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

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A R T I C L E   I N F O

Article history:
Paper received 14 January 2015
Accepted 26 March 2015
Available online 8 April 2015

Keywords:
Augmentation
Enhancement
Filler
Lip

A B S T R A C T

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.

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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.

http://dx.doi.org/10.1016/j.jcms.2015.03.032
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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 hyaluronic 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 (Clinica 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 ‘DermaGel’ OR ‘Pemigal’) OR (‘AlloDerm’ OR ‘Surgesis’ 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.](image-url)
2.2. Selection criteria

were thus examined in this systematic review. With the addition of these 9 articles, a total of 38 articles

3) lip augmentation techniques using
studies: 1) human patients; 2) lips without pathology or patients
reductions after excluding non-academic publica-

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

3. Results

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 I, four studies; level II, four studies; level III, 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 McCollough, 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, facial tissue, tendon tissue, muscular tissue, or osseous tissue. Autologous subdermic tissue removed from patients who underwent direct lip lift (DIL) (Kesselering, 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 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.
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, Perlane) or particulate form (Cymetra,1 2 3 mm 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

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Technique</th>
<th>LOE</th>
<th>Patients *</th>
<th>Age (years)**</th>
<th>Sex **</th>
<th>FU (months)</th>
<th>Efficacy outcome measurement</th>
<th>Complications</th>
<th>Time direction of the study</th>
<th>Randomized</th>
<th>Control</th>
<th>Blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1998</td>
<td>Dermal: upper eyelid repair</td>
<td>IV</td>
<td>14</td>
<td>67 (58 to 79)</td>
<td>0</td>
<td>6</td>
<td>Average lip score (10 point scale)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>2</td>
<td>1998</td>
<td>Alloderm</td>
<td>IV</td>
<td>12</td>
<td>62</td>
<td>1.6%</td>
<td>7</td>
<td>Satisfaction survey patient</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>1999</td>
<td>Alloderm</td>
<td>IV</td>
<td>87</td>
<td>52</td>
<td>8.2%</td>
<td>12</td>
<td>Anthropometric measurements, frontal and lateral view</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>4</td>
<td>2000</td>
<td>Cymetra / Ziplast</td>
<td>Ib</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
<td>Patient satisfaction survey (clinician)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>2006</td>
<td>Collagen: Perlane</td>
<td>IV</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>Satisfaction survey patient</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>2006</td>
<td>Collagen: Perlane</td>
<td>IV</td>
<td>76</td>
<td>32-61</td>
<td>0</td>
<td>3</td>
<td>Satisfaction survey patient (3)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>2009</td>
<td>Collagen: Perlane</td>
<td>IV</td>
<td>15</td>
<td>52.3</td>
<td>0</td>
<td>3</td>
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<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>2009</td>
<td>Collagen: DermisR55</td>
<td>IV</td>
<td>51</td>
<td>82.2</td>
<td>3%</td>
<td>10</td>
<td>Satisfaction survey patient (clinician)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Double Blind</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>9</td>
<td>2010</td>
<td>Collagen: PRF-1, PRO-2, Ziplast, Perlane</td>
<td>Ib</td>
<td>79</td>
<td>NR</td>
<td>0</td>
<td>9, 12</td>
<td>Satisfaction survey patient (3)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Compensated</td>
<td>No</td>
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<tr>
<td>10</td>
<td>1999</td>
<td>Hyal: Restylane</td>
<td>IV</td>
<td>192</td>
<td>46</td>
<td>0</td>
<td>6, 8</td>
<td>Percentage of patients 1 year</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>2004</td>
<td>Hyal: Restylane</td>
<td>IV</td>
<td>1146</td>
<td>485</td>
<td>56.1/-</td>
<td>30.7</td>
<td>28.8%</td>
<td>3, 6, 9</td>
<td>Four point scale physician evaluator score</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Cochrane Series</td>
</tr>
<tr>
<td>12</td>
<td>2008</td>
<td>Hyal: Restylane</td>
<td>IV</td>
<td>66</td>
<td>43.8/-</td>
<td>NR</td>
<td>0.1%</td>
<td>9</td>
<td>Patient satisfaction survey (5)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Cochrane Series</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>2011</td>
<td>Hyal: Restylane</td>
<td>Ib</td>
<td>180</td>
<td>135</td>
<td>47.6/-</td>
<td>21.8</td>
<td>0.6%</td>
<td>8w, 16w, 26w, 36w</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>2013</td>
<td>Hyal: Restylane</td>
<td>Ib</td>
<td>80</td>
<td>56</td>
<td>0</td>
<td>6, 9, 12</td>
<td>Overall satisfaction (11)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>2013</td>
<td>Hyal: Restylane</td>
<td>Ib</td>
<td>50</td>
<td>47</td>
<td>24.4/-</td>
<td>4%</td>
<td>6, 5</td>
<td>Lip fullness scale (4)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>16</td>
<td>1996</td>
<td>Calcium and nitrates</td>
<td>IV</td>
<td>42</td>
<td>31.5/-</td>
<td>6%</td>
<td>10,5%</td>
<td>19</td>
<td>Quantitative analysis of upper lip projection and vermilion area</td>
<td>No</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>2003</td>
<td>Palmaris longus tendon</td>
<td>IV</td>
<td>31</td>
<td>11</td>
<td>25</td>
<td>28</td>
<td>Quantitative analysis</td>
<td>No</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>18</td>
<td>2010</td>
<td>SMAS from thyroidectomy</td>
<td>IV</td>
<td>10</td>
<td>(11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>Single blind analysis</td>
<td>No</td>
<td>No</td>
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<tr>
<td>19</td>
<td>2013</td>
<td>Temporalis fascia</td>
<td>IV</td>
<td>19</td>
<td>31.5/-</td>
<td>5%</td>
<td>10,5%</td>
<td>19</td>
<td>Quantitative analysis of upper lip projection and vermilion area</td>
<td>No</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
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<tr>
<td>20</td>
<td>2008</td>
<td>Palmaris longus tendon</td>
<td>IV</td>
<td>78</td>
<td>(21)</td>
<td>59</td>
<td>Cosmetic assessment</td>
<td>No</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
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<td>21</td>
<td>1995</td>
<td>Abdominoplasty</td>
<td>Ib</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
<td>Aesthetic: Yes</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
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<td>2005</td>
<td>Abdominoplasty</td>
<td>IV</td>
<td>102</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
<td>Aesthetic: Yes</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>23</td>
<td>2010</td>
<td>Abdominal surgery</td>
<td>IIb</td>
<td>50/25</td>
<td>NR</td>
<td>24</td>
<td>Frontal and lateral anthropometric measurements</td>
<td>Yes</td>
<td>Retrospective</td>
<td>Cochrane Series</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>24</td>
<td>2004</td>
<td>CADH: Radiesse</td>
<td>IV</td>
<td>100</td>
<td>15.5/-</td>
<td>NR</td>
<td>6</td>
<td>Paper's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>25</td>
<td>2006</td>
<td>CADH: Radiesse</td>
<td>IV</td>
<td>338</td>
<td>133</td>
<td>NR</td>
<td>8</td>
<td>Paper's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>26</td>
<td>2006</td>
<td>CADH: Radiesse</td>
<td>IV</td>
<td>120</td>
<td>NR</td>
<td>18</td>
<td>Patient satisfaction (3)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>2009</td>
<td>Aromasin: Newfull</td>
<td>IV</td>
<td>66</td>
<td>NR</td>
<td>72%</td>
<td>4.4%</td>
<td>Store of satisfaction (10)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>1992</td>
<td>Silosome: Biostaple</td>
<td>IV</td>
<td>18</td>
<td>18</td>
<td>NR</td>
<td>12</td>
<td>Satisfaction survey patient (5)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>29</td>
<td>2005</td>
<td>Silosome: Silkon 1000</td>
<td>IV</td>
<td>608</td>
<td>38</td>
<td>2.9%</td>
<td>72</td>
<td>Surgeon and patient's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>30</td>
<td>2010</td>
<td>Silosome: Silkon 1000</td>
<td>IV</td>
<td>179</td>
<td>33%</td>
<td>0.5/-</td>
<td>10</td>
<td>Satisfaction survey patient (5)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>31</td>
<td>1992</td>
<td>Teflo: Gore-Tex</td>
<td>IV</td>
<td>15</td>
<td>21.5/-</td>
<td>9.4%</td>
<td>4.7%</td>
<td>14</td>
<td>Surgeon's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
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<td>Teflo: Gore-Tex</td>
<td>IV</td>
<td>17</td>
<td>36.7</td>
<td>0</td>
<td>4</td>
<td>Anthropometric measurements</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>33</td>
<td>2001</td>
<td>Teflo: Softform</td>
<td>IV</td>
<td>31</td>
<td>NR</td>
<td>NR</td>
<td>SR</td>
<td>Surgeon's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>34</td>
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<td>IV</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>94%</td>
<td>4.6%</td>
<td>26</td>
<td>Surgeon's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
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<tr>
<td>35</td>
<td>2006</td>
<td>Teflo: Advanta</td>
<td>IV</td>
<td>802</td>
<td>NR</td>
<td>NR</td>
<td>94%</td>
<td>4.6%</td>
<td>26</td>
<td>Surgeon's *</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
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<td>36</td>
<td>2008</td>
<td>Teflo: Advanta</td>
<td>IV</td>
<td>33</td>
<td>33</td>
<td>NR</td>
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<td>30</td>
<td>Patient satisfaction survey (5)</td>
<td>Yes</td>
<td>Retrospective</td>
<td>No</td>
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<td>37</td>
<td>2004</td>
<td>PMMA: Artecoll /control</td>
<td>Ib</td>
<td>69</td>
<td>59 lip control</td>
<td>NR*</td>
<td>1, 3, 6, 12</td>
<td>Masked observer ratings using the FPAS (6)</td>
<td>Yes</td>
<td>Prospective Multicenter (6 centers)</td>
<td>No</td>
<td>Yes</td>
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<td>38</td>
<td>2006</td>
<td>PMMA: Artecoll /control</td>
<td>Ib</td>
<td>55</td>
<td>63 lip control</td>
<td>NR*</td>
<td>1, 3, 6, 12</td>
<td>Masked observer ratings using the FPAS (6)</td>
<td>Yes</td>
<td>Prospective Multicenter (6 centers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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</table>

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 hydroxylapatite; DLL direct lip lift; EPITE: 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.
Table 2
Classification of fillers for facial and lip augmentation.

<table>
<thead>
<tr>
<th>FILLER SUBSTANCE</th>
<th>Main features</th>
<th>Cross link</th>
<th>PS (μm)</th>
<th>LIFE (m)</th>
<th>NAME</th>
<th>Year</th>
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<td><strong>DERMIS</strong></td>
<td>CONNECTIVE TISSUE</td>
<td>Human autologous, from white lip skin after direct lip lift</td>
<td>≥27</td>
<td>Upper and lower lip connective tissue</td>
<td>1966</td>
<td>X</td>
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<td>Human autologous, from pre/post auricular skin after rhinoplasty</td>
<td>≥27</td>
<td>Pre and post-auricular connective tissue</td>
<td>1975</td>
<td>X</td>
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<td>Human autologous, from strap muscle after mastectomy</td>
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<td>Upper and lower connective tissue</td>
<td>1975</td>
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<td>Human autologous, from breast implant capsule after removal.</td>
<td>≥27</td>
<td>Breast implant capsule</td>
<td>1996</td>
<td>X</td>
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<td><strong>FIBROCARTILAGENSIS</strong></td>
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In green: autologous materials; in red: the producer has discontinued manufacture. discontinued (Gilbert et al., 2012); **Collagenics Inc went out of business in 2006; Sanofi-Aventis acquired Candlemm Pharma; ** the product is no longer available on catalog; ** studies found for a specific filler in facial augmentation; Superf: superficial; Semip: semipermanent; Sem: semipermanent; Scm: sternocleidomastoid muscle; US: United States of America.
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 16.4% for placebo (p < 0.05) (Weiss et al., 2007). These results were consistent with an animal study where capillary-associated macrophages, as observed by electron microscopy, were observed 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). Dermol 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 Cosmorderm (non-cross-linked human collagen) and Cosmoplast (cross-linked human collagen). Cosmorderm was used for the correction of upper lip rhytids, and Cosmoplast was used for lip augmentation. The duration of Cosmorderm 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, Cosmorderm, 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., 2005). 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, 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.
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 (Minnews.com, 2009). This product failed to be marketed, but FG-5016, another cross-linked rhII 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.

Hyaluronic or hyaluronic acid (HA) is a glycosaminoglycan polysaccharide composed of alternating residues of the mono- saccharides 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 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 Ágerup, 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 mono- densified 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 Juvederm (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 (Ecleston 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 mono- phasic polydensified HAs.

The polydensification process creates a gel with different den- sity 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 persist for 4–6 months. A hypothesically 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. Revenasene (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 Ellenboghenin (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 ‘liposculture’ was described by Cole- man: 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 with DDL (jacobs and Quartzel, 2004). Only one study among 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 Rabhan, 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 (Ponzzielle 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 (Citarrella 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 re- sults of these flaps have been quite acceptable (Botti and Villedieu, 1995). The use of an orbicularis oris flapping was recently
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 (TGFB) 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) (Midick, 1992; Ersek and Beissang, 1992; Ersek et al., 1997) became a common procedure after 1991 (Alke, 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 (Fluroron) (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; Bigata, 2001). Solid tube-shaped silicone has also been used in lip enhancement, under the name Perma Facial Implant (Surgisol, 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 FizioMed (US) under the name Laresse (previously Profil 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/Polytuf. 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 (PLA) and e-polycapronolactone (PCL), are currently used as soft tissue fillers.

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 Atletane, 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 Atletane 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 hydroxyapatite (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 Gravier, 2006), but a high rate of nodularity has been found (Jacovella et al., 2006; Jansen and Gravier, 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 (TGFB-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).
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 Ellanse, 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 Artex/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; Nacul 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 Artex, 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 Dermadep (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 polyethylene glycol/diacrylate (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 Polynekon 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).

Polyacrylamine 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). Polyalkylamide 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 Sardesi, 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 (Bosniak 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 LFCS (lip fullness grading scale (LFCS) (Recupero and McCullough, 2010); the peri oral lines scale (POLS) and oral commissures severity scale (OCSU) (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 Firooz, 2001; Recupero and McCullough, 2010), the softness in one scale (Moscona and Codro, 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) mm3 for facial and (60–65) mm3 for lip. For tubular shape implants (Silicone, ePTFE), the volume was approximately (30–35) mm3 for facial and (10–15) mm3 for 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-
<table>
<thead>
<tr>
<th>Reference Technique</th>
<th>Efficacy outcome measurement</th>
<th>Result</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fezza Dermis: upper eyelid skin de-epithelialized with CO₂ laser</td>
<td>Average postoperative lip score (10 points scale. No detailed description of the survey is given).</td>
<td>Average lip score pre-operative 2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>De Benito Galea and subgalea</td>
<td>Satisfaction survey patient (3 point scale, not validated)</td>
<td>Excellent 26%</td>
<td>NR</td>
</tr>
<tr>
<td>Leaf SMAS from rhytidectomy</td>
<td>Questionnaire (only 54 responders; 2 point scale; not validated)</td>
<td>Fuller lips 77%</td>
<td>NR</td>
</tr>
<tr>
<td>Trussler Palmaris longus tendon</td>
<td>Upper lip measurements:</td>
<td>Fuller lips</td>
<td>Non fuller lips</td>
</tr>
<tr>
<td></td>
<td>% augmentation mean (postoperative vertical measurement/preoperative vertical measurement) × 100</td>
<td>Midlateral lip left 190 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Cupid’s bow left</td>
<td>194 ± 4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Tubercle</td>
<td>198 ± 4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Cupid’s bow right</td>
<td>193 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Midlateral lip right</td>
<td>189 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Cupid’s bow (left/right): distance from the intermediate point of the upper vermilion border (between Ls’ and Ch) and Stos’</td>
<td>Mean vertical height</td>
<td>192 ± 3</td>
</tr>
<tr>
<td></td>
<td>Midlateral lip (left/right): 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°</td>
<td>Lateral projection</td>
<td>184 ± 7</td>
</tr>
<tr>
<td>Recupero SMAS, PAF, DLL + SMAS, DLL + PAF</td>
<td>Upper lip dynamic smile outcomes</td>
<td>Mean lip mobility scale in post-op 4.7</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>1) Lip mobility score (5 point scale)</td>
<td>Mean lip mobility at 12 months 4.8</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>2) Smile strength</td>
<td>Smile strength in post-op 98</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>Formula: [[(ch–ch smile)/(ch–ch rest)] × 100]</td>
<td>Mean satisfaction at 12 months post-op 3.4</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>Physician satisfaction (5 point scale: 0 dissatisfaction; 4 totally satisfied)</td>
<td>Mean satisfaction at 1 day post-op 3.6</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>Patient satisfaction assessment (5 point scale: 0 dissatisfaction; 4 totally satisfied)</td>
<td>Mean satisfaction post-op 3.7</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>Lip fullness grading scale (5 point scale (validated [Kesselring, 1986]))</td>
<td>Mean satisfaction at 12 months FU 3.4</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>0 very thin</td>
<td>Pre-op SMAS 0.81</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>1 thin</td>
<td>1.1 1.76</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>2 moderately thick</td>
<td>PAF 3.2</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>3 thick</td>
<td>DLL + SMAS 0.3</td>
<td>p = 0.05</td>
</tr>
<tr>
<td></td>
<td>4 full</td>
<td>DLL + PAF 1.04</td>
<td>p = 0.05</td>
</tr>
</tbody>
</table>

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.
Preoperative Postoperative Change
Mean SD Mean SD
Upper lip projection ±1.30 21% 0.001

/Ch0

[20] Upper lip projection: distance between the white roll and the lowest point in the upper lip (LST to S), less than the Steiner’s line (Cm to P) and the most anterior upper lip vermillion point (Lsa), being the two lines orthogonal. The points LST and S are positive values.

Quantitative analysis of vermillion show (frontal view) and upper lip projection (lateral view). The results are expressed in % of increase between pre-op measurement (in mm) and post-operative measurement (in mm).

Frontal view: vermillion show, upper and lower lip (left and right sides) and a 23% increase in upper lip projection, mm (LST 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.

Bohluli Temporalis fascia Quantitative analysis of vermillion show (frontal view) and upper lip projection (lateral view). The results are expressed in % of increase between pre-op measurement (in mm) and post-operative measurement (in mm).

In red: not statistically significant.

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; 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.

Twelve good quality studies evaluated the efficacy of connective tissue matrix (two studies), collagen fillers (four studies), hyaluronic 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 Zyplast with Zyplast (control), Scala et al. (2002) reported that at 12 months after surgery, 85% of patients treated with Zyplast 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 Dermicoll-P35 in one study and Evolence Breeze in another study (Landau et al., 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 Dermicoll P-35 and very good or good in 86.8% of patients treated with Evolence Breeze. In his study of Dermicoll 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>
<thead>
<tr>
<th>Reference</th>
<th>Technique</th>
<th>Efficacy outcome measurement</th>
<th>Result</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rohrich Alloderm</td>
<td>Satisfaction survey patient (2 categories for each survey) not validated</td>
<td>Overall satisfaction with the results</td>
<td>Yes</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Would you repeat the procedure?</td>
<td>Yes</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discomfort lasted in 1 week?</td>
<td>Yes</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>23%</td>
</tr>
<tr>
<td>Scalfani Cymetra/Zyplast</td>
<td>Anthropometric measurements, frontal and lateral view at 12 months post-operation.</td>
<td>Change in vermillion % at midline from baseline (%[% \Delta (d-c)(d)])</td>
<td>Cymetra</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zyplast</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change in vermillion height at midline from baseline (%[% \Delta (d-c)])</td>
<td>Cymetra</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zyplast</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change in nasolabial angle from baseline, (\langle \Delta m \rangle)</td>
<td>Cymetra</td>
<td>16.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zyplast</td>
<td>16.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change in anterior projection mm ((\Delta ))</td>
<td>Cymetra</td>
<td>69.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zyplast</td>
<td>27.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change in vermillion surface area from baseline (lateral view) % (% \Delta ))</td>
<td>Cymetra</td>
<td>53.3%</td>
</tr>
<tr>
<td>Landau Collagen: DermicolP35</td>
<td>Patient satisfaction with the results (3 point scale)</td>
<td>Very good</td>
<td>69.2%</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfactory</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td>De Boulle Collagen: DermicolP35</td>
<td>Improvement survey clinician (6 point-scale)</td>
<td>Improvement of lip enhancement</td>
<td>Yes</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not improvement of lip enhancement</td>
<td>Yes</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfied/very satisfied with results</td>
<td>Yes</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not satisfied with results</td>
<td>Yes</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfied/very satisfied with results</td>
<td>Yes</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not satisfied with results</td>
<td>Yes</td>
<td>6%</td>
</tr>
<tr>
<td>Landau Collagen: Evolence Breeze</td>
<td>Patient satisfaction survey patient (4-point scale): very satisfied, satisfied, unsatisfied.</td>
<td>Very good</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfactory</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Downie Collagen: PRI-1, PRI-2 and Zyplast, Hyaluronic acid: Perlane</td>
<td>3D stereophotogrammetry Average upper lip volume</td>
<td>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</td>
<td>Perlane</td>
<td>CI 95%</td>
</tr>
<tr>
<td></td>
<td>2D analysis (CKC scale)</td>
<td>Upper lip size (5 point scale; – 2 very thin, to 2 extremely full)</td>
<td>Perlane</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower vermillion body (5 point scale; – 1 tight almost unlined to 3 severe wrinkles)</td>
<td>Perlane and PRI-1</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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)</td>
<td>PRI-1 less longevity than Perlane</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Satisfaction survey patient (5 point scale; 1 very satisfied to 5 very dissatisfied)</td>
<td>Very satisfied</td>
<td>PRI-1 and PRI-2 more dissatisfied than Perlane or Zyplast</td>
<td>p = 0.052</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfied</td>
<td>Neither satisfied or dissatisfied</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dissatisfied</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very dissatisfied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosniak Hyal: Restylane</td>
<td>Physician evaluation score (4 point scale; 0 no improvement/effect to 3 complete improvement/effect)</td>
<td>0 no improvement</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 minimal improvement</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 moderate improvement</td>
<td>20.15</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 complete improvement</td>
<td>76.50</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Patient satisfaction rating (3 point scale: unsatisfied, satisfied, very satisfied)</td>
<td>Unsatisfied</td>
<td>22.2</td>
<td>49.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfied</td>
<td>39.6</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very satisfied</td>
<td>38.2</td>
<td>8.03</td>
</tr>
<tr>
<td>Jaco</td>
<td>Hyal: Restylane</td>
<td>Patient satisfaction (5 point scale: 5 most satisfied to 1 dissatisfied. The rest of the description of the survey is not given)</td>
<td>Mean satisfaction score ± SD</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Glogau</td>
<td>Hyal: Restylane/Placebo (No treatment)</td>
<td>MLFS: Medicis lip fullness scale (5 point scale; validated)</td>
<td>Treatment success (at least a 1 point improvement) at week 24 compared to control</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAI: global aesthetic improvement scale (9 point scale; not validated)</td>
<td>Treatment success (at least a 1 point improvement) at week 24 compared to control</td>
<td>74%</td>
</tr>
<tr>
<td>Eccleton</td>
<td>Hyal: Juvederm Volvella</td>
<td>Overall satisfaction (11 point scale; not validated. 0 very dissatisfied, 10 very satisfied)</td>
<td>7–10 in month 3</td>
<td>94.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–3 (not satisfied)</td>
<td>7–10 in month 6</td>
<td>93.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4–6</td>
<td>7–10 in month 9</td>
<td>89.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7–10 (satisfied)</td>
<td>7–10 in month 12</td>
<td>82.8%</td>
</tr>
<tr>
<td>Fagien</td>
<td>Hyal: Juvederm Ultra</td>
<td>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 &gt;40% of the subjects, they were considered responders</td>
<td>Baseline</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks</td>
<td>0%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 weeks</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 weeks</td>
<td>10%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POL: 12 weeks compared to baseline</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POL: 24 weeks compared to baseline</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCS: 12 weeks compared to baseline</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCS: 24 weeks compared to baseline</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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 &gt;40% of the subjects, they were considered responders</td>
<td>Lip volume (cm²)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lip surface %</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper lip projection %</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower lip projection %</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) 3D digital images changes from baseline (measures of baseline are considered magnitude zero)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients satisfaction at week 2, 12 and 24, in a 11 point scale (0 very dissatisfied to 10, very satisfied)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaconella</td>
<td>Radiess</td>
<td>Patient satisfaction survey at 18-month (3-point scale. description of survey not given)</td>
<td>n (%)</td>
<td></td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Reference</th>
<th>Technique</th>
<th>Efficacy outcome measurement</th>
<th>Mean score</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mladick</td>
<td>Siloxane: Bioplastique</td>
<td>Satisfaction survey patient (5 points scale; 1 poor results, 5 excellent results)</td>
<td>4.5</td>
<td>NR</td>
</tr>
<tr>
<td>Moscona</td>
<td>Siloxane: Siluron 1000</td>
<td>Satisfaction survey patient (5 point scale)</td>
<td>66.5%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excellent</td>
<td>18.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good result</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild improvement</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No improvement</td>
<td>2.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Softness lips scale (5 point scale: 1 soft as before, 5 very hard)</td>
<td>1 Soft as before</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>18.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 Very hard</td>
<td>0.6%</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>Eptfe: Gore-Tex</td>
<td>Anthropometric measurements (mean increase in mm)</td>
<td>0.98 mm</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean increase of lip projection (in mm) at 6th month.</td>
<td>1.94 mm</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference among the mean increases in the 1st, 3rd, 6th month of follow-up.</td>
<td>Yes</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean increase in width of exposed vermillion (mm)</td>
<td>1.94 mm</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference among the mean increases in the 1st, 3rd, 6th month of follow-up.</td>
<td>Yes</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td>Verret</td>
<td>Eptfe: Advanta</td>
<td>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)</td>
<td>8.8%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Minimal improvement</td>
<td>74.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Significant improvement</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Redbord</td>
<td>Eptfe: Advanta</td>
<td>Patient satisfaction survey (5 point scale: 5 very satisfied to 1 very unsatisfied)</td>
<td>76%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>15.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Cohen</td>
<td>PMMA: Artcoll/Control (Collagen: Zyplast)</td>
<td>Improvement in investigator ratings using the facial fold assessment scale (FAAS) (5 point scale: 1 – completely successful to 5 – not at all successful)</td>
<td>1.47 ± 0.09</td>
<td>1.32 ± 0.334</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 month</td>
<td>1.28 ± 0.009</td>
<td>0.43 ± 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 month</td>
<td>1.34 ± 0.12</td>
<td>0.05 ± 0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 month</td>
<td>1.41 ± 0.12</td>
<td>0.48 ± 0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improvement in mask observers ratings using the FAAS (5 point scale: 1 – very satisfied to 5 – very dissatisfied)</td>
<td>0.31 ± 0.07</td>
<td>0.25 ± 0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 month</td>
<td>0.08 ± 0.08</td>
<td>0.22 ± 0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 month</td>
<td>0.24 ± 0.09</td>
<td>NR NR</td>
</tr>
<tr>
<td>Cohen</td>
<td>PMMA: Arthefill/Control (Collagen: Zyplast)</td>
<td>Improvement in investigator ratings using the facial fold assessment scale (FAAS) (5 point scale: 1 – completely successful to 5 – not at all successful)</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 month</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 month</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 month</td>
<td>2.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>
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 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 CAIS. 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
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 Redbold 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 microspher filler Artecoll, investigator ratings using the validated FFAS showed greatest improvement (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 (Bouquet and Ägerup, 1999; Solish and Swift, 2011; Eccleston and Murphy, 2012; Fagien et al., 2013) and a 34.5% rate of erythema (Bouquet and Ägerup, 1999; Solish and Swift, 2011). The higher rate of swelling with hyaluronate may be explained by the time when the swelling was measured: Bouquet 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 (Bouquet and Ägerup, 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 (Ponielli 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 hyalurionate (Solish and Swift, 2011; Eccleston and Murphy, 2012; Fagien et al., 2013) and 4.4% of patients injected with agarose (Sarano 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 spp.) (Pedana 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 amoxicillin-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% (Bosnacki 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% /C19 and Prilocaine 2.5%; AstraZeneca, Wilmington, US) on the injection site 15 min before the injection is given (Jacovella et al., 2006). Some fillers, such as Restylane-L, Perlane-L, Juvederm 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-Sanze, 1996). A temporary hypoesthesia was reported in 3.5% of patients with Dermisol-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 (Redbold and Hanke, 2008).
Table 6
Complications reported in each study.

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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 vermilion 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 Olshinsky, 2012) which is similar to the incidence reported for other fillers. Steroid injections, simple excision of the granuloma, special surgical techniques (Moor and Olshinsky, 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. Hydroxyapatite 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).
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 lip shape (Trussler et al., 2006). Despite this, hyaluronate seems to be the preferred filler, according to the ranking of nonsurgical 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 Boule 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), ePTFE implants were inserted in 17 patients and a total of 23 lips;
granulomas associated with silicone use was approximately 3
innovative
number of patients may have masked some important in-
excluding some studies based on their failure to include a mini-
This may
letters to the editor published about the original research articles.

divided the
ve fold lower than the 5.8% extrusion rate if one divided the
Thus, silicone implantation has taken on a negative connotation,

ection. Fifth, our exclusion of studies that included patients who
dict of interest for the studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Technique</th>
<th>COE</th>
<th>Type of COE</th>
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<tr>
<td>Tobin</td>
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<td>Jaco</td>
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<td>Glogau</td>
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<td>2006</td>
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<td>Yes</td>
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Abbreviations: COE: conflicts of interest; NR: not reported.

Table 7

Conflicts of interest reported for the studies.

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 floating 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 peripheral 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
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 particular 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

The authors have no financial interest regarding the content of this article.

Acknowledgments

Dr. Joan San Miguel Moragas received financial support of the Cranio-Maxillo-Facial Surgery Chair Prof. Mommaerts of the Vrije Universiteit Brussel to conduct the study.

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Wolter TP, Pallua N: Removal of the permanent filler polyacrylamide hydrogel (Aquamid) is possible and easy even after several years. Plast Reconstr Surg 126(3): 138–139, 2010

