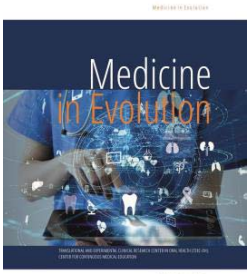
The Impact of Injectable Biostimulatory Substances on Current Trends in Aesthetic Medicine: Focus on Poly-L-lactic Acid, Polycaprolactone, and Calcium Hydroxyapatite



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Abstract

1.Background/Objectives: In recent years, aesthetic medicine has shifted from conventional volumizing fillers to regenerative, biostimulatory approaches, aiming to promote long-term skin health and natural rejuvenation. 2.Methods: This narrative review compares the most commonly used injectable biostimulators—poly-L-lactic acid (PLLA), polycaprolactone (PCL), and calcium hydroxyapatite (CaHA)—by analyzing current evidence on their mechanisms of action, clinical efficacy, safety, and aesthetic indications. 3.Results: These agents stimulate neocollagenesis through controlled inflammatory responses, resulting in enhanced dermal architecture and sustained aesthetic effects. PLLA activates the TGF-β/SMAD signaling pathway to enhance type I collagen synthesis, PCL offers immediate volumization with neovascularization and collagen remodeling, while CaHA promotes fibroblast proliferation and angiogenesis. 4.Conclusion: The findings support a growing preference for minimally invasive yet regenerative treatments. This review emphasizes the significance of personalized therapeutic strategies and ongoing research in improving outcomes and ensuring patient safety in aesthetic practice.

Keywords: Injectable biostimulators, Poly-L-lactic acid, Polycaprolactone, Calcium hydroxyapatite, Aesthetic medicine

INTRODUCTION

In the last few years, there has been a significant change in the field of aesthetic medicine. This transformation is driven by the increasing demand for minimally invasive and effective procedures that deliver natural-looking results and short recovery times. Today's patients are no longer solely focused on visible and quick corrections; they seek regenerative solutions that enhance skin health and slow the aging process [1]. This development marks a shift away from traditional fillers that rely on instant volumization, such as hyaluronic acid, to biostimulatory agents that stimulate the skin's collagen production. This emphasizes stimulating deep and long-term regeneration rather than transient effects. Injectable biostimulators are a distinct class of dermal, biocompatible, and biodegradable substances that act by inducing a controlled local inflammatory reaction, leading to fibroblast activation and neocollagenesis [2]. This mechanism provides a progressive, natural, and long-lasting aesthetic effect, unlike the immediate but temporary volumizing effect of classic fillers [3]. The most commonly encountered biostimulators include polymerized polylactic acid (PLLA), polycaprolactone (PCL), and calcium hydroxyapatite (CaHA), each with unique characteristics in terms of mode of action, durability, and areas of clinical use [4].

This narrative review aims to provide a comparative analysis of these three biostimulatory agents, which are widely used in regenerative aesthetic medicine. The review synthesizes existing clinical data and mechanistic perspectives to clarify their similarities, differences, and roles in current therapeutic protocols.

The significant role of these substances lies in their ability to support the aesthetic correction of the skin and its structural regeneration process by providing gradually improved and natural results. In addition, they are increasingly suited to the needs of a population interested in effectively preventing ageing without resorting to surgery [5]. Moreover, biostimulators are being increasingly integrated into combination protocols, along with botulinum toxin, dermal fillers, and energy-based devices, to enhance treatment efficacy and patient compliance. However, research on the safety and effectiveness of these combination therapies remains limited and varied, underscoring the need for further studies to establish standardized protocols and optimize outcomes [6]. Thus, the transition from traditional volume-focused approaches to regenerative strategies that emphasize long-term skin health and natural rejuvenation is being pursued, leading to the evolution of minimally invasive procedures that not only correct the visible signs of aging but also support the organism's intrinsic regenerative processes [7].

Aim and objectives

This article aims to compare the most used injectable bio-stimulators in modern aesthetic medicine—PLLA, PCL, and CaHA—from the perspectives of mechanism of action, clinical efficacy, safety, and aesthetic applications, thereby contributing to therapeutic guidance tailored to the patient's profile and treatment goals.

MATERIAL AND METHODS

This article presents a narrative review comparing the most popular injectable biostimulators used in aesthetic medicine: poly-L-lactic acid (PLLA), polycaprolactone (PCL), and calcium hydroxyapatite (CaHA). A systematic search was conducted in three core scientific data sources: PubMed, ScienceDirect, and Google Scholar. The search spanned from January 2004 to February 2024. It searched the following terms and combinations thereof: “injectable biostimulants”, “collagen stimulators”, “poly-L-lactic acid”, “polycaprolactone”,

"calcium hydroxylapatite", "aesthetic medicine", "regenerative injectables". The inclusion criteria comprised any peer-reviewed clinical studies, narrative or systematic reviews, and mechanistic or theoretical studies relevant to dermatology, aesthetic surgery, or regenerative medicine. Only English articles were considered. The following exclusion criteria were applied: non-peer-reviewed sources, studies with animals alone that did not have available clinical translation, and those that failed to present a discussion in depth on clinical efficacy or mechanisms involved (either separately or combined). This methodology was chosen to achieve a comprehensive and relevant synthesis of the best available evidence.

MECHANISMS AND CLINICAL APPLICATIONS OF INJECTABLE BIOSTIMULATORS

Poly-L-L-lactic acid (PLLA)

Poly-L-L-lactic acid (PLLA) is a biodegradable and biocompatible synthetic polymer that stimulates the production of type I collagen through a controlled inflammatory process triggered by the subdermal injection of PLLA microparticles. These particles trigger a foreign body reaction, leading to the activation and recruitment of macrophages and the formation of multinucleated giant cells. These immune cells surround the particles and release pro-regenerative biochemical signals. [8,9]. An essential element in this process is the activation of fibroblasts, the cells responsible for maintaining and renewing the extracellular matrix (ECM). In vitro studies have demonstrated that exposure of human fibroblasts to PLLA-SCA leads to increased expression of COL1A1 and COL1A2 genes, responsible for the synthesis of type I collagen, as well as other ECM components such as elastin and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2), in parallel with decreased expression of MMP-1 [10,11].

The PLLA-induced biostimulation primarily functions through the TGF-β/SMAD signaling pathway, a well-studied biochemical pathway that mediates regenerative biology, including collagen synthesis, fibroblast proliferation, and the tissue healing process [12]. Increased TGF-β1, phosphorylated SMAD-1/2, and AKT expression have been demonstrated in vitro and in vivo, suggesting a substantial impact on dermal remodelling and metabolism [13,14]. Furthermore, PLLA would seem to exert an indirect effect on adipogenesis. It has been found to stimulate the differentiation of pre-adipocytes, as well as the synthesis of type VIα1 and type IV collagen associated with the formation of adipose tissue, which may be involved in its long-lasting volumizing effect [15].

The use of PLLA-SCA in aesthetic medicine has expanded considerably in recent decades, evolving from initial indications in reconstructive and orthopedic surgery to aesthetic applications with clinically proven benefits. As a dermal bio stimulator, PLLA-SCA is mainly recommended for correcting facial volume loss, improving skin laxity, and improving skin quality by stimulating endogenous collagen synthesis. Initially approved for the treatment of facial lipoatrophy in HIV patients, PLLA-SCA has subsequently become a popular option in facial rejuvenation due to its ability to induce a gradual and long-lasting biological response. In the aesthetic context, the substance is commonly used in treatments targeting the mid- and lower face, particularly the cheeks, jawlines, and temples, where volume loss is often associated with the ageing process. Subdermal application of PLLA-SCA results in a progressive remodeling of facial contours and a visible improvement in dermal density [16].

A clinical study by Signori et al. demonstrated that PLLA treatments led to significant improvements in wrinkle severity scores, with effects maintained up to 25 months after the last injection, highlighting that PLLA is effective in aesthetic treatments, with long-lasting effects and minimal adverse events [17].

Polycaprolactone (PCL)

Polycaprolactone (PCL) is an innovative dermal biostimulator used in aesthetic medicine for facial volume restoration, contouring, and non-surgical lifting. PCL-based fillers have a dual mode of action: they give an immediate volumizing effect through gel-carrying a carboxymethylcellulose (CMC) and sustained fibroneogenesis through biodegradable PCL microspheres. Studies have shown that this type of filler initially stimulates the formation of type III collagen, followed by a predominant synthesis of type I collagen, the most essential structural collagen of the skin, which has a half-life of approximately 15 years [18,19]. This ability to induce type I collagen explains the durability of the clinical results observed after PCL treatment, which can last for over two years. Compared to other biostimulators, such as CaHA and PLLA, PCL offers both an immediate effect and long-lasting efficacy without requiring multiple sessions; in most cases, a single injection is sufficient [20,21]. An increase in dermal thickness up to 21% on average at 1 year after injection of smooth moulded microspheres also accompanied by active fibroblasts, newly formed type I and type III collagen bundles, elastin fibres and neovascularisation in the neighbourhood of the PCL microsphere has been observed both in clinical and histological studies [22].In addition, histologic analysis of human tissues injected with PCL showed the formation of type I and III collagen around the microspheres, thus supporting the long-lasting effect of the product. These findings confirm PCL's ability to induce neocollagenesis and provide long-lasting aesthetic results [23]. Quantitative 3D assessments also showed a 50-150% increase in volume over the initial injected volume after two years, suggesting progressive tissue remodeling [24].

The duration of the clinical effect of PCL-based filleters varies between 18 and 30 months, depending on the formulation. For example, Ellansé-S (PCL-1) offers visible results for up to 18 months, while Ellansé-M (PCL-2) maintains aesthetic improvements for up to 24 months or longer. A randomized controlled trial comparing the two products for correction of the nasolabial fold demonstrated clinical durability, with 90% of patients achieving continued clinical improvement at 12 months, as well as high satisfaction rates at 24 months (81.7% for PCL-2 and 72.4% for PCL-1) [25].

Polycaprolactone, thus, stands out as a key ingredient in aesthetic medicine due to its unique properties - biocompatibility, slow biodegradability, and ability to stimulate collagen production. Its application in facial rejuvenation treatments offers dual benefits (immediate volumization and long-lasting effects through regeneration), bridging the gap between regeneration and aesthetics, while also providing a viable prospect for personalized, safe, and effective treatments. Evaluations performed on nasolabial folds - one of the most treated areas in aesthetic practice - have shown long-lasting results, with significant improvements maintained even 24 months after injection. The versatility of PCL has also been demonstrated in other facial areas, such as the forehead, temples, jawline, and even the hands, achieving not only volume restoration but also a visible improvement in skin quality. These effects are due to PCL's unique ability to stimulate neocollagenesis, a process that contributes to a natural, long-lasting, and revitalized appearance. In terms of safety profile, data from clinical studies and extensive post-marketing use are encouraging, with adverse reactions being rare, mild, and transient (such as edema or local bruising) [26].

Moreover, more than a decade of clinical experience gained globally has cemented the product's reputation as a safe, stable, and predictable product with no significant complications reported in the literature. Thus, PCL not only offers natural and long-lasting aesthetic results but also a solid safety profile confirmed by clinical data and daily medical practice.

Calcium hydroxyapatite (CaHA)

Calcium hydroxyapatite (CaHA) is a biocompatible synthetic material widely used in aesthetic medicine for wrinkle correction, facial volumization, and skin rejuvenation. It has FDA clearance for the treatment of nasolabial folds, jawline contouring, and hand rejuvenation. Its effectiveness in improving aesthetic scores and patient satisfaction has been emphasized by effects that can last up to 18 months or longer [27]. Unlike other dermal fillers, CaHA offers a dual effect: immediate plumping and progressive stimulation of dermal regeneration, with results that can last 12-18 months or longer. CaHA is composed of calcium phosphate microspheres suspended in a carboxymethyl cellulose gel. After injection, the gel provides an immediate volume effect, while the microspheres act as a biological stimulant, promoting collagen and elastin synthesis. This profound action explains the remarkable improvements in skin texture and quality, even after the filler has been reabsorbed [28,29].

The biological mechanisms of action of calcium hydroxyapatite (CaHA) contribute significantly to explaining its effectiveness in skin regeneration and improvement of skin appearance. A study by Amiri et al. indicates that CaHA can stimulate the proliferation of fibroblasts - the cells responsible for collagen production - a process evidenced by increased expression of the nuclear marker Ki-67, without signs of cell toxicity (no increase in LDH levels). In addition, enhanced EGFR and SMAD2 gene expression is indicative of the temporal activation of growth-signaling pathways essential for cellular proliferation and invasion, with peak gene upregulation occurring approximately 4 weeks following injection. In parallel, CaHA induces the synthesis of type I and III collagen, reflecting a physiological pattern of transition from type III collagen (associated with the initial regeneration phase) to type I collagen (predominant in the dermis and responsible for the mechanical strength of the skin). This process is essential in combating signs of ageing, such as loss of elasticity, dryness, or wrinkles. CaHA also contributes to the regeneration of elastic fibers by stimulating the production of elastin, a structural component critical for skin elasticity, which is degraded with age and environmental exposure [30].

A second important characteristic of CaHA is its ability to induce angiogenesis (formation of new blood vessels) to increase tissue oxygenation and nutrient delivery, both crucial to the healing and dermal remodeling processes. These effects are accompanied by a decrease in local inflammation and edema, both of which are crucial for effective and lasting skin regeneration [31].

CaHA can be administered as a structural filler (undiluted) or as a biostimulator (diluted), depending on the treatment objective. Although approved only for a few areas, its off-label use has been extended to cheek contouring, the temple, neck, and neckline rejuvenation.

DISCUSSIONS

Injectable biostimulators, such as PLLA, PCL, and CaHA, represent a paradigm shift in aesthetic dermatology, transitioning from immediate volumization to regenerative skin restoration. These agents stimulate neocollagenesis, elastogenesis, and extracellular matrix remodeling by activating fibroblasts and pro-regenerative signaling pathways [32].

The increasing demand for minimally invasive aesthetic procedures has led to the emergence of poly-L-lactic acid (PLLA) as a leading biostimulator for facial rejuvenation. PLLA induces neocollagenesis through a controlled inflammatory process, resulting in a gradual and prolonged recovery of age-related volume. A review was conducted to assess the efficacy, longevity, and safety of PLLA in the context of aesthetic use, including randomized clinical trials (RCTs) in adults. The results of the work by Signorini et al. suggest that PLLA is effective for skin tightening and texture improvement, with low and transient adverse effects,

mainly when proper reconstitution and administration techniques are employed. However, differences between protocols and the poor quality of some of the studies support the need for further standardized research to maximize the clinical application of this product [17]. The efficacy of PLLA as a new volumizing filler, as well as an enhancer of skin quality through tissue remodeling, is also confirmed by studies by Syleima et al. Marked improvements in erythema, pores, and texture score were observed 18 weeks after treatment, with a significant change in epidermal layers and reduced parameters associated with elastin fragmentation and angiogenesis effect. These histological changes indicate that the action of PLLA is not superficial but deep, favouring not only neocollagenesis but also dermal regeneration and microvascularization. Treatment tolerability was favorable, and no adverse reactions were reported, further supporting the safety of repeated applications. Due to these dermoregenerative effects, PLLA can be considered for aesthetic protocols not only for volume restoration, but also for use in structural rejuvenation, particularly in patients with photoaging and in cases of early lipoatrophy [33].

In contrast to PLLA, which relies on a controlled inflammatory process to stimulate collagen, PCL acts through physical persistence in the dermis, inducing a prolonged mechanical stimulation effect.

PCL is a biodegradable synthetic polymer that serves as an injectable biostimulator in aesthetic medicine, exhibiting immediate volumizing capacity (due to the carboxymethylcellulose carrier gel) alongside long-term efficacy (by stimulating neocollagenesis induced by PCL microspheres). Histological examinations of human biopsies taken 13 months after injection revealed that the PCL particles remained within the dermis without migration or biodegradation, indicating their favorable safety profile and potential synergistic long-term aesthetic effects. These findings validate the product's ability to remodel tissue by enhancing collagen density. However, use in anatomically mobile areas should be approached with caution, particularly considering recent isolated cases of granulomatous reactions, which underscore the urgent necessity for standardization of administration protocols and long-term patient follow-up [23,34]. Compared to other biostimulants, PCL offers the advantage of lasting rejuvenation while ensuring safety. Nonetheless, injection limitations, side effects, and aesthetic outcomes necessitate adherence to a rigorous injection protocol, appropriate patient selection, and thorough post-treatment follow-up. Therefore, PCL can be regarded as a promising solution for aesthetic medicine, delivering both immediate and enduring effects; however, treatment outcomes can be significantly influenced by the physician's skill in performing the procedures and the protocols implemented [35].

CaHA, in addition to being a known collagen and elastin stimulator, acts as a skin microstructure enhancer. The study by Nowag et al. found that the direct interaction between CaHA microspheres and fibroblasts is crucial in stimulating neocollagenogenesis. Thus, in vivo, the more diluted the microspheres, the higher the dispersion and the higher the probability of cell encounter. In contrast, in vitro, the stimulation of type III collagen synthesis is proportional to the number of activated fibroblasts, independent of the activity of individual cells. This direct relationship between particle distribution, CaHA concentration, and fibroblast activation could serve as the basis for the development of personalized dilution and injection depth protocols tailored to each anatomical area and the patient's skin characteristics [36]. The in vivo results further support the application of CaHA as an effective biostimulatory agent for facial rejuvenation, mainly due to the induction of type III collagen expression in the initial period, followed by type I collagen expression in a manner consistent with the natural physiologic process of dermal regeneration. These results align with the current literature, which reports a rapid and immediate volumizing effect, followed by a persistent skin biostimulation stage, and a clinical gain of 12 to 18 months. Additionally, personalized dilution methods of CaHA are becoming increasingly relevant in the treatment

of sensitive areas, such as the neck and décolleté, thereby highlighting the impact of diffusion on fibroblast activation. CaHA offers the best ratio between immediate aesthetic effects and medium-term collagen-boosting potential, making it particularly suited for patients who want immediate results with long-lasting effects. In parallel, the growing trend for combination treatments, such as the combination of CaHA with PLLA, reflects a three-dimensional, personalized rejuvenation approach and may result in a synergistic effect on skin volume and quality. However, widely observed shortcomings in study methods, small sample sizes, and a lack of standardized protocols underscore the need for further multicenter clinical trials with longitudinal monitoring and objective (imaging) assessment of dermal effects [37].

Therefore, poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL) are the most widely used and experienced collagen biostimulators in minimally invasive facial rejuvenation. Each of these agents has specific characteristics that can be tailored according to the patient's profile and requirements. PLLA is recognized for its ability to gradually regenerate the dermis sustainably, thereby providing a natural appearance. CaHA provides immediate plumping, which is further enhanced by neocollagenesis, making it ideal for fast and versatile treatments. PCL has been shown to have the highest reversibility for esthetic restoration, with the lowest adverse reaction rate, and is therefore a valuable choice for patients seeking long-term results. The main characteristics of these three biostimulators are summarized in a comparative table (Table 1), providing practical support for personalized clinical observations.

Table 1. Comparative Table of Biostimulating Fillers in Aesthetic Medicine

Feature	PLLA (Poly-L-lactic acid)	PCL (Polycaprolactone)	CaHA (Calcium Hydroxyapatite)
Product Type	Synthetic, biodegradable polymer	Synthetic, slow-biodegradable polymer	Biocompatible, synthetic mineral compound
Mechanism of Action	Controlled inflammatory response, macrophage and fibroblast activation, TGF-β/SMAD signaling	Dual action: immediate effect via CMC gel + long-term collagen stimulation via PCL microspheres	Dual action: immediate effect via CMC gel + fibroblast stimulation, angiogenesis, and ECM regeneration
Collagen Type Induced	Mainly Type I	Initially Type III, then predominantly Type I	Type III (early), followed by Type I
Onset of Effect	Gradual, delayed onset	Immediate + progressive improvement	Immediate + progressive improvement
Duration of Effect	18–24 months	18–30 months (depending on formula)	12–18 months
Target Areas	Mid and lower face (cheeks, jawline, temples)	Forehead, temples, cheeks, jawline, hands	Nasolabial folds, cheeks, hands, temples, neck (off-label)
Safety Profile	Good, few adverse events; long clinical use	Excellent; over a decade of use; minimal side effects	Very good; transient edema or bruising; no significant toxicity

CONCLUSIONS

Biostimulators have thus become indispensable tools in modern aesthetic practice, offering not only volumization but also deep stimulation of dermal regeneration. The choice of the appropriate substance should consider the aesthetic goals, the treatment area, and the individual patient profile. A detailed understanding of the characteristics of each product is crucial for optimizing results and minimizing associated risks. Current trends indicate a shift in medical aesthetics toward prevention, tissue regeneration, and subtle enhancements, aligning with the demands of today's generation and the latest advances in regenerative

medicine. Future research directions should include prospective studies on a large cohort to validate the long-term efficacy and safety of biostimulatory fillers, as well as a larger-scale double-blind, randomized, controlled trial. The development of comparative studies, combination treatments, and individual treatment regimens may contribute to the advancement of personalized medicine in the field of aesthetic medicine. Additionally, translational research into the molecular mechanisms underlying regenerative tissue healing will inform the development of optimal filler compositions and their practical application. Addressing these issues will help fill the evidence gaps currently missing and generate new, evidence-based solutions for regenerative aesthetic medicine.

Conflicts of Interest

The authors declare no conflict of interest.

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