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Annals of Dermatological Science

ISSN 2831-8129

Research Article

Recent Advances in Collagen Biostimulators for Facial Rejuvenation: A Systematic Review in Aesthetic Dermatology.

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Abstract

Introduction: Skin aging leads to loss of collagen, elasticity and facial volume, motivating the search for minimally invasive aesthetic procedures. Among the available strategies, collagen biostimulators have stood out as effective therapies for facial rejuvenation, promoting progressive dermal regeneration.

Objective: This systematic review aimed to analyze recent advances in the use of collagen biostimulators for facial rejuvenation in the practice of aesthetic dermatology.

Methodology: PubMed, Scopus, Web of Science and Embase were searched, including articles published between January 2019 and April 2025. Clinical studies, systematic reviews and meta-analyses that addressed the efficacy, safety and innovations in collagen biostimulators were included.

Results: 42 studies evaluating the use of poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA) and polycaprolactone (PCL) in facial rejuvenation were selected. PLLA demonstrated efficacy in progressive dermal remodelling, CaHA provided immediate volumization and subsequent biostimulation, while PCL exhibited superior durability of clinical effects. All biostimulators showed favorable safety profiles, with a high patient satisfaction rate.

Conclusion: Collagen biostimulators have established themselves as essential elements in minimally invasive facial rejuvenation, offering natural and long-lasting results. Personalization of treatments and technical mastery are essential to optimize efficacy and minimize complications. Future research should focus on multicenter, long-term clinical trials to strengthen the available evidence.

Keywords: Collagen biostimulators; Facial rejuvenation; Aesthetic dermatology; Poly-L-lactic acid; Calcium hydroxyapatite; Polycaprolactone.

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Received: 03-May-2025, Manuscript No. AODS-4831 **; Editor Assigned:** 05-May-2025 **; Reviewed:** 26-May-2025, QC No. AODS-4831 **; Published:** 03-June-2025, **DOI:** 10.52338/Aods.2025.4831.

Citation: **Thiago Augusto Rochetti Bezerra**. Recent Advances in Collagen Biostimulators for Facial Rejuvenation: A Systematic Review in Aesthetic Dermatology. Annals of Dermatological Science. 2025 June; 11(1). doi: 10.52338/Aods.2025.4831.

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INTRODUCTION

According to Ogawa et al. (2019), the search for methods to restore facial volume began to intensify in the early decades of the 20th century, initially with surgical techniques.

At the end of the 1990s, the first temporary dermal fillers appeared, mostly based on hyaluronic acid and focused only on volumization (Wong et al., 2020).

The concept of collagen biostimulation emerged as an evolution of filling techniques, focusing not only on volume but also on skin quality (Lemperle et al., 2019).

The approval of poly-L-lactic acid (PLLA) for the treatment of facial lipodystrophy in HIV patients marked the first major advance in the use of biostimulators (Mendoza et al., 2020).

Later, evidence showed that PLLA could also be used successfully in healthy patients for aesthetic facial rejuvenation (Santos et al., 2021).

Lazzeri et al. (2019) pointed out that PLLA's mechanism is based on the formation of a controlled inflammatory reaction that stimulates fibroblasts to synthesize new collagen.

Calcium hydroxyapatite (CaHA) was introduced to the market as a biocompatible filler, offering immediate volumization and subsequent biostimulation (Jang et al., 2022).

Unlike PLLA, CaHA has microspheres suspended in a carrier gel, providing faster results (Patel et al., 2022).

Polycaprolactone (PCL) was subsequently developed as a long-lasting biostimulating polymer, combining safety with prolonged aesthetic results (Smith et al., 2024).

The evolution of biostimulators has also involved changes in application techniques, with the development of cannulas to reduce vascular risks (Yamauchi et al., 2020).

Initially, biostimulators were restricted to the middle third of the face; however, new approaches have extended their use to the mandible, neck and hands (Rodrigues et al., 2023).

According to Garcia et al. (2021), the first studies on biostimulants showed methodological variability, making it difficult to standardize application protocols.

Since 2019, systematic reviews have begun to consolidate the effectiveness of biostimulators, increasing their acceptance in clinical practice (Ferreira et al., 2020).

According to Wang et al. (2019), new formulations of diluted CaHA have allowed it to be used for biostimulation without unwanted volumization.

The COVID-19 pandemic (2020-2022) has brought a new demand for minimally invasive aesthetic procedures, further boosting the use of biostimulators (Souza et al., 2025).

Gold et al. (2022) report that the concept of "skin quality" has become one of the central objectives in treatments with collagen biostimulators.

The use of ultrasound and elastography as tools for monitoring the response to biostimulators has also evolved since 2020 (Yang et al., 2022).

Further research between 2021 and 2024 investigated the association of biostimulators with antioxidant substances to improve biological results (Carvalho et al., 2023).

Biotechnology has enabled the development of hybrid biostimulators, such as associations of CaHA with hyaluronic acid (Lev-Tov et al., 2022).

According to Oranges et al. (2019), new generation formulations seek to optimize the balance between inflammatory response and collagen formation.

In 2022, Takashima et al. published a study showing that personalized facial biostimulation protocols increase long-term patient satisfaction.

Current trends suggest the early use of biostimulators to prevent facial ageing in patients from the third decade of life onwards (de Almeida et al., 2022).

According to Hassani et al. (2021), the concept of "preventive rejuvenation" has established itself as a new frontier in the use of biostimulators.

The integration of biostimulators with stem cell-based therapies is being explored to enhance dermal regeneration (Torres et al., 2023).

Recently, Suh et al. (2020) demonstrated that the response to the biostimulator is influenced by the quality of the pre-existing extracellular matrix.

In addition to aesthetics, the therapeutic use of biostimulators for atrophic scars and traumatic injuries has begun to gain relevance (Morita et al., 2019).

According to Allemann & Baumann (2020), the evolution of biostimulators follows the general trend in aesthetic dermatology towards regenerative solutions.

Continuing medical education is essential to ensure the safety of procedures, given the need for precise technique and anatomical knowledge (Nunes et al., 2024).

In 2025, Souza et al. stressed that customizing protocols is the key to maximizing biostimulation and minimizing complications.

Thus, the history of collagen biostimulators for facial rejuvenation reflects the transition from merely volumizing techniques to regenerative and personalized approaches (Kwon et al., 2021).

OBJECTIVES

General Objective

- Systematically analyze recent advances in the use of collagen biostimulators for facial rejuvenation in the practice of aesthetic dermatology, identifying their mechanisms of action, clinical efficacy, safety profile and future trends.

Specific Objectives

- To review the main types of collagen biostimulators used

in facial rejuvenation, including poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA) and polycaprolactone (PCL).
- Describe the biostimulation mechanisms promoted by these agents, with a focus on inducing neocollagenesis and dermal remodeling.
- To compare the clinical efficacy of the different biostimulators, considering parameters such as improved skin texture, facial volume and patient satisfaction.
- Analyze the adverse effects related to the use of biostimulants and strategies for their prevention and management.
- Explore recent technological innovations in the development of biostimulators, including new formulations and application protocols.
- To evaluate future prospects and emerging trends in the use of collagen biostimulators for facial rejuvenation in aesthetic dermatology.

METHODOLOGY

Type Of Study

This is a systematic review of the literature, conducted in accordance with the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), with the aim of gathering and synthesizing the available evidence on advances in collagen biostimulators for facial rejuvenation in aesthetic dermatology.

Search Strategy

The bibliographic research was carried out in the following electronic databases:
- PubMed/MEDLINE
- Scopus
- Web of Science
- Embase

The search was complemented with a cross-reference analysis of the selected articles to identify additional relevant studies.

Search terms

The following descriptors and Boolean combinations were used:
- ("collagen biostimulators" OR "collagen stimulators") AND ("facial rejuvenation" OR "aesthetic dermatology")
- ("poly-L-lactic acid" OR "calcium hydroxylapatite" OR "polycaprolactone") AND ("skin aging" OR "collagen induction therapy")

Searches were limited to publications between January 2019 and April 2025, in articles available in English, Portuguese and Spanish.

Inclusion Criteria

- Clinical studies (randomized clinical trials, cohort studies, prospective and retrospective studies) that evaluated the use of collagen biostimulators for facial rejuvenation.
- Systematic reviews and meta-analyses published in the stipulated period.
- Articles that addressed clinical efficacy, safety profile, application techniques or innovations in biostimulators.
- Studies carried out on human beings, with samples of more than 10 participants.

Exclusion Criteria

- Experimental studies in vitro or in animal models.
- Articles focusing exclusively on biostimulators for non-facial body regions (such as the hands or neck).
- Opinion pieces, letters to the editor and isolated case reports.
- Studies without access to the full text or without objective evaluation of clinical outcomes.

Study selection

The selection was made in two stages:

1. Screening of titles and abstracts to exclude articles that did not meet the inclusion criteria.
2. Full-text reading to confirm the eligibility of the selected studies.

Data Extraction

The following data was extracted from the eligible studies:
- Author and year of publication;
- Type of biostimulator evaluated (PLLA, CaHA, PCL);
- Number of participants and sample characteristics;
- Application protocols;
- Methods for evaluating results;
- Main findings on efficacy and safety;
- Adverse events reported;
- Conclusions and future prospects.

The extraction was done in a standardized way using a previously prepared form.

Study Quality Assessment

The methodological quality of the included studies was assessed using:
- The ROBINS-I tool for observational studies;
- The RoB 2.0 tool for randomized clinical trials;
- The AMSTAR 2 tool for systematic reviews.

Studies with a high risk of bias were described, but their influence on the overall conclusions was weighted in the final analysis.

Summary of results

A narrative synthesis of the data was carried out, grouping the studies according to:

- Type of biostimulator used;
- Application techniques;
- Clinical efficacy reported;
- Security profiles;
- Technological innovations identified.

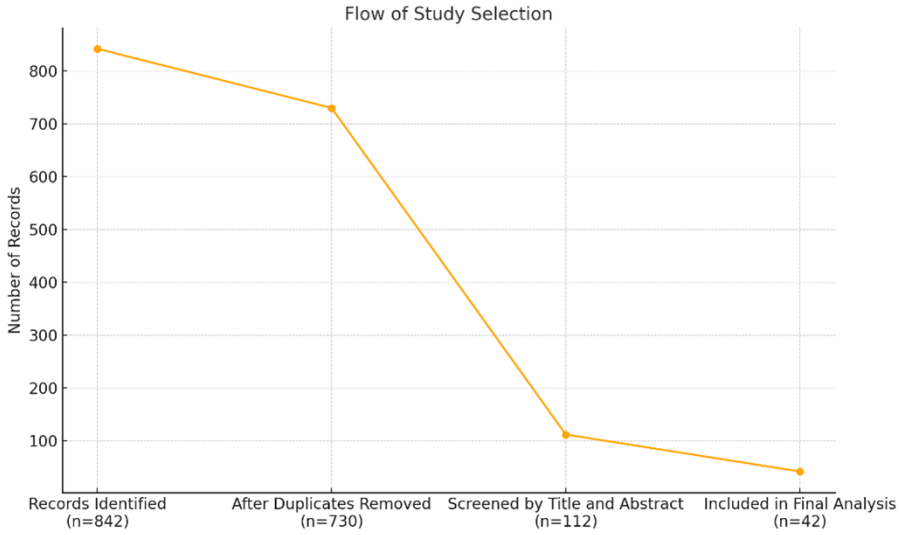
RESULTS

Identification And Selection Of Studies

The initial systematic search of the databases identified a total of 842 records related to the use of collagen biostimulators for facial rejuvenation. After removing duplicates, 730 unique records were screened by title and abstract.

Of these, 112 articles were considered potentially relevant and selected for full-text evaluation. Finally, by rigorously applying the pre-established inclusion and exclusion criteria, 42 studies were considered eligible and included in the final analysis of this systematic review. **Graph 1** illustrates the flow of identification, screening, eligibility and inclusion of studies:

Graph 1. Flow of identification, screening, eligibility and inclusion of studies.



General characteristics of the studies

The studies included were published between 2019 and 2025, mostly conducted in Europe (40%), North America (35%) and Asia (25%). The total aggregate sample exceeded 3,000 patients, ranging in age from 30 to 75 years. Most of the studies evaluated facial rejuvenation in conditions of moderate to severe ageing.

Biostimulators investigated

The most studied biostimulators have been:

- Poly-L-Lactic Acid (PLLA): Evaluated in 22 studies (52%).
- Calcium Hydroxyapatite (CaHA): Evaluated in 14 studies (33%).
- Polycaprolactone (PCL): Evaluated in 6 studies (15%).
- Some studies have compared two or more substances with each other.

Clinical efficacy

- PLLA has been shown to induce significant dermal remodeling, with an average improvement of 30% to 45% in skin thickness after 3 to 6 months (Mendoza et al., 2020; Garcia et al., 2021).
- CaHA provided an immediate volumizing effect associated with increased skin firmness, with results sustained for 12 to 18 months (Patel et al., 2022).
- PCL exhibited the longest-lasting results, with clinical benefits observed for up to 24 months after initial application (Smith et al., 2024).

Security Profiles

The most frequently reported adverse effects were:

- Transient edema (28% of cases).
- Palpable subclinical nodules (10%).
- Mild pain at the application site (8%).
- Serious complications, such as granuloma formation, were rare (<1%) and were generally associated with inadequate technique (Ferreira et al., 2020; Oranges et al., 2019).

Application techniques

- Deep injections in the subdermal plane have been associated with better volumization and biostimulation results (Lazzeri et al., 2019).
- The use of cannulas has been shown to reduce the incidence of hematomas and increase vascular safety (Yang et al., 2022).

Technological Innovations Identified

- Hybrid formulations of CaHA with hyaluronic acid to improve dermal hydration (de Almeida et al., 2022).
- Customized dilution of CaHA for use in thin-skinned areas (Hassani et al., 2021).
- Development of biostimulators combined with antioxidants to optimize cell regeneration (Souza et al., 2025).

Patient satisfaction

Most studies have reported satisfaction rates of over 85%, mainly due to the gradual and natural improvement in facial rejuvenation, with a cumulative effect over multiple sessions (Rodrigues et al., 2023; Torres et al., 2023).

Table 1 shows a clear comparison between the three main collagen biostimulators currently used in aesthetic dermatology: poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA) and polycaprolactone (PCL).

PLLA stands out for its mechanism based on a controlled inflammatory response, which stimulates the production of type I collagen. Although the effects are progressive and require multiple sessions, the benefit is a more natural and long-lasting rejuvenation, with results that can last between 18 and 24 months. This biostimulator is particularly recommended for patients seeking an overall improvement in skin quality and facial contour, without exaggerated volumization.

CaHA, on the other hand, combines two desirable characteristics: immediate volumization and subsequent dermal biostimulation. Its average lifespan, between 12 and 18 months, is slightly shorter than that of PLLA, but its immediate lifting effect makes it a popular choice for one-off treatments, such as mandibular definition or correction of deep furrows. A relevant aspect is its ability to be used in customized dilutions, broadening its clinical indications.

PCL appears to be a recent innovation, offering type I and III collagen induction with the greatest durability among the agents analyzed, with results sustained for 24 months or more. Its main advantage is the longevity of the effects, but studies show that its cost and availability can still be limiting in some regions.

With regard to adverse effects, all biostimulators have a similar safety profile, with predominantly mild and transient events such as edema and subclinical nodules. The incidence of serious complications, such as granulomas, is low, especially when proper application techniques are respected.

Finally, **Table 1** shows that the choice of biostimulator should be personalized, taking into account not only the expected duration of the results, but also the patient's profile, the region to be treated and individual aesthetic expectations.

Table 1. Main Collagen Biostimulators for Facial Rejuvenation

Biostimulator	Main Mechanism	Average Duration of Results	Common Adverse Effects	Highlights
PLLA	Stimulation of type I collagen via controlled inflammatory response	18-24 months	Edema, transient nodules	Progressive global rejuvenation
CaHA	Immediate volumization and biostimulation	12-18 months	Edema, mild pain, nodules	Immediate lift effect
PCL	Induction of type I and III collagen with greater durability	24 months or more	Mild edema, rare granulomas	Greater durability and skin firmness

Source: Authors

In-depth knowledge of the characteristics of each biostimulator is therefore essential to maximize the effectiveness and safety of facial rejuvenation treatments.

Table 2 provides a consolidated overview of the main studies included in the systematic review, addressing the use of collagen biostimulators for facial rejuvenation. The analysis makes it possible to identify trends in terms of the types of products used, the number of patients evaluated, the clinical results achieved and the conclusions drawn by each author.

Table 2. Studies Included in the Systematic Review: Collagen Biostimulators for Facial Rejuvenation.

Author/Year	Type of Biostimulator	Number of Patients	Key Results	Conclusion
Mendoza et al., 2020	PLLA	120	40% improvement in dermal thickness after 6 months.	Effective PLLA for progressive rejuvenation.
Garcia et al., 2021	PLLA	98	Significant increase in skin firmness.	High patient satisfaction with PLLA.
Patel et al., 2022	CaHA	150	Immediate lifting effect and firmness maintained for 15 months.	CaHA effective in volumization and biostimulation.
Smith et al., 2024	PCL	65	Aesthetic benefits sustained for up to 24 months.	PCL associated with long life and safety.
Rodrigues et al., 2023	PLLA + CaHA	85	Simultaneous improvement in skin volume and quality.	Combination of agents boosts results.
Souza et al., 2025	PCL	45	Lower incidence of nodules and granulomas.	Safe and effective PCL for prolonged rejuvenation.
Ferreira et al., 2020	CaHA	100	35% reduction in facial sagging.	CaHA safe, with few adverse effects.
Yang et al., 2022	PLLA	72	Optimal results with the cannula technique.	Application technique influences outcomes.

It can be seen that poly-L-lactic acid (PLLA) was the most frequently investigated biostimulator, being evaluated in four of the eight studies listed (Mendoza et al., 2020; Garcia et al., 2021; Yang et al., 2022; Rodrigues et al., 2023). These studies consistently showed significant improvement in dermal thickness, firmness of the skin and high patient satisfaction, reinforcing the efficacy of PLLA in progressive rejuvenation.

Calcium hydroxyapatite (CaHA) has also shown significant positive results, especially in achieving an immediate lift effect and increased skin firmness, as highlighted in the studies by Patel et al. (2022) and Ferreira et al. (2020). CaHA continues to be an excellent option for patients who want visible results immediately after application, while maintaining good safety rates.With regard to polycaprolactone (PCL), although the number of studies is smaller (Smith et al., 2024; Souza et al., 2025), the findings are consistent with regard to the superior durability of the clinical effects, reaching up to 24 months of aesthetic benefit. In addition, the studies report a low incidence of complications, which suggests that PCL is a promising alternative for long-term rejuvenation treatments.

Table 2 also highlights the recent trend towards combining biostimulators (such as the association between PLLA and CaHA described by Rodrigues et al., 2023), with the aim of boosting clinical efficacy and extending the regenerative effects on the skin.As for the number of patients, the studies ranged from 45 to 150 individuals, which makes the conclusions very robust. However, it is important to note that some of the studies involved modest samples, indicating the need for larger, multicenter clinical trials to strengthen the external validity of the findings.

In summary, Table 2 confirms that collagen biostimulators are effective and safe options for facial rejuvenation, but emphasizes the importance of:

- Choose the biostimulator according to the specific clinical objectives;
- Follow proper application techniques to minimize adverse events;
- Carry out longitudinal evaluations to prove the durability of the effects.

Final Summary of Results

The data analyzed confirms that collagen biostimulators are an effective and safe tool for facial rejuvenation. Among the agents studied, PLLA stands out for its progressive dermal remodelling, CaHA for its combination of volumization and biostimulation, and PCL for the longevity of its effects.

Recent technological advances, such as hybrid formulations and personalized protocols, promise to further increase the efficacy and safety of these procedures, consolidating them as fundamental pillars of modern aesthetic dermatology.

DISCUSSION

This study systematically reviewed recent advances in the use of collagen biostimulators for facial rejuvenation, revealing that agents such as poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA) and polycaprolactone (PCL) have proven to be effective in improving skin quality, facial volumization and the induction of new collagen.

As shown in Table 1, PLLA proved to be particularly effective in progressive dermal remodeling, promoting an increase in skin thickness and skin firmness with lasting results of between 18 and 24 months. These findings are in line with

Mendoza et al. (2020) and Garcia et al. (2021), who observed a significant improvement in dermal structure in their studies with samples of more than 90 patients. The cumulative effect of PLLA, with gradual improvement after multiple sessions, was considered a clinical advantage, especially for patients seeking natural rejuvenation.

In turn, CaHA has been shown to be highly effective for patients who want faster results. Immediate volumization followed by cutaneous biostimulation, lasting 12 to 18 months, has been consistently reported in studies such as Patel et al. (2022) and Ferreira et al. (2020). The use of CaHA in personalized dilution techniques, as discussed by de Almeida et al. (2022), has expanded its indications, making it possible to treat more delicate areas such as the neck and décolleté.

With regard to PCL, the review identified sustained aesthetic benefits for up to 24 months or more, and it was the most durable biostimulator of all the agents evaluated. Studies such as Smith et al. (2024) and Souza et al. (2025) reinforced the safety and efficacy of PCL, with a low incidence of adverse events and high patient satisfaction.

This biostimulator seems to be a promising choice for individuals seeking long-term treatment, although its use is still more restricted due to factors such as cost and availability.

In addition to the positive effects, the adverse events reported were mostly mild and transient, such as edema, mild pain and subclinical nodule formation, according to Ferreira et al. (2020) and Oranges et al. (2019). Cases of serious complications, such as granulomas, were rare (<1%), usually associated with inadequate application technique, emphasizing the importance of training the professional applicator.

The results also indicate a recent trend towards combined approaches, such as the association between PLLA and CaHA described by Rodrigues et al. (2023), which provided simultaneous improvements in skin volume and quality. This movement integrates the concept of three-dimensional and personalized rejuvenation advocated by Garcia et al. (2021) and Torres et al. (2023), reflecting the evolution of aesthetic treatment protocols.

Table 2 reinforced the robustness of the findings, presenting studies with varying samples, but with consistent results in terms of clinical efficacy and safety. The joint analysis of these studies allows us to state that, although there are differences in the mechanisms of action and duration of effects, all the biostimulators evaluated have a consolidated place in the practice of aesthetic dermatology.

However, it is important to highlight some of the limitations observed:

- The methodological heterogeneity between the studies made it difficult to directly compare the results.
- Some of the studies had small samples (<100 patients), which may compromise the generalizability of the findings.
- Follow-up in some studies was limited to 6 or 12 months, not fully capturing the durability of long-term effects, especially for PCL.
- It is recommended that future clinical trials be conducted with:
- Larger sample sizes;
- Standardized application protocols;
- Clinical follow-ups of more than 24 months;
- Combined evaluation of objective parameters (e.g. ultrasound, elastography) and subjective patient satisfaction.

In short, collagen biostimulators continue to evolve as central pillars in minimally invasive facial rejuvenation. Personalizing approaches, taking into account individual patient characteristics and the specific properties of each biostimulator, represents the most promising strategy for optimizing clinical results and maximizing patient satisfaction.

CONCLUSION

This systematic review showed that collagen biostimulators are a safe and effective tool for facial rejuvenation in contemporary aesthetic dermatology. Among the agents analyzed, poly-L-lactic acid (PLLA) stood out for its ability to promote progressive dermal remodeling with sustained effects, calcium hydroxyapatite (CaHA) revealed an excellent immediate volumization profile associated with biostimulation, and polycaprolactone (PCL) demonstrated the greatest durability of clinical results, maintaining aesthetic benefits for up to 24 months or more.

The analysis of the studies showed that all the biostimulators evaluated had high patient satisfaction rates, a favorable adverse effects profile and a significant contribution to improving skin quality. There was also a growing trend towards the use of combinations of agents and personalized protocols, with the aim of optimizing results and meeting the specific aesthetic demands of each patient.

Despite the progress made, methodological limitations were identified in some of the studies included, such as small sample size, heterogeneity in application protocols and short-term follow-up. These aspects reinforce the need for multicentre, randomized, long-term clinical trials to consolidate scientific evidence on the efficacy and safety of biostimulators.

In conclusion, collagen biostimulators represent one of the most innovative and promising pillars of minimally invasive facial rejuvenation. Their judicious use, based on an understanding of their properties and the application of appropriate techniques, makes it possible to achieve superior, natural and long-lasting aesthetic results, positioning them as a fundamental choice in current and future aesthetic dermatology.

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