

# Perspectives and challenges in lip rejuvenation: a systematic review

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**Abstract. – OBJECTIVE:** There is an abundance of information on facelifts, blepharoplasties, rhinoplasty, and other cosmetic surgical procedures for the upper third of the face, but little is known about perioral lip rejuvenation. The aim of this article is to examine the existing literature on lip rejuvenation and perioral procedures related to lip rejuvenation. Additionally, this article aims to highlight the importance of addressing perioral areas alongside lip rejuvenation procedures, rather than solely focusing on lip rejuvenation. We also discussed the extensive procedures and materials used for lip rejuvenation, such as hyaluronic acid, botulinum toxin A, abobotulinum, onabotulinum, incobotulinum, prabobotulinum, fat grafts, silicone fillers, human collagen, collagen stimulating procedures such as derma pens and derma rolls, radiation frequency, stem cells, and plasma therapy, as well as the underlying factors that contribute to varying success rates.

**MATERIALS AND METHODS:** A thorough literature search was done using PubMed, Cochrane, Ebsco search, Google Scholar, Scopus, and Web of Science for the articles pertaining to facial and lip cosmetic surgeries 1995-2020. Keywords for the search included anatomy of the face, facial aging, perioral areas, lip rejuvenation, botox, grafts, facelift, plastic surgery, stem cell therapy, plasma treatment, and cosmetic surgery.

**RESULTS:** 37 articles met the study criteria. 14 out of 37 studies included procedures for lip and perioral region rejuvenation. The remaining 23 studies either involved lip procedures alone or lip procedures in conjunction with facial cosmetic procedures. Lip rejuvenation with perioral enhancement with hyaluronic acid gel demon-

strated a 94.3% improvement on the lip fullness scale (LFS) one month after re-treatment. The amalgamation of lip and perioral region rejuvenation produces a synergistic effect. Whereas, sole lip rejuvenation procedures showed short-term results with less patient satisfaction, calling for secondary lip rejuvenation procedures. It was also observed that hyaluronic acid was the most commonly used agent for lip rejuvenation procedures with minimal or no side effects.

**CONCLUSIONS:** In conjunction with perioral rejuvenation, lip rejuvenation procedures produce more aesthetically appealing results. However, any cosmetic surgical or non-surgical procedure is limited by the nature and composition of the products used. The use of FDA-approved products for rejuvenation is strongly advised to avoid undesirable side effects. Further extensive research is required on the long-term outcomes and adverse effects of stem cell transplants, such as tumor development.

## Key Words:

Lip augmentation, Rejuvenation, Lip fillers, Botox, Hyaluronic acid, Graft, Lip implants, Plasma therapy, Stem cell therapy, Cosmetic lip corrections, Facial plastic surgery.

## Introduction

In facial cosmetic procedures such as blepharoplasty, facelift, and brow lift, the outer ring of the face is addressed, unfortunately focusing least on the inner ring or perioral areas<sup>1</sup>. To understand facial cosmetic procedures, it is very important to

precisely evaluate facial bone and soft tissue anatomy and the effect of external and internal factors on the facial region. Aging is associated with multiple factors such as genetics, and environmental such as exposure to sunlight, diet, smoking, and drinking alcohol.

Age-related facial changes include:

- Facial bone resorption
- Anatomical dissolution or atrophy of mandibular fat compartments (superior and inferior)
- Gradual disappearance of jawline contour
- Dehiscence of mandibular septum
- Loss of skin elasticity and sagging
- Gradual reduction in the tissue volume over the face and neck regions
- Wrinkles at the corners of eyes (crow's feet)
- Perioral wrinkles
- Loss of jawline contour
- Double chin
- Drooping and thinning of lips
- Muscular weakness
- Prominence of nasolabial folds
- Lip lengthening and obliteration of nasal columella

Facial soft tissues and muscles undergo senile changes with the underlying skeletal system, which influences the aging process<sup>1,2</sup>. The muscles and ligaments of the lower part of the face are inserted into the inferior border of the mandible and mandibular septum. This is covered by the subcutaneous tissues, fat, and skin giving shape and volume to the lower part of the face. As age advances, these compartments begin to disintegrate, resorbing the bone and getting filled by colloids. Musculature begins to loosen the underlying support, increasing the depth of the labiomental sulcus, jowls, and marionette lines, and deepening pre-jowl lines. The skin loses its youthful appearance. Devolumization further in the chin area causes a “witch’s chin” appearance. In response to the muscular atrophy, there is compensatory hypertrophy of other muscles such as mentalis, *depressor anguli oris*, and *depressor labii inferioris*. The resultant effect of atrophy and hypertrophy of muscles creates deep creases such as a melo-mental crease, labiomandibular crease, and mental crease. These factors contribute to the senile features in an individual<sup>1</sup>.

The upper lip extends from the subnasale to the lower free vermilion border of the upper lip superior-inferiorly and nasolabial folds laterally. At the center of the lip is a V-shaped depression called a cupid’s bow. The lower lip extends from the upper free vermilion edge to the lower border

of the mandible superoinferiorly and to the commissures of the mouth laterally. In between the red vermilion border of the lip and the skin is a thin white roll. The upper lip is shorter than the lower lip. The anatomy of the lip, perioral structures, and senile changes must be borne in mind during lip rejuvenation procedures.

## Materials and Methods

Based on the PRISMA guidelines, a systematic review was conducted. A thorough literature search was conducted using PubMed, Cochrane, EBSCO search, Google Scholar, Scopus, and Web of Science for the articles pertaining to facial and lip cosmetic surgeries between 1995-2020. Keywords for the search included anatomy of the face, facial aging, perioral areas, lip rejuvenation, Botox, grafts, facelift, plastic surgery, stem cell therapy, plasma treatment, and cosmetic surgery.

### Study Selection

Only peer-reviewed articles in English were included in the study. All the human randomized, quasi-randomized clinical trials, case reports, and case series were included in the study. Articles were first selected based on the key terminologies and criteria for selection. The abstracts were screened first, followed by the screening of the full-text papers reporting lip and perioral rejuvenation procedures.

### Inclusion criteria

- Lip, perioral lip rejuvenation procedures with advantages, disadvantages, complications, and steps taken to manage them.
- Lip rejuvenation procedures in combination with other facial cosmetic procedures.

### Exclusion criteria

- Age and gender not taken into consideration during the database search.
- Duplicated studies by the same author.

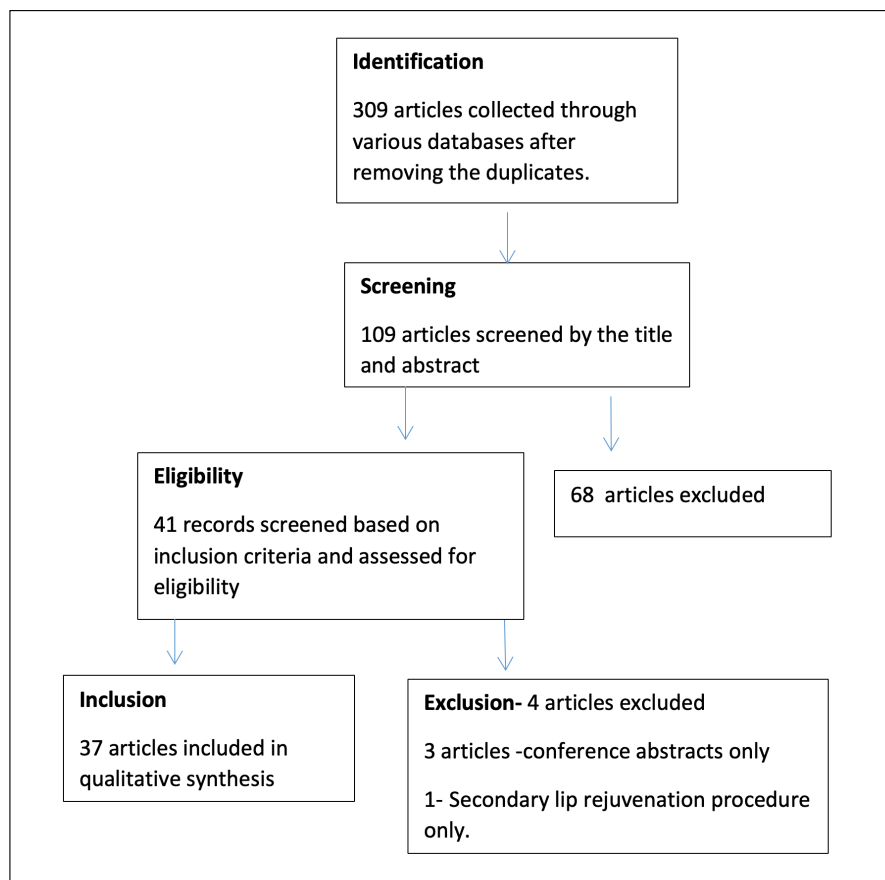
Upon perusing the titles and abstracts, they were further filtered. Any conflicts regarding article selection were resolved with the professor, a co-author of this study. Relevant topics were investigated in each of the selected article’s citations to determine if they contained pertinent information. Before being included in this systematic review ([Supplementary Table I](#)), each selected article was thoroughly read and evaluated.

## Results

From the initial database search, 309 articles were identified. A PRISMA flowchart (Figure 1) illustrates the identification and selection of relevant articles and the final screening. 106 met the criteria for inclusion. There were 37 articles<sup>1-37</sup> that met all the study's criteria. The rest of the articles were either conference abstracts or articles pertaining to secondary lip revision procedures. 14 out of 37 studies included procedures for lip and perioral region rejuvenation<sup>1,3,6,7,10,11,13,16,22,25,26,28,33,35</sup>. The data pertaining to the age changes in young and old lips and perioral anatomy in terms of upper and lower lip proportions, volume, projection of upper lip, philtrum, nasal base to vermilion shape, cupid's bow were compared, concluding that, as age advances, the loss of lip volume, projection, fading of philtral columns, sagging in the upper lip increase in vertical length, showing the impact of how the amalgamation of these two methods produces a synergistic effect<sup>7</sup>.

The first application of stromal vasculature derived from adipocytes in facial cosmetic procedures was made by Cohen in 2003<sup>9</sup>. This neurotoxin was later applied for cosmetic corrections. Neurotoxins such as abobotulinum, onabotulinum, incobotulinum, parabotulinum are used in the correction of crow's feet (caused by the contraction of orbicularis oculi muscle), brow rejuvenation nasal bunny lines, nasal flaring, gummy smile, neck and mentalis muscle, perioral rhytids and asymmetric smiles<sup>10</sup>. Lip and perioral enhancement with hyaluronic acid gel demonstrated a 94.3% improvement on the lip fullness scale (LFS) one month after re-treatment, compared to an 82.2% improvement one month after the initial treatment<sup>10</sup>.

Lip and perioral rejuvenation procedures were reported to have minor disadvantages in comparison to lip rejuvenation procedures<sup>16</sup>. Face granulomas, hypersensitivity, and nodule formations were reported in one study. A study<sup>35</sup> identifies calcium hydroxyapatite complications such as nodule formation, hematoma formation, and extrusion of a treated nasolabial fold.



**Figure 1.** PRISMA flowchart showing the screening of articles for the systematic review.

## Discussion

Perioral and lip aging is a multifactorial process, each factor interrelated with the other. External and internal soft tissue changes are associated with the underlying bony changes. Atrophy of the philtrum columella and the orbicularis oris muscle contribute to the increase in the upper lip length<sup>36,37</sup>. Hence all the surrounding structures, including pre-maxillary, nose, and perioral areas, should be addressed during lip rejuvenation procedures.

Nasolabial and labiomental creases, perioral rhytids, jowls, and underlying bone resorption contribute to the perioral aging process. Hence, the use of only the fillers without addressing associated contributing factors would give an un-aesthetic appearance. Surgical and non-surgical lip rejuvenation procedures carry their own advantages and disadvantages. Surgical perioral lip correction procedures might lead to scarring<sup>38</sup>. Adipose stem cells have the potential for scarless wound healing<sup>39</sup>. Lip rejuvenation extending to cleft lip corrections using botulinum toxins has shown excellent results. Chemical denervation paralyzes the targeted muscles supplied by that nerve, thus reducing the hyperactivity of the muscle. The use of denervating agents in the perioral region helps in fading the perioral rhytids<sup>40</sup>.

Dermal fillers are categorized as follows:

- Permanent fillers: i.e., silicone, polymethyl-methacrylate, polyalkalimide.
- Short-term fillers: i.e., collagen, hyaluronic acid, calcium hydroxyapatite.

Various authors suggested a combination of fillers with varying injection depths and techniques to obtain successful results<sup>40,41</sup>. The most commonly used fillers are hyaluronic acid and polyacrylamide. However, owing to the adverse effects such as granuloma formations, polyacrylamide use is restricted<sup>42</sup>. The use of hyaluronic acid fillers is gaining worldwide popularity, but comparative studies are scarce.

Use of synthetic fillers such as hyaluronic acid derivatives, polyvinylsiloxane, homologous preserved fascia lata, dermis, heterologous and homologous collagen tend to exhibit complications such as siliconomas, granuloma, migration, hypersensitivity, granulomatous reactions, infection and inflammation, and pain, dyschromia, migration, connective-tissue disease, hypercalcemia, lupus miliaris disseminatus and sicca complex and even death<sup>22,43</sup>. Bovine collagen, however, shows a lesser degree of allergic reactions, up to 2%, which necessitates a pre-patch test before the procedure, and

5% of the disproportionate distribution and nodule formation of the bovine collagen resulting in the unesthetic appearance postoperatively<sup>44</sup>.

As mentioned in the article published by Suzuki<sup>45</sup>, Dr Alan Scott was the 1<sup>st</sup> surgeon to use botulinum toxin for the correction of strabismus. Stem cells play a diversified role in corrective restorative and esthetic cosmetic procedures. The earliest discoveries of the clinical implications of stem cells, genetic engineering, and stem cell transplantations were made by Owen<sup>46</sup>. The role of stem cells in cosmetic lip rejuvenation procedures is remarkable too. Stem cells are either unipotent, multipotent, or pluripotent. Unipotent stem cells produce cells of one type only. They possess the capacity to renew. Multipotent ones differentiate into limited types of cells (e.g., mesenchymal cells). While, pluripotent cells differentiate cells from all the 3 germ layers (e.g., embryonic or induced pluripotent stem cells). Human mesenchymal cells possess the ability to differentiate into adipocyte, chondrocyte, and osteocyte cell lines. Stem cells derived from adipose cells demonstrate antiaging properties. They differentiate into collagen-producing skin cells. Stem cell application at the site of the healing wound accelerates the process and fades the scar<sup>47</sup>. Bone marrow stem cells and fibroblasts possess excellent wound-healing properties through increased collagen and growth factor production. Adipose stem cells enhance granulation tissue formation, angiogenesis, and collagen formation, thus accelerating wound healing<sup>48</sup>.

As stated earlier, fat volume loss is one of the contributing factors to the aging process. Fat grafts can be used to rejuvenate these areas. However, fat compartments resorb eventually, disproportionately creating an unesthetic appearance. This can be reduced by the addition of stem cells, such as cell-assisted lip transfer (CAL) to the fat graft. These stem cells enhance the life of the graft, reducing its absorption<sup>49,50</sup>.

Stem cells also reduce the immunosuppression and rejection of composite alloplastic tissues (CTA)<sup>51</sup>.

Platelet-rich plasma is obtained by the centrifugation and isolation of concentrated platelets from the patient's own blood. Vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF- $\beta$ ), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), are growth factors (GFs), epidermal growth factor (EGF), concentrated in platelet-rich plasma (PRP) and platelet rich fibrin matrix (PRFM)

preparations. They help in the chemotaxis of fibroblasts, stem cells, endothelial cells, and osteoblasts and are mitogenic for fibroblasts, monocytes, smooth muscle cells, osteoblasts, endothelial cells, and keratinocytes. They enhance the production of collagen and fibronectin and hasten wound healing by increasing angiogenesis and vascular permeability. They diminish the effect of erythema and edema post-operatively<sup>52,53</sup>. A study conducted on split-thickness graft with platelet rich plasma (PRP) showed increased epithelization and angiogenesis<sup>54</sup>. However, some studies showed that PRF has little or no effect on wound breaking-incision site strength nor showed increased epithelization in their randomized clinical control study and provided no histological support for their study<sup>55</sup>. Neuromodulators are used for the correction of perioral rhytids, marionette lines, turned-down oral commissures, and dimples and depressions over the chin. Solid implants-in correcting pre-jowl sulcus and other mandibular anatomical abnormalities, depending on the anatomic presentation by the patients<sup>56</sup>.

Lip rejuvenation grafts/products have some drawbacks. For instance, the use of botulinum toxin only provides short-term effects<sup>57,58</sup>. Fat graft shows inflammatory response, neurovascular injury abscess, cysts/nodule formation<sup>59</sup>. Chemo denervation causes paralysis of the adjacent non-targeted muscles, headaches, erythema at the site of injection, and the production of antibodies<sup>60</sup>.

Perioral rejuvenation procedures include facial resurfacing as an adjunctive to facial rejuvenation procedure, botulinum toxin A chemo-denervation, fat grafting, surgical facelift, and soft tissue fillers such as silicone. The author Luthra<sup>61</sup> presented various studies showing the superior performance of calcium hydroxylapatite over hyaluronic acid for the correction of nasolabial folds. Silicone granulomas, hypersensitivity, nodule formations on the face. Calcium hydroxylapatite complications noted in a study include nodule formation, hematoma formation, and extrusion of a treated nasolabial fold<sup>61</sup>. Hyaluronic acid fillers give immediate results and safe, effective, and reversible treatment. More than 2 million of the world's population uses hyaluronic acid fillers<sup>62</sup>.

### **Limitations**

Comparative investigations between lip rejuvenation and lip with perioral rejuvenation were not included, so individual-level data were lacking.

## **Conclusions**

In conjunction with perioral rejuvenation, lip rejuvenation procedures produce more aesthetically appealing results. However, any cosmetic surgical or non-surgical procedure is limited by the nature and composition of the products used. Therefore, both the patient and the operating surgeon must abide by these restrictions and embrace realistic cosmetic restorations. The use of FDA-approved products for rejuvenation is strongly advised to avoid undesirable side effects. Further extensive research is required on the long-term outcomes and adverse effects of stem cell transplants, such as tumor development.

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### **Conflict of Interest**

The Authors declare that they have no conflict of interests.

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### **Authors' Contributions**

The conception and design of the study: NT, VCJ, SA, SMK. Acquisition of data: NT, AAS, SMK, MMA, DMA, LAN. Analysis and interpretation of data: NT, VCJ, SA, LAN. Drafting the article or revising it critically for important intellectual content: NT, VCJ, SMK, MMA. Final approval of the version: NT, SA, SMK, LAN, SA, DMA.

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### **Funding**

This research received no external funding.

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### **Acknowledgments**

The authors extend their appreciation to the Deanship of Postgraduate and Scientific Research at Dar Al Uloom University for their support of this work.

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### **Ethics Approval and Informed Consent**

Not applicable.

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