR 'Esthelis' OR 'Captique' OR 'Belotero' OR' Restylane' OR 'Perlane' or 'Puragen' OR 'Emervel') OR ('elastin' OR 'Endoplast-50') OR ('Collagen' OR 'Zyplast' OR 'Zyderm' OR 'Cosmoplast' OR 'Cosmoderm' OR 'Autologen' OR 'Dermalogen' OR 'Evolence' OR 'Dermicol' OR 'Permacol') OR ('Alloderm' OR 'Surgisis' OR 'Cymetra' or 'Matrix') OR ('Fibroblasts' OR 'Isolagen') OR ('Agarose' OR 'Easy

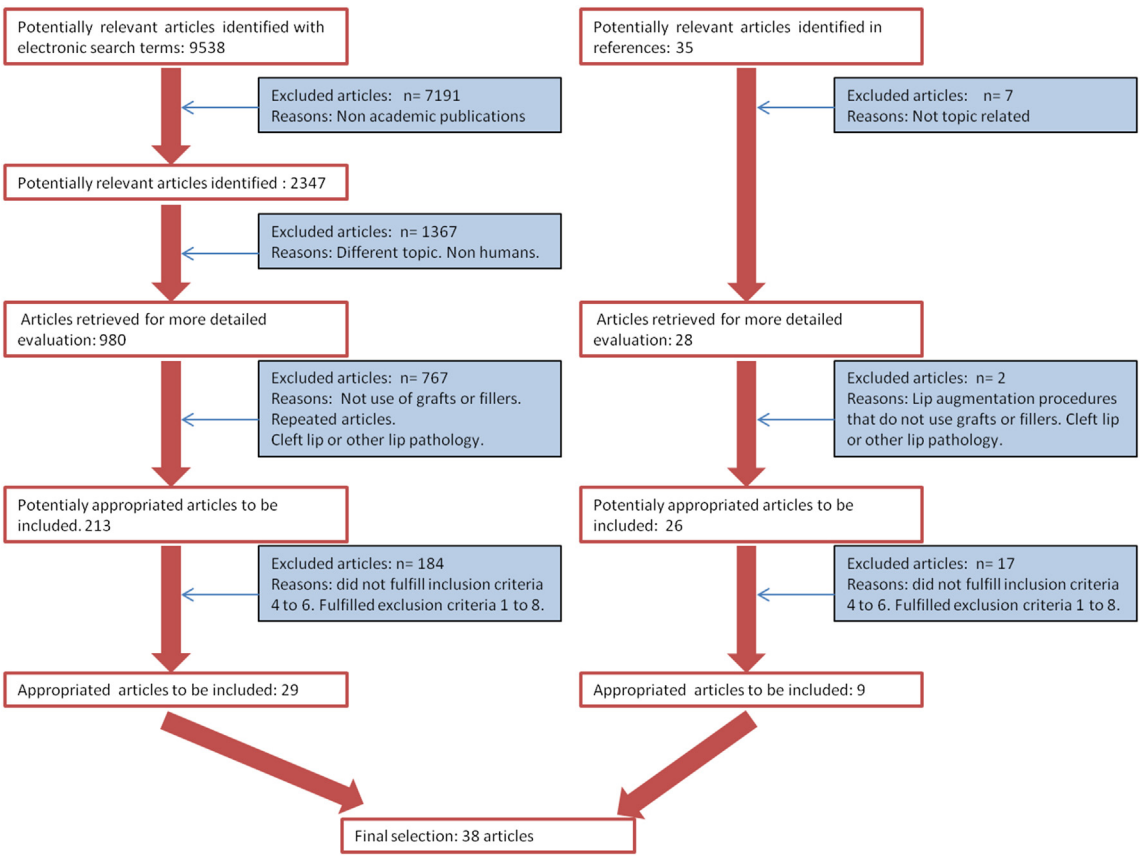

Fig. 1. QUOROM-flow diagram. Flow diagram according to QUOROM statement (Moher et al., 1999) providing information about the number of articles identified, included, and excluded and the reasons for excluding them. Abbreviations: n = number of studies.

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Filler' OR 'Easy Agarose' OR 'Dextran' OR 'Matridex' OR 'Sephadex' OR 'crmDEX' OR 'Alginate') OR ('Paraffin' OR 'Vaselin') OR ('Silicone' OR 'Silikon' OR 'Bioplastique' OR 'Adatosil' OR 'Siluron' OR 'PMS 350' OR 'Silksin') OR ('e-ptfe' OR 'expanded polytetrafluoroethylene' OR 'Gore-Tex' OR 'Softform' or 'Ultrasoft' OR 'Advanta' OR 'SAM') OR ('Calcium Hydroxylapatite' OR 'Radiance' OR 'Radiesse') OR ('HEMA' OR 'Dermalive' OR 'Dermadeep' OR 'Polymethylmethacrylate' OR 'PMMA' OR 'Artefill' OR 'Artecoll' OR 'Arteplast') OR ('polyethylenglycol' OR 'PEG') OR ('acid poly-L-lactic' or 'Sculptra' OR 'NewFill' OR 'polycaprolactone' OR 'Ellansé') OR ('Polyvinyl alcohol' OR 'Bioinblue') or ('Polyacrylamide' OR 'Aquamid' OR 'Amazingel' OR 'Formacryl' OR 'Kosmogel') OR ('Polyalyklimide' OR 'Bioalcamid' OR' Bio Alcamid')]}.

Our initial search identified 9538 publications, which were reduced to 2347 articles after excluding non-academic publications. Excluding studies not involving humans or discussing a different topic reduced the number of potential studies to 980, and excluding studies discussing cleft lip, other lip pathologies, and lip augmentation techniques not using fillers or grafts further reduced the articles to 213. Only 29 out of these 213 studies fulfilled inclusion criteria 4–6 but did not meet exclusion criteria 1–8 (see SELECTION CRITERIA below). To complete the search, we examined every reference from each of the 29 selected studies to determine whether they met the inclusion or exclusion criteria. Using this strategy, we identified an additional 35 studies involving FPLA, only 9 of which fulfilled the inclusion criteria but not the exclusion criteria. With the addition of these 9 articles, a total of 38 articles were thus examined in this systematic review.

2.2. Selection criteria

The following inclusion criteria were used to select appropriate studies: 1) human patients; 2) lips without pathology or patients without pathology that could be ameliorated by lip enhancement; 3) lip augmentation techniques using fillers or grafts; 4) the number of patients was stated; 5) at least 10 patients in the study; and 6) the complication or efficacy rate was reported and the efficacy outcome(s) are quantifiable. Two articles using muscular flaps instead of grafts were included as the flaps functioned as filling substances.

The exclusion criteria were as follows: 1) use of fillers for the nasolabial fold, marionette lines, or corners of the mouth; 2) resurfacing, peeling, laser, botulinum toxin injections, or tattoos; 3) efficacy outcome or complication data related to the lip were not clearly stated; 4) lip lift or V–Y lip advancement; 5) upper lip Z-plasty; 6) level of evidence (LOE) rated as a V; 7) reviews or systematic reviews; and 8) languages other than English, French, Spanish, German, Dutch, Portuguese, Italian. Botulinum toxin for lip enhancement and lip pigmentation techniques does not directly enhance the lip; therefore, studies of these methods were excluded.

2.3. Data extraction

The following data were extracted from the full-text version of each selected study: year of publication, type of material used for filling, number of patients, patients' mean age and sex, efficacy of the FPLA, number of points used for each assessment scale, validation of the scales presented, complication rate, type of study (prospective or retrospective), use of a control group, randomization of groups, blinding, inclusion and exclusion criteria, filler manufacturer, year when the graft or filler was used for the first time, patient satisfaction scale, amount of filling, average life of the filler after injection, average size of micro-particles (for those fillers containing microparticles), study sponsor(s), quantity of filler injected, diameter of the needle used, and market availability of the filler.

To assess the methodological strength of each article, a quality evaluation was performed using the level of evidence (LOE) scale proposed in the 2011 Oxford Centre for Evidence Based Medicine levels of evidence recommendations (Howick et al., 2011). The quality was rated from level I to level IV. Level V studies were excluded from this review.

3. Results

3.1. Included studies

A total of 38 studies were included in this review (Table 1). Of these, 27 had quantifiable data for the effectiveness of the FPLA and were chosen to evaluate the efficacy outcome; 35 stated the specific number of patients with lip complications and were chosen to evaluate complication rates.

The distribution of LOE ratings for the 38 studies was as follows: level Ib, four studies; level IIb, four studies; level IIIb, one study; and level IV, 29 studies. Ten studies were prospective; five of these were multicenter studies and one had a parallel design. The design was double-blind for three studies and single-blind for another three. A control group was used in seven studies: placebo control (saline serum injection), one study (Solish and Swift, 2011); no treatment, one study (Seymour, 2008); active control with a reference filler (the collagen filler Zyplast), three studies (Sclafani et al., 2002; Cohen et al., 2004, 2006); and one study compared a variety of different fillers (three collagen-based fillers and a Zyplast control) (Recupero and McColloug, 2010). Only four studies used randomization to assign patients to treatment (or control) groups.

3.2. Lip enhancement fillers

A number of materials used for soft tissue augmentation have also been used in the lip. Although most cosmetic injectable fillers have been studied in facial augmentation, a smaller number have been tested specifically for lip enhancement. Table 2 summarizes information about all materials used for soft tissue augmentation, including their composition, origin, size of particles (if the material is particulate), degree of permanence after injection into the receptor tissue, major brands and their manufacturers, year of launch onto the market, and whether published studies exist regarding its use in soft tissue augmentation and specifically lip augmentation.

Facial fillers can be classified into two broad categories: biologic substances (e.g. collagen, adipose tissue, or agarose) and non-biologic substances (e.g. silicone oil or agarose). Biological substances are derived from animal or non-animal sources. Animal substances can be obtained from the same person (autologous), another person, which is generally a cadaver (homologous), or another animal (heterologous). They can also be synthetically manufactured. Non-animal biologic substances can be obtained from non-animal organisms (e.g. dextran beads, which are derived from bacteria). Non-biologic substances can be obtained from petroleum (e.g. polytetrafluoroethylene) or minerals (e.g. silicone), or they can be synthesized de novo.

3.2.1. Biologic substances: animal

Animal filler substances include subdermic connective tissue, adipose tissue, fascial tissue, tendon tissue, muscular tissue, or osseous tissue. Autologous subdermic tissue removed from patients who underwent direct lip lift (DLL), (Kesselring, 1986) upper eyelid blepharoplasty or rhytidectomy-blepharoplasty (Fezza et al., 2003) and rhytidectomy (Sykes and Emery, 1995) has been used for lip augmentation. Lip filling with connective tissue from the capsule of

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Table 1
Studies included in the review.

	Reference	Year	Technique	LOE	Patients *n*	Age (years)*	Sex **	FU (months)	Efficacy outcome measurement	Compli-plicatons	Time direction of the study	Rando-mized	Con-trol	Blinded
1	Fezza	2003	Dermis: upper eyelid dermis from blepharoplasty	IV	14	67 (38 to 79)	0	6	Average lip score (10 point scale)	Yes	Retrospective	No	No	No
2	Tobin	1998	Alloderm	IV	12	52	1.6%	7	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
3	Rohrich	2000	Alloderm	IV	47	42	4.2%	12	Satisfaction survey patient	Yes	Retrospective	No	No	No
4	Scalfani	2002	Cymetra / Zyplast	Ib	44	NR	NR	12	Anthropometric measurements, frontal and lateral view	Yes	Prospective, Multicenter	Yes	Yes	Yes
5	Braun	2008	Collagen: Evolence	IV	20	NR	0	NR	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
6	Landau	2008	Collagen: Evolence Brzz	IV	16	42-61	0	3	Satisfaction survey patient (3)	Yes	Retrospective	No	No	No
7	Landau	2009	Collagen: DermicolP35	IV	15	52.3	0	3	Satisfaction survey patient (3)	Yes	Retrospective	No	No	No
8	De Boulle	2009	Collagen: DermicolP35	IV	51	44.2	2%	4, 10	Satisfaction survey patient Satisfaction survey clinician	Yes	Retrospective Multicenter	No	No	No
9	Downie	2009	Collagen: PRI-1, PRI-2, Zyplast, Perlane.	Ib	79	NR	0	9, 12	Satisfaction survey patient (5) 3D stereophotogrammetry, 2D analysis (CKC scale)	Yes	Prospective	Yes	Comparative	Double blind
10	Bousquet	1999	Hylan: Restylane	IV	192	46	0	8, 8	Surgeon and patient´s 'eye'	Yes	Prospective Consecutive series	No	No	No
11	Bosniak	2004	Hyal: Restylane	IV	1146 685 lip	50.5+/-10.2	28.8%	3, 6, 9	Four point scale physician evaluator score	Yes	Retrospective Consec. Series	No	No	No
12	Jacono	2008	Hyal: Restylane	IV	66	45.8+/-NR	6.1%	9	Patient satisfaction (5)	No	Retrospective Consec. Series.	No	No	No
13	Glogau	2011	Hyal: Restylane /Placebo	Ib	180 135 lip	47.6+/-10.6	0.6%	8w, 24w, 9m	Medicis lip fullness scale (5) Global aesthetic improvement scale (9)	Yes	Prospective Parallel	Yes	Yes	Evaluator blind
14	Eccleston	2012	Hyal: Juvéderm volvella	IIb	60	50 21-74	0	6, 9, 12	Overall satisfacton (11)	Yes	Prospective Multicenter	No	No	No
15	Fagien	2013	Hyal: Juvéderm Ultra	IIb	50	47 24-68	4%	6, 5	Lip fullness scale (4) Photographic scales (4) Investigator satisfaction (11) Patient satisfaction (11)	Yes	Prospective Multicenter	No	No	Evaluator blind
16	De Benito	1996	Galea and subgalea	IV	42 (31 FU)	NR	NR	24	Satisfaction survey patient (3)	Yes	Retrospective	No	No	No
17	Leaf	2002	SMAS from rhytidectomy	IV	103 (11FU)	NR	3,8%	24	Questionnaire 54 pcs	Yes	Retrospective	No	No	No
18	Recupero	2010	SMAS, PAF, DLL+SMAS, DLL+PAF	IIb	39 (14/10/8/7)	56, 62, 57.38	NR	6, 12	Lip fullness grading scale (5) : validated	Yes	Prospective Cohort	No	Comparative	Single blind analysis
19	Bohluli	2013	Temporalis fascia	IV	19	31.7+/-7.7	10,5%	19	Quantitative analysis of upper-lip projection and vermillion show	No	Prospective	No	No	No
20	Trussler	2008	Palmaris longus tendon	IV	38 (21cosmetic patients)	39 cosmetic patients	NR	12	Upperlip augmentation measurements outcomes , upper lip dynamic smile outcomes, physician satisfaction, patient satisfaction	No^	Retrospective	No	No	No
21	Botti	1995	Ms Lip-cheek/lip flap	IV	28	NR	NR	NR	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
22	Ponzielli	1997	Ms latissimus dorsii	IV	10	23–51	2%	17	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
23	Argawal	2010	Ms SCM from rhytidectomy(25)/control(25)	IIIb	50 (25/25)	NR	NR	24	Frontal and lateral anthropometric measurements	Yes	Retrospective Cohort	No	Yes	No
24	Sklar	2004	CaHA: Radiance	IV	101 15 lips	NR	NR	6	Patient´s 'eye'	Yes	Retrospective	No	No	No
25	Jansen	2006	CaHA: Radiesse	IV	609 338 Lips	NR	NR	6	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
26	Jacovella	2006	CaHA: Radiesse	IV	10	NR	NR	18	Patient survey (3)	Yes	Retrospective	No	No	No
27	Scarano	2009	Agarose: NewFill	IV	68	52 35–70	4.4%	NR	Score of satisfaction pcs (10)	Yes	Retrospective	No	No	No
28	Mladick	1992	Siloxane: Bioplastique	IV	40 18 lip	NR	NR	12	Satisfaction survey patient (5)	Yes	Retrospective	No	No	No
39	Fulton	2005	Siloxane: Silikon 1000	IV	608	38	2.9%	72	Surgeon and patient´s 'eye'	Yes	Retrospective	No	No	No
30	Moscona	2010	Siloxane: Siluron 1000	IV	179	35% were 20–30	NR	36	Satisfaction survey patient (5) Softness lips scale (5)	Yes	Retrospective	No	No	No
31	Linder	1992	Eptfe: Gore-Tex	IV	15 21 lips	29 18–55	4.7%	14	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
32	Wang	1997	Eptfe: Gore-Tex	IV	17	36.7	0	6	Anthropometric measurements	Yes	Retrospective	No	No	No
33	Brody1	2001	Eptfe: Softform	IV	31 8 lips	NR	NR	NR	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
34	Hanke1	2002	Eptfe: Advanta	IV	11 lips	NR	NR	NR	Surgeon´s 'eye'	Yes	Retrospective	No	No	No
35	Verret	2006	Eptfe: Advanta	IV	102	NR	NR	NR	Photographic comparison pre- and post-rated by independent observers	Yes	Retrospective	No	No	No
36	Redbord	2008	Eptfe: Advanta	IV	33 13lips	NR	NR	60	Patient satisfaction survey (5)	Yes	Retrospective	No	No	No
37	Cohen	2004	PMMA: Artecoll /control Zyplast	Ib	69 lip 59 lip control	NR^	NR^	1, 3, 6, 12	Masked observers ratings using the FFAS (5) Investigator ratings using the FFAS (5)	Yes	Prospective Multicenter (8 centers)	Yes	Yes	Double Blind
38	Cohen	2006	PMMA: Artefill /control Zyplast	IIb	58 lip 53 lip control	NR^	NR^	1, 3, 6, 12	Masked observers ratings using the FFAS (5) Investigator ratings using the FFAS (5)	No^	Prospective Multicenter (8 centers)	No	Yes	Patient and evaluator blinded.

Red squares: no quality data available on complications or no quality data available on outcomes; yellow squares: good quality markers. Age (years)*: mean age of the patients; sex**: % of males included in the study; FU: follow-up, in months; NR^ the variable was not stratified for the subjects who received lip infiltration, and is only described as a general mean of all the subgroups of the study; control: use of a control group.
Abbreviations: CaHA calcium hydroxylapathite; DLL direct lip lift; EPTFE: expanded polytetrafluoroethylene; FFAS facial fold assessment scale; Hyal: hyaluronate; LFS: lip fullness scale; LOE: level of evidence; ms: muscle; PAF post auricular fascia; SCM: sternocleidomastoid muscle; SMAS, superficial muscular aponeurotic system.

a breast implant capsule has also been reported (Isenberg, 1996). Acellular connective tissue matrix of human cadaver origin has been used in lip augmentation, either as sheets (*Alloderm*), particulates (Yoder and Elliott, 2010; Tobin and Karas, 1998; Kridel, 1998; Castor et al., 1999; Rohrich et al., 2000; Wyatt et al., 2002; Duncan, 2003) or particulate form (*Cymetra*, 123 μm particles) (Sclafani et al., 2002). Acellular connective tissue matrix from porcine small intestinal submucosa (*Surgisis*) has also been used for lip augmentation (Seymour, 2008). This product augmentation is composed of type 1 collagen, hyaluronic acid, heparin, heparin

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Table 2
Classification of fillers for facial and lip augmentation.

FILLER SUBSTANCE				Main features					Cross link	PS μm	LIFE (m)	NAME	Year	Sts	Lip
BIOLOGIC	ANIMAL	DERMIS	CONNECTIVE TISSUE	Human autologous, from white lip skin after direct lip lift.							>12?	Upper and lower lip connective tissue	1986	X	X
				Human autologous, from pre/post auricular skin after rhytidoplasty.							>12?	Pre and post-auricular connective tissue	1995	X	X
				Human autologous, from upper eyelid skin after blepharoplasty.							>12?	Upper eyelid connective tissue	2003	X	X
				Human autologous, from breast implant capsule after revision.							>12?	Breast implant capsule	1996	X	X
			FIBROBLASTS	Human autologous, fibroblasts from the retroauricular fold							12-24	Isolagen#, Azficel-T (Fibrogen Sciences, US)	1998	X	-
			ACELLULAR MATRIX	Human cadaver skin	Micronized and injectable					123	12	Cymetra (LifeCell US)	2000	X	X
					Sheets not micronized						6-12	Alloderm (LifeCell US)	1995	X	X
				Porcine	Intestinal mucosa							Surgisis (Cook Biotech Inc, US)	2008	X	X
			ELASTIN	Synthetic	With bovine collagen						12	Endoplast-50 (Filorga Laboratoires, France)#	1998	-	-
			COLLAGEN	Bovine	Non cross linked + lidocaine						3-4	Zyderm (Inamed corporation, US)^	1981	X	-
					3.5% cross-linked collagen + lidocaine						3-4	Zyplast (lip) (Inamed corporation, US)^	1985	X	X
				Porcine	Cross-linked with glycation, type I collagen		Injectable		GA		12-24	Evolence^DermicolP35 (OrthoDermatologics US)	2004	X	X
							Injectable		GA		6-9	Pri 1 Pri 2 (PRI-2 more cross-link) (Covidien US)	2006	X	X
							In sheets		GA		6-9	Permacol (Covidien US)	2003	X	X
				Human	Non-recombinant	Autologous					3-4	Autologen (Collagenesis Inc. US)^^	1995	X	X
						Homologous					3-4	Dermalogen (Collagenesis Inc. US)^^	1995	X	X
					Recombinant	Non cross-linked					4-6	Cosmoderm (Allergan-INAMED, US)^	2003	X	X
						Cross-linked					4-6	Cosmoplast (Allergan-INAMED, US)^	2003	X	X
							Type III collagen				?	FG-5017, FG-5016 (FibroGen US)	2005	-	-
			HYALURONATE	Avian	Cross-linked				DVS		4-6	Hylaform (Inamed Corporation US)^	2004	X	-
				Bacterial (S. equi)	Non cross linked -						6	Revanesse (Boston Medical Group Ltd, US) Hyaluderm (Lca pharmaceutical, France)	2010	-	-
					Cross-linked	Single	Mono-phasic	Monoden-sified.	BDDE	300	6-9	Juvéderm (Allergan, US)	2006	X	X
									BDDE		6-9	Teosyal (Teoxane, Switzerland)	2005	X	-
								Polyden-sified	BDDE		4-6	Belotero (Merz Pharmaceuticals US)	2011	X	-
									BDDE		6-9	Esthelis (Anteis, Switzerland)	2005	X	-
									DVS		3-6	Captique^, Prevelle Silk (Mentor corp, US)	2004	X	-
							Poly-phasic	Superficial	BDDE	250	6-9	Restylane (Medicis Aesthetics, US)	2005	X	X
								Deep	BDDE	550	6-9	Perlane (Medicis Aesthetics, US)	2007	X	X
							?¿		BDDE		6-12	Emervel (Galderma, Switzerland)	2011	X	-
						Double	Mono		DEO		6-9	Puragen, Prevelle Dura(Mentor, US)	2004	X	-
		FAT	GENERAL FAT	Human, autologous, from abdomen, thigh or submental							Semip	General fat	1893	X	X
			BUCHAL FAT PAD	Human, autologous							Semip	Buccal fat pad	2013	X	X
			PRESACRAL FAT	Human, autologous (connective tissue + underlying fat)							Semip	Presacral fat	2000	X	X
		FASCIA	FASCIA LATA	Human cadaver						500	3-4	Fascian (Fascia Biosystems, US)	1994	X	X
			SMAS	Human, autologous							Semip	Smas	2002	X	X
			GALEA	Human, autologous							Semip	Galea and subgalea	1996	X	X
			TEMPORALIS FASCIA	Human, autologous							Semip	Temporalis fascia	2013	X	X
		TENDON	PALMARIS LONGUS	Human, autologous (10% do not have palmaris longus tendon)							Semip	Palmaris longus tendon	1995	X	-
		MUSCLE	LATISSIMUS DORSI	Human, autologous							Semip	Latissimus dorsi	1997	X	X
			ORBICULARIS	Human, autologous, during an upper eyelid blepharoplasty							Semip	Orbicularis oculi	2009	X	X
			SCM	Human, autologous, during a rhytidectomy							Semip	Scm	2010	X	X
			ORBICULARIS ORIS	Human, autologous, superior orbicularis oris plicature 'flipping flap'							Perm	Orbicularis oris	2013	-	X
				Human, autologous, superior or inferior orbicularis oris flap							Perm		1995	-	X
			BUCCINATOR	Human, autologous, with a cheek-lip flap							Perm	Buccinator	1995	X	X
		BONE	B-TCP	With hyaluronic acid gel							NR	Atlean (Stiefel Laboratoires, US)	2007	X	-
			CaHA	Synthetic microspheres						25-45	9-12	Radiance, Radiesse (BioForm, US)	2006	X	X
	NON ANIMAL	AGAROSE	AGAROSE	1–2% Agarose							5	Easy-Filler (Tracom, India) Easy-Agarose (Sifarma, Italy)	2007	X	X
		DEXTRAN	DEXTRAN	Synthetic	2.5% Dextran + 2% Hylan (Bacterial origin)					40	12-24	Reviderm intra (Canderm Pharm Canada)^^	1997	-	-
					Cross linked Dextran (Sephadex)					40-60	12-24	Reviderm (Canderm Pharma, Canada)^^	1997	X	-
					Cross linked + Diethyletanolamine (DEAE)					80-120	12	Matridex+, Crm-DEX (Biopolymer, Germany)	2005	-	-
		ALGINATE	ALGINATE	Reticulate alginate in ringer-lactate solution.							Semip	Novabel (Merz Farmaceuticals, Germany)	2009	-	-
NON BIOLOGIC		PARAFFIN	HENTRIACONTANE	Solid. Fusion threshold at 60º Celsius							Perm	Paraffin	1896	X	-
		PETROLEUM	DIISONONYLPHTHALATE	Solid. Fusion thershold at 40º Celsius							Perm	Vaseline (Chesebrough Manufacturing, US)	1899	X	-
		SILOXANE POLYMERS	PDMS	Liquid							Perm	Adatosil 5000, Silikon 1000 (Alcon, US), Siluron 1000 (Fluoron, Germany)	1997	X	X
				Solid	Tubes						Perm	Permafacial (SurgiSil, US)	1997	X	X
					Microspheres + polyvinylpyrrolidone					100-600	Perm	Bioplastigue (Bioplasty Inc, US)	1990	X	X
		POLYETHER	PE	Solid and rigid synthesized microspheres of PE								Medpor (Stryker corp, US)		X	-
			PEO	+ Carboxymethylcellulose (carrier)							Semip	Profill, Laresse (FZIOmed, US)#	2006	-	-
			E-PTFE (GORE-TEX)	With 22 μm pores.							Perm	SAM, Polytef (W. L. Gore & Associates, US)	1972	X	X
				3.2 mm 22 μm pore tube-shaped (Ultrasoft: thin-wallet version)							Perm	Softform, Ultrasoft (Tissue Tech, US)#	1997	X	X
				With 40 μm (outer layer) and 100 μm (center) pores.							Perm	Advanta (Atrium Medical Corporation, US)	1996	X	X
		POLYESTER	L-PLA	Microparticles						40-63	12-24	Sculptra (for vih) NewFill (Dermik, US)	2004	X	-
			PCL	+ Carboxymethylcellulose (carrier)						25-50	6-12	Ellansé (Aqtis Medical, Holland)	2010	X	-
		ACRYLATE POLYMERS	HEMA + EMA	240% HEMA + 1.14% cross-linked hyaluronic acid (bacterial origin)						45-110	Semip	Dermalive, Dermadeep (Dermatech, Paris)	1998	X	X
			PMMA	20% PMMA + 3.5% bovine collagen (Artefill has 0.3 ml of lidocaine)						30-50	Perm	Artecoll, Artefill, (Suneva Medical US)	2006	X	X
			PEGA	4% PEG + 90% non-pyrogenic water.							18-24	Remake (Innova Pharma, Italy,)	2008	-	-
		POLYVINYL	PVA	8% PVA + 92% water.							12-18	Bioinblue (Polymekon S.r.l. Italy)#	2006	-	-
		AMIDE POLYMERS	PAAG	5% cross-linked PAAG + 95% water. No microspheres							Perm	Aquamid (Contura, Denmark)	2003	X	X
				+Co-DADMA	Without polyvinyl						110	Outline Ultra (Trillium Meditech, Canada)	2001	-	-
					+ 6% polyvinylhidroxide (PVOH) microspheres					5-80	110	Evolution (Trillium Meditech, Canada)	2001	-	-
			PAIG	4% PAIG + rest water (96%)						20	Perm	Bio-alcamid (Polymekon, Italy)#	2003	X	X

In green: autologous materials; in red: the producer has discontinued manufacture. ˆdiscontinued (Gilbert et al., 2012); ˆˆCollagenesis Inc went out of business in 2006; Sanofi-Aventis acquired Canderm Pharma; # the product is no longer available on catalog; **X**: studies found; - no studies found.

Abbreviations: μm: micrometres; BDDE: 1,4-butanediol diglycidyl ether; B-TCP: β tri-calcium phosphate; CaHA: calcium hydroxylapathite; cross-link: substance with which a certain filler is crosslinked; DADMA-co: diallyl dimethyl ammonium chloride; DEO: 1,2,7,8-diepoxyoctane; DVS: divinylsulphone; EMA: ethylmethacrylate; e-PTFE: expanded polytetrafluoroethylene; GA: glutaraldehyde; GORE SAM: gore-tex subcutaneous augmentation material; HEMA: hydroxiethylmethacrylate; LIFE: life of the product after injected; Lip: studies found for lip augmentation; L-PLA: poly-L-lactic acid; m: months; NR: not reported; PAAG: polyacrylamide gel; PAIG: polyalkylimide gel; PCL: polycapronolactone; PDMS: polydimethylsiloxane; PE: polyethylene; PEG: polyethylene glycol diacrylate; PEGA: polyethylene glycol acrylate; PEO: polyethylene oxide; Perm: permanent; PMMA: polymethylmethacrylate; PS: particle size; PVA: polyvinyl alcohol; Rec: recombinant; Sts: studies found for a specific filler in facial augmentation; Superf: superficial; Semip: semipermanent; Scm: sternocleidomastoid muscle; US: United States of America.

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sulfate, chondroitin sulfate, and dermatan sulfate. It contains more glycosaminoglycans than *Alloderm* (Beatty et al., 2002). *Alloderm*, *Cymetra*, and *Surgisis* are terminally sterilized, so they contain no infectious agents (such as human immunodeficiency virus [HIV] or hepatitis C virus [HCV]), and they elicit no immunologic response from host tissue, so they require no skin testing prior to use (Yoder and Elliott, 2010; Beatty et al., 2002; Badylak et al., 1998). Both *Alloderm* and *Surgisis* can be rehydrated in sterile saline or ringers lactate solution in 5 min, and they can be rolled and sutured before being introduced into the lip (Seymour, 2008; Tobin and Karas, 1998).

Since 1998, cultured human dermal fibroblasts have also been used for dermal renovation (of depressed scars) and soft tissue augmentation (Boss et al., 1998; Smith et al., 2012), but no study has focused specifically on their use in the lips. The *Isolagen* autologous cell system (Isolagen Inc., US) requires a small skin biopsy at an inconspicuous site (typically in the post auricular fold) to obtain fibroblast cells that are subsequently cultured to generate several million cells (Weiss et al., 2007) fluctuating the price of the whole procedure between £2500 and £5000 (€3200 and €6000). One study, for patients treated with fibroblast injections in the nasolabial fold, had an 81% positive response rate at 6 months compared with 36.4% for placebo ($p < 0.05$) (Weiss et al., 2007). These results were consistent with an animal study where fibroblast injections reported reductions in large rhytids and depressed facial scars by 10%–85%, as measured by profilometry in Sprague Dawley rats (Boss et al., 1998). Solakoglu (2008) found that injected fibroblasts were well tolerated, stable, and long lasting, and they significantly increased the number of blood vessels and colonization of capillary-associated macrophages, as observed by electron microscopy.

In November 2006, Isolagen Inc. announced the proposed closure of Isolagen Europe Ltd., and in 2009, Isolagen Inc. began operating as a subsidiary of Fibrocell Science, under the name Fibrocell Technologies Inc. This was accompanied by a name change from *Isolagen* to *Azficel-T* (Laviv). In April 2013, Fibrocell Science announced its Phase 2 study to evaluate the safety and efficacy of *Azficel-T* for the treatment of patients with moderate-to-severe acne scars (Munavalli et al., 2013). We believe that the use of self-cultured fibroblasts is a promising strategy, and although research in this field diminished in the past 10 years, it now appears to be increasing again.

Certain connective tissue macromolecules can also be injected to add volume to the lips. The extracellular matrix is primarily composed of three groups of macromolecules: elastin, collagen, and glycosaminoglycans. The latter include hyalurine, heparin, heparin sulfate, dermatan sulfate, keratin sulfate, and chondroitin sulfate. In 1998, Filorga Laboratories (France) launched *Endoplast-50*, filler composed of solubilized elastins combined with bovine collagen (Tordjman, 1998). Elastin appears to influence the proliferation of fibroblasts, increasing collagen production and stimulating endothelial cells (Tordjman, 1998). Filorga Laboratoires does not currently mention *Endoplast-50* on its website, and no study about this filler has been published since 1998, so it is likely that production of this filler has been discontinued.

The fibrillar protein collagen is the main component of connective tissue, comprising approximately 30% of protein in the entire body (Di Lullo et al., 2002), and the major subtype of collagen in connective tissue is type I collagen. A bovine substitute of human type I collagen was patented in the US in 1976 (Daniels and Knapp, 1976), and was used for soft tissue augmentation in 1977 (Knapp et al., 1977). The first commercially available bovine collagen was *Zyderm* in 1981 (Stegman and Tromovitch, 1980), a non-cross-linked prototype used for lip augmentation, which was subsequently followed by *Zyplast* in 1985 (Kligman and Armstrong, 1986), which was cross-linked with glutaraldehyde to resist deterioration. It was assumed that by cleaving the telopeptide from the central helical portion of the bovine collagen molecule, the compound would be non-immunogenic. However, this process probably further destabilized the molecule and yielded incomplete collagen fragments that possibly enhanced immunogenicity. Rates of allergic reactions to bovine collagen ranged from 3% to 10% (Charriere et al., 1989; Barr and Stegman, 1984), so allergy tests were required prior to its use. Another drawback of *Zyderm* and *Zyplast* was their short life after injection: only 3 months.

Human type I collagen fillers were developed at the end of the 1980s. The first of these substances were manufactured by Collagenesis (US) under the names *Autologen* and *Dermalogen*, beginning in 1995. *Autologen*, an autologous injectable human tissue collagen matrix, was a dispersion of collagen fibers and tissue matrix produced from a sample of the patient's skin, which was generally obtained during an aesthetic plastic surgical procedure. The excised skin was sent to Collagenesis, where customized collagen was produced for that patient. Three injections, administered over several weeks, were required to fully correct most dermal defects. The procedure was associated with negligible inflammation and no allergic reactions. Positive aesthetic results persisted for more than 12 months (Fagien and Adams, 2000). *Dermalogen* was an injectable human collagen matrix derived from tissue donors, so it did not require a preceding surgical procedure. Blood samples from donors were screened for several infectious agents and skin tests were recommended before treatment, although allergic or chronic granulomatous reactions had not been reported (Fagien and Adams, 2000). Collagenesis went out of business in 2006 and *Autologen* and *Dermalogen* are no longer available.

In 2003, recombinant type I human collagen was launched on the market under the name *Cosmoderm* (non-cross-linked human collagen) and *Cosmoplast* (cross-linked human collagen). *Cosmoderm* was used for the correction of upper lip rhytids, and *Cosmoplast* was used for lip augmentation. The duration of *Cosmoderm* and *Cosmoplast* after injection was approximately 6 months, which was longer than that of *Zyderm* and *Zyplast* (Bauman, 2004). Since late 2010, Allergan-Inamed Corporation (US) stopped manufacturing *Zyderm*, *Zyplast*, *Cosmoderm*, *and Cosmoplast*, because of the lack of demand for these products (Gilbert et al., 2012).

In 1997, porcine type I collagen was introduced on the market and offered the advantages of a longer life after injection (ranging from 6 to 24 months) and there was no need to perform skin tests prior to use because of its high structural similarity to human collagen. *Permacol* (collagen sheet) was launched by Tissue Science laboratories in 1997 and its use in the lower lip after the excision of an angioma has been described (Benito-Ruiz et al., 2006). Also two *Permacol* injectables launched in 2006, named *PRI-1* and *PRI-2* (*PRI-2* has more crosslinking than *PRI-1*), have been used for lip augmentation (Downie et al., 2009). The duration of *Permacol*, *PRI-1*, and *PRI-2* after injection ranges from 6 to 9 months (Downie et al., 2009). Other porcine collagens had even longer lives: *Evolence* (launched in 2004 by Colban LifeScience, Israel) and *Dermicol-P35* (launched in 2008 by Ortho Dermatologics, US) persisted for 12–24 months after injection and these substances produced promising results in several studies (Landau, 2008, 2009, Braun and Braun, 2008; De Boulle et al., 2009). However, *Evolence* was discontinued by Johnson & Johnson because of poor sales after it purchased Colban LifeScience, and *Dermicol-P35* was discontinued by Valeant pharmaceuticals after it bought Ortho Dermatologics.

Since 2010, no collagen fillers have been available in the US. Nevertheless, in the European Union (EU), two bovine collagen fillers are approved for cosmetic use: *Sunmax i-plus* (2009, Sunmax Biotechnology, Taiwan (Clinicaltrials.gov, 2013)) and *Therafill* (2010,

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Sewon Cellontech Co., South Korea). These substances are also used in the Asian market. Studies are required to assess their efficacy. *FG-5017*, a recombinant human (rh) cross-linked type III collagen developed by Fibrogen Inc. (US), was evaluated for approval in the US as a facial filler for cosmetic surgery (Miinews.com, 2009). This product failed to be marketed, but *FG-5016*, another cross-linked rhIII collagen (Liu et al., 2009) is currently available from Fibrogen Inc., although no studies have been published regarding its use in soft tissue, facial, or lip enhancement.

Hyaluronan or hyaluronic acid (HA) is a glycosaminoglycan polysaccharide composed of alternating residues of the monosaccharides D-glucuronic acid and N-acetyl-D-glucosamine. It is found naturally in the mammalian extracellular matrix and has no species specificity, unlike collagen. The volume-enhancing effects of HA occurs through its considerable ability to bind water. In addition, HA interacts with the fibroblast CD44 receptor, which promotes collagen synthesis and normal skin function. Hylan B is a divinylsulfone (DVS)-cross-linked hyaluronan, derived from rooster combs. It was developed in 1989 (Larsen et al., 1993; Balazs et al., 1989). It was first used as a facial filler in the year 1995 (Larsen et al., 1995) and later entered the market under the name *Hylaform*. It had a duration of up to 4–6 months in the dermis (Manna et al., 1999). Inamed corporationCo (US) stopped producing *Hylaform* in 2004 (Gilbert et al., 2012).

The majority of HA used in cosmetic surgery is produced by fermentation of strains of the bacteria *Streptococcus equi*. Non-animal HA can be cross-linked or not cross-linked with other molecules. Crosslinking of HA impedes the destruction of HA by hyaluronidase. Cross-linked HA products are either biphasic or monophasic. In biphasic products, cross-linked HA is sieved through a screen to isolate particles of a uniform size. *Restylane* is a prototype cross-linked biphasic HA, which has been used as a soft-tissue filler since 1998 (Olenius, 1998; Duranti et al., 1998). *Restylane* (250 μm HA particles) and *Perlane* (550 μm particles) are 1,4-butanediol diglycidyl ether (BDDE) cross-linked HA products that have been extensively used for lip enhancement (Bousquet and Ågerup, 1999; Bosniak and Cantisano-Zilkha, 2001; Bosniak et al., 2004; Jacono, 2008; Solish and Swift, 2011; Glogau et al., 2012; Rzany et al., 2012) and last an average of 6–12 months.

Monophasic HA fillers are not sieved and thus contain a mixture of HA molecules of varying sizes and shapes. Monophasic monodensified HA gels blend and crosslink the HA particles in a single step, whereas monophasic polydensified fillers add additional HA and perform further crosslinking after the initial blend. *Teosyal* (Teoxane, Switzerland) and *Juvéderm* (Allergan-Inamed, US) are monophasic monodensified HA, cross-linked with BDDE, which persist up to 6–9 months when injected in the nasolabial folds (Nast et al., 2011) or the lips (Eccleston et al., 2012; Fagien et al., 2013). Belotero (Merz, US) (Kammerer, 2007), Esthélis (Anteis, Switzerland), (Hasson and Romero, 2010) and Prevelle Silk (previously called Captique, Mentor, US) (Onesti et al., 2009) are monophasic polydensified HAs.

The polydensification process creates a gel with different density zones, which allows for more homogeneous spread throughout the connective tissue, thereby producing less lumpiness. This contrasts with monodensified HA fillers, which fail to fill the smallest spaces in connective tissue, as shown in a blinded punch biopsy study comparing three classes of HA fillers (Flynn et al., 2011). Belotero and Esthélis are BDDE-cross-linked and persist up to 6–9 months after injection; Prevelle Silk is DVS-cross-linked and persists for 4–6 months. A hypothetically longer effect could be achieved with the double cross-linked (with 1,2,7,8-diepoxyoctane) HA fillers, Puragen and Prevelle Dura, but their production was discontinued by Mentor (US) in 2010 and 2012, respectively. Revanesse (Boston Medical Group Ltd, US) and Hyaluderm (LCA Pharmaceutical, France) are examples of non-animal non-cross-linked HAs, but studies evaluating these fillers are lacking. Emervel (Galderma, Switzerland) is claimed to be the longest lasting HA filler on the market, but no quality evidence is available to support this statement (Rzany et al., 2011).

Fat tissue has also been used for face and lip augmentation. The first adipose tissue autograft in the face, using fat that was grafted in a single block, was reported in 1893 by Neuber. In 1919, Brunning reported a grafting technique using small-to-medium-sized adipose pieces. Smaller pieces (4 mm) were used by Ellenbogenin (1986) during his 'greffe en perle' method. Fournier introduced 'Lipofilling' of the face in 1985 after the invention of liposuction. This allowed fat obtained by liposuction to be grafted, without the need for an additional surgical procedure. In 1995, a refined method of lipofilling called 'lipostructure' was described by Coleman: after fat is obtained by liposuction, it is centrifuged to isolate the adipose stem cells layer. However, the survival rate of grafted fat is variable, ranging from 40 to 80% (Gir et al., 2012), depending on the investigator, and the reasons for this variability are unclear. The 'greffe en perle' (Gatti, 1999; Churukian, 1997) and Fournier techniques (Colic, 1999; Fulton et al., 2000; Bertosi et al., 2003) have both been used for lip augmentation, also along with DLL (Jacono and Quartela, 2004; Haworth, 2004). Only one study using the Coleman fat grafting technique has focused specifically on the lips, but in this study, centrifugation of the fat was not performed (Hopping, 2010). Buccal fat pads have also been used for lip augmentation (Rubio-Bueno et al., 2013), as well as a 'block' dermo-adipose graft harvested from the presacral area (Chasan and Rahban, 2000).

Fascial tissue has been used for lip augmentation since 1995 (Hinderer, 1995). De Benito published a retrospective study of his results for grafting galea and subgalea tissue; morbidity at the donor site was the major drawback of the technique (De Benito and Fernandez-Sanza, 1996). The use of superficial muscular aponeurotic system (SMAS) grafts harvested from a simultaneous post-auricular rhytidectomy (Leaf and Firouz, 2002; Recupero and McCullough, 2010), post-auricular fascia grafts (Recupero and McCullough, 2010), and temporalis fascia (Hinderer, 1995; Bohluli et al., 2013) have also been described for lip augmentation. Preserved particulate (2000 μm, 500 μm, and 250 μm) fascia lata, derived from screened human cadavers, was launched on the market under the name *Fascian* (Koontz, 1926). It was first used for lip enhancement in 1997 (Burres, 1999). However, it required the use of wide-bore (18 gauge) needles (Shore, 2000) and it has been reported as low durability, with 50% of the material lost in 3–4 months (Burres, 1997). *Fascian* is no longer being produced, Fascia Biosystems (US) cannot be found anymore.

Sinewy autografts from the palmaris longus tendon have been used for lip augmentation with good results; however, this tendon is not present in 5% of the population and morbidity at the donor site can be problematic (Davidson, 1995; Trussler et al., 2008; Trussler and Bradley, 2009).

Lip augmentation has also been accomplished with muscle autografts. A 1997 report described the use of latissimus dorsi strip grafts for lip augmentation in 10 patients (Ponzielle et al., 1997), and a 2010 study described the placement of sternocleidomastoid muscle and fascia grafts into the lips of 25 patients during a concurrent facial rhytidectomy (Agarwal et al., 2010). The use of Orbicularis oculi strips obtained from the upper eyelid during superior blepharoplasty has also been reported (Citarella et al., 2009; Tarallo et al., 2010). . The use of 'lip–lip' and 'cheek-lip' flaps has been used to bring viable muscle to the lip from the opposite lip or buccinator muscle, respectively. The aesthetic results of these flaps have been quite acceptable (Botti and Villedieu, 1995). The use of an orbicularis oris flipping flap was recently

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reported in a single patient to fill an undeveloped philtrum (Choi et al., 2013).

Although bone grafts have not been used for lip enhancement because of their rigidity, calcium phosphate derivatives have been evaluated. In 2007, ABR Invent (France) developed Atlèan, a β-tricalcium phosphate-based filler for soft tissues. The manufacturer claimed that β-tricalcium phosphate helps stimulate the production of new collagen (Walker, 2009). Stiefel (a company that belongs to GSK, US) subsequently purchased ABR Invent, and Atlèan is no longer being produced. Radiesse (previously called Radiance) (Sklar et al., 2004; Tzikas, 2003), is another bone-like derivative. It has been on the market since 2006. It is a subdermal implant composed of synthetic calcium hydroxylapatite (CaHA) microspheres, 25–45 μm in diameter, suspended in a carrier of carboxymethylcellulose. The manufacturer (BioForm, US) claims that the gel structure dissipates in vivo and is subsequently replaced by soft-tissue, so that the CaHA remaining at the site of injection is surrounded by connective tissue (Probeck and Rothstein, 1989). Radiesse has been used for lip augmentation in several studies, (Jacovella et al., 2006; Jansen and Graivier, 2006), but a high rate of nodularity has been found (Jacovella et al., 2006; Jansen and Graivier, 2006; Sankar and McGuff, 2007; Probeck and Rothstein, 1989).

3.2.2. Biologic substances: non-animal

Non-animal biologic substances have also been used as fillers. Only one study has reported the use of Agarose gel (Easy-Filler) for lip enhancement; it found that complete resorption of the gel occurred in 5 months (Scarano et al., 2009). Since 1997 dextran molecules (of bacterial origin) have been used for soft tissue filling. In 1997, Canderm Industries (Canada) launched Reviderm and Reviderm Intra (40–60 μm microspheres of dextran [Sephadex] embedded in a hylan B carrier) for soft tissue and lip augmentation; however, several undesirable effects have been subsequently reported (Lemperle et al., 2003). For instance, edematous swelling of the implants continued for more than 3 months after insertion with both of these products, and dextran beads produced the greatest amount of granulation tissue of all injectable fillers tested in a comparative histologic study (Lemperle et al., 2003). Consequently Reviderm and Reviderm Intra are no longer under production.

BioPolymer Industries (Germany) launched another biodegradable dextran-based filler, Matridex, which was composed of cross-linked HA and BDDE-cross-linked dextran microspheres (80–120 μm diameter). The efficacy of dextran fillers is at least partly explained by observations in rats that dextran beads attract macrophages to their positively charged surfaces, and the subsequent release of transforming growth factor beta (TGF-β) and interleukins from these macrophages stimulates fibroblasts to produce new collagen fibers (Eppley et al., 1994). Nevertheless, macrophages may also contribute to the delayed inflammatory reactions that have been described with Matridex (Huh et al., 2010), but studies assessing the efficacy and complications of Matridex are lacking. Matridex has more recently been renamed crm-DEX (25 mg/ml of dextran and 17 mg/ml of HA). The manufacturer claims that crm-DEX persists up to 12 months and is beneficial for treating deep wrinkles and folds (such as nasolabial and marionette), as well as for lip augmentation. However, actual clinical trials verifying the efficacy and safety of crm-DEX have yet to be done. Alginate (a seaweed derivative) was introduced in the European market as a dermal filler under the name Novabel; within 2 years, its EU quality certificate was withdrawn (Spain, 2012).

3.2.3. Non-biologic substances

The first non-biologic substance for facial augmentation was paraffin, whose use was originally reported in 1894. Paraffin is a petroleum derivative composed primarily of hentriacontane. It was a popular filler throughout the first two decades of the twentieth century (Legarde, 1903) but its use diminished as the risk of serious complications, including paraffinomas, became apparent (Kach, 1919; Bettman, 1913). Vaseline is another petroleum derivative. Its use as a filler was first described in 1899 (Gersuny, 1900). Vaseline is composed primarily of diisononyl phthalate, and after an initial surge of popularity, it met the same fate as paraffin. It achieved the same poor results as paraffin due to its low melting point (40 °C for Vaseline, versus 60 °C for paraffin) and a tendency to migrate led to poor aesthetic results (Glicenstein, 2007).

Silicone is composed primarily of polydimethylsiloxane. It was discovered in 1901 and first used in plastic surgery in 1961. Twenty-five years later, in 1986, liquid silicone was used for facial augmentation (Webster, 1986). Lip augmentation with silicone microspheres (100–600 μm) wrapped in polyvinylpyrrolidone (Bioplastique filler) (Mladick, 1992; Ersek and Beisang, 1992; Ersek et al., 1997) became a common procedure after 1991 (Alkek, 1991); but several complications, including nodularity and granulomas, have been reported (Rudolph et al., 1999; Hoffmann et al., 1999). Theoretically, increasing the viscosity in silicone could reduce these problems. So the density of liquid silicone was increased from 350 to 1000 cSt (1 centistoke is the density of the water) and launched under the name Adatosil 5000 in 1997. This has since been replaced by Silikon 1000 (Alcon, US) and Siluron 1000 (Fluoron) (Fulton et al., 2005; Christensen, 2007; Barnett and Barnett, 2007). A retrospective study of 179 patients using Siluron 1000 for lip augmentation published in 2010 reported good long-term results (Moscona and Fodor, 2010) and a low complication rate but these results have been questioned (Mercer, 2010). Many other studies have reported high complication rates associated with the use of silicone implants (Baumann and Halem, 2003; Maly et al., 2004; Nitzan et al., 2004; Schmidt-Westhausen et al., 2004; Walter et al., 2008; Bigatà, 2001). Solid tube-shaped silicone has also been used in lip enhancement, under the name Perma Facial Implant (Surgisil, US) (Narsete and Ersek, 2009).

Polyethylene oxide (PEO) is a polyether that was used as a semi-permanent dermal filler, beginning in 2006. It was manufactured by FzioMed (US) under the name Laresse (previously Profill Fziomed, 2007). This product is no longer available and we found no studies evaluating this product. Expanded polytetrafluoroethylene (ePTFE) is another polyether, which has been more successful than PEO. It was discovered in 1967 and introduced to the public under the trademark Gore-Tex/Polytef. It was first used as a prosthesis in 1972 (Soyer et al., 1972), and 20 years later, it was used as a solid, removable lip filler in the form of 1–2 mm thick cut-out sheets (Linder, 1992). In 1995, tube-shaped subcutaneous augmentation material (SAM) (Strand Gore-Tex facial implant) was introduced for lip augmentation (Ellis and Trimas, 1995; Conrad and MacDonald, 1996; Wang et al., 1997). In 1997 Softform (ePTFE with an average pore size of 22 μm) was launched onto the market. It was used for lip enhancement (Lassus, 1997; Brody, 2001) but it was relatively stiff and its small pore size allowed some tissue fixation but no tissue ingrowth. A softer version (Ultrasoft) was therefore launched in 2004. Malposition and infection were not uncommon (Wolf, 1995; Hubmer et al., 1999; Truswell and William, 2002; Rudolph et al., 2003; Fezza, 2004). Since 2001 Advanta ePTFE has a dual porosity design, with a 100 μm pore center surrounded by a smooth, medium-porosity (40 μm) outer sheath. This design gives the implant a softer feel than the previous ePTFE implants, and several authors have described its use for lip enhancement since its introduction in 2001 (Hanke, 2002; Niamtu, 2006; Verret et al., 2006; Redford and Hanke, 2008).

Two polyester compounds, poly-L-lactic acid (L-PLA) and e-polycapronolactone (PCL), are currently used as soft tissue fillers.

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Injected L-PLA hydrogel (Sculptra) stimulates a foreign body reaction, leading to local collagen production, dermal fibrosis, and facial augmentation (Salles et al., 2008). It has been used in the nasolabial folds of unhealthy individuals and in the medial cheek fat compartment in patients with HIV (Levy et al., 2008). No studies in lip augmentation have yet been reported. In 2010, the Dutch company Aqtis Medical developed Ellansé, a 50 μm microparticle PCL-based filler that lasts 6–12 months. Trials assessing its effects in the nasolabial folds are available (Moers-Capri and Sherwood, 2013), but there is a lack of data referring to the lips.

Acrylic compounds have been used for lip augmentation since 1994. Artefill (20 μm microspheres) and Artecoll/Artesense (40 μm microspheres) are acrylic fillers containing polymethylmethacrylate (PMMA). Artefill contains 20% PMMA and 80% porcine collagen and its effects on lip augmentation are well documented (Cohen et al., 2006; Salles et al., 2008; Nácul and Valente, 2009; Park et al., 2012). PMMA microspheres are smoother than other materials (such as Teflon and silicone particles), and they do not have smaller residues that can be phagocytized and thus lead to a chronic granulomatous reaction (Cohen, 2006). The manufacturer of Artefill and Artecoll, Artes Medical, US, went out of business in 2008; Suneva Medical is currently manufacturing Artefill. Artecoll has been discontinued, although a similar product with 40–60 μm PMMA microspheres is sold under the name Metacrill (Biodiet & Contorno Estético S.A., México). In 1998, an acrylic filler containing a blend of hydroxyethylmethacrylate (HEMA) and ethylmethacrylate (EMA) particles became available for use in Europe under the names Dermalive (45–65 μm HEMA-EMA particles and 40% HA) and Dermadeep (80–110 μm HEMA-EMA particles and 60% HA). However, although studies assessing their efficacy in lip augmentation are scarce (Bergeret-Galley et al., 2001; Furmanczyk et al., 2009; Naouri, 2012) production of these products has since been discontinued by their manufacturer, Dermatech (France). The polyethylenglycoldiacrylate (PEGA)-based filler Remake (Attali, 2009) has been sold since 2008 by Innova Pharma (Italy), but no studies of its use are available for review.

Polyvinyl alcohol (Bioinblue) was sold in Europe by Polymekon Research (Italy). No studies have been found regarding its use for lip enhancement and its production was discontinued in 2008 (Rzany and De Mayo, 2006).

Polyacrylamide gel (PAAG) has been sold since 2004 under the name Aquamid (US and EU), Argiform (Russia), Amazingel (Asia), and Outline Ultra/Evolution (Canada). Several complications have been documented with its use and its efficacy in lip augmentation has not been established (Buelow et al., 2005; Kalatar-Hormozi et al., 2008; Pallua and Wolter, 2010; Wolter and Pallua, 2010; Spain, 2007). Polyalkylimide gel (PAIG) entered the market in 2006 under the name Bio-alcamid. It has produced poor results in lip enhancement (Ramires et al., 2005; Ellis and Sardesai, 2008; Ramires and Miccoli, 2010) and there have been reports of complications, such as abscesses (Serrano and Serrano, 2006; Akrish et al., 2009) or granulomas (Akrish et al., 2009).

3.3. Age, sex, and follow-up (Table 1)

According to the cosmetic surgery national data bank (US) statistical report of 2012, 45.4% of patients who underwent soft tissue augmentation with fillers were 35–50 years old and 90.4% were female (Surgery.org, 2011). There is no similar data available referring specifically to FPLA.

In the studies included in this systematic review, the patients treated with lip fillers (excluding the control group patients) had a mean age of 44.7 years. A total of 16 studies either did not report the mean age of their patients, only reported the range of ages, or reported the age of the all patients, without separating those who received lip augmentation from those who underwent filling procedures in other areas of the face. Only three studies reported the standard deviation of the age along with the type of treatment received (Bosnial et al., 2004; Solish and Swift, 2011; Bohluli et al., 2013).

Only 4.17% of the patients receiving fillers were men; the percentage of men ranged from 0% in eight studies to 28% in one study (Bosniak et al., 2004). The sex of the patients was not reported in 41% of the studies.

The mean duration of follow-up was 15.4 months, with a minimum of three months in two studies (Landau, 2008, 2009) and a maximum of 72 months in one study (Fulton et al., 2005). The duration of follow-up mode was 12 months (which was the duration used in 8 of 36 studies).

3.4. Efficacy outcomes

Twenty-seven studies were selected to analyze efficacy outcomes. Only five studies used anthropometric measurements to evaluate the efficacy of the filling procedure. The remaining 22 used qualitative or quantitative surveys to evaluate efficacy. Two studies used two different 2-point scales, six studies used four different 3-point scales, two studies used four different 4-point scales, twelve studies used twelve different 5-point scales, one study used one 6-point scale, two studies used two different 10-point scales, two studies used two different 11-point scales, and one study used one 15-point scale. Only 5 of the 30 scales used have been validated: Medicis lip fullness scale (MLFS) (Kane et al., 2012); the LFGS (lip fullness grading scale (LFGS) (Recupero and McCullough, 2010); the peri oral lines scale (POLS) and oral commissures severity scale (OCSS) (Werschler et al., 2011; Cohen et al., 2011); the FFAS (facial fold assessment scale (FFAS) (Flynn et al., 2009); and the Catherine-Knowles-Clarke (CKC) scale (Downie et al., 2009). The broadly used *global aesthetic improvement scale* (GAIS) scale, which is widely used in cosmetic surgery, has not yet been validated. Patient or physician satisfaction was the feature most commonly assessed (in 20 scales). Other evaluated features were as follows: lip fullness in three scales (Solish et al., 2011; Leaf and Firouz, 2001; Recupero and McCullough, 2010), the softness in one scale (Moscona and Fodro, 2010), the lip mobility in one scale (Trussler et al., 2008) and facial folds in one scale (Cohen and Holmes, 2004; Cohen et al., 2006). The size of the needle used for filler injection generally varied between 27 and 30 gauge, and the quantity of filler injected usually ranged from 0.5 to 15 mL per lip (although fat grafting generally required 5–6 mL per lip) (Fulton et al., 2000). For the fillers produced in sheets (Alloderm, Surgisis, ePTFE), the volume was approximately (30–35)*(60–65)*(1–2) mm^3 per lip, and for tubular shape implants (Silicone, ePTFE), the volume was approximately (30–35)*(10–15)*(10–15) mm^3 per lip. Resorbable fillers usually required one or two follow-up sessions for touch-ups.

3.4.1. Autografts

Seven good quality studies were identified that used autografts as the primary lip filler (Table 3). These included four fascia/aponeurosis graft studies and one study involving each of the following: dermal grafts, tendon grafts, and muscular grafts. No good quality studies involving fat grafts in the lip were found. Only one study for dermal grafts, another for tendon grafts and one for muscular grafts in the lip have been found. As for fascia/aponeurosis grafts, four studies have been found, which makes a total of seven good quality articles about lip fillers whose main material is an autograft (Table 3).

Fezza et al. (2003) evaluates the outcomes of dermal grafts obtained during upper eyelid blepharoplasty, which were de-

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Table 3
Outcomes using autografts.

Reference	Technique	Efficacy outcome measurement				Result	Statistical signifi-cance	
Fezza	Dermis: upper eyelid skin de-epithelialized with CO_2 laser	Average postoperative lip score (10 points scale. No detailed description of the survey is given).	Average lip score pre-operative Average lip score post-operative			score 2.9 5.5	<0.0001	
De Benito	Galea and subgalea	Satisfaction survey patient (3 point scale, not validated) Excellent Satisfactory No difference	Excellent Satisfactory No difference			26% 42% 32%	NR	
Leaf	SMAS from rhytidectomy	Questionnaire (only 54 responders; 2 point scale; not validated) Fuller lips/non fuller lips	Fuller lips Non fuller lips			77% 33%	NR	
Trussler	Palmaris longus tendon	**Upper lip measurements:** % augmentation mean [(postoperative vertical measurement/preoperative vertical measurement) ×100] +/− SD. Vertical measurements: - Tubercle (distance from Ls to Stos) - Cupid's bow (left/right): distance from Ls' to Stos'. - Midlateral lip (left/right): distance from the intermediate point of the upper vermillion border (between Ls' and Ch) and Stos' Lateral measurements: - Lateral projection: distance from the most anterior point of the upper lip (Lsa) to the line that goes from N to ANS, with an angle of 90°.	Midlateral lip left Cupid's bow left Tubercle Cupid's bow right Midlateral lip right Mean vertical height Lateral projection			190 ± 3 194 ± 4 198 ± 4 193 ± 3 189 ± 3 192 ± 3 184 ± 7	<0.05 <0.05 <0.05 <0.05 <0.05 <0.05 <0.05	
		Upper lip dynamic smile outcomes 1) Lip mobility score (5 point scale) 2) Smile strength Fomula: {[(ch−ch smile)/(ch−ch rest)] ×100} **Physician satisfaction** (5 point scale: 0 dissatisfaction; 4 totally satisfied) **Patient satisfaction assessment** (5 point scale: 0 dissatisfaction; 4 totally satisfied)	Mean lip mobility scale in post-op Mean lip mobility at 12 months Smile strength in post-op Smile strength at 12 months post-op Mean satisfaction at 1 day post-op Mean satisfaction at Mean satisfaction post-op Mean satisfaction at 12 months FU			4.7 4.8 98 99 3.4 3.6 3.7 3.4	*p*>0.05 *p*>0.05 *p*>0.05 *p*>0.05	
Recupero	SMAS, PAF, DLL + SMAS, DLL + PAF	Lip fullness grading scale (5 point scale (validated (Kesselring, 1986))) 0 very thin 1 thin 2 moderately thick 3 thick 4 full Pre-op ratings compared to 6 months follow up and 12 months post-operative rating among the four treatment groups (SMAS, PAF, DLL + SMAS, DLL + PAF). They evaluate which is the group that has the largest score increase.		Pre-op	12 m post-op	12 m Post-op	The DLL + SMAS group has the largest score increase at 12 months post-operation.	Every pre- and post-operative score among each group is compared and all of them are statistically significant with $p < 0.001$	All of the comparisons between pre/6 m post and pre/12 m post were P < 0.001
			SMAS	0.81	1.76	1.714			
			PAF	1.1	2.36	2.26			
			DLL + SMAS	0.3	1.792	1.917			
			DLL + PAF	1.04	2.524	2.429			

				Preoperative		Postoperative		Change		
				Mean	SD	Mean	SD			
Bohluli	Temporalis fascia	Quantitative analysis of vermillion show (frontal view) and upper lip projection (lateral view):	Upper lip Vermillion show	3.8 ± 1.33		4.79 ± 1.30		21%		0.001
		- Upper lip vermillion show: distance between the white roll and the lowest point in the upper lip (Ls to Stos).	Upper lip projection	−0.07 ± 1.84		1.08 ± 1.14		52%		<0.001
		- Upper lip projection: the distance between Steiner's line (Cm to Pg') and the most anterior upper lip vermillion point (Lsa), being the two lines orthogonal. The points anterior to the Steiner line are positive whereas the posterior ones have a negative value.								
Argawal	Ms Sternocleidomastoid from rhytidectomy (25) vs. control group (25)	Frontal and lateral anthropometric measurements. The results are expressed in % of increase between pre-op measurement (in mm) and post-operative measurement (in mm)	Upper lip right vermillion show, % (Ls'-sto)					20%		<0.001
			Upper lip left vermillion show, % (Ls'-sto)					22%		<0.001
			Lower lip right vermillion show, % (Li'-sto)					23%		<0.001
			Lower lip left vermillion show, % (Li'-sto)					24%		<0.001
		Frontal view: vermillion show, upper and lower lip (left and right sides)	Upper lip lateral projection, mm (Ls to Sn-Pg line)					0.9 mm		CNBC
			Lower lip lateral projection, mm (Li to Sn-Pg line)					0.9 mm		CNBC
		Lateral view: upper lip and lower lip projection with respect to a line that passes through subnasale and pogonion landmarks.								

In red: not statistically significant.

Abbreviations: ANS: anterior nasal spine; Ch: chelion; CI: confidence interval; CNBC: could not be calculated; DLL: direct lip lift; Li: labrale inferior; Li': labrale inferior lateral (projected from cupid bow); Ls labrale superior central; Ls': labrale superior lateral (cupid bow); m: month; N: nasale; NR: not reported; PAF: post auricular fascia; Pg: pogonion; SD: standard deviation; SMAS: superficial muscular aponeurotic system; Sn: subnasale; Val: validated (if val is not indicated, the scale is not validated); Vs.: versus; w: week.

epithelialized and then inserted into the upper lip. Using a 10-point scale, the difference between the preoperative and postoperative results achieved statistical significance ($p < 0.0001$). Trussler et al. (2008) compared preoperative and postoperative anthropometric measurements of cosmetic and non-cosmetic pre- and post-operative results in patients treated with autologous palmaris longus tendons (although we only considered the cosmetic patients for this review). All measurements improved after surgery ($p < 0.05$), but upper lip dynamic smile outcomes and physician and patient satisfaction showed no significant improvement. De Benito et al. (1996) assessed galea and subgalea grafts for lip augmentation and found that 32%, 42%, and 26% of patients reported 'no difference', 'satisfactory', and 'excellent', respectively, on a 3-point patient satisfaction scale but failed to achieve statistical significance ($p > 0,05$).

In the study by Leaf and Firoz (2002), of lip augmentation using SMAS from patients who underwent rhytidectomy, 77% of patients reported fuller lips postoperatively on a 2-point assessment scale. Recupero and McCullough (2010) compared four groups who underwent lip augmentation with SMAS, pre-auricular fascia, SMAS with DLL, or post-auricular fascia with DLL. Efficacy was assessed by three blinded physicians who used the validated MLFS grading scale to analyze preoperative and postoperative photographs. The postoperative photographs were obtained at approximately 6 and 12 months after surgery. Their results showed that postauricular fascia graft lip augmentation and combined lip advancement and postauricular fascia augmentation produced the highest scores after surgery. The largest mean score increases were found in the lip advancement and SMAS lip augmentation groups: 1.459 at 6 months ($p < 0.001$) and 1.584 at 12 months ($p < 0.001$) respectively. In the Bohluli et al. (2013) study of temporalis fascia grafts in lip augmentation, quantitative analysis demonstrated a 21% change in the upper lip vermillion show and a 52% change in upper lip projection after surgery ($p < 0.001$). Argawal et al. (2010) used SCM muscle from 25 patients and found an increase of 20% and 22% in the right and left upper lip vermillion show, respectively; and a 23% and 24% increase in right and left lower lip vermillion show, respectively ($p < 0.001$). An increase of 0.9 mm in the upper and lower lip lateral projection was also detected, although the statistical significance could not be calculated for the lateral view.

3.4.2. Connective tissue matrix, collagen, hyaluronate, and calcium hydroxylapatite

Twelve good quality studies evaluated the efficacy of connective tissue matrix (two studies), collagen fillers (four studies), hyaluronate fillers (five studies), and CaHA fillers (one study) when used for FPLA (Table 4). Rohrich et al. (2000) inserted Alloderm sheets for lip augmentation in 47 patients. According to a 2-point questionnaire, 53% of patients were satisfied with the results and 71% indicated that they would repeat the procedure in the future. In their study comparing Cymetra with Zyplast (control), Scalfani et al. (2002) reported that at 12 months after surgery, 85% of patients treated with Cymetra had an increased percentage of red lip in the midline and 85% exhibited an increased vermillion height in the midline. Both percentages were significantly greater than those in the Zyplast group ($p = 0.01$). The rest of the measurements failed to achieve statistical significance. As for collagen fillers, Landau (2009) found similar satisfaction rates with Dermicol-P35 in one study and Evolence Breeze in another study (Landau, 2008) at three months after surgery, using the same non-validated 3-point scale in both studies. The results were rated as very good or good in 86.6% of patients treated with Dermicol P-35 and very good or good in 86.9% of patients treated with Evolence Breeze. In his study of Dermicol P-35 injections, De Boulle et al. (2009) reported that 90% of clinicians were satisfied or very satisfied with the results; 94% of patients

Table 4
Outcomes using connective matrix, collagen, hyaluronate, and CaHA.

Reference	Technique	Efficacy outcome measurement			Result	Statistical significance
Rohrich	Alloderm	Satisfaction survey patient (2 categories for each survey) not validated	Overall satisfaction with the results	Yes	53%	NR
				No	47%	
			Would you repeat the procedure?	Yes	71%	NR
				No	29%	
			Discomfort lasted in 1 week?	Yes	77%	NR
				No	23%	
Scalfani	Cymetra/Zyplast	Anthropometric measurements, frontal and lateral view at 12 months post-operation.	Change in vermillion % at midline from baseline (%[%Δ[100*{(d-c)/d}]])	Cymetra	84%	<0.01
				Zyplast	39%	
			Change in vermillion height at midline from baseline %(%Δ[d-c])	Cymetra	84%	<0.01
				Zyplast	38%	
			Change in nasolabial angle from baseline, °(Δm)	Cymetra	46%	0.07
				Zyplast	16.6%	
			Change in anterior projection mm (Δj)	Cymetra	69.2%	0.02
				Zyplast	27.7%	
			Change in vermillion surface area from baseline (lateral view) % (%Δl)	Cymetra	69.2%	0.048
				Zyplast	33.3%	
Landau	Collagen: DermicolP35	Patient satisfaction with the results (3 point scale)		Very good	53.3%	NR
				Good	33.3%	
				Satisfactory	13.3%	
De Boulle	Collagen: DermicolP35	Improvement survey clinician (6 point-scale)		Improvement of lip enhancement	98%	NR
				Not improvement of lip enhancement	2%	
		Satisfaction survey clinician (4-point scale): very satisfied, satisfied, unsatisfied.		Satisfied/very satisfied with results	90%	
				Not satisfied with results	10%	
		Satisfaction survey patient (4-point scale): very satisfied, satisfied, unsatisfied.		Satisfied/very satisfied with results	94%	
				Not satisfied with results	6%	
Landau	Collagen: Evolence Breeze	Patient satisfaction survey (3 point scale; not validated)				NR
		Very good		Very good	53%	
		Good		Good	33%	
		Satisfactory		Satisfactory	2%	
Downie	Collagen: PRI-1, PRI-2 and Zyplast. Hyaluronic acid: Perlane	3D stereophotogrammetry	Average upper lip volume	Significantly higher average upper lip volume gain from baseline to week 1 compared to the other three groups, which persisted throughout the 12-month study period	Perlane	CI 95%
		2D analysis (CKC scale)	Upper lip size (5 point scale; −2 very thin, to 2 extremely full)	Largest average changes from baseline throughout the follow-up period.	Perlane	$p < 0.01$
			Lower vermillion body (5 point scale; −1 tight almost unlined to 3 severe wrinkles)	Longevity of effect on the lower vermillion body compared to the other groups	Perlane and PRI-1	0.007
			Upper vermillion border (5 point scale; −1 protruding and/or creating peri oral shadow, to 3 indistinct and severely lined, with/without shadow from mid lower lip)	Less longevity of effect	PRI-1 less longevity than Perlane	0.05
		Satisfaction survey patient (5 point scale; 1 very satisfied to 5 very dissatisfied)		Very satisfied	PRI-1 and PRI-2 more dissatisfied than Perlane or Zyplast	$p = 0.052$
				Satisfied		
				Neither satisfied or dissatisfied		
				Dissatisfied		
				Very dissatisfied		
Bosniak	Hyal: Restylane	Physician evaluation score (4 point scale; 0 no improvement/effect to 3 complete improvement/effect)		3m / 6m / 9m	Best at 3 months	NR
				0 no improvement: 0 / 25 / 44.4		
				1 minimal improvement: 3.4 / 35 / 38.8		
				2moderate improvement: 20.15 / 35.5 / 16.8		
				3 complete improvement: 76.50 / 5.5 / 0		
		Patient satisfaction rating (3 point scale: unsatisfied, satisfied, very satisfied)		Unsatisfied: 22.2 / 49.2 / 63.4	Best at 3 months	NR
				Satisfied: 39.6 / 42.8 / 31.97		
				Very satisfied: 38.2 / 8.03 / 4.67		

Jacono	Hyal: Restylane	Patient satisfaction (5 point scale: 5 most satisfied to 1 dissatisfied. The rest of the description of the survey is not given)	Mean satisfaction score ± SD			4.5 ± 0.6	NR	
Glogau	Hyal: Restylane/ Placebo (No treatment)	MLFS: Medicis lip fullness scale (5 point scale; validated) 5 very full 4 full 3 medium 2 thin 1 very thin	Treatment success (at least a 1 point improvement) at week 24 compared to control			70%	$p < 0.001$	
		GAIS: global aesthetic improvement scale (9 point scale; not validated) +4 complete improvement +3 substantial improvement +2 definite +1 some 0 unchanged −1 slight worsening −2 moderate −3 marked −4 very marked	Treatment success (at least a 1 point improvement) at week 24 compared to control			74%	<0.001	
Eccleston	Hyal: Juvéderm Volvella	Overall satisfaction (11 point scale; not validated. 0 very dissatisfied, 10 very satisfied)	7–10 in month 3			94.6%	NR	
		0–3 (not satisfied)	7–10 in month 6			93.2%		
		4–6	7–10 in month 9			89.8%		
		7–10 (satisfied)	7–10 in month 12			82.8%		
Fagien	Hyal: Juvéderm Ultra	1) Investigator assessment of lip's appearance on the lip fullness scale (4 point scale, validated; minimal fullness, mild, moderate, marked fullness). If an improvement of ≥1 grade from baseline was achieved in >40% of the subjects, they were considered responders		Min	Mil	Mod	Mar	Improvement	
			Baseline	30%	64%	6%	0%		
			2 weeks	0%	14%	56%	30%		
			12 weeks	0%	31%	49%	20%	80%	$p < 0.05$
			24 weeks	10%	38%	42%	10%	56%	$p < 0.05$
		2) Investigator assessment of lip photographs on the POL (Peri oral lines) and OCS (oral commissures severity) 4-grade scales (validated; none, mild, moderate, severe). If an improvement of ≥1 grade from baseline was achieved in >40% of the subjects, they were considered responders	POL: 12 weeks compared to baseline					51%	$p < 0.05$
			POL: 24 weeks compared to baseline					46%	$p < 0.05$
			OCS: 12 weeks compared to baseline					64%	$p < 0.05$
			OCS: 24 weeks compared to baseline					59%	$p < 0.05$
		3) 3D digital images changes from baseline (measures of baseline are considered magnitude zero)			2 w	12 w	24w	Increase with respect to baseline	$p < 0.05$ in all compari-sons
			Lip volume (cm^2)		0.94	0.74	0.73		
			Lip surface %		34	27	25		
			Upper lip projection %		40	31	21		
			Lower lip projection %		31	30	24		
		4) Evaluator's satisfaction at week 2 in repose and animation in a 11 point scale (0 not satisfied at all, to 10 very much satisfied)	Baseline evaluator's satisfaction					42%	NR
			2 weeks evaluator's satisfaction					96%	
		Patients satisfaction at week 2, 12 and 24, in a 11 point scale (0 very dissatisfied to 10, very satisfied)	2 weeks patient's satisfaction					92%	
			12 weeks patient's satisfaction					82%	
			24 weeks patient's satisfaction					81%	
Jacovella	Radiesse	Patient satisfaction survey at 18-month (3-point scale. description of survey not given) n (%)	Very good					80%	NR
			Good					20%	
			Acceptable					0%	

In red: not statistically significant.

Abbreviations: Δ: difference; Δc: distance from subnasale to Ls; Δd: distance from Ls to Stos; Δj: shortest distance from reference line (pronasale-pogonion) to anteriormost point of lower lip; Δm: nasolabial angle; 2D: two dimensional; 3D: three dimensional; CKC: Catherine Knowles Clarke; m: month; NR: not reported.

Table 5
Outcomes using connective matrix, collagen, hyaluronate, CaHA, continued.

Reference	Technique	Efficacy outcome measurement					Result	Statistical signifi-cance
Mladick	Siloxane: Bioplastique	Satisfaction survey patient (5 points scale; 1 poor results, 5 excellent results)	Mean score				4.5	NR
Moscona	Siloxane: Siluron 1000	Satisfaction survey patient (5 point scale)	Excellent				66.5%	NR
		Excellent	Good result				18.4%	
		Good result	Mild improvement				7.8%	
		Mild Improvement	No improvement				4.5%	
		No Improvement	Worse				2.8%	
		Worse						
		Softness lips scale (5 point scale: 1 soft as before, 5 very hard)	1 Soft as before				76%	NR
			2				18.4%	
			3				4.5%	
			4				0.6%	
			5 Very hard				0.6%	
Wang	Eptfe: Gore-Tex	Anthropometric measurements (mean increase in mm)	Mean increase of lip projection (in mm) at 6th month.				0.98 mm	$p < 0.01$
			Difference among the mean increases in the 1st, 3rd, 6th month of follow-up.				Yes	$p>0.05$
		A) Lip projection calculated as the line that goes from the most anterior point of upper vermillion lip to the line that unites the Sn and Pg landmarks, in lateral view.	Mean increase in width of exposed vermillion (mm)				1.94 mm	$p < 0.01$
			Difference among the mean increases in the 1st, 3rd, 6th month of follow-up.				Yes	$p>0.05$
		B) Width of exposed vermillion calculated as the curved distance from superior point of cupid bow to the wet line at the midline of the upper lip, in lateral view.						
Verret	Eptfe: Advanta	Photographic comparison of pre-surgery and post-surgery frontal photos of the patients, rated by independent observers. (3 point scale: 0 no improvement to 2 significant improvement)	0 No improvement				8.8%	NR
			1 Minimal improvement				74.5%	
			2 Significant improvement				16.7%	
Redbord	Eptfe: Advanta	Patient satisfaction survey (5 point scale: 5 very satisfied to 1 very unsatisfied)	5				76%	NR
			4				7.6%	
			3				15.3%	
			2				0%	
			1				0%	
Cohen	Pmma: Artecoll/Control (Collagen: Zyplast)	Improvement in investigator ratings using the facial fold assesment scale (FAAS) (5 point scale: 1 = completely successful to 5 = not at all successful)		PMMA Mean ± SE		Control Mean	SE		
			1 month	1.47	0.09	1.32	0.334	PMMA	$p=0.338$
			3 month	1.28	0.009	0.43	0.12	PMMA	$p < 0.001$
			6 month	1.34	0.12	0.05	0.13	PMMA	$p < 0.001$
			12 month	1.41	1.02	NR	NR	–	NA
		Improvement in masked observers ratings using the FFAS (5 point scale: 1 = very satisfied to 5 = very dissatisfied)	1 month	0.31	0.07	0.48	0.08	PMMA	$p=0.205$
			3 month	0.18	0.09	0.25	0.07	PMMA	$p=0.454$
			6 month	0.08	0.08	0.22	0.07	PMMA	$p=0.176$
			12 month	0.24	0.09	NR	NR	–	NA
Cohen	Pmma: Artefill/Control (Collagen: Zyplast)	Improvement in Investigator ratings using the facial fold assesment scale (FAAS) (5 point scale: 1 = completely successful to 5 = not at all successful)	1 month	The results are not displayed in a table. The graphic where they are displayed is not useful to calculate the means and SE.				PMMA	$p>0.05$
			3 month					PMMA	$p < 0.001$
			6 month					PMMA	$p < 0.001$
			12 month					–	NA
		Improvement in masked observers ratings using the FFAS (5 point scale: 1 = very satisfied to 5 = very dissatisfied)	1 month	2	0.1	2	0.1	PMMA	NS
			3 month	2	0.2	3.1	0.3	PMMA	<0.01
			6 month	2	0.2	3.9	0.3	PMMA	<0.01
			12 month	2.3	0.2	NR	NR	–	NA

Scarano	Agarose: NewFill	Score of satisfaction pcs (10 point scale; from 1 to 10)	Immediately after treatment	8–10	NR
			1 month	7–8	
			2 months	6–8	
			3 months	4–5	
			6 months	3–4	
			12 months	2–3	

In red: not statistically significant.
Abbreviations: NA: not applicable; NR not reported; NS: not statistically significant; PMMA: polymethylmethacrylate; SE: standard error.

were satisfied or very satisfied; and 98% of patients had improved lip enhancement.

Downie (2009) randomized a total of 79 patients, by using a computerized interactive voice response system, to one of four treatment groups that received the following injections to the upper lip line (vermillion) border: group A, PRI-2; group B, Perlane; group C, PRI-1; and group D, Zyplast. A double-blind clinical evaluation of lip augmentation was performed using mathematically-derived facial volume and shape measurements obtained by 3D stereophotogrammetry, and ratings of 2D images using the validated CKC scale. This scale contains five ordinal categories for the size of the lips, the vermillion body, and the vermillion border. All treatment groups exhibited a shift towards larger, less wrinkled, and more prominent lips, with the effects dissipating during the follow-up period. Patients administered collagen derivatives had similar upper lip volume gains over baseline, whereas Perlane produced a significantly higher upper lip volume gain from baseline than the other groups at all times from 1 week to 12 months after injection ($p < 0.01$).

Three studies assessing the efficacy of Restylane in lip augmentation were found. Bosniak et al. (2004) injected Restylane into 685 lips and assessed the outcomes at 3, 6, and 9 months using non-validated physician evaluation and patient satisfaction rating scales. In the physician evaluation score, complete improvement was achieved in 76.5% of patients at 3 months, which decreased to 5.5% at 6 months and 0% at 9 months (although 35.5% and 16.8% of patient evaluations were of a moderate effect at 6 and 9 months, respectively). Similar results were obtained for the patient satisfaction ratings. A mean patient satisfaction of 4.5 (out of 5) was reported by Jacono et al. (2008) in 66 patients who underwent lip augmentation with Restylane. Glogau et al. (2012) injected Restylane in 135 lips and compared the results with a no treatment group; outcomes were assessed with the MLFS (a validated scale) and the GAIS. Significantly more individuals in the treatment group achieved at least a 1-point or greater improvement than in the control group at 24 weeks after surgery ($p < 0.001$).

Two recent studies have suggested that positive results after Juvéderm Volbella and Juvéderm Ultra injection persist longer than after Restylane. In 2012, Eccleston et al. (2012) found that 94.6%, 93%, 90%, and 83% of patients reported overall satisfaction at 3, 6, 9, and 12 months after injection of Juvéderm Volbella, using an 11-point non-validated scale. Fagien et al. (2013) assessed the outcomes of Juvéderm Ultra in 2013. They found an 80% improvement in LFGS at 12 weeks after the injection of Juvéderm Ultra and a 56% improvement at 24 weeks, compared with baseline ($p < 0.05$). Lip volume, surface, and projection, as seen on 3D digital images, were increased above baseline ($p < 0.05$). Patient satisfaction rates were 82% and 81% at 3 and 6 months, respectively (determined by an 11-point scale survey), which were slight lower than the satisfaction rates obtained with Juvéderm Volbella. Using the CaHA *filler Radiesse*, Jacovella et al. (2006) found 80% 'very good' and 20% 'good' results in a 3-point patient satisfaction survey at 18 months follow-up. Of note, the categories for this scale were 'very good', 'good', and 'acceptable', so poor outcomes could not be identified.

3.4.3. Non-animal materials

Only eight good quality studies involving non-animal materials were selected. They evaluated the following filler materials: agarose, one study; siloxane, two studies; ePTFE, three studies; and PMMA, two studies (Table 5). In the Scarano et al. (2009) study, the agarose gel NewFill was injected into the lips of 78 patients. On a ten-point patient satisfaction scale, the score was 5 or higher (more satisfied) up to and including 3 months after injection, but less than

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5 at 6 and 12 months; this correlates with the short life of NewFill. Mladick et al. (1992) found a mean score of 4.5 on a non-validated 5-point patient satisfaction survey in 18 patients at 12 months after lip injection with Bioplastique. In Moscona and Fodor's (2010) study of Siluron 1000 lip injections, they found 66% of 179 patients reported excellent results on a 5-point patient satisfaction survey at 36 months after injection. This was the only study that assessed the softness of the lips; using a non-validated patient subjective lip softness scale, 76% of patients indicated that their lips were as soft as before treatment with Siluron 1000. After SAM lip implants, Wang et al. (1997) found a significantly increased lip projection and width of exposed vermillion (0.98 mm and 1.94 mm, respectively; $p < 0.01$), which remained constant at 1, 3, and 6 months after insertion. One study of Advanta ePTFE implants reported that 74.5% of patients achieved only minimal improvement, when rated on a 3-point scale by independent observers who viewed photographs of the patients (Niamtu, 2006). This contrasts with Redbord and Hanke's (2008) results in 13 patients with Advanta lip implants: 76% of these patients were very satisfied, based on their 5-point scale rating (5, very satisfied; 1, unsatisfied). In the Cohen et al. (2004) study of the PMMA microsphere filler Artecoll, investigator ratings using the validated FFAS showed greater improvement at 3 and 6 months after injection of Artecoll than after injection of the control substance (Zyplast) ($p < 0.001$); however, independent observers using the same FFAS rated the improvement as similar for the Artecoll and control groups at both 3 and 6 months. Superior results were found by the same authors (Cohen et al., 2006) in a separate study evaluating Artefill: the improvement in FFAS was greater after Artefill injection than after control, when assessed by both the investigators and independent observers ($p < 0.001$ and $p < 0.01$).

3.5. Complications

A broad range of complications have been reported after lip filling procedures (Table 6). The vast majority of these complications can be considered mild, with only a very low percentage of severe adverse events, such as hemorrhage, abscess, or cellulitis. The complications are described below.

3.5.1. Swelling and erythema

Swelling and erythema are common during the immediate postoperative period and they generally persist for 3–15 days after surgery. Swelling after SMAS grafting has been reported to range from 1 to 40% (Recupero and McCullough, 2010). However, this 40% value may be at least partly explained by the concomitant DLL procedure that was performed in two of the groups in this study (Recupero and McCullough, 2010).

Connective tissue matrix fillers were associated with a 5.2% rate of swelling and a 0.5% rate of erythema (Sclafani et al., 2002), whilst collagen fillers had a mean rate of swelling of 3.64% (Sclafani et al.; De Boulle et al., 2009; Downie et al., 2009) Hyaluronate fillers had a 61.5% rate of swelling (Bousquet and Ågerup, 1999; Solish and Swift, 2011; Eccleston and Murphy, 2012; Fagien et al., 2013) and a 34.5% rate of erythema (Bousquet and Ågerup, 1999; Solish and Swift, 2011). The higher rate of swelling with hyaluronate may be explained by the time when the swelling was measured: Bousquet et al. demonstrated the decreasing rate of swelling substantially over time, from 86% at 24 h, to 14% at 5 days, and 1% at 10 days (Bousquet and Ågerup, 1999). CaHA fillers produced a 13% rate of swelling in one study (Sklar et al., 2004). Siloxane was associated with a low rate of swelling: only 0.6% (Moscona and Fodor, 2010). After ePTFE implants, swelling was reported to be between 3.2% (Brody, 2001) and 9% (Hanke, 2002) of the patients, and erythema was reported to be between 5.8% (Wang et al., 1997) and 9% (Brody, 2001). 6% of patients required further excision of the implant.

3.5.2. Hemostatic disorders

Problems with hemostasis can occur during and after lip filling surgery. No hemorrhage has been reported for SMAS grafts (Leaf and Firouz, 2002; Recupero and McCullough, 2010) or lip-cheek flaps, but a 10% incidence of bleeding was reported with latissimus dorsi grafts (Ponzielli et al., 1997), which required further drainage. Nearly half of patients who were given Cymetra injections developed an ecchymosis (Sclafani et al., 2002), while no hemostatic complications have been reported in association with the use of Alloderm. Only one-quarter of patients treated with Zyplast developed an ecchymosis (Sclafani et al., 2002; Downie et al., 2009), but in 5% of all patients, the ecchymosis persisted for 6 months. No patients suffered from these complications with Alloderm. Only one-quarter of the patients treated with Zyplast had ecchymosis, No hemorrhage has been reported with CaHA fillers. Bruising has been reported in a mean of 34.5% patients injected with hyaluronate (Solish and Swift, 2011; Eccleston and Murphy, 2012; Fagien et al., 2013) and 4.4% of patients injected with agarose (Scarano et al., 2009). A 3.4% incidence of bleeding was reported with the injection of Siluron 1000 and 2.8% of patients required drainage for bleeding. A 9% rate of bleeding has been reported with Advanta e-PTFE implants (Hanke, 2002).

3.5.3. Infection

Dermis implants have been associated with a 7% rate of abscesses (*Staphylococcus* ssp.) (Fezza et al., 2003) requiring treatment with drainage and oral antibiotics. Palmaris longus tendon grafts have been associated with a 4.7% rate of infection (Trussler et al., 2008) that led to upper lip cellulitis treated with amoxicilin-clavulanic. Infection rates for the connective tissue matrix has shown a rate of infection from 0% (Rohrich et al., 2000; Duncan, 2003) to 8.3% (Tobin and Elliott, 2010), collagen fillers, ranged between 0% (Sclafani et al., 2002; Downie et al., 2009) to 5.2% (Downie et al., 2009; Sclafani et al., 2002). For hyaluronate fillers, the mean infection rates were between 0% (Downie et al., 2009) to 0.2% (Bosniak et al., 2004), and for e-PTFE fillers the mean infection rate was 7.3% (Linder, 1992; Brody, 2001; Hanke, 2002; Verret et al., 2006). No infection was reported in the studies selected for this review involving silicone or CaHA; however, Schmidt-Westerhausen (2004) reported a case of delayed silicone abscess in the lower lip after silicone injection. Reactivation of human herpes virus 1 (HHV-1) infection has also been reported after FPLA, with rates as follows: 11.4% after connective tissue matrix grafts (Tobin and Karas, 1998; Sclafani et al., 2002), 12.3% after collagen injections (Downie et al., 2009; De Boulle et al., 2009), 21.7% after Perlane (Downie et al., 2009) and 0.1% with PMMA (Cohen and Holmes, 2004).

3.5.4. Pain and neurologic disorders

Pain during the insertion of lip filler material is normal. This pain can be reduced by placing some EMLA cream (Lidocaine 2.5% and Prilocaine 2.5%; AstraZeneca, Wilmington, US) on the injection site 10–15 min before the injection is given (Jacovella et al., 2006). Some fillers, such as Restylane-L, Perlane-L, Juvéderm Ultra Xc, and Artefill, are formulated so they contain 0.2–0.3% lidocaine or xylocaine. Residual pain during mouth opening or smiling was reported with galea/subgalea grafts in 16% of patients (De Benito and Fernandez-Sanza, 1996). A temporary hypoesthesia was reported in 3.5% of patients with Dermicol-P35 (De Boulle et al., 2009) and in 1% of patients with SMAS graft (Leaf and Firouz, 2002), 7.6% of patients with Advanta e-PTFE grafts required excision of the implant (Redbord and Hanke, 2008).

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Table 6
Complications reported in each study.

Reference	Technique		Swelling	Erythema	Hemorrhage	Bruising	Infection	Herpes labialis	Pain	Hypoesthesia	Tension	Assymetry	Malposition	Lumpiness	Scarring	Reoperated	Others
Fezza	Dermis: upper eyelid						7HKI		0								Inclusion cyst 7J
Tobin	Alloderm						8.3	16.6							0		
Rohrich	Alloderm				0		0						2.12			8.51	
Scalfani	Cymetra	Initial injection	5.2	10.5	47.3		0		15.7		10.5	5.2					
		6 month	0	0	6.2		0	6.2	0		0	6.2					
	Zyplast	Initial injection	8	0	28		0		12		2	8					
		6 month	0	0	5		5		5		5	0					
Landau	Collagen: DermicolP35							0									Touch-up 13.3
De Boulle	Collagen: DermicolP35		5			10P		2	19P	3.5T				12			
Landau	Collagen: Evolence Breeze													93Q			
Braun	Collagen: Evolence	Postop												80			
		12 m												30			
Downie	PRI-1		5.2I				0	21									Blistering 5.2; Allergy 5.2
	PRI-2		0				5.2L	21									Mouth ulcer 5.2
	Zyplast		0				0	5.5									
	Perlane		0				0	21.7									Miscarriage 4.3; Dry lips 4.3
Bousquet	Hyal: Restylane		86/ 14/ 1M	52, 36, 12N													
Bosniak	Hyal: Restylane		??				0.2C,J										
Glogau	Hyal: Restylane /placebo		58	17		44			22		22						
Eccleston	Hyal: Juvéderm volvella		8.3			51.7								TAB 8.3			
Fagien	Hyal: Juvéderm Ultra		94			92					88			32			
De Benito	Galea and subgalea								16*								Tight smiling 52
Leaf	SMAS from rhytidectomy		1		0		0			1%		2		1**			
Trussler	Palmaris longus tendon						4.7A				4.7B		0				Stiff lip 10m
Recupero	SMAS				0								0				0 revision
	PAF														10C		
	DLL+SMAS, DLL+PAF		40									20					Multiple injections 33
Botti	Ms Lip-cheek/lip flap				0		0			0							Partial necrosis 3.5; Narrow lateral part of the lip 25
Ponzielli	Ms latissimus dorsi				10D		0					0			0		
Argawal	Ms SCM													4C			
Sklar	CaHA: Radiance		13										0	20C			
Jansen	Radiesse													12.4C			Radial lip lines 3.6C
Jacovella	CaHA: Radiesse													10F			
Mladick	Siloxane: Bioplastique													5.5F		5.5	
Fulton	Siloxane: Silikon 1000													0.6J			
														0.8C			
														0.3F			
Moscona	Siloxane: Siluron 1000		0.6		3.4. 2.8D									2.2			
Linder	Eptfe: Gore-Tex						13			0			6.6				
Wang	Eptfe: Gore-Tex			5.8F												5.8	Stiffness 5.8
Brody	Eptfe: Softform		3.2	9.6F			6.4						16.1			9.6	
Hanke	Eptfe: Advanta		9G,F		9		9										
Verret	Eptfe: Advanta						0.9					1.9	0.9F			3.8	Bubbles 0.9

(*continued on next page*)

Table 6 (*continued*)

Reference	Technique	Swelling	Erythema	Hemorrhage	Bruising	Infection	Herpes labialis	Pain	Hypoesthesia	Tension	Assymetry	Malposition	Lumpiness	Scarring	Reoperated	Others
Redbord	Eptfe: Advanta								7.6F			7.6F				Too small 15.2F
Cohen	Pmma: Artecoll						0.1						0.1			
Scarano	Agarose gel				4.4		0						0	0		

*Pain when opening mouth or when smiling; **with secondary excision A – upper lip cellulitis: ttm amoxicilin-clavulanic; B – operative sectioning of the graft through multiple vermillion incisions and postop frequent stretching exercices with a facial flex; C- treated with steroid injection; D – hemorrhage post surgery, treated with drainage; F – treated with excision; G-diferred >4 weeks; H – abscess treated with drainage; I – Cheilitis angularis; &– Herpes labialis; J – resolved spontaneously; K – treated with oral antibiotic; L – staphylococcus; L – bacterian stomatitis; M 86% at 24 h, 14% at 5 days, 1% at 10 days; N 52% following the 24 h, 36% following the 48 h, 12% following 72 h; P following the first 24 h after injection; Q the lumpiness only lasted the first fortnight; T temporary.

Abbreviations: m: month; ms: muscle; postop: postoperative period; SCM: sternocleidomastoid muscle; CaHA: calcium hydroxylapatite.

3.5.5. Mechanical complications

Tight smiling was reported in 52% of patients who received galea/subgalea grafts (De Benito and Fernandez-Sanza, 1996). Palmaris longus grafts were associated with a 4.7% incidence of tight and stiff lip (Trussler et al., 2008), which was treated with operative sectioning of the graft through multiple vermillion incisions and frequent postoperative stretching exercises. A 5.8% rate of stiffness was reported after ePTFE implants (Wang et al., 1997) and a 5% incidence of lip tension was reported at 6 months after Zyplast injection (Sclafani et al., 2002). Cymetra was associated with a 10.5% incidence of tight lips (Sclafani et al., 2002), whereas hyaluronate was associated with a higher rate of stiffness: 22% with Restylane (Solish and Swift, 2011) and 88% with Juvéderm Ultra (Fagien et al., 2013), as well as a 5% lip tension with Zyplast at 6 months postoperatively (Sclafani et al., 2002). Tight lips were reported by 10.5% of patients treated with Cymetra (Sclafani et al., 2002), while more stiffness was reported following treatment with hyaluronate: 22% Restylane (Solish and Swift, 2011) and 88% Juvéderm (Fagien et al., 2013).

Asymmetry was reported with: Cymetra, 6.2% at 6 months (Sclafani et al., 2002); SMAS/PAF + DLL, 20% (Leaf and Firouz, 2001); SMAS, 2% (Recupero and McCullough, 2010); and e-PTFE, 1.9% (Verret et al., 2006). Malposition was a complication of Alloderm, 2.1% (Rohrich et al., 2000) and e-PTFE was associated with an extrusion rate of 7.6% (Linder, 1992; Brody, 2001; Verret et al., 2006; Redbord and Hanke, 2008).

3.5.6. Lumpiness and granulomas

An inclusion cyst developed in 7% of patients who underwent dermis grafting using a graft from an upper eyelid blepharoplasty (Fezza et al., 2003), but this resolved spontaneously. Postauricular fascia grafts led to a 10% incidence of scars requiring treatment with steroid injections (Recupero and McCullough, 2010); ECM muscle grafts were associated with a 4% rate of scar tissue which was treated with steroid injections (Agarwal et al., 2010); and SMAS from rhytidectomy led to 1% nodularity in 1% of patients, which was treated with secondary excision (Leaf and Firouz, 2002). Silicone was associated with a 3.1% rate of granulomas (Moor and Olhsinka, 2012) which is similar to the incidence reported for other fillers. Steroid injections, simple excision of the granuloma, special surgical techniques (Moor and Olshinka, 2012) as well as the use of ultrasound (Kornstein, 2012) have all been proposed to reduce or eliminate the development of chronic silicone granulomas. Hyaluronan was associated with transient lumpiness, at rates of 8.3%–32% with Juvéderm (Eccleston and Murphy, 2012; Fagien et al., 2013) that has not lead to a true granulomatous reaction. Landau et al. (2009) reported that the transient lumpiness disappeared spontaneously by the fourth week in 15 women. Hydroxylapatite produced a relatively high rate of nodularity in the face, with 36% of patients reporting minimal nodularity and 8% reporting moderate nodularity in one study (Tzikas, 2003). 20% (Jansen, 2006), 12.4% (Sklar and White, 2004) and 10–20% (Jacovella et al., 2006) of patients treated with CaHA fillers in the lips were treated with either excision or steroid injections. PMMA fillers were associated with a low incidence of nodularity, 0.1% in the lips (Cohen and Holmes, 2004), which became symptomatic at variable times after placement. Salles et al. (2008) reported that the interval between injection and the first symptoms varied from 1 month to 6 years).

3.5.7. Removal

Some fillers act as implants, which can be easily removed if complications arise. Removal of lip implants was reported for Alloderm, 8.5% (Rohrich et al., 2000), Bioplastique, 5.5% (Mladick, 1992), and ePTFE, 10.7% (Wang et al., 1997; Brody, 2001; Verret et al., 2006; Redbord and Hanke, 2008).

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3.5.8. Other complications

Allergic reactions are a classic complication of bovine collagen fillers (Kligman and Armstrong, 1986; Charriere et al., 1989). Charriere et al. (1989) found a 3.8% incidence of positive skin tests and a 2.3% rate of allergic reactions in a group of 705 patients injected with collagen bovine filler. Downie et al. (2009) reported that PRI-1 lip injections led to a 5.2% incidence of allergic reactions, as well as a 5.2% incidence of blistering at the injection site. Perlane injection was associated with dry lips and a 4.3% rate of miscarriage (Downie et al., 2009). Cheek-lip and lip−lip flaps were complicated by partial necrosis in 3.5% of the patients, and 25% of patients required a second operation to reduce excess tissue at the lateral part of the lip (Botti and Villedieu, 1995). Salles et al., likewise reported partial necrosis of the upper lip, in a study describing complications after PMMA injection, but no necrosis was reported with this agent in the studies included in this review (Salles et al., 2008). CaHA fillers were associated with the presence of radial lip lines that remained visible several months after surgery in 3.6% of the patients; these lines were successfully treated with steroid injections (Sklar et al., 2004). Verret et al. (2006) reported that 0.9% of patients receiving Advanta implants exhibited bubbles along the lip.

4. Discussion

In this systematic review with meta-regression analysis, we examined the effectiveness of each type of filler material. A primary problem with examining this issue involves the methods that have been used to assess efficacy. Many studies that we initially examined did not have quantifiable methods of efficacy assessment: for instance, a number of authors simply made claims that 'all the patients were satisfied with the results' or 'we think that the results were excellent'. To obtain meaningful results, we therefore excluded studies that did not use quantifiable or precise assessment methods.

Although we did include studies that used patient or surgeon surveys to evaluate effectiveness, data obtained from such surveys must be viewed with caution. These types of surveys are subject to the possibility of self-serving bias. Researchers have described self-serving attributional bias, in which people tend to make more internal, stable, and global attributions for positive events than for negative events; the variable '*d*' has been defined as the mean attribution for positive/successful events minus the mean attribution for negative/failure events, divided by the mean standard deviation (Hedges, 1981). In their meta-analysis of 266 studies, Mezulis et al. found that self-serving attributional bias is pervasive in the general population ($d = 0.96$), and the maximum bias ($d = 1.38$) was observed in people more than 55 years old (Mezulis et al., 2004). Self-serving attributional bias may certainly be applicable to lip augmentation surgery, as no patient wants to think that the considerable money and time expended for the procedure has been in vain, and no surgeon wants to think that their results are poor. Therefore, when one uses a survey to evaluate the efficacy of a cosmetic outcome, it is most appropriate to use a validated scale that is completed by an independent observer who was not involved in the surgical process (i.e. not patients or their nurses or doctors). However, one drawback of validated scales is that none of the current available scales assesses the degree of 'fakeness' of the final cosmetic appearance. A result can be rated as 'good' in terms of fullness, but if it does not appear natural, then the overall results may be considered poor. In our current review, the types of efficacy assessment surveys varied considerably from author to author, and most were not validated. Thus, meaningful comparisons between studies were not possible.

In contrast to surveys, anthropometric measurements are a more accurate and objective way to assess the outcomes of FPLA. However, we identified only five studies (Fagien et al., 2013; Trussler et al., 2008; Bohluli et al., 2013; Agarwal et al., 2010; Wang J et al., 1997) in our review which used anthropometric measurements, and the variability of the 'end-points' used in these studies was substantial. The reference line used to measure profile landmarks differed among three studies ('nasale' landmark with the anterior nasal spine (Trussler et al., 2008), columella to the pogonion (Bohluli et al., 2013) and subnasale to the ogonion (Agarwal et al., 2010; Steiner, 1953)), and one author (Wang J et al., 1997) used a curved line from the labrale superius to the stomion, a line which is generally not used in facial anthropometry. We prefer the Steiner line as the reference line, as it is reliable and broadly used in anthropometry, but it was used in only one study in this review (Bohluli et al., 2013). Anthropometric measurements also have a limitation. They fail to measure the shape of the lip, which can be a major determinant of the ultimate aesthetic outcome after FPLA. Similarly, unless anthropometric measurements are obtained when patients are smiling or talking, they do not fully assess the aesthetic effects of FPLA. In this review, no study evaluated the change in lip shape after lip augmentation (either by anthropometric measurements or by another method) and only one study evaluated patients while smiling, but this evaluated smile strength, not appearance (Trussler et al., 2008). Despite this, hyaluronate seems to be the preferred filler, according to the ranking of non-surgical procedures reported by the American Society of Aesthetic Plastic Surgeons (Surgery.org, 2012).

Another type of bias that one must consider when evaluating the outcome of lip augmentation is reporting bias (Sterne et al., 2008), which may arise when studies are sponsored by the filler manufacturers (Buchkowsky and Jewesson, 2004; Sterne et al., 2008). This sponsoring may also lead to ghostwriting of clinical trials, which may enhance the possibility that data is manipulated to favor the manufacturer's product (McHenry and Jureidini, 2008). In this review, 58% of the selected studies acknowledged that at least one author was sponsored by, or a consultant for, a filler manufacturer (Table 7). In another 13% of the studies, the possible existence of a relationship with the manufacturer was not mentioned. Of note, all studies that did not mention sponsoring were written before 1999; all subsequent studies included a conflict of interest statement. Our results found that porcine collagen had different reported rates of lumpiness, depending on whether the study was sponsored. The only non-sponsored study of bovine collagen found a 30% rate of lumpiness after 12 months (Bauman, 2004), whereas the other two studies reported rates of 0% (Landau, 2009) and 12% (De Boulle et al., 2009) after 10 months. Similarly, our only non-sponsored CaHA study reported the largest rate of lumpiness (20%), compared with the rates reported for the two other sponsored studies (10% and 12.4%). Although these findings suggest the possibility of bias, alternative explanations should be considered. For example, the definition of 'lumpiness' may have differed for different investigators, leading to errors in classification, or simple random variation may have occurred, especially because the size of the groups varied considerably (e.g. 110, 338, and 10 patients for the three CaHA studies) (Wang et al., 1997; Jansen and Graivier, 2006; Jacovella et al., 2006).

An outcome reporting bias was observed in the Jacovella et al. (2006) study of Radiesse filler. The satisfaction scale used in this study contained only three categories, 'acceptable results', 'good results', and 'excellent results', but did not include options such as 'no difference' and 'worse results'. Hence, by using this survey, it was not possible to obtain a poor surgical result. Another way to distort the data is to calculate the rate of complications for a specific filler, based on the number of fillers or filler segments placed, not the number of patients. For example, in one study (Wang et al., 1997), e-PTFE implants were inserted in 17 patients and a total of 23 lips;

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Table 7
Conflicts of interest reported for the studies.

Reference	Year	Technique	COE	Type of COE
Tobin	1998	Alloderm	NR	
Rohrich	2000	Alloderm	No	
Scalfani	2002	Cymetra/Zyplast	Yes	Sponsored by LifeCell corp
Braun	2008	Collagen: Evolence	No	
Landau	2008	Collagen: Evolence Breeze	Yes	Speaks for Johnson & Johnson in congresses presenting clinical experience with the product
Landau	2009	Collagen: DermicolP35	Yes	Speaks for Johnson & Johnson in congresses presenting clinical experience with the product
De Boulle	2009	Collagen: DermicolP35	Yes	Sponsored by ColBar science
Downie	2009	Collagen: PRI-1/−2,Zyplast, Perlane	Yes	Sponsored by Tissue science laboratories
Bousquet	1999	Hylan: Restylane	Yes	Sponsored by Q med
Bosniak	2004	Hyal: Restylane	Yes	Is a consultant to Medicis, Has received travel grants for lectures from Qmed AB
Jacono	2008	Hyal: Restylane	No	
Glogau	2011	Hyal: Restylane/Placeb	Yes	Sponsored by Medicis aesthetics
Eccleston	2012	Hyal: Juvéderm volvella	Yes	Sponsored by Allergan
Fagien	2013	Hyal: Juvéderm Ultra	Yes	Sponsored by Allergan Merz Aesthetics consultant
Sklar	2004	CaHA: Radiance	No	
Jansen	2006	CaHA: Radiesse	Yes	Sponsored by Bioform Medical Inc
Jacovella	2006	CaHA: Radiesse	Yes	Sponsored by Bioform Medical Inc.
Scarano	2009	Agarose: NewFill	No	
Mladick	1992	Siloxane: Bioplastique	NR	
Fulton	2005	Siloxane: Silikon 1000	No	
Moscona	2010	Siloxane: Siluron 1000	No	
Linder	1992	Eptfe: Gore-Tex	NR	
Wang	1997	Eptfe: Gore-Tex	NR	
Brody	2001	Eptfe: Softform	No	
Hanke	2002	Eptfe: Advanta	No	
Verret	2006	Eptfe: Advanta	No	
Redbord	2008	Eptfe: Advanta	No	
Cohen	2004	Pmma: Artecoll/Control Zyplast	Yes	Sponsored by Artes Medical Inc.
Cohen	2006	Pmma: Artefill/Control Zyplast	Yes	Sponsored by Artes Medical Inc.

Abbreviations: COE: conflicts of interest; NR: not reported.

however, as 3 segments of filler were implanted into each lip, the total number of filler segments was 69 segments. The authors' reporting of a 1.3% extrusion rate, representing 1 in 69 segments was almost five fold lower than the 5.8% extrusion rate if one divided the number of extrusions (one) by the number of patients (17).

Additionally, some fillers have been the subject of 'media' bias. For example, silicone implants have received much negative publicity, demonizing the secondary effects of silicone (Huffman, 2003). However, this negative publicity may not be consistent with the scientific data. For example, our review found that the rate of granulomas associated with silicone use was approximately 3–4%, which was lower than the 10–20% rate reported for CaHA. This media bias has even permeated scientific journals, as reflected in letters to the editor published about the original research articles.

This review has limitations. First, there was a language bias (reporting bias) introduced by our exclusion of studies not written in one of the eight languages used as selection criteria. This may have prevented good quality studies written in other languages from being included; in particular, emerging studies from China and South Korea may have been underrepresented. Second, excluding some studies based on their failure to include a minimum number of patients may have masked some important information. The innovative flipping flap technique proposed by Choi et al. (2013) is a good example of this: the authors reported their results in an extremely comprehensive manner, but the article was based on only one patient and thereby was not included in our review. Third, our exclusion of studies in which patients had perioral pathology or were undergoing surgery that could affect the shape of the lips may have concealed valid information. One study, performed by Rubio-Bueno et al. (2013), was excluded because the patients were undergoing orthognathic surgery; however, it is the only currently available study about buccal fat pad grafts for lip augmentation with good quality data.

A common question in the field of plastics or aesthetic surgery is whether a filler or similar implant should be long-lasting. Theoretically, a long-lasting filler is preferable if the filler exhibits ideal mechanical and biological attributes. However, if a filler is not ideal, and perfect results are difficult or impossible to achieve – as is the status with fillers in current use – then it is more appropriate for the filler to persist for approximately 6–12 months. There is definite need to develop new filler materials, potentially coupled with advances in tissue engineering and the administration of growth factors, to improve the outcome of either hard or soft facial tissue augmentation. The primary components of many of the fillers used in the current review were developed during the first half of the twentieth century: for example, silicone was developed in 1901, PMMA in 1902, and PCL in 1934 (Woodruff and Hutmacher, 2010).

Although advances have been made over the years in this field, innovative new strategies for soft tissue augmentation are necessary to improve outcome. In addition to the attributes of the ideal filler material discussed above, the ability to increase sarcomere production and thus promote muscle function may also be advantageous. Myoblasts develop and eventually fuse to form myofibrils through a cascade of events that is not well understood, but researchers have used cultivated myoblasts for Duchenne myopathy and urinary incontinence with success (Schneider, 2002; Pavlath, 2011; Posey et al., 2001). The use of growth factors to stimulate the differentiation of connective stem cells into muscular cells, adipose cells, or fibroblasts is another potentially useful strategy for soft tissue augmentation, including augmentation of the lip.

5. Conclusion

This systematic review has summarized the currently available quality data from FPLA studies. However, the quality of the studies

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we examined was not high: only 21% of the articles had a level of evidence quality rating of level IIc or higher. Fortunately, the quality of studies may be increasing, as 29% of our studies published since 2004 had a level of evidence rating of IIc or higher, whereas only 7% of studies published prior to 2004 exhibited these levels. Because of the considerable diversity of procedures, no definitive comparisons or conclusions were possible. More high quality prospective studies and clinical trials are required to more fully understand the efficacy and safety associated with this popular procedure. It is likewise critical that all surgeons or other healthcare professionals who perform FPLAs have a thorough understanding of the evolving world of aesthetic fillers.

Disclosure

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