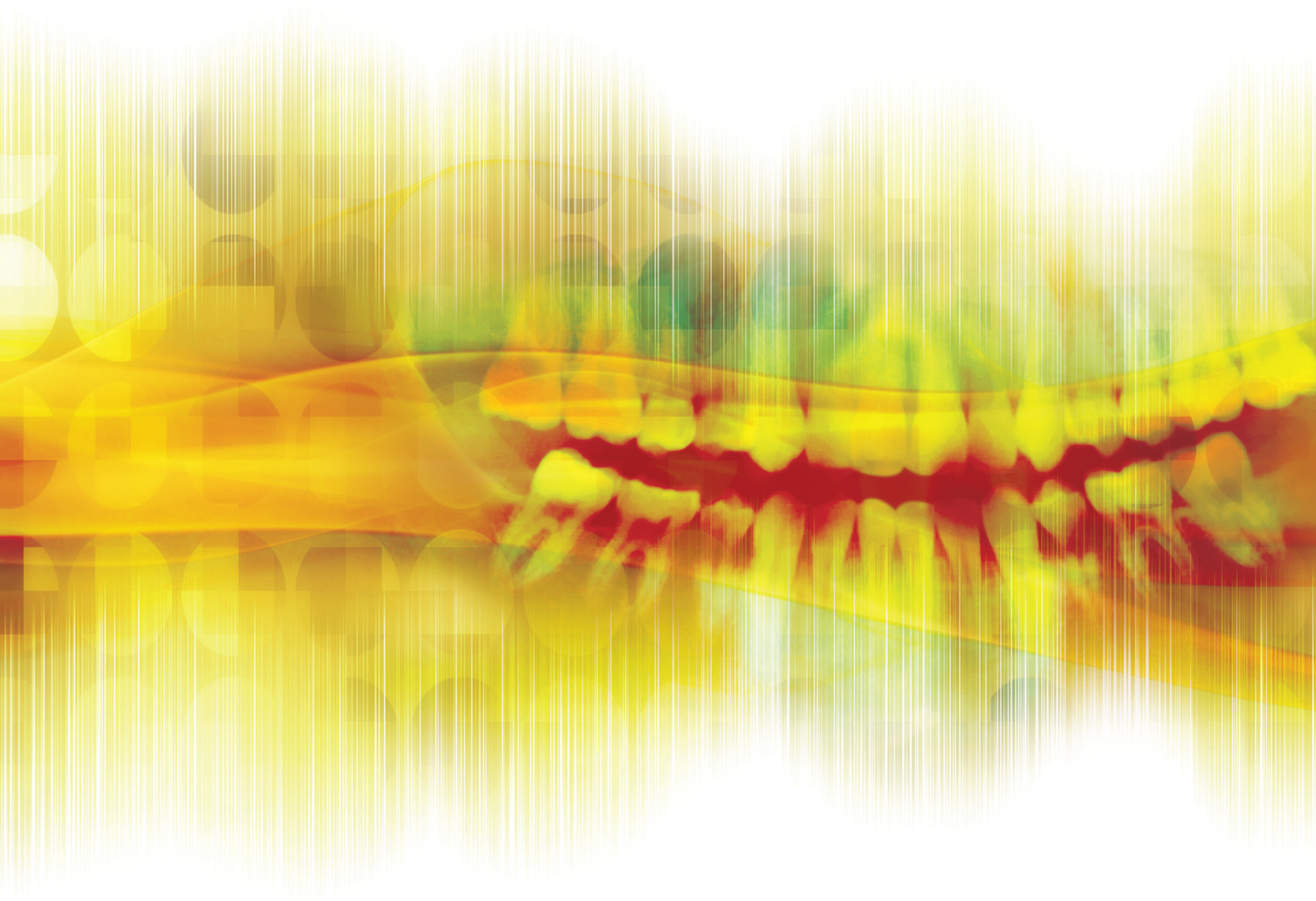
International Journal of Dentistry

Current CAD/CAM Research in Dentistry

Guest Editors: Heng Bo Jiang, Eui-Seok Lee, and Hongxin Cai



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Research Article

Tissue Surface Adaptation and Clinical Performance of CAD-CAM Milled versus Conventional Implant-Assisted Mandibular Overdenture

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Purpose. To evaluate the surface adaptation and maximal biting force of CAD-CAM milled mandibular overdenture (CAD-CAM MOD) compared to conventional compression mold mandibular overdenture (CC MOD). *Materials and Methods*. Ten completely edentulous subjects with persistent complaints of their complete mandibular dentures were received four dental implants in the anterior mandible. Three months after osseointegration, subjects were randomly received either conventional compression mold or CAD-CAM MOD in a crossover design. To assess tissue surface adaptation, the fitting surfaces of each denture base were scanned and placed on the reference master cast. Three and six months after each overdenture was inserted, clinical performance in the form of maximum biting force was evaluated. *Results*. The results of this study indicated that the tissue surface adaptation of the CAD-CAM MOD bases was significantly better than the conventional (compression mold technique) processed bases where ($P = 0.0001$). Regarding clinical performance (maximum biting force), the CAD-CAM MOD exhibited better clinical performance ($P = 0.0001$). *Conclusions*. In denture processing methods, the CAD-CAM overdenture delivered more precise adaption and clinical performance than the compression mold technique.

1. Introduction

Removable denture adaptation is well established to be the most important element in determining the quality of the prosthesis [1]. A well-adapted denture has higher primary wearing comfort and a lower incidence of traumatic ulcers [2]. Adequate denture tissue fit is also important for denture retention, stability, and support [3]. Denture retention has a significant impact on masticatory performance and speaking capacity, and thus on the subjects' quality of life [4]. As a result, one of the key goals of denture manufacture is to achieve maximum mucosal adaptability.

Removable dentures can be produced from a variety of materials and processing techniques. With the type of acrylic resin used and different construction procedures, denture adaption was considerably varied [5]. The compression molding technique, which has been used for decades, is the most extensively utilized processing technique. Although this method has several benefits, dentures might be distorted during processing [6, 7]. Dimensional changes can occur due to polymerization shrinkage and expansion, thermal shrinkage, water absorption, and internal stress release [8]. Denture base adaption to the underlying mucosa is reduced as a result of this deformation, resulting in decreased denture stability and retention. [3, 9].

By digital superimposition, the materials and techniques employed in 3D Printing produced diverging results and the lowest value for accuracy of the fitting surface of the denture foundation in comparison to the CAD/CAM milled base, injection, and compression mold techniques [10]. CAD-CAM produced dentures provide the best denture base adaptation [11–15]. Through the use of prepolymerized blocks of polymethyl methacrylate (PMMA), computer software, and a 5-axis milling machine, CAD-CAM produced dentures have emerged as a popular choice [16, 17], due to advancements in dental technology. In the dentistry field, CAD-CAM dentures have quickly acquired popularity [18, 19]. For both the maxillary and mandibular arches, CAD/CAM denture bases milled from PMMA blocks performed better adaptation than 3D printed, wax milled, and conventionally fabricated heat polymerized denture bases [9, 16].

In addition, the convenience of constructing additional dentures utilizing digitized recorded patient clinical data is one of the merits of CAD-CAM dentures compared to conventional dentures. As a result, if the denture is lost or broken, a replacement prosthesis can be made without the need for new clinical records [20, 21]. CAD-CAM dentures can be completed in two appointments rather than five using the traditional method, saving time for the dentist, technician, and patient [16, 17]. Furthermore, the least amount of distortion during CAD-CAM denture processing, which is critical for mucosal adaptation [14, 22].

The implant-assisted overdenture (IOD) is a well-known treatment option for overcoming the functional inefficiencies that come with traditional dentures [23, 24]. Despite the numerous advantages of implant-assisted prostheses, stress transfer and distribution due to occlusal pressures is expected to differ from that of a traditional complete denture [25]. Under functional forces, the implant acts as a fulcrum of rotating movement, causing concentration of great stresses in the attachment housing area and bone resorption on the edentulous area due to the greater resiliency of the mucosa covering the edentulous ridges compared to the rigid implant abutments. Furthermore, implant fracture, peri-implant bone loss, and subsequent implant failure are possible complications [26–29]. As a result, the goal of this study was to demonstrate the basic adaptability of overdenture.

Denture adaptation is one of the most critical factors determining the clinical performance of complete dentures. Well-fitted dentures provide comfort with fewer traumatic ulcers and greater chewing efficiency [30]. Many factors can influence chewing efficiency, including occlusal contact number, bite force, and masticatory muscle work to grind and break food [31]. The most accurate indicator of occlusal force is the maximal bite force (MBF) [32, 33].

Completely edentulous patients have a masticatory force that is 20%–40% that of healthy dentate people. As a result, complete denture wearers require up to seven times more chewing strokes than dentulous patients to masticate the food [26]. Two mandibular implants dramatically increase bit force and quality of life [34, 35]. Telescopic prostheses were similarly linked to increased MBF [36].

Researchers investigated the adaptation of maxillary [14, 22, 37] or mandibular [38] CAD-CAM complete dentures compared with conventional complete denture bases using superimposition analysis of scanned denture bases [14, 22, 38]. However, the research has not evaluated the tissue surface adaptation of implant-assisted mandibular overdenture bases fabricated by the CAD-CAM technique. Also, most of the studies carried out in CAD-CAM complete dentures are in vitro studies [14, 22, 38, 39], thus more clinical research is necessary to find out the situation. Studies assessing the tissue surface adaptation and clinical performance of CAD-CAM implant-assisted PMMA mandibular overdentures are required and hence emerged the aim of this study. Also, as previously stated, there is a correlation between denture base adaptation and chewing efficiency, which is influenced by biting force. There is a lack of clinical research of denture adaptation and its effect on the biting forces. As a result, the research initiative was created.

This study was aimed to evaluate the CAD-CAM processing technique of prepolymerized PMMA with respect to the denture base adaptation and maximum biting force of implant-assisted overdentures compared to conventional techniques for fabricating overdenture bases. The null hypothesis in this clinical trial is that there will be no differences in the above mentioned tissue adaptation, maximum biting force, and clinical performance with milled CAD-CAM or conventional compression mold manufactured implant-assisted overdenture.

2. Material and Methods

2.1. Study Design and Subjects' Criteria. This prospective clinical study compared two mandibular complete overdentures constructed with two different techniques: milled CAD-CAM or conventional compression mold techniques, using a randomized crossover study design to assess mandibular overdenture base adaptation and maximum biting force. Subjects' selection, treatment procedures, and subjects' evaluation were summarized in Figure 1.

Ten completely edentulous subjects between the ages of 55 and 65 were chosen from the outpatient clinic of the Prosthodontic Department, Faculty of Dentistry, and Mansoura University. NCSS PASS Professional 2021 Software was used to compute the sample size for this investigation, which provided 80 percent power and a 0.05 alpha (α) for the paired t-test. The sample size was determined based on the program calculation and the previous research [40, 41].

Subjects included in their study were using conventional complete dentures at their presentation but desired to improve their mandibular dentures'sretention and stability. Included subjects were required to fulfill the following criteria: the subjects wore complete dentures, had sufficient bone quantity and quality in the mandibular interforaminal area required for standard implants of at least 10 mm length and 3.6 mm diameter provided by cone beam computed tomography, healthy keratinized mucosa, class I maxillo-mandibular relationship, adequate interarch space, and parallel residual alveolar ridges. The exclusion criteria included one or more of the following: subjects with severely atrophied ridges, class II and III

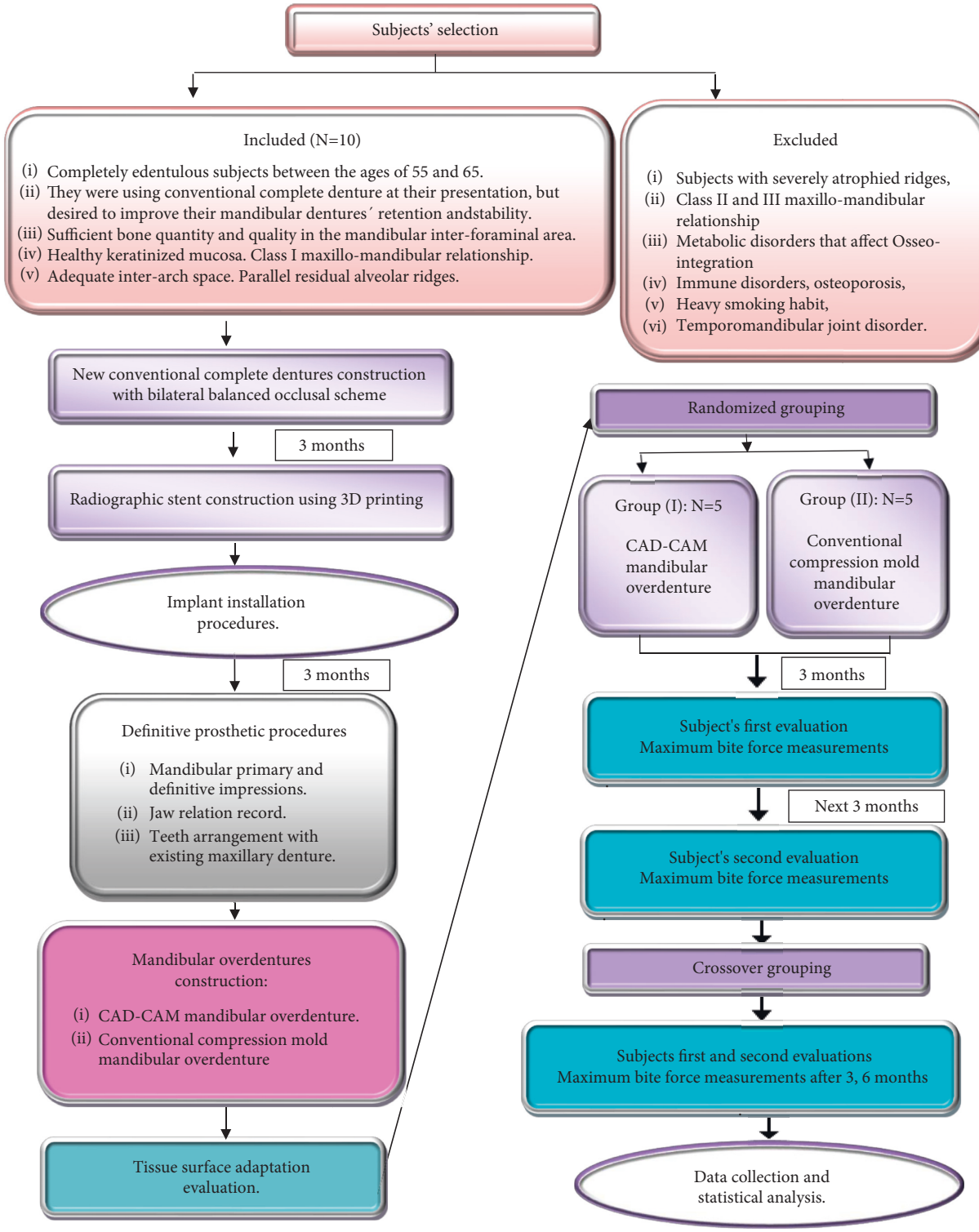


Figure 1: Subjects' selection, treatment procedures, and subjects' evaluation.

maxillo-mandibular relationship, metabolic disorders that affect osseointegration such as uncontrolled diabetes mellitus, immune disorders, osteoporosis, heavy smoking habit, and temporomandibular joint disorder.

This study was approved by the ethical committee of the University of Mansoura, Faculty of Dentistry. The subjects signed an informed consent for participation in this study after they were informed about the full details of study procedures. Clinical study guidelines were followed.

2.2. Surgical and Prosthetic Procedures. New conventional complete dentures with a bilateral balanced occlusal scheme were fabricated for all subjects. Subjects were informed

about the importance of wearing the dentures for 3 months before implant placement to improve neuromuscular adaptation.

As a radiographic stent, clear acrylic resin was employed with gutta percha markers. The individuals were scanned using cone beam computed tomography in accordance with the dual scan protocol [42]. Using 3D image planning software, the implants were virtually placed parallel to each other and perpendicular to the occlusal plane at the canines and lateral incisor locations (OnDemand 3D). Rapid prototyping was used to create a surgical stent with four sleeves positioned over possible implant locations (In2Guide).

Four implants (Dentium Co., Seoul, Korea) were inserted in the mandibular lateral incisors and canine regions bilaterally using a flabless technique and conventional loading protocol. Implants were inserted using the surgical stent which was fixed to the underlying bone using anchor pins. Osteotomy was done using the universal surgical kit supplied with the surgical stent. Implant fixtures were then inserted.

Healing abutments were screwed to the implants, and the mandibular dentures were relieved over the implant sites and relined using a soft liner material (promedica, Germany) to be used as a provisional denture.

Three months thereafter, the mandibular impression was started. The primary impression was recorded and poured to obtain the primary cast. A closed custom tray was constructed on the primary casts. The positioner attachments (Dentium, Co., Seoul, Korea) were screwed to the implants and the processing caps and metal housings were secured over the attachments (Figure 2). The definitive impression was recorded at abutment level using silicon impression material (Silaxil Light Body–LASCOD, Italy) in a border molded custom tray. The impression was poured with extra hard scannable dental stone (Kimberlit extra hard high-density die stone, Girona, Spain) after removing the processing caps and the metal housings from the impression to get the master cast. Maxillo-mandibular relations were recorded on mandibular conventional record blocks opposing the existing maxillary complete denture. Semianatomical acrylic teeth (Ruthinium acrylic teeth, Acry Rock Company, Italy) were set up in bilateral balanced occlusion and tried-in in the patient's mouth.

According to the mandibular denture base material and the processing technique, each subject was randomly given their mandibular overdentures in a crossover study design: five subjects were randomly given the CAD-CAM mandibular overdenture (CAD-CAM MOD) first, and the other five were given the conventional compression mold mandibular overdenture (CC MOD). After 3 and 6 months, maximum bite force was measured, and at 6 months, subjects who woreCAD-CAM MOD received CC MOD and vice versa. After another 3 and 6 months, the measurements were repeated. The sequence of delivering the mandibular overdentures was performed randomly to avoid impact of the prosthesis order on maximum bite force measurements. The randomization was performed using generated numbers in the Excel spread sheet by a person who was blinded to treatment groups.

For the CAD-CAM MOD group, the mandibular master cast and record block were scanned both separately and while biting onto the recorded jaw relation, using an intraoral digital scanner (Medit I 500, Corea). The scanned data were saved as standard tessellation language (STL) file format. These data were uploaded into the design software (EXOCAD DentalCAD DB 2.2 valletta), where the undesirable scanned areas that outside the area of concern were detached and the files were merged using best-fit method. The virtual master cast that was used as a reference cast scan was created (Figure 3(a)). The anatomical landmarks were plotted on the reference cast and the denture base outline was determined. Finally, the mandibular denture base was designed virtually, and the teeth selection and setup were carried out (Figure 3(b)). Based on the virtually designed mandibular denture base, the final denture base was milled with a 5-axis milling machine with an accuracy of ±5 mm (MILL Box 2018 milling machine: ARUM 400, Corea) from gingival-colored prepolymerized PMMA blocks (PMMA Disc, bio HPP, Germany) (Figure 4(a)). Denture teeth were also milled from tooth-colored prepolymerized PMMA blocks (Figure 4(b)), finished, and then bonded into the milled base with a bonding agent (Visio Lign: Bredent).

For the CC MOD group, heat-cured polymethyl methacrylate resin (Major Prodotti Dentari S.P.A; Italy) was used [42]. The same master cast and record block that were previously scanned for CAD-CAM overdenture construction were used for conventional overdenture construction. Mandibular teeth were set up in a balanced occlusion with the existing maxillary denture. The waxed up denture was flasked using the compression mold technique. The acrylic resin polymer and monomer were thoroughly mixed according to the manufacturer's directions. The heat-cured acrylic resin was then packed and polymerized using the long curing cycle. Finishing and polishing were then done.

After the mandibular overdentures were constructed, the fitting tissue surface of each mandibular overdenture base was digitally scanned using the same intraoral digital scanner that was previously used. The obtained scanned 3D images were exported to a standard tessellation language (STL) file. The unwanted scanned points that were outside the area of interest (internal surface) were removed before superimposition.

2.3. Tissue Surface Adaptation Evaluation. Each STL file of the entire fitting surface of the scanned denture base was superimposed on the STL file of the reference scanned mandibular cast for each subject, with surface matching software [38, 43–45] (Geomagic verify; 3D system). Each scanned overdenture base was assessed for positive and negative average deviation values.

At the insertion appointment, any adjustments that may be needed were carried out to ensure proper denture base fit, border extension, even occlusal contact and patient comfort. Self-cure acrylic resin was used to pick up the female housing attachment to the fitting surface of the mandibular overdenture bases (Figure 5(a), 5(b)). The white processing cap was removed and replaced by a blue one. The mandibular overdenture was delivered to each subject according to the included group.

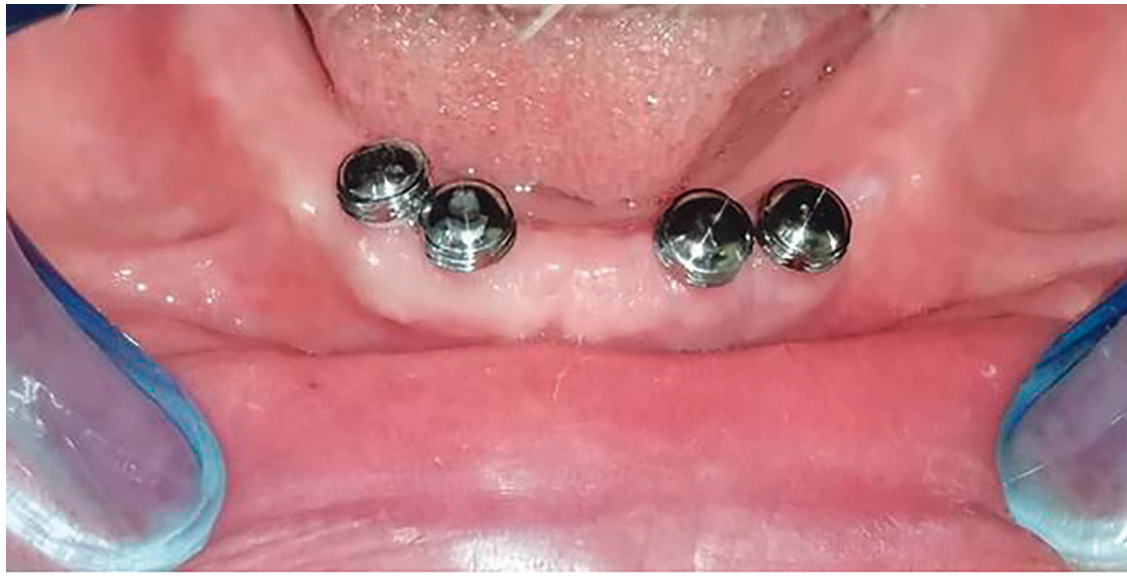


Figure 2: The processing caps and metal housings were inserted on the implant abutments.

2.4. Maximum Biting Force (MBF) Evaluation. A force transducer occlusal force meter (GM10, Nagano Keiki Co, Tokyo, Japan) was used to measure the subject's maximum biting force (MBF) (Figure 6). A digital hydraulic pressure gauge and a vinyl biting element with a plastic sheath make up this instrument. The pressure gauge's little digital screen displayed the maximum bite force values in Newtons (N). The participants sat in a dental chair in an upright position. The right side of the body was measured first, followed by the left side. Subjects were told to bite maximally for a few seconds while the transducer was placed horizontally between the occlusal surfaces in the first molar area. The measurement was done three times on each side, with a two-minute break in between. On the screen, the greatest bite force was recorded for each time. The highest of the three numbers was chosen. The mean of the left and right maximal bite force signals was used for statistical analysis.

2.5. Statistical Analysis. Collected data was analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). The parametric data was displayed as mean (M) and standard deviation (±SD). Positive and negative average deviation means of the CAD-CAM MOD group and the CC MOD group were statistically compared using a paired t-test. Maximum bite force (MBF) within each group with different time measurements was compared using a paired t-test while comparison of MBF between the two groups at each evaluation time was performed using a t-test. P value was significant when ≤0.05 level.

3. Results

3.1. Tissue Surface Adaption of CAD-CAM MOD and CC MOD. The descriptive analysis (mean ± standard deviation) of positive and negative average deviations of CAD-CAM MOD and CC MOD is presented in Table 1.

The mean ± standard deviation of measured positive average deviation of the CC MOD was(0.099 mm ± 0.01), while the negative average deviation values were (−0.081 mm ± 0.009), respectively. The positive mean value of the CAD-CAM MOD was (0.034 mm ± 0.003) while the negative mean values were −0.055 mm ± 0,004.

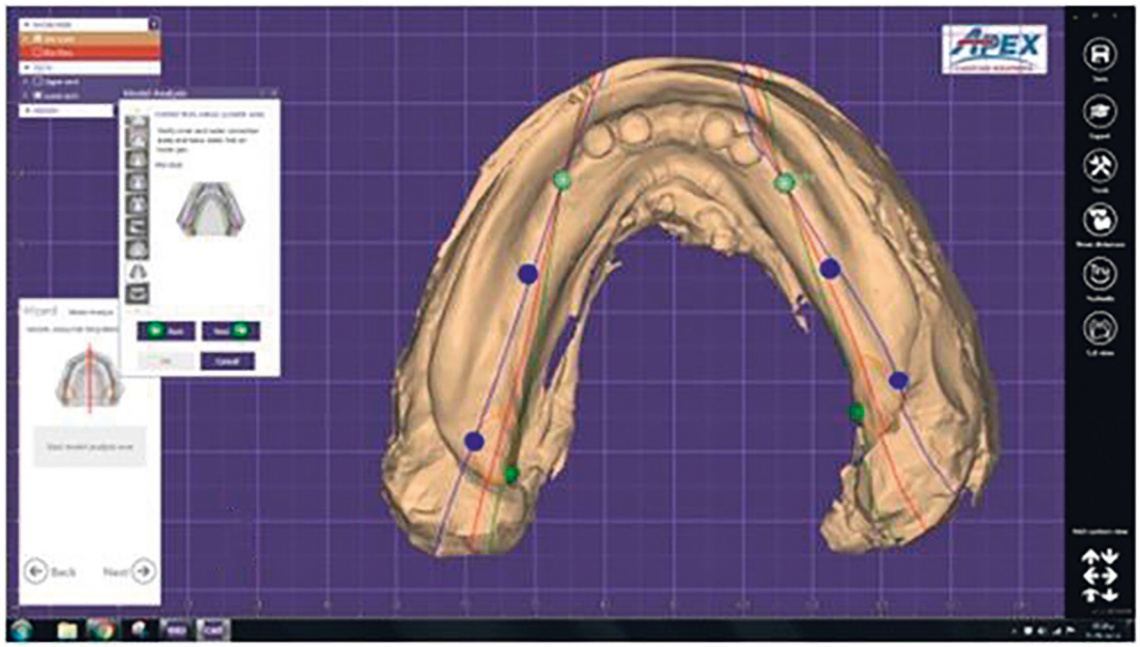
Regarding positive average deviation values, the CAD-CAM MOD group was significantly lower than the CC MOD group ($P = 0.0001$). Regarding negative average deviation values, the CC MOD group was significantly higher than those for the CAD-CAM MOD group ($P = 0.0001$).So that, on the basis of analytical statistics, surface matching revealed that the CAD-CAM MOD group presented the higher values of tissue surface adaptation compared to the CC MOD group. The difference between the two tested groups was statistically significant.

3.2. Maximum Biting Force (MBF) by CAD-CAM PMMA Resin and Conventional Heat-Cured Processed Implant-Assisted Overdentures. The descriptive analysis (mean-± standard deviation) of MBF of CAD-CAM MOD and CC MOD is presented in Table 2.

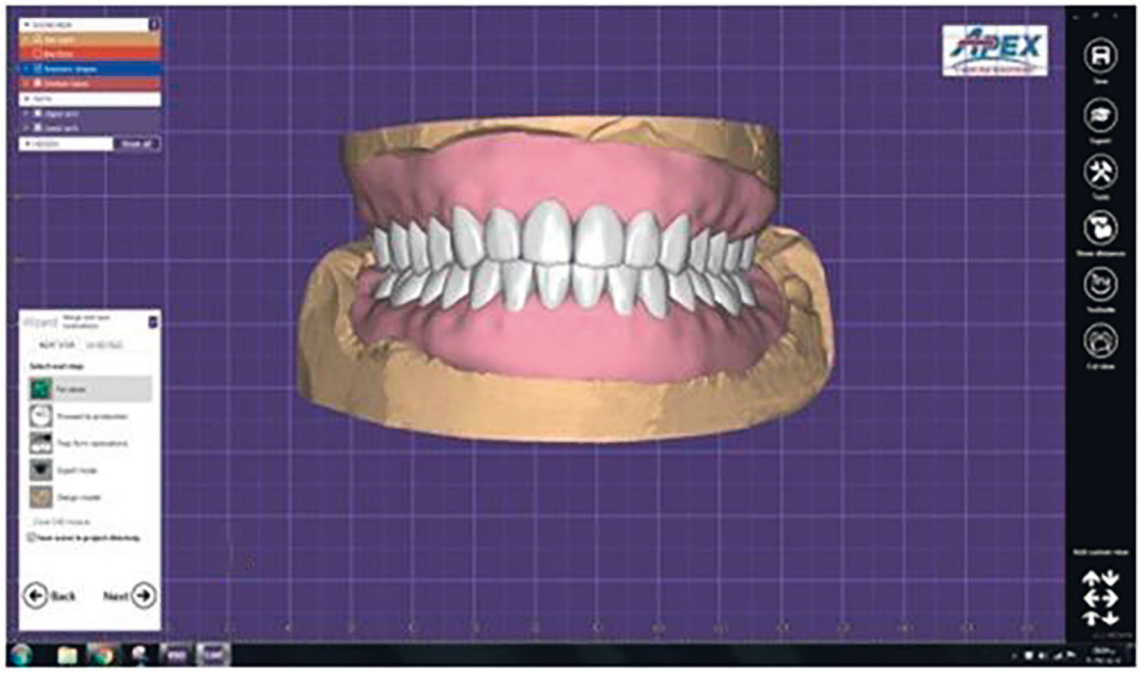
CAD-CAM MOD group (Group I) presented the higher value of maximum biting force (208 ± 3.17), (225 ± 3.45) at 3 and 6 months, respectively, compared to CC MOD (Group II) (166 ± 4.19), (170 ± 4.30) at 3 and 6 months, respectively. The difference between the two tested groups was statistically significant ($P = 0.0001$). The MBF was higher significantly at 6 months than at 3 months in both groups.

4. Discussion

The development of computer-aided technologies for constructing removable prosthesis is now progressing. More prospective clinical trials, however, are required to validate this method. The mechanical properties [46], trueness and tissue surface adaptation [40, 41], retentive quality [47],



(a)

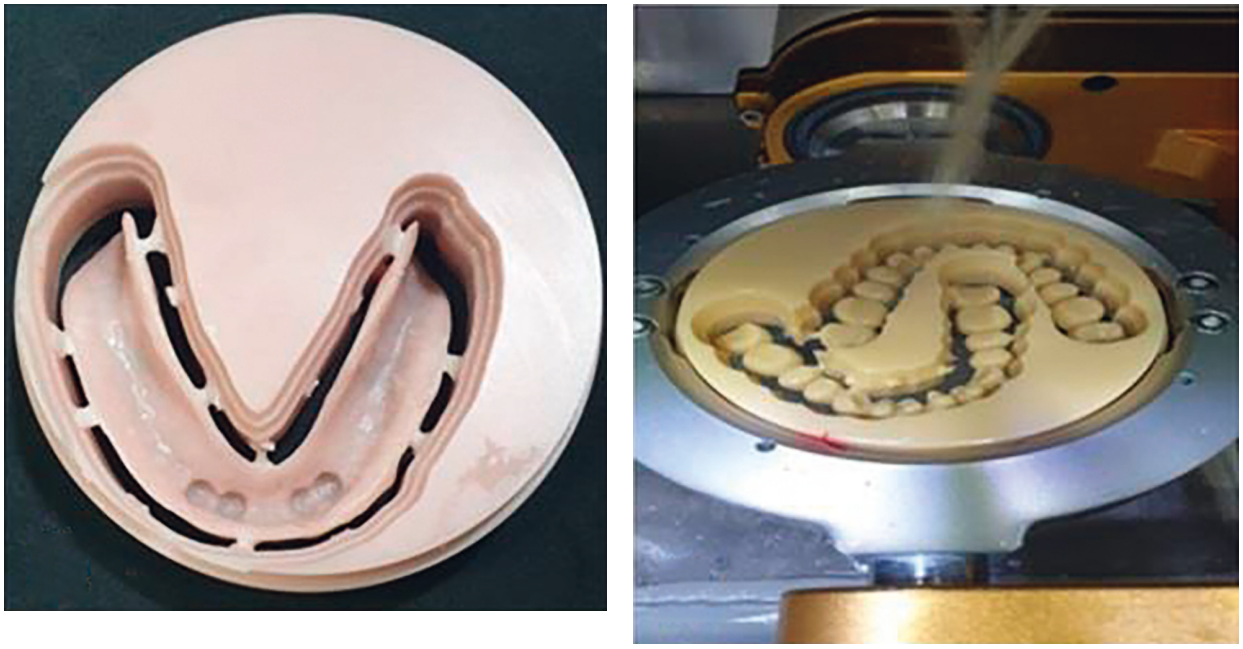


(b)

Figure 3: The virtual master cast (a) and virtual trial denture (b).

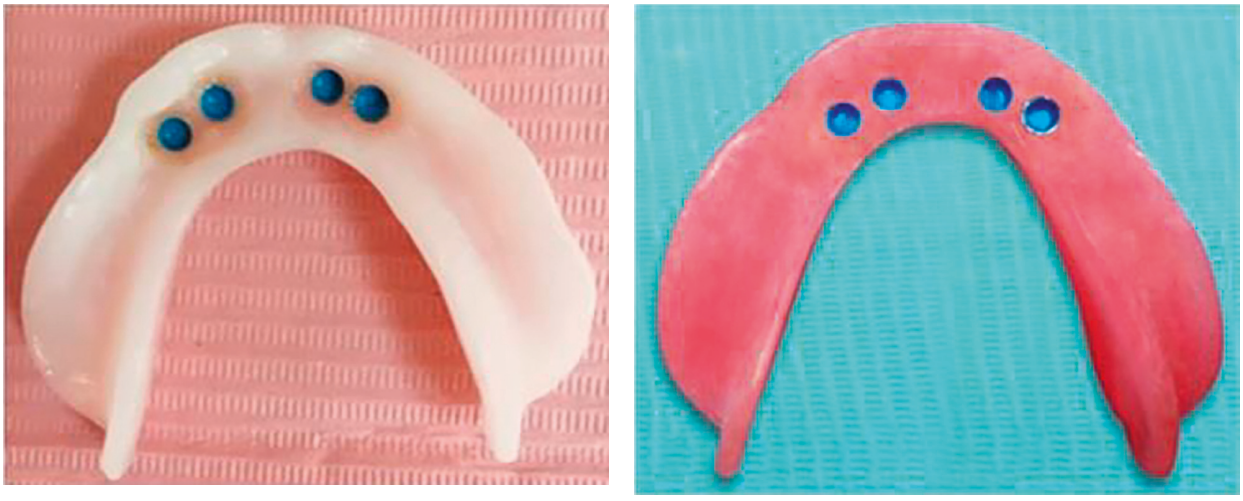
biocompatibility and microbial colonization [48], clinical outcomes and patient satisfaction [49, 50], and clinical complications and quality assessments [51, 52], of CAD-CAM complete dentures compared to conventional dentures were assessed.

However, there is a lack of evidence in the dental literature about implant-assisted overdenture base adaptation fabricated using the CAD-CAM technique and the resulting clinical performance when these dentures are supported by implants. The aim of this study was to evaluate implant-assisted overdenture base adaptation and, as a result, the clinical performance of these overdentures that are supported by implants when constructed using the CAD-CAM technique versus the conventional technique. In this study, the CAD-CAM-milled mandibular overdentures showed better fit and clinical performance compared to conventional compression molded overdentures so that the null hypothesis was rejected.



(a) (b)

Figure 4: Denture base was fabricated from gingival-coloured prepolymerized PMMA blocks (a). The denture teeth were milled from tooth-colored prepolymerized PMMA blocks (b).



(a) (b)

Figure 5: (a) Fitting surface of CAD-CAM milled mandibular overdentures with picked up attachments. (b) Fitting surface of conventional, compressed mold technique, constructed mandibular overdentures with picked up attachments.

The unique manufacturing approach could be responsible for the superior fit of CAD-CAM produced dentures observed in this study. Because the denture base is milled from a fully prepolymerized resin puck that was polymerized at high temperature and pressure in a subtractive technique, as a result, volumetric variations associated with denture base processing are no longer an issue. As a result, when CAD-CAM manufactured dentures were compared to conventional dentures, the fitting surface of the CAD-CAM fabricated dentures revealed a higher similarity to the master cast surface, as previously explained [14, 22, 53].

This finding was in agreement with previously published articles comparing CAD-CAM processing techniques with pack and press [14] and reporting that CAD-CAM for denture fabrication process was more accurate and reproducible denture fabrication technique [14, 52].

On the other hand, conventionally fabricated dentures undergo distortion during processing [7], resulting in a

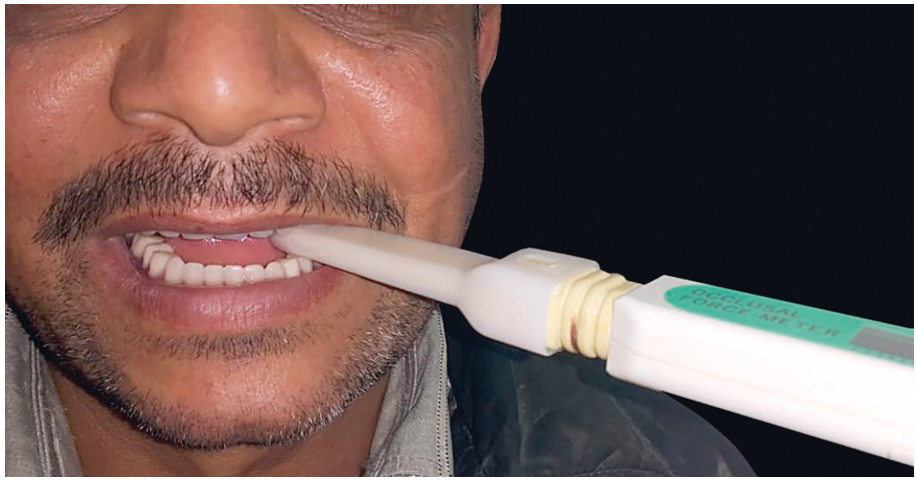


Figure 6: Patient exerts a maximum biting force on the bite force transducer.

Table 1: Descriptive analysis of measured surface deviations between scanned master casts and scanned overdenture bases fabricated by conventional and CAD/CAM milled techniques.

	Positive average values			Negative average values		
	CC MOD	CAD-CAM MOD	t value (*P* value)	CC MOD	CAD-CAM MOD	t value (*P* value)
M	0.099	0.034	20.77 (0.0001)*	−0.081	−0.055	10.22 (0.0001)*
±SD	0.01	0.003		0.009	0.004	

*Statistically significant difference. M, mean; SD, standard deviation; CC MOD, conventional compression mold overdenture; CAD-CAM MOD:CAD-CAM mandibular overdenture; (-) average, negative average values; (+) average, positive average values.

Table 2: Descriptive analysis of maximum biting force (MBF) values and*P* values of conventional PMMA and CAD/CAM PMMA implant overdenture prostheses along the various follow-up periods.

Time of measurement	Processing technique (denture type)			
	CC MOD M ± SD	CAD-CAM MOD M ± SD	t value	*P* value
3 months	166 ± 4.19	208 ± 3.17	30.96	(0.0001)*
6 months	170 ± 4.30	225 ± 3.45	31.54	(0.0001)*
t value	2.16	11.47		
P value	(0.05)	(0.0001)*		

*Statistically significant difference. M,mean; SD, standard deviation; CC MOD, conventional compression mold overdenture CAD-CAM MOD: CAD-CAM mandibular overdenture.

negative impact on the denture base adaptation to the underlying mucosa [54, 55].

The significant increase in the maximum biting force while subjects wearing the CAD-CAM overdentures compared to conventional overdentures may be attributed to improvement in denture adaptation that in turn resulted in more patient comfort and more ability to bite without discomfort that was accompanied with the conventional denture [49]. This result was in accordance with Allahyari and Niakan who found better clinical retention and a reduced incidence of denture-related traumatic ulcers with CAD-CAM dentures and a[56] reduced number of post-insertion adjustment appointments [16].

Another explanation for biting force increasing after CAD-CAM denture wearing may be due to physical retention improvement of the prosthesis; hence, less effort was required from the muscles to retain or stabilize the prosthesis [47].

This is confirmed by Al Helal et al. [47] who reported that retention offered by milled complete denture bases from prepolymerized polymethyl methacrylate resin was significantly higher than conventional heat polymerized denture bases.

On the contrary, the conventionally fabricated dentures show a combination of some areas of more adaptation than others, resulting in some mucosal impingement in some areas which results in sore spots and patient discomfort, and others that were out of contact creating compromised retention. This most likely increases the clinician's chair time because of additional adjustments [56]. This may explain why conventional dentures have reduced bite force.

The significant increase in the biting force for conventional fabricated dentures and CAD-CAM fabricated dentures with time from three to six months may be owing to the progressive experience establishment in addition to increased denture base adaptation by time as confirmed by many earlier studies [57, 58].

This study has some strengths. The crossover design utilized in this study was aimed to reduce human variability and to standardize the tested prosthetic appliances for clinical performance evaluation, using two identical overdentures for each subject.

The clinical performance evaluation was initiated three months after overdenture insertion to provide adequate time for proper neuromuscular accommodation to the new prosthesis as previously reported [59].

Another important strength in this study was the use of laser scanners for assessing the dimensional changes that occur during denture production. Many methods have been developed previously, but the recently introduced laser scanners have been proven to be a reliable means of determining denture base adaption. This technology is used for measurements by superimposing and analyzing scanned information using cutting-edge computer software [44, 60].

Also, in this study, instead of using geometric reference points for surface matching [15], the entire fitting surfaces of the master cast and constructed denture bases were evaluated [23, 26, 27]. Thus all possible deviations over the entire fitting surfaces of the denture bases were recorded.

However, one inherent limitation in this study was the relatively small number of participants. However, because a crossover study was utilized, a small sample size can be used compared to parallel group studies [61].

Another limitation in this study was that the effect of the previous prosthesis type on the MBF of the current prosthesis was not measured. A rest period may be needed before making the crossover. This factor should be considered in future research.

Further long-term clinical trials with increased sample size are needed to evaluate further clinical aspects of CAD-CAM milled overdentures.

5. Conclusion

Within the limitations of the current study, it can be stated that restoring the edentulous mandible with CAD-CAM constructed implant-assisted overdentures increases tissue surface adaption and maximal biting force when compared to conventionally fabricated acrylic resin overdentures.

Data Availability

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Application of Nonsurgical Modalities in Improving Facial Aging

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Objective. This review aims to summarize different kinds of applications of minimally invasive surgery in improving facial aging to provide a comprehensive and accurate introduction on the issue of esthetic treatment of facial skin. *Overview*. In the twentieth century, facial rejuvenation has become a new beauty trend. Facial cosmetology has entered a period of antiaging and rejuvenation therapies and microplastic surgery. The pursuit of beauty has promoted the development of minimally invasive plastic surgery. This review introduces the possible causes of facial aging and its related topics with a focus on facial injectable drugs, such as botulinum toxin, main filler materials (hyaluronic acid, calcium hydroxyapatite, poly L-lactic acid, collagen, autologous fat, and polymethyl methacrylate), and some current antiwrinkle technologies, such as thread lift and radiofrequency rhytidectomy. *Conclusions*. Despite the difference in mechanisms of action, each technique can address facial aging involving the loss of collagen, displacement and enlargement of fat, and muscle relaxation. Combinations of these treatments can provide patients with reasonable, comprehensive, and personalized treatment plans.

1. Introduction

Beauty is an eternal theme for humans as we tend to increasingly focus on their appearances and hope to stay younger as they age. Facial plastic surgery improves facial appearance and function and has been practiced since more than 100 years ago. Jacques Joseph is considered the father of modern facial plastic surgery, and he developed many of the earliest surgical technologies. In recent years, minimally invasive facial beauty has evolved rapidly. In the past two decades, the use of injectable botulinum toxin has increased by 621% [1]. Compared with traditional facial cosmetic surgery, nonsurgical modalities results in more natural, nonstiff, and smoother results with very small trauma and significantly shorter recovery, therefore its preference by patients [2]. This technique is directed toward adjusting the various details of the face, such as wrinkles and fine lines, asymmetry, and excess fat [3]. In recent years, many novel, nonsurgical, antiregional aging treatments have emerged to address the signs of aging. This study analyzes the main reasons and good hair part of facial aging and introduces several hotter minimally invasive wrinkles: injection filler technology, including facial injections, several major facial injection filler materials, linear conduct, radiofrequency rhytidectomy, and other methods. Their mechanisms of action, indications, contraindications, complications, advantages, and disadvantages are discussed.

2. Aging of the Face

2.1. Possible Causes of Facial Aging

2.1.1. Skin. External environmental factors and the body's internal factors can affect the aging process of facial skin. Indoor and outdoor air pollution [4, 5], such as skin exposure to soot, can lead to more obvious pigmentation spots and wrinkles. Sunlight and smoking can also accelerate the aging of the skin, which results in weakness, thinning, and wrinkling [5, 6]. The elasticity of the skin primarily depends on the dermis with collagen playing the primary role. With

internal aging of the skin, the synthesis rate of collagen decreases and its degradation rate increases [7]. Moreover, the decomposition of collagen was increased by upregulating protease [8]. By the age of 40–50 years, the biosynthesis of elastin begins to decline sharply. Elastin is lost via natural degradation [9], which results in the loss of skin elasticity. Glycosaminoglycans play a crucial role in the absorption of water by the skin. With the degradation of hygroscopic glycosaminoglycans, the moisture in the skin is also gradually lost. Additionally, poor quality of sleep can also affect skin quality [10].

2.1.2. Fat. Facial fat is divided into superficial fat and deep fat by the superficial fascia system (Figure 1) [11]. Both shallow and deep fat tissues are separated into multiple smaller pieces of fat [12]. Fibrous tissue supports the fat in all parts. With the increase of age, the change of fat interval position leads to the change of adipose tissue contour [13]. Generally, these changes include atrophy of the deep fat tissue and displacement and hypertrophy of the shallow fat tissue [11, 13]. The continuous pressure of the deep layer of fat tissue on the bones and its relative inertia as a space-filling interface may explain the tendency of its selective atrophy with time [11, 14].

The shallow fat tissue of the forehead and the orbital and perioral fat also undergo atrophy [15]. The formation of facial wrinkles is also related to a reduction in the volume of white adipose tissue [16]. The reduction in subcutaneous fat leads to the relaxation of the skin around the nose, orbit, and chin and the formation of wrinkles [8]. The volume of the lower part of the nasolabial fat tissue increases, which results in the protrusion of the nasolabial groove, maxilla, and mandible of the inferior margin of the orbicularis oculi muscle and the deepening of the nasopharyngeal folds are the results of the downward displacement and volume loss of the buccal fat cavity [17]. The volume loss of the nasolabial sulcus and the head of the medial buccal adipose septum may also lead to lacrimal groove deformities, which aggravates facial aging and makes the nasopharyngeal folds and palpebral sulcus more obvious [18]. The loss of volume results in a lack of support for the medial and middle chambers of the cheek fat, thus resulting in a downward displacement of the facial septum, which is also an important factor in the development of wrinkles [19]. Gravity can also cause downward movement of the facial fat [20]. Due to the separation of fat parts, the change of fat content will be shown in the corresponding facial areas [21].

2.1.3. Muscle. Facial muscles can be divided into expressive and masticatory muscles. The formation of facial wrinkles is mainly due to the relaxation of the superficial expressive muscles located in the superficial myofascial system, which connects the skin with the fat septum [8], which causes sagging of the skin and the formation of wrinkles. Muscle aging mainly results from changes in muscle tension and repetitive movements of the muscle [22]. Specifically, as age increases, the facial muscles lengthen, the muscle tension increases, the motion amplitude shortens, and the muscle tension at rest is closer to the maximum contraction tension [23]. However, facial muscle exercises have limited effects in restoring muscle tension [24]. In addition, the changes in facial muscles may also be a result of adaptation in response to the changes in facial ligaments and bones [13].

2.1.4. Bone. Facial bones support the facial soft tissues. In the aging of facial bones, the most obvious change is the change in the mandibular angle from an L-shape to an I-shape, which leads to mandibular protrusion and changes in the mandibular line [7]. In addition, the zygomatic arch undergoes anteroposterior reconstruction, thus deepening the zygomatic fossa. After 30 years of age, there may be pit regression [25] and maxillary retrusion, which may lead to flat cheeks as well as depression and widening of the upper lip [26].

Between the ages of 30 and 50 years, the lower forehead may begin to flatten out as the angle between the eyebrows decreases. Additionally, there may be drooping of the nasal tip and widening of the alar base [27]. On the right side, these changes cause the face to rotate clockwise relative to the skull base: the brow, orbit, piriform hole, and maxilla rotate downward, thus resulting in a flattened facial angle [28, 29]. The nasal cavity expands outward and forward, and the upper and olfactory cavities remain intact, thus resulting in the enlargement of the piriform foramen. The rim of the eye socket expands downward and outward, thus causing the socket to lose its roundness, and the chin becomes more protrusive, oblique, and short [7].

2.2. Areas of Aging. There are several signs of aging on the face. Of them, the more obvious and significant ones include the appearance of a vertical line in the interbrow and the atrophy of the upper cheeks or midface and the nasolabial folds. Other more common signs of facial aging include horizontal forehead creases, temporal or brow hollows, tear troughs, nasal wrinkles, vertical lip lines, thinning lips, irregular jawline, atrophy of the preauricular fat, and thinning earlobes [30, 31].

The upper face consists of the forehead, interbrow, ocular, and temporal regions. The aging of the upper face is mainly reflected on the forehead [32]. The skin of the forehead loses its elasticity over time, resulting in an irregular and wrinkled forehead with changes in its color [33, 34]. The lower third of the forehead also appears slightly concave due to the formation of more wrinkles on the forehead and plateauing between the eyebrows [35]. Although it is fixed by facial loose tissue, the interval of facial loose tissue will shrink and decrease over time, resulting in skin wrinkling [36]. In this area, a combination of fillers and botulinum toxin injections will be more effective than fillers alone.

The middle of the face refers to the area between the lower eyelid and corners of the mouth where fillers are most commonly used [37]. Volume loss of the soft tissues is an essential aspect of facial aging [38]. Aging of the midface leads to an overall drooping of the soft tissues, particularly the orbicularis oculi and the soft tissue of the zygomatic

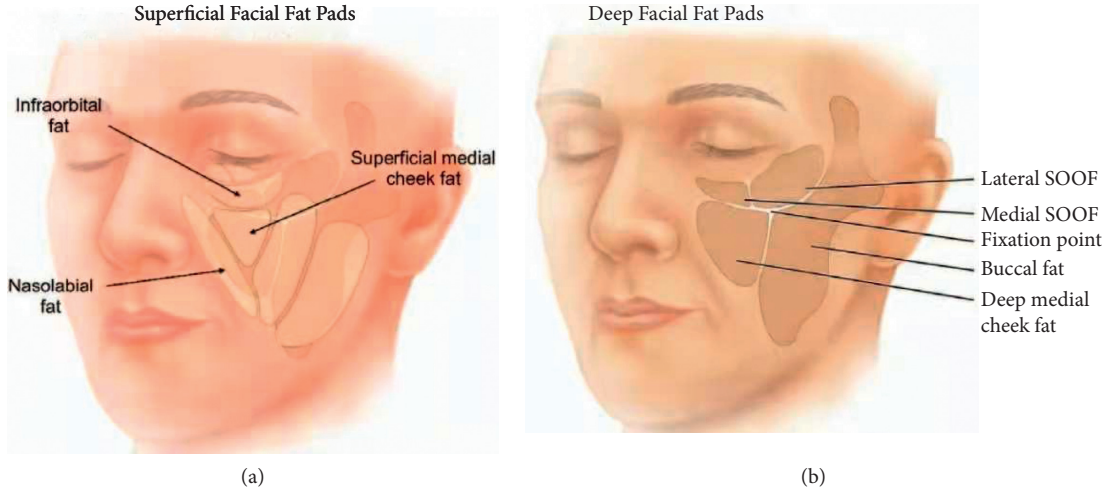


Figure 1: (a) The superficial fat (light beige) in the middle of the face includes the superficial fat on the inner side of the cheek, the fat in the nasolabial groove, and the fat within the orbit. (b) The midface deep fat (dark tan) compartment consists of the deep fat compartment of the inner cheek and the inner part of the buccal fat pad [11].

complex. The decline in these tissues causes, in part, a widening in the laughter line or the nasolabial groove [26]. With aging, the orbital width increases, and the contours of the eyes gradually change [39]. The reduction of fat in this area can also be a cause of thinning of the temples, which results in an emaciated look [40].

The lower face is the area between the corners of the mouth and the neck. Most symptoms of aging in the lower face, such as perioral wrinkles, are also caused by atrophy of the soft tissues and bones. Perioral wrinkles are more commonly treated with fillers to slow the signs of aging. Volume fillers in the lips are also very common [41, 42]. In the jaw and chin, chin augmentation and filling of the anterior jawline are common procedures [43]. However, studies have demonstrated that chin deformities can result when the jaw's soft tissue drops to overfill the chin [44].

3. Facial Injections

3.1. Botulinum Toxin. Botulinum toxin, like other natural substances such as atropine and paclitaxel, was first recognized for its toxicological effects and was used as a powerful biological weapon 70 years ago [45]. It was first used to treat strabismus in the 1970s [46] and was finally approved for human use by the US Food and Drugs Safety Administration (FDA) in 1989.

Facial expressions: muscle contractions move the skin over the face and create wrinkles and folds perpendicular to the shape of the muscles. Obligate anaerobic *Clostridium botulinum* can produce seven serotypes of botulinum toxin (A, B, C, D, E, and F); of them, type A is the most toxic and commonly used (Table 1) [48]. Although different serotypes of botulinum toxin have unique biochemical properties, all have a semblable mechanism of action: they cause muscle paralysis and relaxation by blocking cholinergic nerve transmission. This mechanism can be used to reduce the hyperactivity of muscles of expression, thus improving and eliminating wrinkles. The effect is persistent but reversible to some extent [49]. The formation of SNARE protein is necessary for the binding of acetylcholine to the presynaptic membrane as well as the release of acetylcholine. Botulinum toxin cleaves the substrate of this protein, thus inhibiting the release of acetylcholine. Over time, the effects of botulinum toxin decrease with the formation of new axons and motor endplates [50].

3.1.1. Indications. Botulinum toxin is most commonly used to treat the upper part of the face to eliminate or reduce frown lines (prebrow and wrinkle muscles), forehead lines (frontal muscles), and periorbital or crow's feet lines (lateral to the orbicularis oculi muscle). Common therapeutic muscles include the frontalis, procerus, corrugators, and orbicularis oculi. Figure 2 shows the injection of botulinum toxin into the five glabella sites and 3-4 sites on each side of the face. The use of short, small-bore needles can help minimize the trauma. In the middle part of the face, the reduction in the volume of facial fat and sagging caused by gravity are the main causes of aging [47]. In this part, it is limited for botulinum toxin to treat facial aging, whereas fillers are more commonly used. Treatment of the lower part of the face is usually focused on the perioral wrinkles (orbicularis oris, proximalis, and mentalis muscles) and requires greater skill and small doses.

Generally, a combination of such treatments can produce better results. Botulinum toxin injection into the lower part of the orbicularis oculi muscle, static crow's feet, and deeper frontal lines combined with skin peeling therapy, such as laser or chemical peeling therapy, can improve the efficacy of static lower eyelid wrinkles. Botulinum toxin is better in raising the lateral eyebrows and treating static lip lines in combination with dermal filler injections.

3.1.2. Contraindications. Patients with neuromuscular diseases, such as myasthenia gravis, Eton–Lambert syndrome, and multiple sclerosis, are unsuitable for botox injections

Table 1: Botulinum toxin injectable products.

Trade name	Toxin component	Molecular weight	Approved by FDA	Storage time
Botox	OnabotulinumtoxinA	900 kDa	+	>2 weeks
Dysport	AbobotulinumtoxinA	500/900 kDa	+	>2 weeks
Xeomin	IncobotulinumtoxinA	150 kDa	+	4 years

Information from references. [45, 47].

[52]. Additionally, it is not suitable for women who are menstruating and pregnant. It is also not suitable for people who are allergic to albumin and botulinum toxin. It is not recommended for patients with a blood disease or abnormal coagulation function; severe diabetes; heart, liver, kidney, or lung diseases; and severe hypertension. It is not appropriate in emaciated people because the muscle is too thin. Furthermore, the injection can easily spread to the surrounding muscles, thus resulting in side effects.

3.1.3. Complications. Treatment with botulinum toxin is safe. Most adverse reactions to botulinum toxin are usually due to exaggerated action of the drug and its spread to unintended areas, often with significant or disfiguring complications. One of the commonest complications is posttreatment facial drooping [53]. For example, the most important complications in the glabellar complex and forehead area are drooping of the upper eyelid and eyebrows. In the treatment of crow's feet, an improper injection may result in diplopia, incomplete closure of the eye, lateral drooping of the lower eyelid, and asymmetrical smile when injected into the zygomaticus major muscle [52]. It has also been noted that, after treatment for wrinkles around the lips, some patients reported feeling abnormal after speaking; however, this situation resolved after multiple treatments [54].

It is important to note that normal reactions after such treatments are not true complications; however, needle marks, swelling, bruising, and early discomfort are generally considered complications by the patients. Many patients consider the normal response after the treatment to be abnormal, which may be related to their expectations.

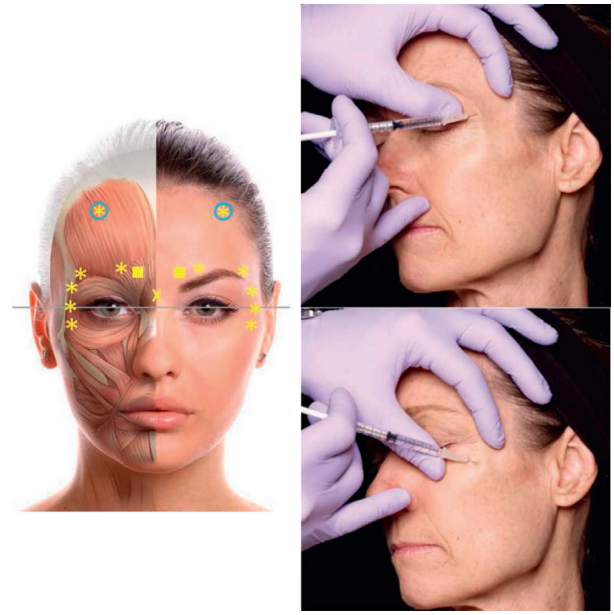


Figure 2: Botox was injected into five eyebrow areas and eight crow's feet (four on each side) for eyebrow lift. The symbols represent different injection depths: the squares represent the full depth of the needle; X represents half needle depth; asterisk indicates one-third of the needle depth [51].

4. Facial Fillers

The main facial filler materials include hyaluronic acid, calcium hydroxyapatite, poly-L-lactic acid, collagen, autologous fat, and polymethyl methacrylate. Different types of facial filler products are used in different fields of microinvasive surgery for facial rejuvenation. Each of them offers unique advantages and disadvantages (Table 2) and can solve different aspects of facial aging, such as the loss of collagen, fat displacement, and hypertrophy.

4.1. Hyaluronic Acid. In 1934, Carl Meyer and his assistant John Palmer separated a newly discovered glycosaminoglycan from the glass of a bull's eye and named this substance "hyaluronic acid" [73]. Hyaluronic acid is a natural linear polysaccharide polymer consisting of repeated diglucan units of N-acetyl-D-glucosaminoglucose and D-glucuronic acid linked by β (1, 4) as well as β (1, 3) glycosidic bonds [74]. It differs from other glycosaminoglycans as it lacks sulfated groups and covalently linked peptides [75]. Hyaluronic acid is an integral component of the extracellular matrix in most mature organisms and is found naturally within most body tissues, including the skin [76]. In addition, hyaluronic acid has been used extensively in the treatment of various conditions, such as infrabony periodontal defects. [77, 78].

Although hyaluronic acid may undergo volume changes due to natural decomposition processes, it has a relatively long shelf-life [79, 80]. It also attracts moisture into the skin [81]. Hyaluronic acid injections can, therefore, be used to replace the loss of volume on the face to restore its youthful appearance [82]. Most hyaluronic acid products are injected by mixing powdered hyaluronic acid in a particular ratio with water to produce a solution. There are two main sources of hyaluronic acid used in facial injections: animal-derived and non-animal-derived sources. Animal-origin hyaluronic acid is obtained from the crowns of chickens, which may also be responsible for the rare allergic reactions in avian animals [83]. Nonanimal sources of hyaluronic acid are of bacterial origin. Such hyaluronic acid may contain very small amounts of bacterial proteins, which may also trigger an allergic reaction [84, 85].

Table 2: Major facial filler materials.

Filler product	Type	Composition	Allergy test required	Indication	Advantages	Disadvantages
Perlane® (medicis, montreal, CA)	HA (bacteria)	Hyaluronic acid (8000 gel Particles/mL), 0.3% lidocaine	No	Deep layer	Long-lasting effects, suitable for use in deep tissue and paracone, minimal reactions	Heavy edema; persists for 3–5 days
Restylane® (medicis, montreal, CA)	HA (bacteria)	Hyaluronic acid (100,000 gel Particles/mL)	No	Superficial layer	Long-lasting effects, suitable for use in deep tissue and paracone, minimal reactions	Heavy edema; persists for 3–5 days [55]
Restylane fine lines® (medicis, montreal, CA)	HA (bacteria)	Hyaluronic acid (200,000 gel Particles/mL),0.3% lidocaine	No	Dermo-epidermal junction layer	Particularly suitable for the area between the eyebrows and for fine lines, not suitable for parabones	Shorter duration than restylane or perlane [56]
Radiesse® [57] (medicis, montreal, CA)	CaHA	Hydroxyapatite calcium microspheres, water, glycerin, and carboxymethyl cellulose	Yes	Facial soft tissue filling [58] stimulates collagen production in facial skin [59] pigmentation due to malformation of the lacrimal passage [60]	Good compatibility with the human body compared with hyaluronic acid, it has a greater modulus of elasticity [58]	Easy degradation and short maintenance time
Sculptra® (galderma, fort worth, TX)	PLLA	150 mg of PLLA microparticles, sodium, carboxymethylcellulose and non-pyrogenic mannitol [56]	No	Zygomatic and cheek depression, lower facial relaxation and fold, lower orbital depression, neck lines (venus chain) and hand aging	Long-term results, safe, no allergy test needed [61]	Inflammatory response and edema last for a long time (3–5 days), irregular appearance (depending on injection technique), requires multiple treatments
ZydermI® (INAMED, santa barbara, CA)	Bovine collagen	3.5% bovine dermal collagen suspended in physiological phosphate buffer sodium chloride solution and lidocaine [62]	Yes	Superficial skin lines [63] (eyebrow lines, horizontal forehead lines, crow's feet, fine lines, and scars)	Safe, reliable, contains lidocaine (lidocaine inhibits eosinophilic activation and reduces the risk of swelling and crusts), ease of administration [64]	Requires allergy test, more inflammatory response, short duration
Zyderm II® (INAMED, santa barbara, CA)	Bovine collagen	6.5% bovine dermal collagen, suspended in physiological phosphate buffer sodium chloride solution and 0.3% lidocaine [62]	Yes	Moderate-to-deep wrinkles	Same as zyderm I	Same as zyderm I
Zyplast® (INAMED, santa barbara, CA)	Bovine collagen	Cross-linked with 0.0075% glutaraldehyde, other ingredients are the same as in ZydermI [62]	Yes	Deeper wrinkles [63] (nasolabial furrows, deep acne scars, and red lip edges)	Same as zyderm I but more viscous and harder to degrade [64]	Same as zyderm I
CosmoDerm I® (INAMED, santa barbara, CA)	Bioengineered human collagen	3.5% collagen, phosphate buffer saline, and lidocaine [65]	No	Superficial wrinkles [65]	Safe, reliable, contains lidocaine (lidocaine inhibits eosinophilic activation and reduces the risk of swelling and crusts), no allergy test needed, ease of administration [64]	Short duration
CosmoDerm II® (INAMED, santa barbara, CA)	Bioengineered human collagen	6.5% collagen, phosphate buffer saline, and lidocaine [66]	No	Same as CosmoDerm I [65]	Same as CosmoDerm I [65]	Same as CosmoDerm I
CosmodPlast® (INAMED, santa barbara, CA)	Bioengineered human collagen	Cross-linked with 0.0075% glutaraldehyde, other ingredients are the same as in CosmoDerm I	No	Medium-depth wrinkles and red lip edges	Same as CosmoDerm I, more viscous and harder to degrade [64]	Same as CosmoDerm I
Cymetra® (INAMED, santa barbara, CA)	Human cadaveric collagen	Micropowdered cadaver collagen [67]	No	Lip, nasolabial groove, and deep wrinkles [67]	Safe, contains lidocaine (lidocaine inhibits eosinophilic activation and reduces the risk of swelling and crusts), no allergy test needed	Skin necrosis if used in glabella, expensive, and often lumps in the needle
Isologen (isologen technologies inc., paramus, NJ)	Autologous collagen	A culture of autologous fibroblasts extracted from the patient's own skin [68]	No	Moderate-to-deep wrinkles	Safe, no allergy test needed	High cost, long processing time, injection pain, difficulty in immediate correction, and uncertain long-term efficacy [62,68]
Autologous fat	Autologous fat	Glycerol and fatty acids [69]	No	Facial contour deformities, scarring, and wrinkles [70]	Highest biocompatibility [71]	High resorption rate [71]

Table 2: Continued.

Filler product	Type	Composition	Allergy test required	Indication	Advantages	Disadvantages
Bellafill® (suneve medical, San Diego, CA)	PMMA	Smooth microsphere of PMMA (20% volume) and 3.5% bovine collagen (80% volume) and 0.3% lidocaine matrix suspension [72]	Yes	Nasolabial groove, frown line, radial lip line, and the corners of the mouth [72]	Long-term effects or even permanent [65]	Requires allergy test, non-degradable components have safety risks [61]

HA, hyaluronic acid; CaHA, calcium hydroxyapatite; PLLA, poly-L-lactic acid; PMMA, polymethyl methacrylate.

4.1.1. Indications. Skin wrinkles caused by the loss of collagen and elastin fibers in the fine dermis can be effectively addressed using hyaluronic acid fillers [3]. The increasing sophistication and varieties of modern hyaluronic acid injections have made injectable fillers an appropriate intervention to address various aspects of facial aging, such as contouring, balance, and feature positioning, rather than just diminishing the skin wrinkles (Figure 3) [86]. Generally, a person's lips shrink and wrinkle with age. Filling the lips with hyaluronic acid can achieve lip volume restoration and contouring [41, 86]. Facial aging causes variations in the distribution of subcutaneous tissue, particularly around the temporal area, orbits, cheeks, and corners of the mouth [42]. The appearance of lines can result in an aged look of the face [87]. Hyaluronic acid is very popular among beauty seekers because of its good performance as a filler. It can also be used to fill scars caused by trauma and surgery, asymmetries resulting from congenital defects, and pits from acne scars [35]. Hyaluronic acid injections are administered in rhinoplasty. This method includes the advantages of quick shaping, no surgery, and a painless procedure [88]. Hyaluronic acid is injected into the forehead where it fuses with the preexisting hyaluronic acid, thus producing a skin swelling and forehead augmentation effect [89]. It is noted that a physician's knowledge of hyaluronic acid's specific properties in terms of rheology is crucial in selecting the appropriate hyaluronic acid products as well as determining the facial areas eligible for their use [90].

4.1.2. Contraindications. Patients with past medical experience with cosmetic surgery for rhinoplasty are at risk of skin necrosis [91]. Several factors may contribute to the risk of skin ischemia, gangrene, and vascular embolism after hyaluronic acid injections, such as the unpredictability of vascular localization [92].

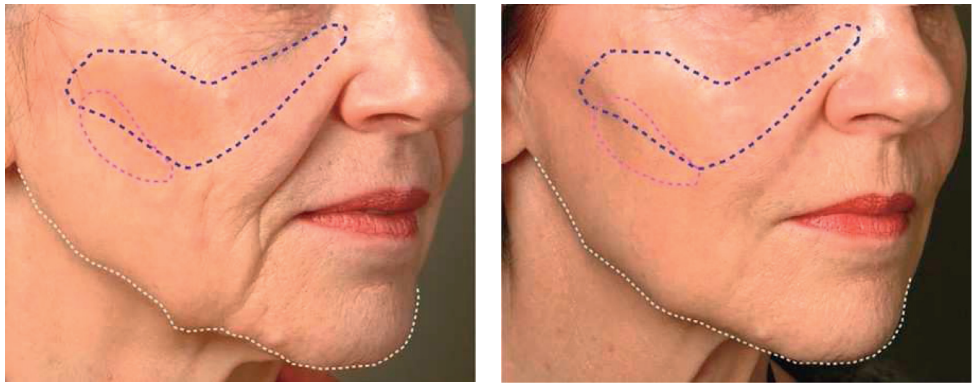
4.1.3. Complications. Acute complications with hyaluronic acid injections are rare; they include nerve damage, pain due to venous and lymphatic injury, severe bruising due to vascular injury, partial pressure necrosis of the skin, and distal soft tissue necrosis, which can have serious functional and esthetic implications [93, 94]. Hyaluronic acid carries a very low risk of allergic reactions; therefore, preprocedural skin testing is hardly required [95, 96]. Redness and swelling are common side effects of filler injections. They usually have no sequelae but can lead to temporary local bleaching of the skin that has responded to manipulation and hyaluronidase and potential scarring. Additionally, there may be bruising, nodulation, and irregularities [97]. If hyaluronic acid is carelessly injected into a blood vessel, it may lead to necrosis, delayed reticular erythema, and pain in distant skin [98]. If the arterial blood flow is connected to the ophthalmic system, it may lead to retrograde retinal arteries, ocular muscle paralysis, or even unilateral blindness [99, 100]. Activation of herpes may occur after hyaluronic acid injection with symptoms of erythema and crusted papules that require antiviral treatment with acyclovir. Although this is extremely rare, it should be taken seriously by practitioners to ensure proper prevention and timely diagnosis and treatment [101]. When administered by a board-certified expert dermatologist, hyaluronic acid is extremely safe as an injection, and the incidence of side effects is extremely low [102].

4.2. Calcium Hydroxyapatite. Compared with other facial fillers, calcium hydroxyapatite plays a unique role in increasing action time and filling effect. It is the main mineral in human bones and teeth; therefore, it has good biocompatibility with the human body. Radiesse® (Merz Aesthetics, New York, USA) is composed of hydroxyapatite calcium microspheres of 25–45 mm suspended in water containing glycerol and carboxymethyl cellulose-containing hydrogels. As calcium hydroxyapatite is utilized immediately for the repair of facial appearance, the residual microspheres form a scaffold for the growth of fibroblasts. Additionally, the collagen fibers that are formed can fix the microspheres and prevent them from moving. These microspheres dissolve in a piecemeal manner into calcium and phosphorus ions within a few months to a year [57]. In 2011, Radiesse® was approved by the FDA for the treatment of facial fat atrophy in patients with infection with human immunodeficiency virus (HIV) and the treatment of moderate-to-severe facial wrinkles. Compared with hyaluronic acid, calcium hydroxyapatite has a higher elastic modulus [58].

4.2.1. Indications. There is no doubt that Radiesse® can be used for filling soft tissues. [58] Additionally, it is now more commonly used to stimulate collagen production within the facial skin to improve the quality of the skin [59]. One periorbital treatment uses calcium hydroxyapatite to treat pigmentation caused by lacrimal duct malformation [60]. Radiesse® has been used in treating the puppet line, premaxillary groove, oral commissure, and posterior mandible. It is reported that some people believe that when injected into the temple and zygomatic area, it will also produce positive clinical effects [58].

4.2.2. Contraindications. Although hydroxyapatite calcium has become the second most popular filling agent after hyaluronic acid due to its short marketing time and good biocompatibility with the human body, its use is limited to the lacrimal groove area of the lip and the lower orbital margin. Additionally, injections should be avoided at sites of inflammation [12].

4.2.3. Complications. The most common postinjection side effects are usually limited to 2 weeks and include erythema, ecchymosis, and edema. Tzikas et al. [103] examined 1000 patients who were injected with calcium hydroxyapatite and noted only minor side effects of bruising, redness, and itching. The incidence of nodule formation was 5.9% in the lip and 0.002% in other parts. Improper injection methods may lead to the formation of nodules; therefore, lip injections should be avoided. If it is injected at a site of



(a) (b)

Figure 3: (a) 67 year-old patient shows multiple signs of aging due to loosening of the soft tissues in several areas, such as sagging in the mid and lower face, and resorption of the upper and lower jaws. (b). The patient's face 10 months after hyaluronic acid injection. No surgery was performed. The changes are due to providing prominence or lift, restoring the structure and volume to the cheek mound and mid-cheek (marked in blue), weakening the shadows of the cheeks (marked in purple), and repairing the borders of the mandible (marked in white) [35].

inflammation, it will worsen the inflammation further. It can also cause long-term swelling and bruising which can be avoided by selecting the appropriate technique and method of injection [12]. Rare complications of these injections include palpable vascular occlusion and nodules. Larger nodules can be injected with lidocaine and 5-fluorouracil to reduce the fibroblast activity and break them down [58].

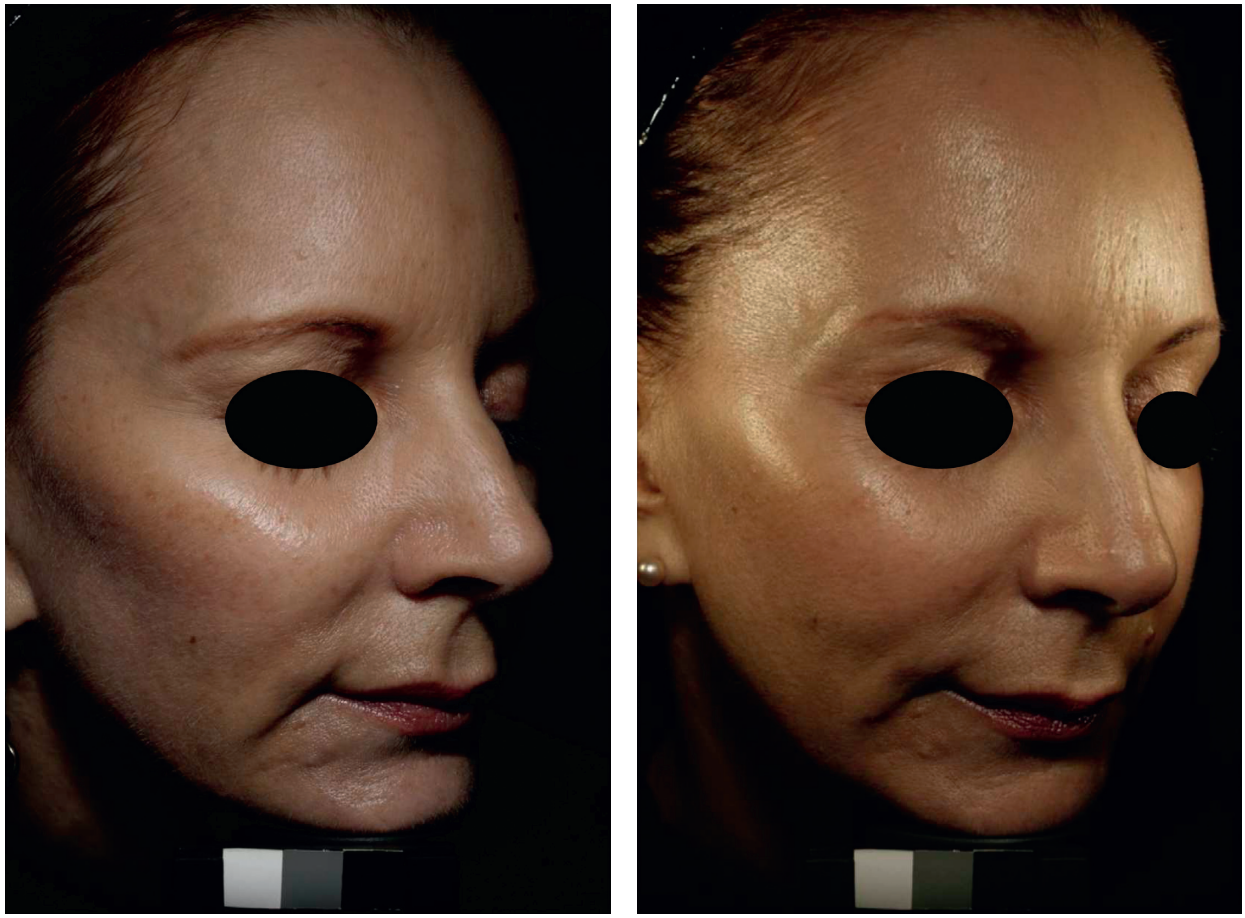
4.3. Poly-L-Lactic Acid. Poly-L-lactic acid (PLLA) is a biocompatible, biodegradable, α-hydroxyl-based synthetic polymer, which has been used clinically as the main component of some surgical absorbable sutures for over 20 years [58]. A PLLA filling layer is placed within the deep dermis or subcutaneous layer. PLLA microparticles are large enough to avoid phagocytosis and immediately result in subclinical foreign body inflammation, which leads to encapsulation of the microparticles, fibrous tissue hyperplasia, and type I collagen deposition in the extracellular matrix to achieve the esthetic effect of filling. Furthermore, some studies have reported the presence of type III collagen near the PLLA microparticles [66]. After the injection, the volume of the patient's face may increase immediately due to mechanical expansion of the particle suspension, which settles within a few hours to days. The level of expansion is an approximation of the overall results after three treatments; therefore, it can be used to predict the number of treatments needed to reach the expected results [66]. Having received the injection, the initial effects appear gradually after one month and are more remarkable over 3–6 months (Figure 4). PLLA particles are metabolized by the same metabolic pathway as that of lactic acid; they reduce by 6%, 32%, and 58% at 1, 3, and 6 months, respectively, and degrade completely by approximately 9 months [66].

The effects of PLLA are long-lasting and can achieve effect that lasts for 2 years after three consecutive sessions. Skin tests can be avoided for sources that are made by nonhumans or nonanimals. PLLA can also be applied to deep tissues and around the bones. However, drawbacks of PLLA include typical features of injectable dermatological agents, such as ecchymosis, transient pain, mild-to-moderate hematomas, inflammatory response, edema that lasts for 3–5 days, irregular appearance (depending on the injection technique), and multiple treatments. The FDA approved PLLA as the only injectable implant for correcting HIV-associated facial fat atrophy in 2004 but also introduced it for cosmetic uses, including facial wrinkles, nasolabial creases, and other facial contours [104].

4.3.1. Indications. PLLA can be used in patients with or without HIV infection (including retroviral treatment) with facial lipoatrophy; they will need sufficient patience, however, due to the time required for the gradual effects of PLLA to manifest. The applicable parts include the zygomatic and cheek depressions, lower facial relaxation and fold, lower orbital depression, neck lines (venus chain), and hands.

4.3.2. Contraindications. PLLA is contraindicated in patients with collagen allergy, related immune system diseases, scar hyperplasia, hematologic diseases, and coagulation disorders during pregnancy and lactation. Orbital infarction with loss of vision has been reported after unexpected intravascular PLLA injections around the nasal and periorbital areas [104]. Treatments should be avoided over the nose, suborbital areas, and lips as these areas are at higher risk of overcorrection, nodules, and intravascular injections that are attributed to continual muscle contractions [104].

4.3.3. Complications. PLLA has been used for a long time with a good safety record. Common complications are generally mild and mostly resolve spontaneously. Granuloma and nodular formation are major complications with PLLA. They occur occasionally and are related to incorrect injection areas and techniques. Postoperative swelling, redness, pain, itching, discoloration, scab formation, and peeling are common phenomena. As long as a reasonable



(a) (b)

Figure 4: (a). Before Sculptra (Galderma, Fort Worth, TX, USA) injection. (b). 13 months after PLLA. Each of temporal, midface, and submalar areas received two vials of Sculptra [102].

dosage is injected, these symptoms resolve spontaneously within a few days. Some patients can have an acne outbreak after treatment for 10 days, which is related to abnormal stimulation leading to vigorous metabolism. It is suggested that PLLA should be injected into the deep or underlying dermis to establish the supporting structures. If the injection level is too shallow, skin nodules and/or fever are likely. Skin nodules can easily appear, if the dose or concentration is too large or the preparation time is insufficient.

Dermal thickening is slow and progressive. Therefore, according to the principle of "a small number of times," which has been designed to strictly prohibit "over-correction," there should be 3-4 weeks of observation between two injections. According to the degree of tissue atrophy, usually, 3-4 continuous treatments are required to achieve the most satisfactory effects. Standard volumetric solutions require a maximum of four treatments 4–6 weeks apart [58]. Some researchers also recommend higher reconstitution volumes (5–9 mL with a maximum of 10 mL) and longer hydration times (24–48 h). All these techniques have been demonstrated to be effective in reducing the incidence of nodules [58, 66]. The injection areas should be deep and should never be used in areas with extremely thin skin, such as the lips and eyes. Therefore, comprehensive training is required for physicians. The correct injection method should be mastered, and its abuse must be avoided. PLLA injections should be avoided in areas where other fillers have been injected or sites of inflammation.

Ice compression is required immediately after the injection, and direct sunlight should be avoided as much as possible for half a month. After administering the injection, the areas must be gently massaged for even distribution of PLLA in the skin and minimize the formation of nodules and granulomas. The following massage principles should be followed: instruct patients to use over-the-counter petrolatum-based ointment 5 minutes at a time, five times a day, for 5 days to promote even distribution of the injected substance [58]. If there is a significant nodule or mass, it usually takes months or more to resolve spontaneously. If necessary, a small dose of corticosteroids can be injected for relief.

4.4. Collagen. Collagen, the main component of the dermal extracellular matrix, is an ideal biological scaffold that can provide space for fibroblasts' growth and is also a good medium for cellular growth. Injecting collagen into the

human body results in not only the filling of valleys or wrinkles but also the induction of host cells and capillaries to migrate into the injected collagen. With adequate oxygen and nutrients delivered by capillaries, the host fibroblasts can undergo normal activities and synthesize the host's collagen and other extracellular stromal components.

Collagen improves the skin's elasticity, increases water content, and reduces wrinkles (Figure 5). Collagen, one of the first injectable fillers used, has been used for more than 30 years and can be used alone or in combination with other facial fillers. The main collagen injectable products include bovine, human, and pig collagen products of different concentrations.

After 1-2 weeks of injection, collagen begins to mix with the host's collagen and is gradually absorbed and degraded by the skin tissue, making the skin feel increasingly natural. After 1-2 months, it will result in a softer and more natural feel than other types of fillers. Collagen does not easily absorb water and swell, so when used in tissues around the eyes that have slow water metabolism and can easily develop edema, there will subsequently be no water absorption and edema, which can reduce postoperative adverse reactions. When collagen is used for mesotherapy, the whitening and skin rejuvenation effects are stronger than those with hyaluronic acid. Collagen is an excellent coagulant with hemostatic effects, does not easily diffuse distally, and does not easily embolize (does not mean that it will not embolize). Therefore, it is relatively safe in areas with rich blood vessels, such as the eyelids and around the eyes, or in patients prone to bruising. Repeated injection of collagen can stimulate dermal fibroblasts to produce new collagen, form new tissues, and perform their functions of repair and regeneration.

Collagen injections can only be used against skin aging caused by superficial wrinkles, such as the small and shallow shrinkage skin defects of brow lines, nasolabial groove wrinkles, crow's feet, or superficial scars and brow lines. For deeper wrinkles, such as forehead wrinkles in elderly patients, and older or deep scars, such as those of cystic acne or postoperative scars, the effects are not perfect. Collagen has a short duration of action in the tissues, only 3–6 months, and continues to reduce in volume. Therefore, several injections are required, and the optimal time of satisfaction is short. Early collagen was derived from bovine or human cadavers, which are species-specific and tissue-specific. Certain people may develop allergic reactions; therefore, skin tests must be performed before its use. It may also have hidden dangers of animal-derived pathogens, such as mad cow disease. It must be stored in cold storage, which is inconvenient for transportation.

4.4.1. Indications. The applications of collagen vary according to the filling level of different products and collagen compositions. The product that fills the dermo-epidermal junction is used for superficial skin lines (eyebrow lines, fine lines, crow's feet, scars, and horizontal forehead lines), while the product that contains more collagen is better suited for moderate and deep lines. Products with filling levels of the *epidermis* to the deep dermis are suitable for deeper wrinkles (nasolabial furrows, deep acne scars, and red lip edges) [67].

4.4.2. Contraindications. Contraindications of bovine collagen and bioengineered human collagen include allergy to their ingredients, including lidocaine. Human cadaveric collagen is contraindicated in patients with gentamicin allergy, treated site infection, and collagen vascular disease. Autologous collagen has a low risk of hypersensitivity and is relatively safe [67].

4.4.3. Complications. Complications are generally similar between the types of collagen injections. Common adverse reactions are injection overdose, irregularities, sclerosis, and unsatisfactory effects but are not extremely serious problems due to collagen's fast absorption rate. Therefore, serious complications associated with collagen products are rare. The commonest complication is hypersensitivity, which is commonly known as an allergy. Once serious allergies appear, the biggest advantage of collagen—that it can directly replenish the collagen in the skin leading to integration between the cells of collagen—becomes its most tragic shortcoming. Collagen injection products in the human body are very difficult to remove using operations and procedures, and they cannot dissolve as hyaluronic acid does; hence, such reactions are only managed with continuous allergy treatment to control the symptoms. Therefore, skin tests must be performed before using bovine and porcine collagen [105].

There are three types of collagen currently available:

Bovine collagen: bovine collagen products were the first soft tissue filling injections approved by the FDA. Before the development of hyaluronic acid, bovine collagen was often used as the gold standard for such injections [64, 67]. Bovine collagen is extracted from cowhide and has been used as a biomaterial for more than 30 years [62]. Most experts recommend that patients who receive bovine collagen injections undergo two skin tests 2–4 weeks apart [62]. Local allergy occurs in 3%–5% of patients. Adverse reactions to bovine collagen include allergy, bruising, local necrosis, bacterial infections, and reactivation of herpes virus infection [62].

Porcine collagen: following the development of bovine and human-derived bioengineered collagen, new pig-derived collagen appeared in the market. However, the data available on its use as an intradermal filler are scarce, and none are available in dermatological practice from the US. Porcine collagen is biodegradable and lasts for approximately 1 year in soft tissues. It has demonstrated good safety, is less immunogenic than bovine collagen, and has never resulted in allergic reactions. However, its main product, Evolence™ (ColBar LifeScience Ltd, Herzliya, Israel) was withdrawn from the American market by its manufacturer in 2009, just 1 year after it was approved [106].

Human-derived bioengineered collagen

(1) Bioengineered human collagen: cultured bioengineered human fibroblasts derive nutrition from the culture medium and produce collagen and

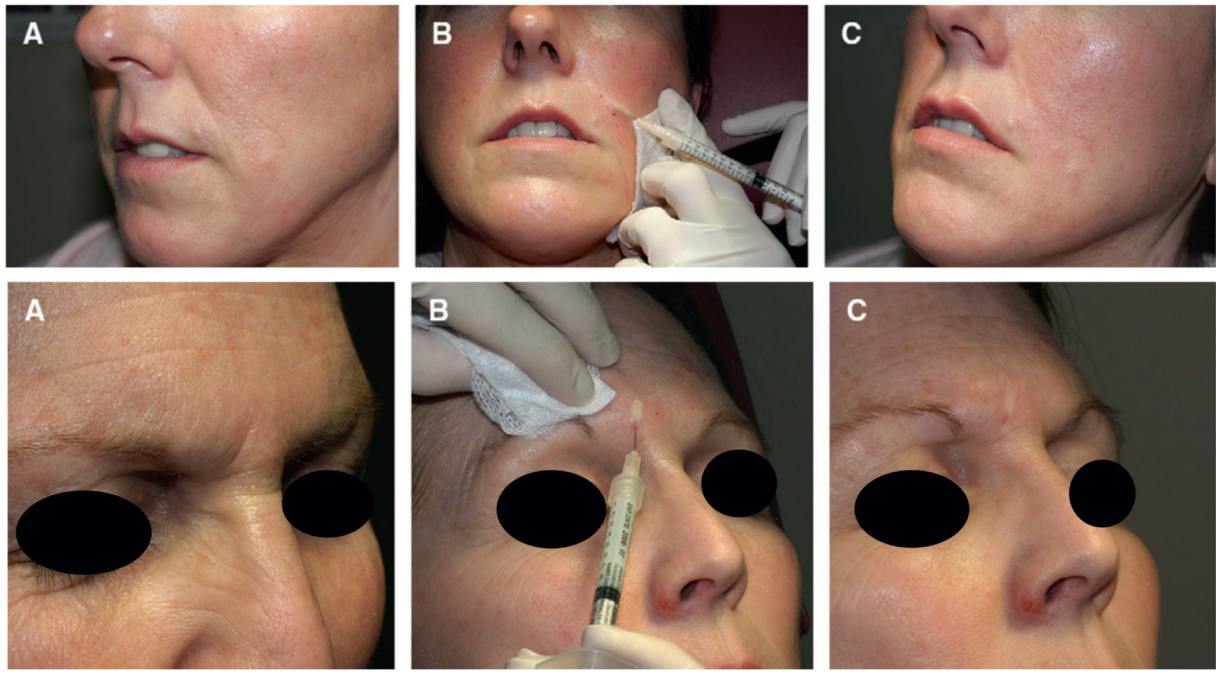


Figure 5: (a) Nasolabial fold fine lines and glabellar lines before collagen injection. (b) During collagen superficial injection, skin blanching is observed. (c) Immediately after collagen injection, remarkable results can be observed [105].

extracellular matrix proteins, which can be used to manufacture the required face-filling implants. Pathogen screening is needed for fibroblasts, and the collagen they produce is affected by the suppression of the virus. The fibroblasts need to be screened for pathogens, and the collagen they produce is affected by viral inhibition. Allergy testing is not required because it is derived from human skin fibroblasts [62, 67].

(2) Human cadaveric collagen: this type of collagen product is an injection of a cell-free allogeneic dermal matrix tablet originating from human cadaver derma and marketed in 2000.

(3) Autologous collagen: the autologous collagen product is derived from a culture of autologous fibroblasts extracted from the skin of the patients. A 3 mm needle biopsy is performed, usually behind the ear, and sent to a laboratory for culture after being frozen. After approximately 6 weeks, 1–1.5 cm^3 fibroblasts and extracellular matrix are usually obtained and returned to the doctor to be injected. Injections are to be administered within 24 hours of receipt of the product, and three injections with 2-week intervals are recommended [62, 67]. The disadvantages of the product are high costs, slow processing rates, painful injections, difficulties with immediate correction, and uncertain long-term efficacy [62].

4.5. Autologous Fat. Autologous fat has gained considerable popularity because it is an ideal filler with perfect biocompatibility. Autologous fat has many properties of an ideal filler and can be removed when necessary [107].

Autologous fat grafting was used at the beginning of the twentieth century to treat congenital deformities following oncologic surgery and has since been one of the procedures favored by plastic and maxillofacial surgeons [70, 107]. The clinical longevity of fat grafts, however, is highly uncontrollable; additionally, fat grafts have a high rate of absorption, and the results are operator-dependent [108]. A new technique was introduced by Coleman in the 1980s and is still the preferred method for fat filling and liposuction, which is constantly undergoing improvements [70, 71, 107].

Clinically, fat is often obtained from areas that have high fat content and no significant effects on the overall shape following aspiration. The inside of the thigh and lower abdomen are ideal supply sites because of the high concentrations of stromal vascular cells [108, 109]. To reduce pain and control bleeding, a swelling anesthetic technique is required. The swelling solution usually contains low concentrations of epinephrine, lidocaine, and saline.

Fat processing is necessary because unfiltered fat can cause inflammation at the recipient site. Current mainstream techniques for fat processing include centrifugation, filtration, washing, and gravity settling (Figure 6). Each of these methods has its own drawbacks. Wang et al. reported that filtration and centrifugation techniques had better retention results [110, 111].

To improve the viability of fat cells, the fat tissue should be placed close to the blood supply during fat reimplantation. Multiple microinjections which are no more than 1 mL are preferable over a single injection [107].

4.5.1. Indications. The main indication of facial autologous fat grafting is to correct facial contour deformities, such as

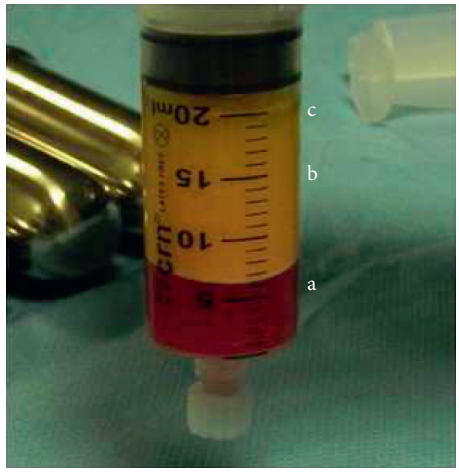


Figure 6: Centrifuged adipose tissue extract. From bottom to top: (a) First layer of blood and local anesthetics, (b) Second layer of fatty tissue, and (c) Third layer of lipids [62].

craniofacial shortening, to eliminate scarring, wrinkles, and changes associated with aging. While the traditional approach relies on the removal of fat, mainly for subtraction, a more natural result is achieved by filling the hollow facial spaces. Fat grafting can fill the hollow spaces in the orbital and temple areas and improve the contours of the cheekbone areas and jaw.

The important injection areas include the lips, anterior jawline, and labial jawline. The deep "muscle-related" folds usually do not disappear completely with soft tissue enhancement. However, the texture of the fold can be improved [112]. Patients with mild brow ptosis and skin laxity can be rejuvenated using fat transfer. In these patients, fat grafting is often preferred [113].

4.5.2. Complications. Lipotransfer is a very safe facial filler, and several trials have demonstrated that this method results in a good prognosis with few complications [114]. The commonest complication of autologous fat injections is fat necrosis that may be accompanied with hematoma and infection. Mild postoperative erythema and volume asymmetry have also been reported [110]. However, very rare and serious complications, such as blindness, sepsis, and hemiparesis, can also occur. Another study reported a rare case of ipsilateral external carotid artery (ECA) embolism following autologous facial fillers.

4.6. Polymethyl Methacrylate. Polymethyl methacrylate (PMMA) is a permanent filler. Its safety is similar to that of hyaluronic acid or calcium hydroxyapatite [115]. PMMA is very popular in facial filling because of its low price, easy availability, and simple usage [116].

The filling layer of PMMA is either the deep dermis or subcutaneous space. After injecting PMMA, the volume is initially provided by collagen, which is absorbed within 1–3 months. Meanwhile, the round, smooth PMMA microspheres are wrapped in the connective tissues of the host and are not degraded or excreted, thus becoming stable, permanent, and irreversible [115].

PMMA is not engulfed by human macrophages and does not undergo gradual degradation; therefore, its effects last for a long term or even are permanent (Figure 7). It can, however, ensure the softness of some tissues, and the effects are lasting in deep folds and acne scars. It is easy to implant but difficult to remove, and its nondegradability poses safety risks. It includes the risk of late granuloma and nodules that require steroid treatment or surgical resection. It has been marketed as a permanent skin filler in the US since 2007 and received FDA approval for treating acne scars in December 2014 [117].

4.6.1. Indications. Injectable PMMA is suitable for the nasolabial groove as well as for the frown line, radial lip line, and corner of the mouth [72]. It can permanently resolve facial wrinkles, nasolabial creases, scars, and other skin defects.

4.6.2. Contraindications. Complications of beading or masses have been reported with PMMA when injected around the eyes. If it is used for lip augmentation, it may result in a large number of nodules. Therefore, injections in these areas are not recommended [118].

4.6.3. Complications. Immediate complications include ecchymosis and hematoma in patients who consume alcohol or are on antiplatelet aggregators, vitamin *E*, ticlopidine, and nonsteroidal anti-inflammatory drugs a few days before or after the implantation, which usually resolve spontaneously after 2–7 days [116]. For approximately 7 days after the implantation, most patients may develop swelling, which can be alleviated with ice and compression [116].

Infections can also result from an overdose of the injection and early local compression due to poor blood circulation. The potential risk of embolism cannot be excluded theoretically although it has not been reported. Rarely, advanced granuloma and tissue necrosis may also occur; the former occurs due to an allergic reaction to bovine collagen and PMMA, and the latter is mainly due to intravascular fillers or excessive compression of the surrounding blood vessels [116].

The late complications include the following. Approximately 6–24 months after implantation, PMMA microspheres may result in granuloma due to foreign body reactions, which can be treated with corticosteroid injections [116]. Many years after the implantation, migration of PMMA microspheres may occur because the particles are surrounded by collagen fibers and are often difficult to be absorbed by human body, which can present as sclerosis or nodules that require surgical interventions [116].

5. Thread Lift

As more patients opt for minimally invasive rejuvenation procedures, thread-lifting techniques have emerged as an excellent option. Thread lift has been used in medical esthetic surgery since the early 11010s [119]. Sulamanidze's

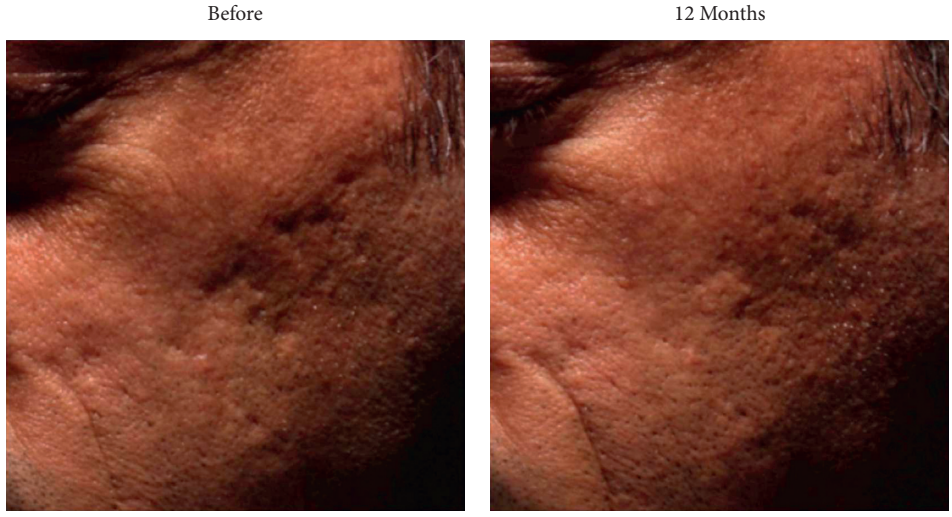


Figure 7: (a). Before and (b). 12 months after treatment of sectional scars using Bellafill® (Suneve Medical, San Diego, CA), significant recovery of scars can be observed in the cheek [115].

Antiptosis (Aptos) Subdermal Suspension Thread hooks a special thread on the skin to make it tense, which counteracts the laxity of the tissue and finally achieves a cosmetic effect of eliminating wrinkles. Thread lift is popular because of its many advantages, such as smaller incisions and shorter recovery time [120]. Sasaki and Cohen originally used a hookless sharp thread for cheek fat pad lifts. However, its retention was not good; therefore, attention was turned to barbed sutures, which were named Aptos according to the number of barbs on the polypropylene threads [121]. A surgeon needs to have a good knowledge and understanding of the superficial musculoaponeurotic system (SMAS) because the threads are fixed underneath the skin tissue in the face and neck [122].

5.1. Types of Threads

5.1.1. Aptos Threads. The Aptos thread is made of a cut 2-0 polypropylene thread. The thread has small, angled barbs in the same direction. Sulamanidze et al. [123] described the procedure as making a small incision in the temporary temple and drawing out several sutures under the skin. After the deeper threads and sutures appear, the remainder of the underlying line is clipped and the superior line is sewn to the temporalis muscle fasciatus using moderate traction. The recovery period with Aptos threads is short; however, patients need to follow their doctor's advice, such as avoiding sudden chewing and adhering to a massage for 1-2 weeks, to ensure that the results last longer. Indications for Aptos sutures in the face and neck are sagging, lax, flattened soft tissues, and less visible esthetic landmarks of the facial and cervical areas; lifting of the facial area is more common than lifting of the entire face. Examples include correction of significant nasolabial grooves or marionette wrinkles, lifting the cheeks, fixing the eyelids, and lifting fat from the lower eyelids [124]. The Aptos approach is considered by Sulamanidze et al. [125] to be the most effective in the midface region.

5.1.2. Contour Threads. The contour thread is an isometric thread approved by the FDA in October 2004. It consists of 25 cm of 2-0 polypropylene suture with 50 intermediate 10 cm sections of unidirectional spiral barbs secured to the fascia. Carmina et al. [120] described its use as placing a 3 mm incision in the temporal hairline for upper and midface lifts and a surgical incision behind the latissimus dorsi muscle for a submental lift. The stitches are advanced in a 'Z' shape in the subcutaneous plane as this shape is thought to maximize the number of hooks in touch with the subcutaneous tissues. The thread is finally truncated at the proximal end of the incision and secured to the deep fascia.

5.1.3. Silhouette Sutures. The silhouette suture consists of junctions and tapers and is composed of approximately 82% PLLA and 18% poly (lactic-co-glycolic acid). The silhouette suture was approved by the FDA in April 2015 for use in draping midface tissue. The suture is conceived with 8, 12, or 16 tapers that are evenly spaced on either side within a 2 cm taper-free central area and are designed to reduce the risk of migration and extrusion. The cones are arranged in the opposite direction, and the tip of the cone points to the end of the suture. The degradable component of the sutures stimulates collagen production during the degradation process, which facilitates suture fixation. Silhouette sutures are indicated for moderate midfacial tissue declines, such as nasolabial folds, declining oral continuity, and marionette wrinkles. [126].

5.1.4. Multianchor Suspension Sutures. Multianchor suspension suture is made from a 3-0 polypropylene suture. It has nine knots in the middle and spans 8 cm (knots are

approximately 10 mm apart). Every knot is inset into an assimilable hollow cylinder made of copolymers containing levulinic acid and acetyl cross-esters. The sutures have a semicircular pin at the near terminus, which allows them to be fixed to a nonabsorbable synthetic knitted surgical mesh during the procedure. Multianchor suspension sutures are often indicated to lift the midface, for example, to decrease the width of the nasolabial groove, increase the definition of the mandible, and increase the temporal projection [127]. The technique can also be useful in static correction of nerve palsy of the face when recovery of the neurological functions is impossible.

5.2. Complications. The most common complications are the same as those with most logical surgical procedures, such as pain, swelling, and bruising. The most common complications are temporary. Additionally, depression of the skin and breakage or migration of the threads may also occur [120]. The incidence of nerve damage is lower than that of conventional debridement (0.7%–2.5%) [128]. Persistence of foreign objects can lead to many side effects as well as unsatisfactory esthetic effects [129]. Wu et al. [130] have demonstrated that complications, such as infection or granulomas, can also occur. Due to tissue remodeling, there is an increased likelihood of scar formation, hyperpigmentation, and suture extrusion.

6. Conclusion

Minimally invasive facial surgery mainly uses drug injections, fillers, thread lift, and radiofrequency to improve facial function and appearance. Compared with traditional cosmetic surgery, such as face-lifting, non-surgical modalities is increasingly favored by cosmetic surgeons and patients because of its advantages, such as small wound surface, short recovery period, and more natural effects.

Facial aging is mainly caused by the breakdown of collagen, elastin, and glycosaminoglycans, run-off of fat volume and displacement of fat in different locations, changes in muscle tension and length, and changes in the shape of bones. The different parts of the face experience different levels and likelihood of aging. In this article, the authors have listed the commonest areas of facial aging.

This paper summarizes the injectable drugs (botulinum toxin) and facial fillers (hyaluronic acid, calcium hydroxyapatite PLLA, collagen, autologous fat, and PMMA) in the treatment of facial aging along with their mechanisms, indications, contraindications, and complications as well as introduces thread lift and radiofrequency anti-wrinkle applications in treating facial aging. Botulinum toxin blocks cholinergic nerve transmission and causes muscle paralysis and relaxation, thus reducing hyperactivity of the muscles of expression and eliminating wrinkles. The main purpose of facial implants is to plump the face. Hyaluronic acid is naturally present in body tissues, including the skin, and has good compatibility with the human body. It is the most widely used facial filler currently, and the application range of calcium hydroxyapatite is second only to that of hyaluronic acid. The main action place of the thread lift is the SMAS. The cosmetic effects of fading wrinkles are achieved by hooking special threads under the skin to make it taut. The role of radiofrequency rhytidectomy removal is to heat the dermis and stimulate the regeneration of collagen so that the skin recovers its elasticity gradually and skin wrinkles are eliminated.

Although the mechanism of action of various drug materials is relatively clear, the indications, contraindications, and complications of their effects remain unclear for some clinicians. The comprehensive summary of injectable drugs, facial fillers, thread lift, and radiofrequency rhytidectomy presented in this paper can act as a reference for clinicians.

The combined application of facial nonsurgical modalities has good clinical prospects. Additionally, minimally invasive rhinoplasty, lip surgery, and lower eyelid lifting are becoming increasingly popular among patients.

Data Availability

All data, figures, and tables in this review paper are labeled with references.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Mr. Kelun Li had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design was made by Kelun Li and Heng Bo Jiang. Acquisition, analysis, and interpretation of data were made by all authors. Kelun Li, Fanyu Meng, Yu Ru Li, Yueyi Tian, Hao Chen, Qi Jia, and HongXin Cai drafted the manuscript. All authors critically revised the manuscript for important intellectual content. Heng Bo Jiang provided administrative, technical, and material support and supervised the study.

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