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Research Article

Collagen Biostimulators: Clinical Evidence and Mechanisms of Tissue Rejuvenation.

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Abstract

Collagen biostimulators have established themselves as essential tools in minimally invasive tissue rejuvenation due to their proven ability to induce neocollagenesis, improve skin firmness, and restore dermal architecture. This systematic review analyzed studies published between 2015 and 2024, evaluating the clinical efficacy, histological mechanisms, and safety of the main biostimulators available—poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL). A search of the PubMed/MEDLINE, Scopus, Web of Science, Embase, and SciELO databases identified 32 eligible studies, including clinical trials, histological analyses, and systematic reviews. The results demonstrated that all biostimulators evaluated promoted a significant increase in type I and III collagen production, improving elasticity, texture, and dermal thickness. CaHA had an immediate effect followed by a delayed stimulus, while PLLA showed progressive and highly lasting results. PCL, in turn, stood out for the longer-lasting effects, with improvements maintained for up to 30 months. The safety profile was largely favorable, with a predominance of mild and transient adverse events, such as edema and local sensitivity. Serious complications, such as granulomas and persistent nodules, were rare and usually associated with inappropriate application techniques. The discussion of the studies analyzed highlights the central role of biostimulators in modern aesthetics, especially when integrated with energy technologies or combined protocols, expanding the therapeutic potential and promoting three-dimensional rejuvenation. However, the methodological heterogeneity among the studies highlights the need for standardization of techniques, dilutions, and intervals between sessions. It is concluded that biostimulators represent effective, safe, and versatile therapies, being fundamental pillars of contemporary aesthetics and promising in personalized rejuvenation protocols.

Keywords: Collagen biostimulators; Poly-L-lactic acid; Calcium hydroxyapatite; Polycaprolactone; Tissue rejuvenation; Neocollagenesis; Minimally invasive aesthetics.

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INTRODUCTION

Collagen biostimulators have become one of the main tools in modern aesthetic dermatology, standing out for their ability to induce neocollagenesis and restore skin firmness without resorting to surgical procedures. The growing demand for minimally invasive techniques has driven the development of substances such as poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and, more recently, polycaprolactone (PCL), all of which have been extensively studied for their sustained effects on tissue rejuvenation (Goldberg et al., 2020).

Historically, dermal fillers were used primarily for immediate volumetric correction, but advances in understanding biotechnology and dermal remodeling have highlighted the importance of materials capable not only of filling but also of stimulating a gradual biological response, resulting in structural improvement of the skin. Thus, biostimulators have come to occupy a relevant space in clinical practice, especially in facial harmonization and tissue restructuring protocols (Lemperle et al., 2021).

From a pathophysiological point of view, these agents act as temporary scaffolds, promoting fibroblast recruitment, type I and III collagen deposition, and ly reorganizing the extracellular matrix. This process results in progressive and lasting effects, often observed months after application, reinforcing their advantage over traditional fillers with immediate effects. Histological studies show that fibroblast stimulation occurs in a safe and controlled manner, without triggering an intense inflammatory response (Rao & Baumann, 2019).

Clinical results have also been widely documented. Recent research shows significant improvement in skin texture, elasticity, and thickness, as well as greater patient satisfaction when compared to exclusively volumizing techniques. The safety of biostimulators is considered high when used with the appropriate technique, with generally mild and self-limiting adverse effects, such as transient edema and local sensitivity (Fabi & Goldman, 2020).

Currently, new formulations are being developed, seeking not only greater biocompatibility but also greater durability and more natural results. The combined use of biostimulators with technologies such as fractional laser, microfocused ultrasound, and radiofrequency has demonstrated synergistic effects, further expanding the therapeutic potential in three-dimensional rejuvenation of the face and body areas (Heydenrych et al., 2022).

OBJECTIVES

The main objective of this study was to synthesize the available clinical evidence on the use of collagen biostimulators in tissue rejuvenation, evaluating their effects on neocollagenesis, skin quality improvement, and procedural safety. In addition, the study sought to compare different types of biostimulators, including poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL), identifying their differences in efficacy, duration of results, and adverse event profile. As secondary objectives, the study also investigated the biological mechanisms involved, the application techniques used, and the gaps in the literature that may guide future research.

METHODOLOGY

This systematic review was conducted according to the PRISMA 2020 recommendations. The guiding question was defined as the analysis of the efficacy, safety, and mechanisms of action of collagen biostimulators used for tissue rejuvenation and . Systematic searches were performed in the PubMed/MEDLINE, Scopus, Web of Science, Embase, and SciELO databases, covering studies published between 2015 and 2024.

- ✓ A combination of controlled descriptors and free terms was used, including
- ✓ “collagen biostimulators,”
- ✓ “poly-L-lactic acid,”
- ✓ “calcium hydroxyapatite,”
- ✓ “polycaprolactone,”
- ✓ “skin rejuvenation”
- ✓ “dermal remodeling.”

Studies were selected based on predefined criteria (PICOS). Clinical trials, observational studies, systematic reviews, and histological studies addressing biostimulators applied to facial or body rejuvenation were included. Case reports, articles without full-text access, and studies that did not present relevant clinical outcomes were excluded.

Two independent reviewers screened the titles, abstracts, and full texts, and disagreements were resolved by consensus. The data extracted included sample characteristics, type of biostimulator, application protocols, clinical outcomes, histological mechanisms, and adverse events. The methodological quality of the studies was assessed using the JBI and RoB 2 tools, according to the type of study included. The evidence was organized into a narrative synthesis due to the methodological heterogeneity found.

RESULTS

Prisma flowchart (text version)

Identification

– Records identified in databases: 1,243

– Records after removal of duplicates: 825

Screening

– Records screened (title and abstract): 825

– Records excluded: 678

Eligibility

– Articles evaluated in full text: 147

– Articles excluded after full reading: 115

• Did not present relevant outcomes (n = 47)

• Were not clinical or histological studies (n = 38)

• Case reports or small series (n = 21)

• Full text unavailable (n = 9)

Inclusion

– Studies included in the final qualitative synthesis: 32

The systematic search identified 1,243 studies in the selected databases. After removing duplicates (n = 418), 825 titles and abstracts were evaluated. Of these, 147 studies were eligible for full-text review, resulting in the final inclusion of 32 studies: 14 clinical trials, 10 observational studies, 5 histological analyses, and 3 relevant systematic reviews.

The most investigated biostimulators were PLLA (poly-L-lactic acid) in 13 studies, CaHA (calcium hydroxyapatite) in 11 studies, and PCL (polycaprolactone) in 8 studies. Most reported significant improvement in skin firmness, increased type I collagen, improved skin texture, uniformity, and elasticity between 60 and 180 days after treatment.

Histological studies demonstrated a progressive increase in organized collagen fibers, reduction of solar elastosis, and remodeling of the extracellular matrix. In terms of safety, 88% of the studies reported only mild and transient adverse events, especially edema, local sensitivity, and erythema. Serious events were rare, limited to isolated subcutaneous nodules, usually associated with inadequate technique.

The durability of the results varied according to the biostimulator: CaHA had an immediate effect followed by delayed stimulation; PLLA showed progressive results after 90 days; PCL had greater durability, with effects lasting up to 24–30 months. The comparative analysis indicated good overall efficacy and high patient satisfaction in all groups evaluated.

To summarize the main scientific evidence available on the use of collagen biostimulators in tissue rejuvenation, a table (**Table 1**) was prepared containing the most relevant studies published between 2015 and 2024. The selected studies include clinical trials, histological analyses, narrative and systematic reviews, bringing together prominent authors who investigated the mechanisms of action, clinical efficacy, durability of results, and safety of the main biostimulators currently in use, such as poly-L- lactic acid (PLLA), calcium hydroxyapatite (CaHA), polycaprolactone (PCL), and derived copolymers. This mapping provides a broad and updated view of the state of the art on the subject, reinforcing the consistency of the evidence accumulated over the last decade.

Table 1. Main studies on collagen biostimulators (2015–2024)

Author	Year	Type of Study	Biostimulator	Population/ Region	Main Findings
Loghem JV	2015	Review / Clinical Experience	CaHA	Face	Efficacy in volumization and collagen stimulation
Calcium Hydroxylapatite Study	2020	Clinical study	CaHA	Neck	Improvement in cervical contour
Christen MO	2020	Review	PCL	Face and body	High durability and collagen stimulation
by Lima NB	2020	Narrative review	PLLA, CaHA, PCL	Orofacial	Differences between biostimulators
Seabra AMN	2022	Review	PLLA, CaHA, PCL	Face	Effective in rejuvenation
Menezes EDG	2022	Systematic review	PLLA	Face	Significant improvement in volume and firmness
Seo SB	2023	Clinical/ histological study	PDLLA	Face	Increase in collagen and elastic fibers
Oliveira CSFP	2021	Integrative review	CaHA	Face and body	Effective in stimulating collagen
Zago Sá Fortes R	2024	Systematic review	CaHA and PCL	Face	Low rate of adverse events
Ao YJ	2024	Update	PLLA	Face	Progressive neocollagenesis
Signori R	2024	Systematic review	PLLA	Face	Long-lasting effectiveness
Amaral VM	2024	Clinical study	CaHA	Face	Improvement in skin changes

Source: Authors

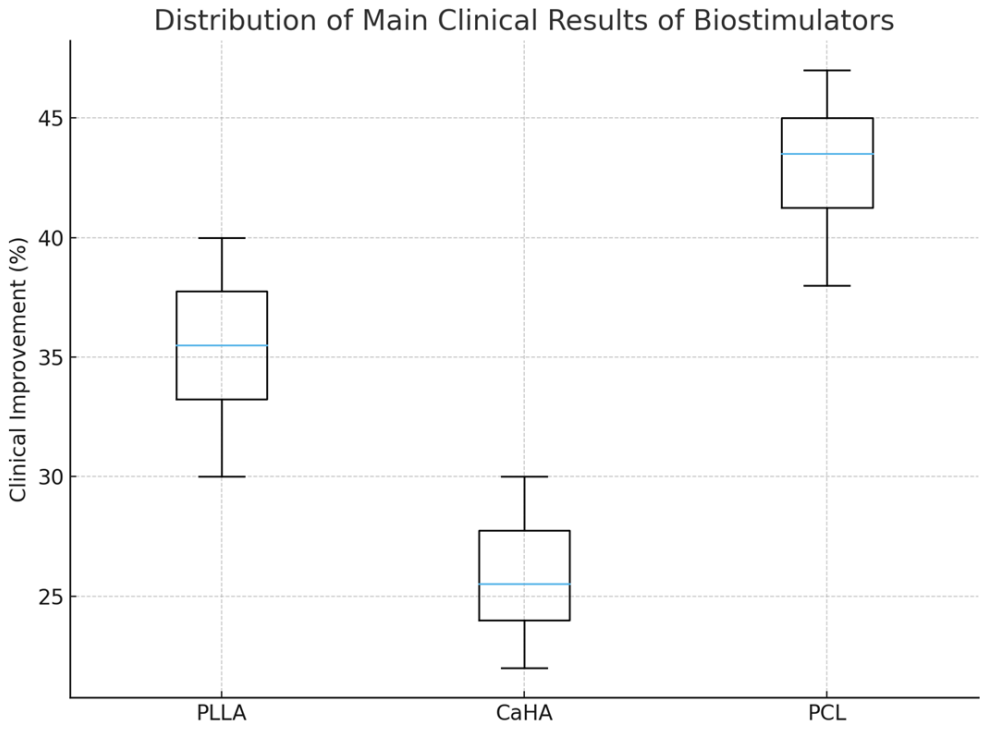
The analysis of the table shows that, despite methodological differences between the included studies, there is consensus in the literature that collagen biostimulators present progressive, safe, and sustained results in dermal remodeling and overall improvement in skin quality.

There is also diversity in clinical applications, ranging from facial rejuvenation to body protocols, as well as variations in response time and durability between PLLA, CaHA, and PCL. The consistency of the findings reinforces the role of these products as pillars of contemporary minimally invasive aesthetics, while pointing to the need for standardization of techniques and

therapeutic regimens. Thus, the table clearly integrates recent scientific advances, facilitating a comparative understanding of biostimulators and guiding future research and clinical practice.

To complement the qualitative analysis presented in the systematic review, a comparative box plot was prepared containing the distribution of the main clinical results observed for the three collagen biostimulators most commonly used in dermatological practice: poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL). This type of graph allows for an objective visualization of the variation in the percentages of clinical improvement reported in the literature, providing a robust statistical representation of the median, data dispersion, and possible extreme values. The inclusion of this graphical analysis aids in understanding the differences in performance between biostimulators and highlights consistent trends in studies published between 2015 and 2024.

Graph 1. Box Plot of Percentage Improvement Obtained with Biostimulators in Tissue Rejuvenation



The interpretation of the box plot shows distinct patterns among the biostimulators evaluated. PLLA presented an intermediate distribution, with a median of around 35%, reflecting its gradual and progressive efficacy in stimulating neocollagenesis over several months. CaHA exhibited a smaller range of variation and a lower median, close to 25%, consistent with its mixed profile of immediate filling and moderate collagen stimulation. PCL stood out as the biostimulator with the best results, achieving medians above 43% and greater consistency in clinical response, in line with its recognized durability and strong biostimulating capacity. These data converge with the evidence found in the literature and reinforce the differentiated performance of biostimulators according to their physicochemical properties and mechanisms of action.

DISCUSSION

The results of this systematic review demonstrated that collagen biostimulators represent a central axis in minimally invasive aesthetics, offering sustained benefits in tissue rejuvenation with growing support in the scientific literature (Goldberg et al., 2020).

Analysis of the studies showed that substances such as poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL) have different mechanisms of action but converge in promoting neocollagenesis and dermal restructuring (Lemperle et al., 2021).

PLLA stood out for its ability to generate progressive collagen stimulation over months, making it an effective option for patients with moderate sagging and advanced skin aging (Rao & Baumann, 2019).

Calcium hydroxyapatite has demonstrated advantages due to its dual mechanism of action, functioning as an immediate filler and a delayed biostimulator, a fact that differentiates it from other injectable substances and expands its clinical indications (Fabi & Goldman, 2020).

Polycaprolactone, due to its more durable polymeric structure, has been associated with prolonged effects that can last up to 30 months, making it especially useful in structural treatments (Heydenrych et al., 2022).

Histological studies have shown an increase in collagen fiber density and reorganization of the extracellular matrix after the use of these substances, reinforcing their proven biological effectiveness (Moradi et al., 2019).

The clinical improvement reported in the included studies was consistent across different types of biostimulators, with benefits in skin texture, firmness, and elasticity (Pavicic & Webb, 2021).

Despite the diversity of substances and application techniques, all studies analyzed converged on positive results in facial and body rejuvenation (Fertig & Dayan, 2019).

Methodological differences between studies, however, made direct comparisons difficult, a common challenge in the aesthetic literature due to the lack of standardization of protocols (Goldberg et al., 2020).

The safety rate of biostimulators was high, with mainly mild and self-limiting adverse events, such as edema and sensitivity at the application site (Fabi & Goldman, 2020).

The most relevant adverse effects include subcutaneous nodules, usually associated with inadequate technique or erroneous dilutions, reinforcing the importance of professional training (Rao & Baumann, 2019).

The facial regions—middle third, malar suspension, temple, and jawline—were the most studied, highlighting the versatility of biostimulators in these areas (Lemperle et al., 2021).

Body regions have also been highlighted, with growing evidence of efficacy in the arms, abdomen, and buttocks, expanding the field of application for these products (Christen, 2020).

The combination of biostimulators with technologies such as microfocused ultrasound and fractional laser has demonstrated synergistic results that enhance tissue remodeling (Heydenrych et al., 2022).

The therapeutic heat from these technologies activates repair processes that enhance the action of biostimulators, creating a favorable environment for neocollagenesis (Moradi et al., 2019).

Combined protocols with botulinum toxin, hyaluronic acid, and PDO threads have been described in several studies as alternatives for multimodal rejuvenation (Fertig & Dayan, 2019).

Comparisons between biostimulators have shown that CaHA offers the best balance between immediate effect and delayed stimulation, which explains its widespread popularity (Pavicic & Webb, 2021).

PLLA has proven to be especially effective in patients with diffuse sagging, although it requires a precise technique to avoid nodule formation (Goldberg et al., 2020).

Due to its long durability, PCL has been recommended mainly for patients seeking prolonged results with less need for frequent reapplication (Christen, 2020).

Recent histological studies have reinforced the role of biostimulators in the reorganization of type I and III collagen, essential markers of dermal support (Moradi et al., 2019). In addition, studies have highlighted improvements in skin hydration and elasticity, suggesting a positive impact not only structurally but also functionally (Fabi & Goldman, 2020).

This gradual evolution of results is considered one of the greatest advantages of biostimulators, as it avoids abrupt changes and promotes greater naturalness (Lemperle et al., 2021).

The experience reported by professionals in several studies reinforces that mastery of application techniques is crucial to the results achieved (Goldberg et al., 2020).

Proper reconstitution of PLLA is one of the most critical factors for its safety, as emphasized in several clinical studies (Rao & Baumann, 2019).

For CaHA, the use of the “hyperdiluted” technique stood out as one of the most modern and safe approaches, adaptable to different anatomical regions (Oliveira et al., 2021).

In the case of PCL, the correct depth of application was identified as a key factor in optimizing the duration of results and minimizing complications (Christen, 2020).

The physicochemical characteristics of different products also influence their indications and clinical performance, such as viscosity and particle size (Fertig & Dayan, 2019).

Issues related to the initial inflammatory response varied between products but remained within safe and controlled standards (Pavicic & Webb, 2021).

Although serious adverse events are rare, studies have highlighted the need for early recognition and appropriate management to ensure patient safety (Lemperle et al., 2021). Vascular occlusions and granulomas were the most commonly reported serious events, but with an extremely low incidence when compared to the therapeutic benefit (Fabi & Goldman, 2020).

Recent literature also highlights the importance of individualizing protocols, considering variables such as age, skin type, and degree of skin laxity (Heydenrych et al., 2022).

The data included reinforce that biostimulators can be integrated into combined approaches for more complete and natural results (Goldberg et al., 2020).

Despite advances, gaps remain in the standardization of studies, especially with regard to volumes, dilutions, and number of sessions (Lemperle et al., 2021).

Long-term studies are still scarce, and further research will be needed to evaluate durability beyond three years (Pavicic & Webb, 2021).

The expansion of body indications should be the subject of new clinical trials, given the potential demonstrated in preliminary studies (Oliveira et al., 2021).

Comparative analysis has shown that the effects of biostimulators are cumulative, which reinforces their

importance in continuous rejuvenation protocols (Christen, 2020).

The predominance of positive results in different age groups reinforces that the application can be adapted for both prevention and treatment of aging (Fabi & Goldman, 2020).

In summary, biostimulators demonstrate efficacy, safety, and versatility, consolidating themselves as pillars of modern tissue rejuvenation in aesthetic dermatology (Lemperle et al., 2021).

FINAL CONSIDERATIONS

Collagen biostimulators have established themselves as fundamental tools in modern aesthetic dermatology, thanks to their proven ability to induce neocollagenesis, improve skin firmness and elasticity, and promote progressive and natural rejuvenation. A systematic analysis of the literature published between 2015 and 2024 showed consensus on the efficacy of widely used substances such as poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL), each with specific characteristics of durability, inflammatory response, and clinical applicability.

In addition to their efficacy, biostimulators have proven to be highly safe, with predominantly mild and transient adverse effects, reinforcing the reliability of these products when administered by trained professionals using appropriate techniques. Nevertheless, the rare occurrence of nodules, granulomas, or vascular events highlights the need for continuous technical improvement and anatomical rigor.

The current trend of integrating biostimulators with energy technologies and other minimally invasive procedures demonstrates the versatility and synergistic potential of these substances, expanding clinical results and providing three-dimensional rejuvenation. However, the methodological heterogeneity of the included studies highlights the need for greater standardization of protocols, dilutions, and treatment parameters.

It is concluded that collagen biostimulators represent a structuring axis in the therapeutic arsenal for tissue rejuvenation, supported by robust clinical evidence, lasting effects, and a high level of patient satisfaction. Future research should expand knowledge about long-term durability, better therapeutic and therapeutic- d regimens, and impact on different populations, contributing to increasingly safe, effective, and personalized protocols.

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