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Precise Biomaterial Strategy for Midface Rejuvenation: A Treatment Series on Collagen Stimulators Alone or Combined with Hyaluronic Acid for Aging Signs

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Abstract

Background: The midface is a key area where aging signs first appear, involving multi-layered changes such as epidermal fine lines, volume loss leading to hollowing and sagging, and deep structural support weakening resulting in nasolabial fold deepening. Single-material treatments often fail to address this complexity comprehensively. While hyaluronic acid (HA) effectively restores volume, its impact on skin texture is limited; collagen stimulators promote long-term collagen regeneration but lack immediate shaping capability.

Objective: Through six typical cases, this study systematically investigates the precise application strategies of HA and collagen stimulators, either alone or in combination. It designs layered treatment plans based on different aging characteristics to evaluate the clinical efficacy and safety of combined therapy for addressing single or compound midface aging concerns, aiming to provide a clinical framework for achieving comprehensive, natural, and long-lasting rejuvenation.

Methods: This case series analysis included six patients with typical midface aging. A layered combination treatment plan was developed according to the anatomical levels of aging signs: one case of infraorbital static fine lines (intradermal injection of a hyaluronic acid-based nutrient complex solution); one case of pigmented dark circles (subdermal injection of the same nutrient complex); two cases of infraorbital hollowing (sub-orbicularis oculi PCL injection); one case of tear trough deformity (combined periosteal HA and submuscular PCL injection); and one case of compound aging (combined HA, PCL, and PLLA treatment). Efficacy was assessed blindly by independent physicians using standardized scales (GAIS, Merz, Hirmand, MVDSS, WSRS). Safety records included early reactions and delayed complications.

Results: All cases showed clear improvement in target aging signs, such as fine lines, dark circles, hollowing, and contour laxity, with significant enhancement in overall aesthetic scores. Treatments were well-tolerated, with only transient, mild expected reactions like redness and swelling observed, and no serious or persistent complications occurred.

Conclusions: This study demonstrates that a combined/layered treatment strategy based on anatomical levels and problem-specific classification using hyaluronic acid and collagen stimulators offers a safe, effective, and personalized comprehensive solution for multidimensional midface rejuvenation.

1. Introduction

The midface represents a focal point in facial aging, where the earliest and most perceptible signs of senescence emerge [1]. Anatomically, aging in this region unfolds across multiple tiers, the epidermis and dermis undergo thinning and textural change due to collagen and hyaluronic acid depletion, presenting as fine lines and loss of luminosity; the subcutaneous soft tissue compartments suffer from volume attenuation and gravitational descent, leading to infraorbital hollowing, malar fat pad ptosis, and tear trough

formation; and the deep structural foundation---comprising retaining ligaments and bony architecture---weakens over time, accentuating nasolabial fold depth and midface flattening [2-4]. This multidimensional, layered progression poses a significant clinical challenge, as monotherapeutic approaches often prove insufficient to address the full spectrum of aging manifestations.

Currently, two principal classes of injectable agents are employed in midface rejuvenation: HA and collagen stimulators. HA fillers excel in providing immediate volume restoration and structural repositioning, yet their capacity to improve skin quality and texture remains limited. Conversely, collagen stimulators promote neocollagenesis and gradual tissue restoration, offering sustained improvements in skin elasticity and mild volumetric correction, but they lack the immediate lifting and contouring effect of fillers [5]. Given these complementary mechanisms---where HA addresses the "space" and collagen stimulators target the "structure"-a rational, layer-adapted combination of both modalities may yield synergistic benefits, enabling more holistic and durable rejuvenation outcomes [6].

Accordingly, this case-series study was designed to systematically evaluate a structured, problem-oriented treatment framework that integrates HA and collagen stimulators, either alone or in combination, based on the specific aging phenotype and anatomical depth of involvement. Through the presentation of six representative clinical cases, we aim to illustrate how a stratified approach---tailoring material selection and injection plane to individual aging signs---can optimize efficacy, enhance safety, and support reproducible clinical decision-making in the management of multidimensional midface aging.

2. Materials and Methods

2.1. Case Selection

2.1.1. Inclusion and Exclusion Criteria and Rationale for Case Selection

Inclusion Criteria

Age Range: 25-50 years old (adult to middle-aged women).

Primary Aging Signs: Presence of at least one clearly defined, patient-identified midface aging sign with a positive desire for treatment.

Representativeness: The presenting aging sign must be clearly classifiable into a typical anatomical-clinical subtype of midface aging.

Exclusion Criteria

Pregnancy or lactation.

Active facial infection, inflammatory skin disease, or unhealed wounds in the treatment area.

Uncontrolled systemic diseases (e.g., severe diabetes, autoimmune disorders) or coagulation disorders.

Known allergy to hyaluronic acid, collagen stimulators, or any component of their formulations.

History of permanent filler implantation in the treatment area or presence of scar tissue that would interfere with assessment.

2.1.2. Rationale for Case Selection

This study aims to systematically present and analyze precise treatment strategies for different layers and mechanisms of midface aging through a series of highly representative cases. These 6 cases were not randomly selected but were deliberately chosen to correspond to and illustrate five distinct yet classic clinical presentations of midface aging, thereby constructing a comprehensive treatment strategy map.

2.1.3. Case 1 Epidermal and Superficial Dermal Aging

Represented Problem Fine lines and wrinkles, stemming from dermal matrix (collagen, HA) degradation leading to textural deterioration.

2.1.4. Case 2 Dermal-Subcutaneous Junction Pigmentation and Microcirculation Issues

Represented Problem Pigmented dark circles, involving factors like dermal pigmentation, subcutaneous vascular prominence, and soft tissue thinning.

2.1.5. Cases 3 & 4 Subcutaneous and Submuscular Soft Tissue Volume Loss

Represented Problem Infraorbital hollowing.

2.1.6. Case 3 (Physiological) Represents primary, age-related fat pad atrophy.

2.1.7. Case 4 (Iatrogenic) Represents secondary, structural fat deficiency following surgery, a common sequela in East Asian populations.

2.1.8. Case 5 Multi-Layer Composite Defect (Ligamentous Laxity with Mild Volume Deficiency)

Represented Problem Tear trough deformity, with a pathological basis combining deep tear trough ligament laxity and superficial SOOF fat pad atrophy.

2.1.9. Case 6 Full-Layer, Multidimensional Composite Aging

Represented Problem Pan-facial aging involving skin, fat, ligaments, and bony support, manifesting as multiple signs including tear trough, malar fat pad descent, and nasolabial fold deepening.

2.2 Materials

The following materials were utilized in the corresponding cases.

1. For fine lines, wrinkles, and dark circles. NCTF® 135 (FILLMED Laboratories, France), a sterile solution containing hyaluronic acid, vitamins, antioxidants, amino acids, and coenzymes, was employed for intradermal or subdermal injection.
2. For infraorbital hollowing and sub-orbicularis oculi volumization. Polycaprolactone (PCL) - based collagen stimulator (Purajuve, Shandong Guyuchun Biotechnology Co., Ltd., China) was used after dilution with sterile normal saline.
3. For deep structural support and volume restoration. Hyaluronic acid dermal filler (FILLMED® UNIVERSAL, FILLMED Laboratoires, France) was applied in the periosteal or deep fat compartment.
4. For large-area skin tightening and collagen stimulation. Poly-L-lactic acid (PLLA) injectable (PULIYAN, Puliya (Nanjing) Medical Technology Co., Ltd., China) was administered subdermally after reconstitution.

All products were used in accordance with manufacturers' instructions and applicable medical device regulations in China.

2.3. Treatment Strategy and Technique

2.3.1. Case 1 Epidermal and Superficial Dermal Aging

A 34-year-old female presented with infraorbital fine lines and wrinkles. She was otherwise healthy with no prior history of cosmetic or surgical procedures. (Figure 1 and Table 1)

Table 1: Etiological Analysis and Injection Details/Strategy for Case 1

Represented Problem	Material	Level & Gauge & Injection Technique	Dosage
Fine lines and wrinkles	NCTF® 135	Intradermal/32G/Needle	0.8ml per side

2.3.2. Case 2 Dermal-Subcutaneous Junction Pigmentation and Microcirculation Issues

A 42-year-old female presented with pigmented dark circles. She was otherwise healthy with no prior history of cosmetic or surgical procedures. (Figure 2 and Table 2)

Table 2: Etiological Analysis and Injection Details/Strategy for Case 2

Represented Problem	Material	Level & Gauge & Injection Technique	Dosage
Pigmented dark circles	NCTF® 135	Intradermal/27G/Cannula	2.5ml per side

2.3.3. Cases 3 & 4 Subcutaneous and Submuscular Soft Tissue Volume Loss

Case 3 (Physiological) Represents primary, age-related fat pad atrophy.

Case 4 (Iatrogenic) Represents secondary, structural fat deficiency following surgery, a common sequela in East Asian populations.

(Figure 3, Figure 4 and Table 3)

Table 3: Etiological Analysis and Injection Details/Strategy for Case 3 & 4

Represented Problem	Material	Level & Gauge & Injection Technique	Dosage
Infraorbital hollowing			
Case 3 Congenital	PCL+0.5ml NS	Sub-orbicularis oculi/27G/Cannula	0.2ml per side
Case 4 Acquired	PCL+0.5ml NS	Sub-orbicularis oculi/27G/Cannula	0.4ml per side

Case 5 Multi-Layer Composite Defect (Ligamentous Laxity with Mild Volume Deficiency) (Figure 5 and Table 4)

Table 4: Etiological Analysis and Injection Details/Strategy for Case 5

Represented Problem	Material	Level & Gauge & Injection Technique	Dosage
Tear trough deformity	AFU	Periosteum/23G/Needle	0.1ml per side
	PCL+0.5ml NS	Sub-orbicularis oculi/27G/Cannula	0.2ml per side

Case 6 Full-Layer, Multidimensional Composite Aging (Figure 6 and Table 5)

Table 5: Etiological Analysis and Injection Details/Strategy for Case 6

Represented Problem	Material	Level & Gauge & Injection Technique	Dosage
tear trough, malar fat pad descent, and nasolabial fold deepening	AFU	Periosteum/23G/Needle	0.2ml per side
	PCL+0.5ml NS	Sub-orbicularis oculi/27G/Cannula	0.4ml per side
	PLLA+6ml NS	Subcutaneous/27G/Cannula	3ml per side
Supplementary injection at 3 months	AFU	Periosteum/23G/Needle	0.2ml per side
	PCL+0.5ml NS	Sub-orbicularis oculi/27G/Cannula	0.4ml per side
Supplementary injection at 10 months	AFU	Periosteum/23G/Needle	0.2ml per side

2.4 Evaluation and Follow-up

Evaluation Methods. Standardized photography, clinical rating scales.

Follow-up Time Points. Determined based on the specific treatment protocol, commonly at 3 months, 6 months, and 10 months post-treatment [7].

2.4.1. Evaluation Methods and Rating Systems.

- **Global Aesthetic Improvement Scale (GAIS)**: -2: Much Worse, -1: Worse, 0: No Change, +1: Improved, +2: Much Improved [8].
- **Merz Infraorbital Hollow Assessment Scale**: Grade 0: None to Minimal, Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Extreme [9].
- **Midface Volume Deficit Severity Scale (MVDSS):** Grade 0: None/Minimal, Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Very Severe [10].
- **Hirmand Tear Trough Deformity Severity Scale (HIRMAND)**: Grade 1: None/Mild, Grade 2: Moderate, Grade 3: Severe [11].
- **Wrinkle Severity Rating Scale (WSRS):** Grade 1: No wrinkles, Grade 2: Shallow wrinkles, Grade 3: Moderately deep wrinkles, Grade 4: Deep wrinkles, well-defined folds, Grade 5: Very deep wrinkles, redundant folds [12].

3. Results

3.1. Case 1

Immediate post-treatment swelling around the eyes and slight bruising at some needle puncture sites were observed, both resolving spontaneously within 72 hours, with no other discomfort reported. At the three-month follow-up, a reduction in fine lines and dryness of the lower eyelid was noted. Compared with the pre-treatment condition, a GAIS score of 1 (Improved) was recorded. (Figure 1)

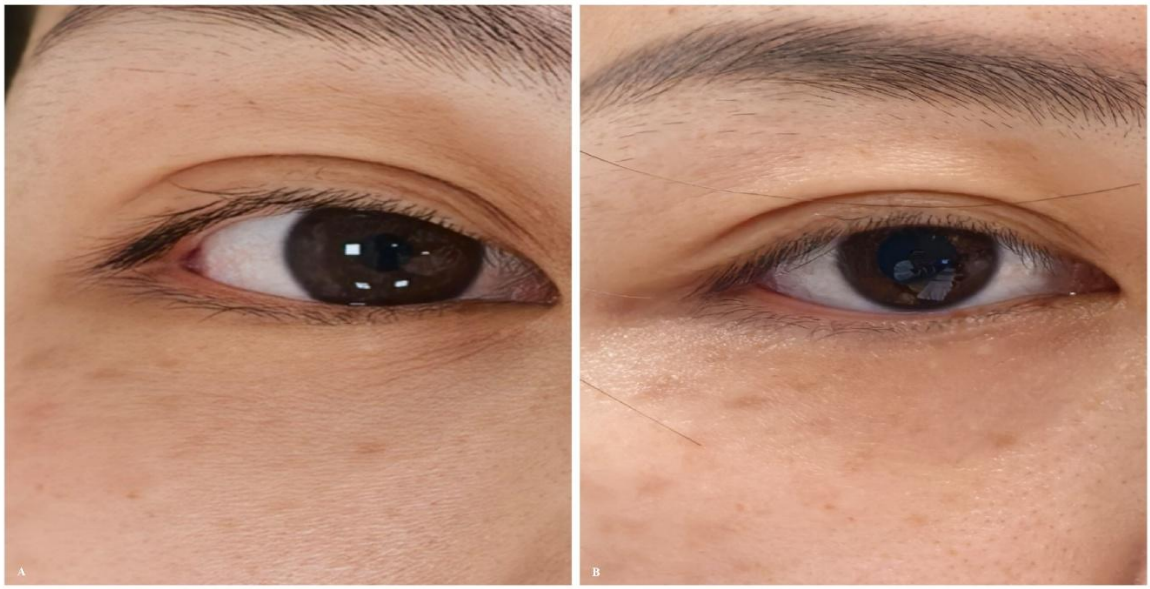

Figure 1: (A) Pre-treatment baseline. (B) Three-month follow-up

3.2. Case 2

Immediate post-treatment swelling around the eyes and slight bruising along the blunt cannula tracks were noted, resolving spontaneously within 72 hours, with no other discomfort. At the three-month follow-up, pigmented dark circles were visibly lightened. A GAIS score of 1 (Improved) was given compared to the pre-treatment state. (Figure 2)

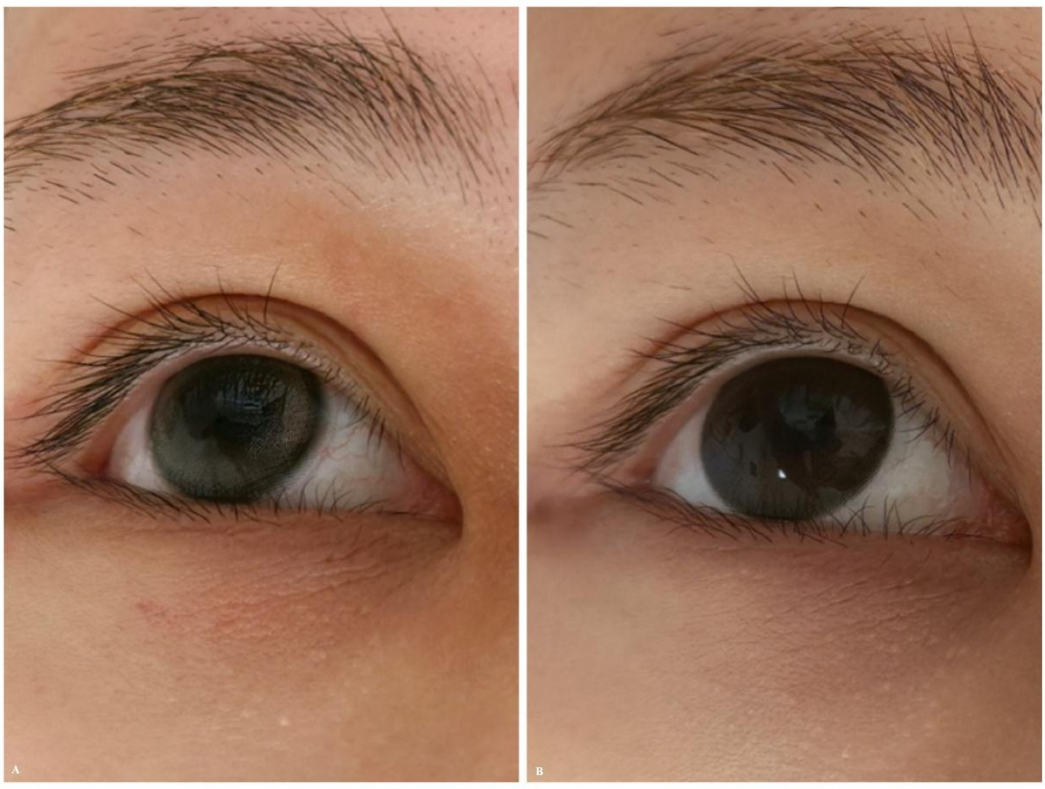

Figure 2: (A) Pre-treatment baseline. (B) Three-month follow-up

3.3. Case 3

Mild periorbital swelling occurred immediately after treatment and resolved within 72 hours, with no other discomfort reported. At the three-month follow-up, infraorbital hollowing was improved. In cases of physiological infraorbital hollowing, treatment resulted in an improvement in the Merz score from 2 (moderate) to 1 (mild).

(Figure 3)

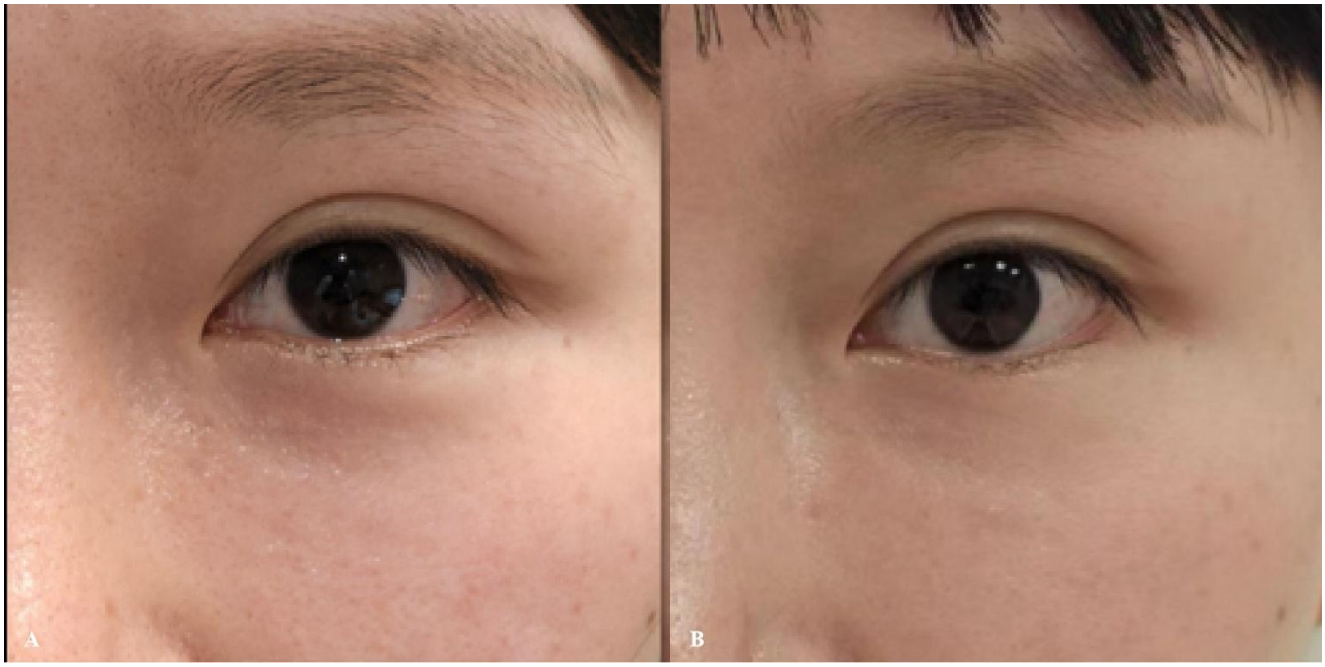

Figure 3: (A) Pre-treatment baseline. (B) Three-month follow-up

3.4. Case 4

Immediate post-treatment periorbital swelling was observed and resolved within 72 hours, with no other discomfort. At the three-month follow-up, significant improvement in infraorbital hollowing was noted. In cases of iatrogenic infraorbital hollowing, treatment led to a significant improvement in the Merz score from 4 (extreme) to 1 (mild). (Figure 4)

Figure 4: (A) Pre-treatment baseline. (B) Three-month follow-up

3.5. Case 5

Post-treatment periorbital swelling occurred and resolved within 72 hours, with no other discomfort. At the three-month follow-up, tear trough improvement was observed, with the Hirmand score decreasing from 2 to 1. At the six-month follow-up, the Hirmand score further improved to 0. (Figure 5)

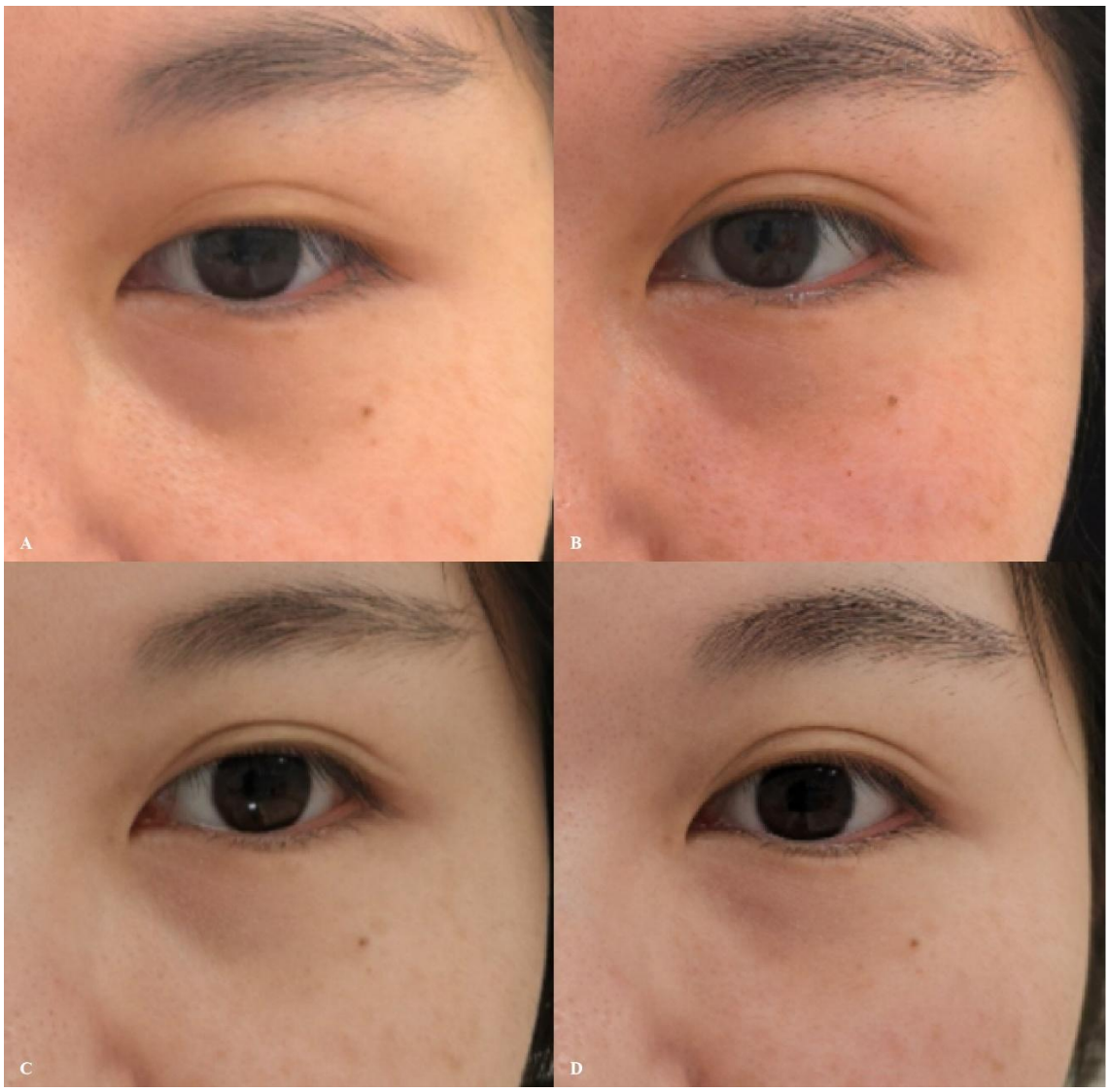

Figure 5: (A) Preoperative baseline. (B) Immediate postoperative appearance. (C) Appearance at 3-month follow-up. (D) Appearance at 6-month follow-up

3.6. Case 6

Immediate post-treatment swelling of the periorbital area and lateral face was noted, resolving within 72 hours without other discomfort.

3.7. Three-month follow-up after initial treatment: Tear trough improvement, Hirmand score decreased from 3 to 2. Improvement in malar fat pad ptosis, MVDSS score decreased from 3 to 2. Nasolabial fold improvement, WSRS score decreased from 4 to 3. Overall improvement, GAIS score was 1 (Improved). (Figure.6)

3.8. Comparison between pre-treatment, 10-month follow-up, and immediate post-injection at 10 months: Tear trough continued to improve, Hirmand score decreased progressively from 3 to 2 to 1. Malar fat pad ptosis continued to improve, MVDSS score decreased progressively from 3 to 2 to 1. Nasolabial folds continued to improve, WSRS score decreased progressively from 4 to 3 to 2. Significant overall improvement: GAIS score was 2 (Much Improved). (Figure 6)

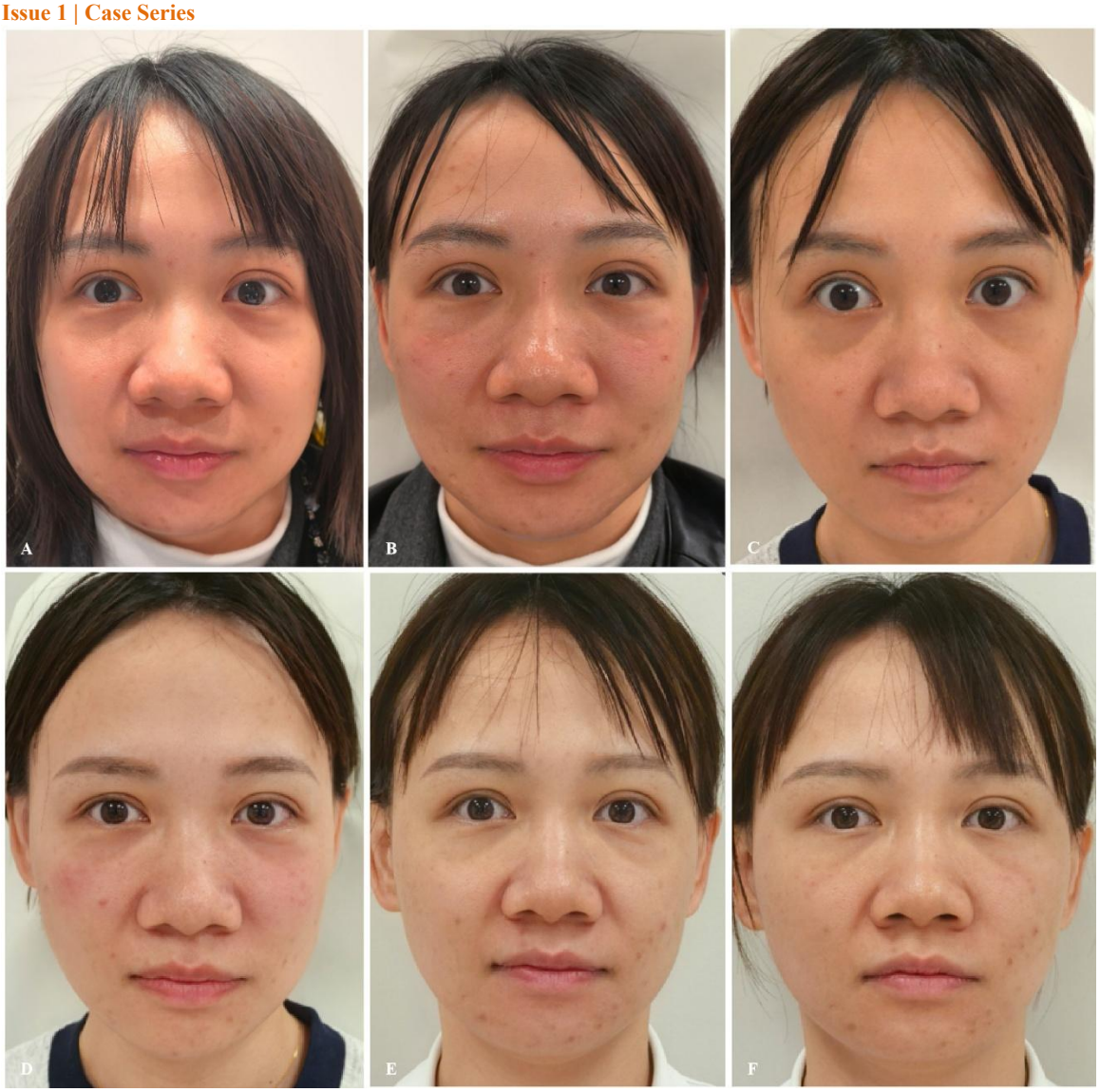

Figure 6: (A) Preoperative baseline. (B) Immediate postoperative appearance. (C) Appearance at preoperative assessment of the 3-month follow-up session. (D) Appearance immediately after retreatment at the 3-month follow-up session. (E) Appearance at preoperative assessment of the 10-month follow-up session. (F) Appearance immediately after retreatment at the 10-month follow-up session

4. Discussion

In the field of facial rejuvenation, the evolution of injecTablele filler materials has been ongoing. Fat grafting, once an early mainstream approach, remains limited by unpredicTablele survival rates (reported in the literature to range between 20%–80%) [13]. Variability in procedural protocols, processing techniques, and physician experience further contributes to outcome inconsistency [14]. Consequently, in China's current practice of pursuing refined and predicTablele facial volumization, synthetic fillers have become the more prevalent choice.

Initially, HA fillers were widely used [15]. However, over the past decade, certain excessive or inappropriate injection techniques have led to the emergence of "facial overfilling syndrome" [16]. NoTablely, driven by marketing strategies, some institutions or brands have attributed this phenomenon to HA itself, promoting the so-called "regenerative material" era and claiming that such materials can avoid the "dough-like" overfilled appearance [17]. In reality, these "regenerative materials" primarily refer to various collagen stimulators—injecTablele products containing microspheres (e.g., PMMA, PLLA, PCL, CaHA). Yet, if composed solely of microspheres, do these materials possess immediate mechanical support? The answer is clearly negative—just as coffee powder dissolved in water remains liquid and cannot provide structural support. Therefore, commercially available "regenerative materials"

can be broadly categorized into two types: those without immediate support (e.g., traditional PLLA “Sculptra”) and those with immediate support (e.g., composite CaHA or PCL products). The supporting capacity of the latter precisely derives from their carrier gel—whether Carboxymethyl Cellulose (CMC) gel or HA gel [18]. Studies have shown that as a microsphere carrier, HA gel significantly outperforms CMC gel in terms of inducing tissue regeneration, maintaining volume sTableility, and promoting angiogenesis.[13] Thus, the “dough-like” overfilled appearance should not be simplistically blamed on HA alone, but is more likely related to injection depth, dosage, product selection, and technical execution [15].

Next, we compare and analyze the key differences between collagen stimulators and HA in clinical applications. Regarding immediate effects, HA provides good immediate support, precise shaping, and lifting capacity, with reversible outcomes that allow for treatment adjustments [14]. In contrast, collagen stimulators-particularly pure microsphere formulations without a pre-mixed carrier gel-lack immediate mechanical support and shaping ability [19]. Their effects rely on the gradual induction of fibroblast activity and neocollagenesis, resulting in a slow onset and an inability to make immediate corrections [20]. In terms of safety and mechanism of action, HA exhibits high biocompatibility with minimal inflammatory response and a relatively predicTablele meTableolism, allowing for better predicTableility of medium- to long-term outcomes [21]. Collagen stimulators, however, function through a controlled foreign-body reaction that stimulates collagen production; thus, a certain degree of inflammation is inherent to their mechanism [22]. NoTablely, large-volume injection or bolus deposition of microspheres may increase the risk of medium- to long-term granuloma formation, making these materials unsuiTablele for substantial volumization [23]. Regarding applicable tissue layers and long-term effects, the two categories are complementary. Cross-linked HA is generally not recommended for superficial areas such as the periorbital region, where thin skin increases the risk of visible lumps or the Tyndall effect [24]. Appropriately diluted collagen stimulators, however, can be used cautiously in superficial layers to improve skin texture and mild volume deficits [25]. Furthermore, collagen stimulators offer a unique long-term benefit: through sustained collagen induction, they can achieve progressive tissue tightening and quality improvement—an effect not attainable with HA [26].

5. Conclusion

The findings of this study indicate that a single therapeutic agent is often insufficient to fully address the multidimensional and layered manifestations of midface aging. In such cases, the combined use of hyaluronic acid and collagen stimulators is not merely an option but a necessary strategy. HA plays an irreplaceable role in achieving immediate aesthetic improvements and precise structural repositioning, while collagen stimulators esTablelish the foundation for long-lasting rejuvenation by inducing tissue regeneration and internally supporting the dermal structure. A layered treatment approach-precisely selecting materials based on the specific anatomical depth of aging-represents the key to moving beyond monotherapy, enabling comprehensive rejuvenation that is not only natural in appearance but also structurally sTablele and enduring. Therefore, in clinical practice, the focus should shift from selecting a single "optimal" material to designing an "optimal" combination strategy tailored to the patient’s unique aging phenotype, with the goal of achieving holistic, safe, and predicTablele aesthetic outcomes. This aligns with the imagery depicted in a classical Chinese poem: “Sunset clouds fly with the lone duck, autumn water blends with the vast sky”. Similarly, in facial rejuvenation, collagen stimulators and hyaluronic acid, like the sunset clouds and the lone duck, the autumn water and the boundless sky-each with distinct properties-complement each other harmoniously when applied in combination and with clear layering, together creating a cohesive and long-lasting overall aesthetic effect.

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