BRAZILIAN JOURNAL OF IMPLANTOLOGY AND HEALTH SCIENCES

ISSN 2674-8169

TISSUE INTEGRATION AND CELLULAR RESPONSE TO COLLAGEN BIOSTIMULATORS IN OROFACIAL HARMONIZATION: AN INTEGRATIVE REVIEW

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https://doi.org/10.36557/2674-8169.2025v7n8p934-960
Artigo recebido em 11 de Julho e publicado em 21 de Agosto de 2025

ARTIGO DE REVISÃO INTEGRATIVA

RESUMO

Introdução: Os bioestimuladores de colágeno são dispositivos biomédicos fundamentais na harmonização orofacial, reconhecidos por sua capacidade de induzir atividade biológica que favorece a regeneração tecidual e a melhora da qualidade da pele. Entre os bioestimuladores mais utilizados destacam-se o Ácido Poli-L-Lático (PLLA), a Hidroxiapatita de Cálcio (CaHA) e a Policaprolactona (PCL). Esses materiais apresentam características de biocompatibilidade, biodegradabilidade e biofuncionalidade, possibilitando a proliferação celular e a produção de colágeno, processos que impulsionam a neocolagênese e a neoelastogênese. **Pergunta da Revisão:** Qual é o impacto dos bioestimuladores de colágeno na integração tecidual, cicatrização e resposta de corpo estranho em humanos e animais no contexto da harmonização facial e estudos experimentais? **Materiais e Métodos:** Esta revisão integrativa seguiu o método PCC, incluindo estudos sobre bioestimuladores de colágeno, regeneração tecidual, reparo, cicatrização e respostas a corpo estranho. Foram excluídos estudos que abordassem patologias, alterações sistêmicas de saúde, harmonização corporal, enxertos ósseos, preenchedores dérmicos, toxina botulínica ou que tivessem foco exclusivamente clínico. As fontes de pesquisa incluíram PubMed, Google Scholar, SciELO, Biblioteca Virtual em Saúde, Dimensions e BASE. **Resultados:** Dos 246 registros identificados, 11 estudos atenderam aos critérios de inclusão. O PLLA esteve associado ao aumento da síntese de colágeno por meio da polarização de macrófagos M2 e da modulação da resposta inflamatória. A CaHA demonstrou bioatividade, interagindo com os tecidos para estimular a neocolagênese e a neoelastogênese. O PCL facilitou a regeneração tecidual ao fornecer propriedades de arcabouço e biodegradação controlada, apoiando a formação da matriz extracelular. **Considerações Finais:** Esses biestimuladores apresentaram respostas celulares e teciduais distintas, refletindo seus diferentes mecanismos de ação. Os biestimuladores de colágeno apresentam significativo potencial para melhorar a integração e a regeneração tecidual na harmonização orofacial, embora seus efeitos sejam específicos de cada material.

Palavras-chave: Bioestimuladores de colágeno, Regeneração tecidual, Harmonização

orofacial, Polarização de macrófagos, Bioatividade.

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ABSTRACT

Introduction: Collagen biostimulators are fundamental biomedical devices in orofacial harmonization, recognized for their ability to induce biological activity that promotes tissue regeneration and improves skin quality. Among the most commonly used biostimulators are Poly-L-lactic Acid (PLLA), Calcium Hydroxyapatite (CaHA), and Polycaprolactone (PCL). These materials exhibit characteristics of biocompatibility, biodegradability, and biofunctionality, enabling cell proliferation and collagen production, processes that drive neocollagenesis and neoelastogenesis. **Review Question:** What is the impact of collagen biostimulators on tissue integration, healing, and foreign body response in humans and animals within the context of facial harmonization and experimental studies? **Materials and Methods:** This integrative review followed the PCC method, including studies addressing collagen biostimulators, tissue regeneration, repair, healing, and foreign body responses. Exclusion criteria comprised studies that focused on pathologies, systemic health alterations, body harmonization, bone grafts, dermal fillers, botulinum toxin, or those with an exclusively clinical focus. The research sources included PubMed, Google Scholar, SciELO, Virtual Health Library, Dimensions, and BASE. **Results:** From 246 identified records, 11 studies met the inclusion criteria. PLLA was associated with increased collagen synthesis through M2 macrophage polarization and modulation of the inflammatory response. CaHA demonstrated bioactivity by interacting with tissues to stimulate neocollagenesis and neoelastogenesis. PCL facilitated tissue regeneration by providing scaffold properties and controlled biodegradation, supporting extracellular matrix formation.
Final Considerations: These biostimulators exhibited distinct cellular and tissue responses, reflecting their different mechanisms of action. Collagen biostimulators show significant potential to enhance tissue integration and regeneration in orofacial harmonization, although their effects are material-specific.

Keywords: Collagen biostimulators, Tissue regeneration, Orofacial harmonization, Macrophage polarization, Bioactivity.

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INTRODUCTION

Collagen biostimulators are biomedical devices that have gained prominence as biomaterials in orofacial harmonization due to their ability to induce biological activity, particularly in promoting tissue regeneration and improving skin quality[1]. The application of collagen biostimulators is based not only on achieving visual restoration but also on delivering functional outcomes to counteract the aging process[2]. These outcomes rely directly on effective interactions between the biomaterials and the target tissues[3].

Among the most widely used collagen biostimulators in orofacial harmonization are Poly-L-lactic acid (PLLA)[4], Calcium Hydroxyapatite (CaHA)[5], and Polycaprolactone (PCL)[6]. These biomaterials are renowned for their biocompatibility, biodegradability, biofunctionality, and their ability to stimulate cell proliferation and collagen production, ultimately leading to neocollagenesis and neoelastogenesis[7]. However, depending on the nature of cellular interactions, tissue responses may vary, resulting in distinct clinical outcomes, such as fibrointegration, fibrosis, or, in some cases, a lack of biocompatibility that could lead to treatment failure[8].

Despite the widespread clinical use of collagen biostimulators, significant gaps remain in understanding the cellular mechanisms underlying the differentiation of tissue integration processes. This lack of systematic data hinders the optimization of clinical protocols[4,5].

In this context, the present study aims to explore the cellular interaction processes associated with collagen biostimulators, with a particular focus on their mechanisms of action and the tissue responses they elicit. By deepening the understanding of these interactions, the goal is to consolidate existing knowledge and identify critical gaps that could inform future research, thereby advancing both clinical practices and scientific insights in the field of orofacial harmonization. Consequently, this integrative literature review seeks to analyze the cellular and tissue interaction processes mediated by collagen biostimulators.

MATERIALS AND METHODS

This integrative review used the PCC method (Table 1). Studies that met the following inclusion criteria were included in this review: collagen biostimulators; cell integration process compatible with the process of tissue regeneration and repair; tissue healing; foreign body response. The exclusion criteria for the studies were as follows: addressing some pathology; systemic health alterations; body harmonization; bone grafts; dermal fillers; botulinum toxin; clinical focus only.

Table 1. Election Criteria with the PCC Method

Participants	Concept	Context
Humans and animals undergoing facial harmonization or experimental studies with collagen biostimulators.	Cell and tissue interaction (tissue integration, healing, foreign body response).	Use of biostimulators in aesthetic or experimental contexts, with a focus on tissue regeneration and inflammatory response.

Review Question

What is the impact of collagen biostimulators on tissue integration processes, healing and foreign body response in humans and animals in the context of facial harmonization and experimental studies?

Search Strategy and Data Extraction

The search was carried out in the following databases: PubMed MEDLINE (high quality biomedical articles), Google Scholar (broad sources and less indexed studies such as books, theses, conferences), SciELO (focus on regional literature in Portuguese and Spanish), Virtual Health Library (VHL): (integrates regional databases such as LILACS, SciELO and MEDLINE), Dimensions (whitelists scientific articles, preprints and citation impact metrics), and Bielefeld Academic Search Engine (BASE) (gray literature and open repositories such as theses and dissertations). The search strategy was carried out by two independent researchers and adapted for each database (Table 2). Thus, studies without language or time restrictions will be included. After searching the literature, the titles and abstracts were then examined by two independent reviewers to assess them

according to the review's inclusion criteria. Duplicate articles were removed as the first step. The full text of the selected citations was assessed in detail against the inclusion criteria by two independent reviewers. Any disagreements that arose between the reviewers at each stage of the selection process were resolved through discussion or with an additional reviewer. For the purpose of this review, studies involving humans, animals, and in vitro models were considered eligible, provided they addressed collagen biostimulators and their effects on tissue regeneration, repair, healing, or foreign body response. A formal risk of bias or methodological quality assessment was not conducted, as the aim of this integrative review was to provide a comprehensive synthesis of the available evidence to explore conceptual trends and biological responses related to collagen biostimulators. Nevertheless, the inclusion criteria were designed to ensure the relevance and scientific validity of the selected publications, and data extraction was carried out independently by two reviewers to minimize selection bias.

Table 2. Methodology and Search Key by Digital Platform

Database	Search Keys	Inclusion Criteria	Exclusion Criteria	Total	Selected
PubMed MEDLINE	("Collagen Biomaterials" OR "Biostimulators") AND ("Facial Rejuvenation" OR "Aesthetics")	Complete texts with no language or time restrictions	Involvement of some pathology or systemic complication, use of biomaterials for bone grafting	22	5
	("PLLA" OR "Poly-L-lactic acid" OR "CaHA" OR "Calcium Hydroxyapatite" OR "PCL" OR "Polyprolactone") AND ("Facial Aesthetics" OR "Facial Rejuvenation")				
Google Scholar	"Collagen Biostimulators" OR "Collagen Stimulation" OR "Collagen Biomaterials" AND "Facial Rejuvenation" OR "Facial Aesthetics" OR "Aesthetic	Complete texts with no language or time restrictions	Clinical approaches that solely report outcomes often overlook the intricate cellular	80	3

	Medicine" AND "PLLA" OR "Poly-L-lactic Acid" OR "CaHA" OR "Calcium Hydroxyapatite" OR "PCL" OR "Calcium Polyprolactone" AND "Tissue Regeneration" OR "Wound Healing"		interactions and are predominantly centered on non-facial harmonization		
SciELO	((((Collagen Biostimulators) OR (Collagen Stimulation)) AND (Facial Rejuvenation) OR (Facial Aesthetics) OR (Aesthetic Medicine)) AND (PLLA) OR (Poly-L-lactic Acid) OR (CaHA) OR (Calcium Hydroxyapatite) OR (PCL) OR (Polycaprolactone)) AND (Tissue Regeneration) OR (Wound Healing)	Complete texts with no language or time restrictions	Articles that were unresponsive or outside the scope of the research	27	0
VHL	tw:(Collagen) AND tw:(Facial Rejuvenation OR Facial Aesthetics) AND tw:(Tissue Regeneration) AND (tw:(PLLA) OR tw:(Calcium Hydroxyapatite) OR tw:(Polycaprolactone))	Complete texts with no language or time restrictions	Articles that focused on non-facial harmonization procedures or bone grafting	5	1
Dimensions	("Collagen Biostimulators" OR "Collagen Stimulation") AND ("Facial Aesthetics") AND ("PLLA" OR "Poly-L-lactic acid" OR "Calcium Hydroxyapatite" OR "Polycaprolactone") AND ("Tissue	Complete texts with no language or time restrictions	Approaches with purely clinical results, did not address cellular interaction, and focused on non-facial harmonization	30	2

	Regeneration" AND "Fibrosis" OR "Neocollagenesis")				
BASE	("Collagen Stimulation" AND "Facial Rejuvenation") AND ("PLLA" OR "Poly-L-lactic acid" OR "CaHA" OR "Calcium Hydroxyapatite" OR "Polycaprolactone") AND ("Tissue Regeneration" AND "Neocollagenesis") AND ("Harmonization" OR "Soft Tissue Remodeling")	Complete texts with no language or time restrictions	Articles or books not available, focus on clinical satisfaction, use of dermal fillers or botulinum toxin	82	0

RESULTS AND DISCUSSION

A total of 246 articles were identified during the search. After screening by reading the title and abstract, 151 articles were excluded (including duplicates), then 95 articles were selected to be read in full and, after applying the inclusion and exclusion criteria, as well as excluding repeated articles, 11 articles were selected.

The studies included in this integrative review are summarized in Table 3. The collagen biostimulators described were: Poly-L-lactic acid (PLLA), Poly-D-lactic acid (PDLA), Poly-D,L-lactic acid (PDLLA), Calcium Hydroxyapatite (CaHA), and Polycaprolactone (PCL). Most of the results specified PLLA as the main collagen biostimulator. However, this does not create a bias since the general characteristics of the biomaterials were taken into account singularly when interpreting the results.

Table 3. Tissue Integration Process Relation in the 11 Selected Studies

Reference (Author and Year)	Biomaterials Considered	Tissue Integration Process
McCarthy *et al*., 2024[8]	PLLA and CaHA	Particles that are more spherical, more regular and smoother have a lower macrophage response when compared to more irregular particles.

Ao *et al*., 2024[9]	PLLA	Neocollagenesis from an inflammatory response with the presence of pro-inflammatory macrophages.
Dong *et al*., 2024[10]	PLLA	M2 macrophage polarization induction and IL-4, IL-13 and TGF-β up-regulation.
Jeon *et al*., 2020[11]	PLLA	The main difference between a normal response and a negative response is the presence of a granuloma and/or a nodule.
Lee *et al*., 2023[12]	PLLA-based hydrogel	Association of ceramic nano-particles to induce anti-inflammatory and angiogenic effects, providing regeneration without fibrosis.
Wang *et al*., 2024[13]	PLLA and PDLLA	The biological response, as well as the mechanism of action, can be modified by altering the morphology without changing the composition of the material.
Christen & Vercesi, 2020[14]	PCL	The process of tissue integration is described in three overlapping phases: inflammation, tissue formation (or proliferation phase) and tissue remodeling. In addition, the process of neocollagenesis through fibrosis or mechanotransduction is more closely linked to the characteristics of the particles than the composition of the material.
Corduff, Niamh, 2023[15]	CaHA	It considers that adult tissues do not regenerate, but that they automatically undergo the process of fibrosis (scarring) for tissue regeneration. And it highlights the potential of biomaterials that can propose tissue regeneration rather than a fibrotic response.
Lee *et al*., 2024[16]	PLLA, PDLA and PDLLA	Changes in the composition of materials can propose different mechanisms of action.
Mathews-Steiner *et al*., 2021[17]	PLLA	The reorientation of collagen fibers in the tissue integration process improves the skin's tensile strength. In addition, biostimulants such as

		PLLA are considered to be “collagen dressings” and not a process of tissue regeneration.
Zheng *et al*., 2023[18]	Unspecified	The main events involved are the angiogenic, inflammatory and immunological response, and the interaction between biomaterials and cells.

The results show that the tissue integration process following the implantation of collagen biostimulators follows the classical pattern of tissue regeneration, similar to what occurs with other biomaterials, such as osseointegrable implants[3]. However, specific characteristics of each biomaterial directly influence the tissue response.

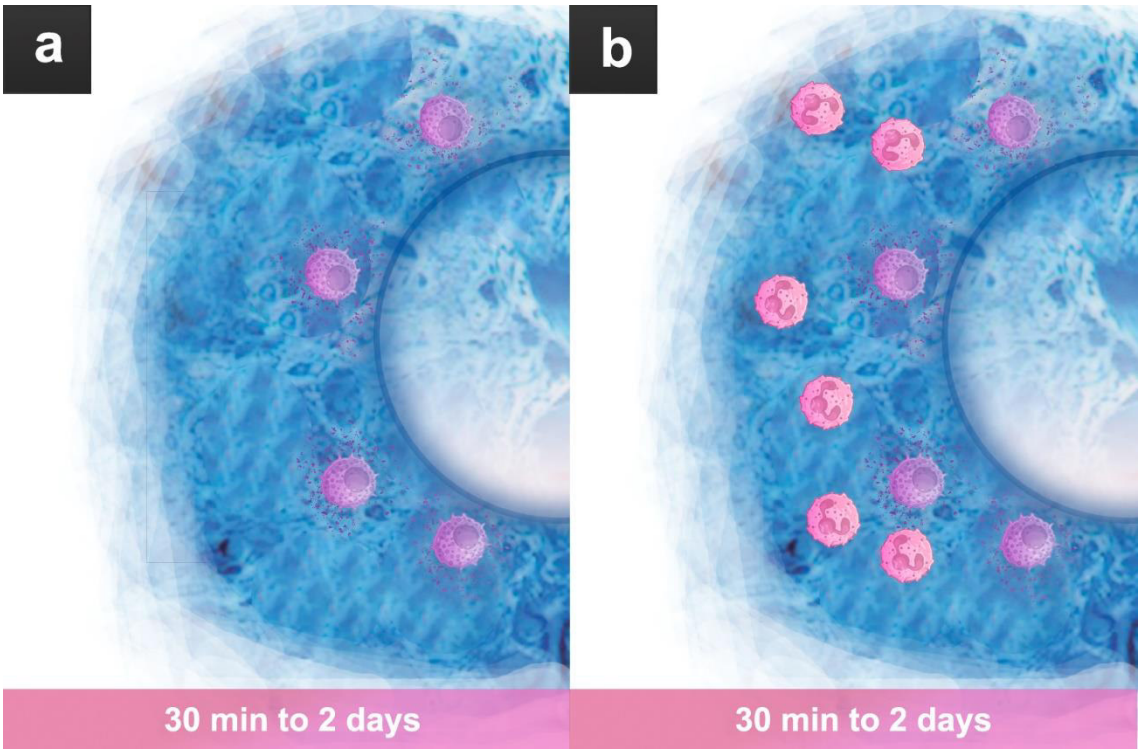
When the biomaterial is implanted in the body, as in the case of collagen biostimulators, a cellular-level interaction occurs between the biomaterial and the cells. The process begins with the adsorption of proteins onto the surface of the material, known as the Vroman effect. Angiogenesis follows, forming a provisional matrix of fibrin associated with type III collagen fibers, leading to the development of granulation tissue[3-19]. The tissue remodeling process gradually replaces these type III collagen fibers with type I collagen fibers, providing greater resistance and stability to the regenerated tissue[8].

The migration of recognition cells, such as mast cells, then occurs. These cells move to the implantation site, begin degranulation (releasing histamine), and secrete pro-inflammatory mediators such as IL-4. This triggers neutrophil migration to the region, initiating the acute inflammation phase[7]. Macrophages also play a critical role in tissue integration, functioning initially in the M1 phenotype, which is pro-inflammatory, and transitioning to the M2 phenotype, which is anti-inflammatory and regenerative. M2 macrophages release cytokines such as TGF-β, IL-4, and IL-13, promoting fibroblast proliferation and extracellular matrix production, supporting tissue regeneration[20].

The phases of the tissue integration process are described as overlapping: the inflammation phase (initial moment), the tissue formation phase (or proliferation phase), and the tissue remodeling phase[14]. During the remodeling phase, the biomaterial either undergoes progressive degradation or integrates into the regenerated tissue, depending on its specific characteristics. Achieving a balance

between inflammatory and regenerative processes and the interaction with the biomaterial is crucial for successful tissue regeneration[8]. Figure 1 illustrates the initial process of biomaterial implantation.

Figure 1. Biomaterial-cell interaction representing the initial tissue integration response.



Legend: (a) Mast cell degranulation (histamine) with release of inflammatory mediators and participation of the complement system. (b) Recruitment of neutrophils characterizing acute inflammation. Source: elaborated by the authors.

The second stage, described as tissue formation, depends on the tissue integration process, which is also influenced by the characteristics of the biomaterial[14].

PLLA is a semicrystalline polymeric material widely used in orofacial harmonization due to its biocompatibility and biodegradability. It has a molecular structure composed of repetitive units of L-lactide, providing suitable mechanical properties such as high tensile strength[9]. PLLA stands out as a biostimulator by promoting collagen production through cellular interactions that induce neocollagenesis, resulting in improved skin quality and tissue regeneration[10]. The chemical composition of PLLA influences its clinical performance by releasing lactic acid

during degradation. This creates a localized acidic environment that stimulates collagen production and tissue remodeling. PLLA is particularly effective in areas like the lower third of the face, where progressive tissue regeneration is crucial.

Its controllable degradation profile, with the release of metabolizable lactic acid, and its versatility for functional adaptations make it a strategic choice for aesthetic treatments aimed at safe and lasting results[11].

CaHA, on the other hand, is a bioceramic material used in dentistry as a bone graft and is widely applied in orofacial harmonization due to its biocompatibility, bioactivity, and ability to stimulate tissue regeneration[8]. With a composition similar to the mineral matrix of bone, CaHA exhibits excellent interaction with tissues, promoting both collagen production and temporary mechanical support[15]. It is used as a biostimulator in injectable suspensions, where its microspheres stimulate fibroblasts to produce collagen, contributing to improved skin elasticity and firmness[21].

Its bioactive nature enables it to interact directly with tissues, inducing specific immune responses that enhance collagen production and tissue integration. CaHA is particularly suitable for immediate volumization in areas like the cheeks and chin. Its controlled degradation allows for progressive and long-lasting aesthetic results, while its clinical safety is well-established due to its predictable behavior and low rate of adverse reactions[22].

PCL, in turn, is a biodegradable semicrystalline polymer widely applied in orofacial harmonization as a collagen biostimulator. Its unique chemical structure, based on aliphatic polyesters, provides a slower degradation rate compared to other biomaterials, enabling the gradual release of regenerative stimuli over time[23]. PCL is used in injectable formulations that promote neocollagenesis, resulting in significant improvement in skin quality, including enhanced firmness, elasticity, and the smoothing of fine lines[15]. Unlike PLLA, PCL degrades slowly, providing prolonged tissue stimulation and supporting gradual neocollagenesis over time. It offers exceptional benefits for long-term rejuvenation in areas with pronounced laxity. Moreover, PCL is recognized for its clinical safety, exhibiting a high biocompatibility profile and a low rate of complications, making it a reliable choice for long-term aesthetic treatments[24].

Each material has unique properties that make them suitable for different clinical scenarios. PLLA is often preferred for progressive tissue regeneration in areas with significant laxity[13], while CaHA is ideal for applications requiring immediate volumization and temporary mechanical support[8]. PCL, with its slower degradation rate, is particularly suitable for long-term aesthetic results[15].

All three biostimulators interact with the immune system in distinct ways[18]. PLLA and PCL modulate tissue regeneration through controlled inflammatory responses[13,14], characterized by a transition from pro-inflammatory (M1) to regenerative (M2) macrophages[20]. In contrast, CaHA bioactivity directly interacts with tissues, stimulating specific immune responses to enhance collagen production and tissue integration[15].

Although these materials have similar actions, they exhibit different biological properties. Table 4 presents the types of biological interactions among these biostimulators.

Table 4. Biological Interaction of Materials

	PLLA	CaHA	PCL
Biactive		x	
Bioinerte			
Bioreasorbable	x	x	x

Source: elaborated by the authors.

Biomaterials can be classified into three main categories based on their interaction with biological tissues: bioactive, bioinert, and bioabsorbable, each playing distinct roles in skin regeneration. Bioactive materials, such as CaHA and certain bioglasses, form a direct biochemical bond with skin tissues by creating a layer of apatite at the interface, enhancing stable integration and promoting neocollagenesis. Bioinert materials, including polymers like ultra-high molecular weight polyethylene (UHMWPE) and metals such as titanium, exhibit minimal interaction with the skin, acting as passive scaffolds without significant degradation or biological activity, which limits their regenerative potential. Bioabsorbable materials, such as PLLA and PCL, are biodegradable and support controlled skin regeneration by gradually degrading while stimulating cellular processes, including fibroblast proliferation, collagen deposition, and angiogenesis, contributing to tissue repair and aesthetic improvements[14-18-25,26].

Moreover, another relevant characteristic is the type of biological activity these materials can exhibit. Table 5 shows the differences among the biostimulators.

Table 5. Biological Activity of the Materials

	PLLA	CaHA	PCL
Genesis	x	x	x
Induction		x	
Conduction		x	

Source: elaborated by the authors.

Biomaterials used in collagen biostimulators promote skin tissue regeneration through three main activities: genesis, induction, and conduction. Genesis refers to the biomaterial's ability to directly interact with differentiated skin cells, such as fibroblasts, stimulating the production of new collagen and extracellular matrix, enhancing skin firmness and elasticity. Induction describes the biomaterial's capacity to influence undifferentiated cells, such as mesenchymal stem cells, to specialize into fibroblasts, guided by biochemical signals released during controlled biodegradation, such as TGF-β. Lastly, conduction involves tissue stimulation without the need for cells, where the structure of the biostimulator, such CaHA, particles, creates a physical scaffold that promotes the reorganization and deposition of collagen fibers, contributing to skin regeneration and aesthetic improvement[10-14-18-27].

The tissue formation stage can be identified based on the clinical outcomes shown in Figure 1. Tissue integration may lead to either regeneration and repair[3] - when the tissues of the surgical wound return to their original state, matching the adjacent tissues (e.g., the epidermis regenerates as epidermis, and the dermis as dermis) - or fibrointegration[3], which can be further categorized as follows[7]:

1. **Healing:** in this process, the adjacent tissues are not restored to their original state but are replaced by fibrous connective tissue, characteristic of tissue fibrosis. This substitution often results in reduced functional capacity in the affected area.

The degree of fibrosis depends on the intensity and duration of the inflammatory response, which is influenced by the properties of the biomaterial.

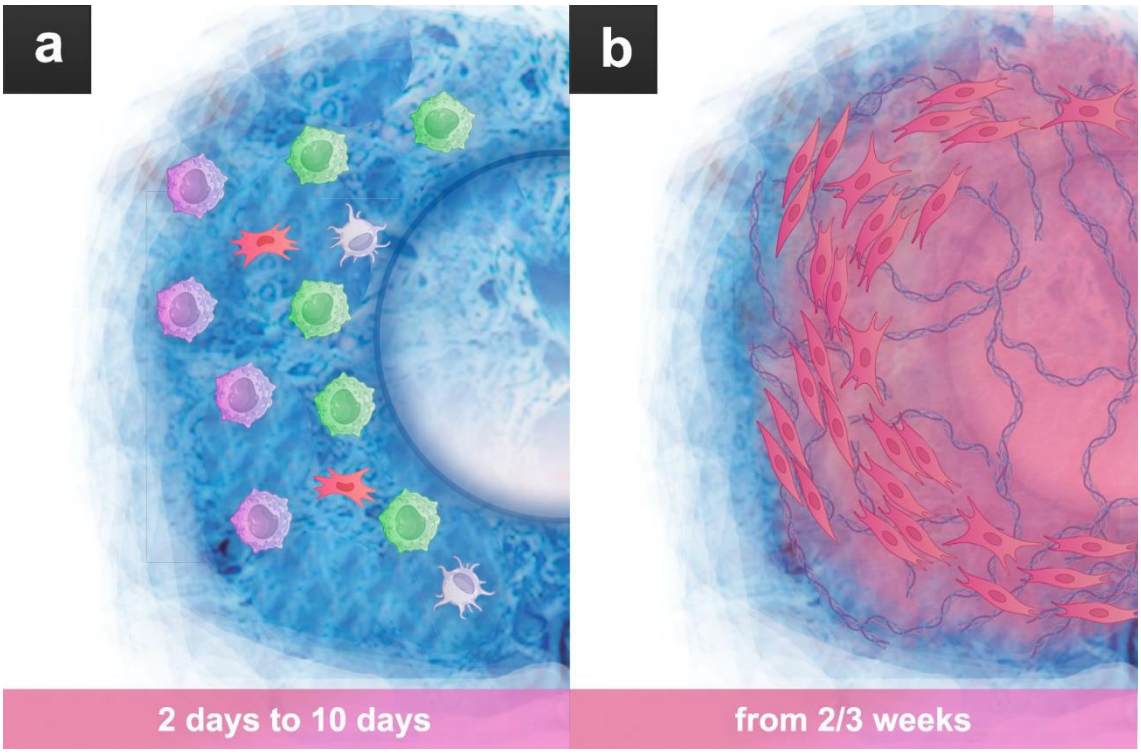
2. **Foreign body response:** this occurs when the biomaterial or biomaterial-cell interaction results in complications that compromise the tissue's compatibility, leading to chronic inflammation, fibrotic encapsulation, or biomaterial rejection. Surface irregularities or poor biocompatibility are often contributing factors to this outcome.

The type of tissue integration - whether regenerative, fibrotic, or reactive - is determined by both the biological response and the properties of the biomaterial. Factors such as surface chemistry, degradation rate, and bioactivity play a critical role. For example, bioactive biomaterials like hydroxyapatite can stimulate osteoblasts for bone regeneration, whereas bioinert materials may require surface modifications to enhance cellular responses[7].

These processes are mediated by cellular mechanisms. Regeneration typically involves the recruitment of stem cells and their differentiation into tissue-specific cells, while healing and fibrotic responses rely on fibroblasts depositing collagen to form scar tissue. In cases of foreign body response, macrophages and giant cells dominate the inflammatory environment, further preventing effective tissue integration[3].

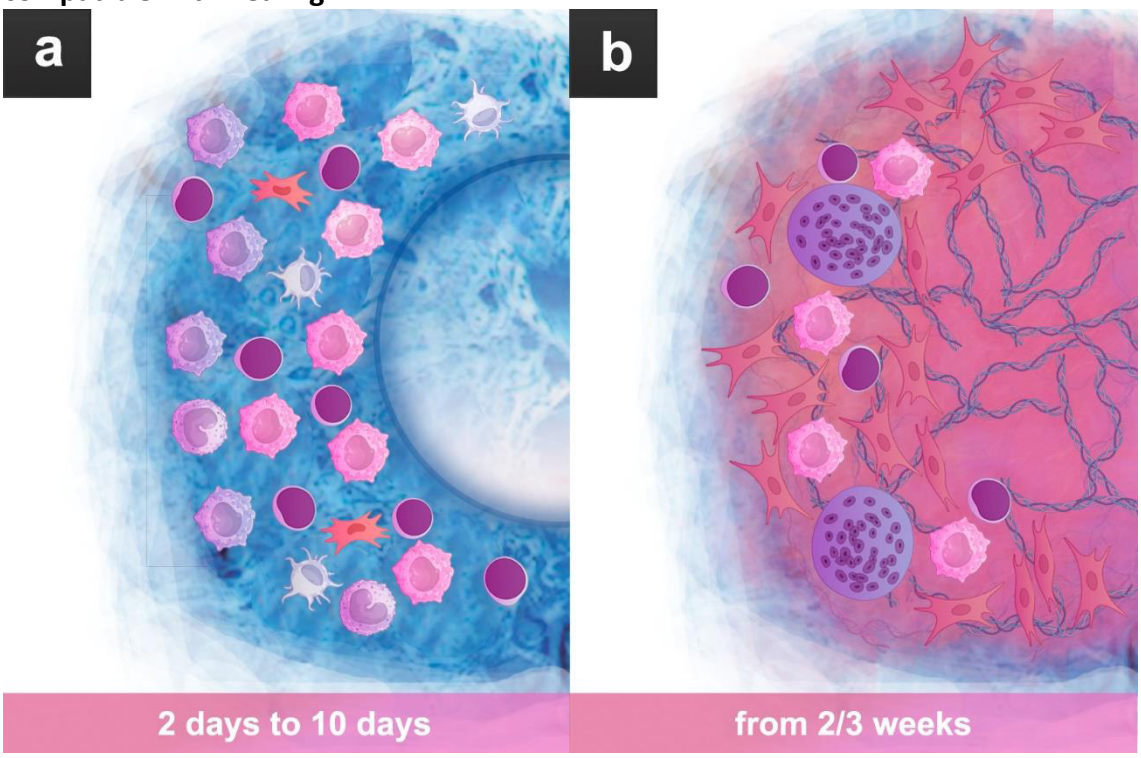
Figure 2, Figure 3 and Figure 4 illustrate these pathways of tissue integration and their clinical outcomes, depending on the interaction between the biomaterial and the surrounding tissue environment.

Figure 2. Biomaterial-cell interaction representing the process of tissue integration compatible with tissue regeneration and repair.



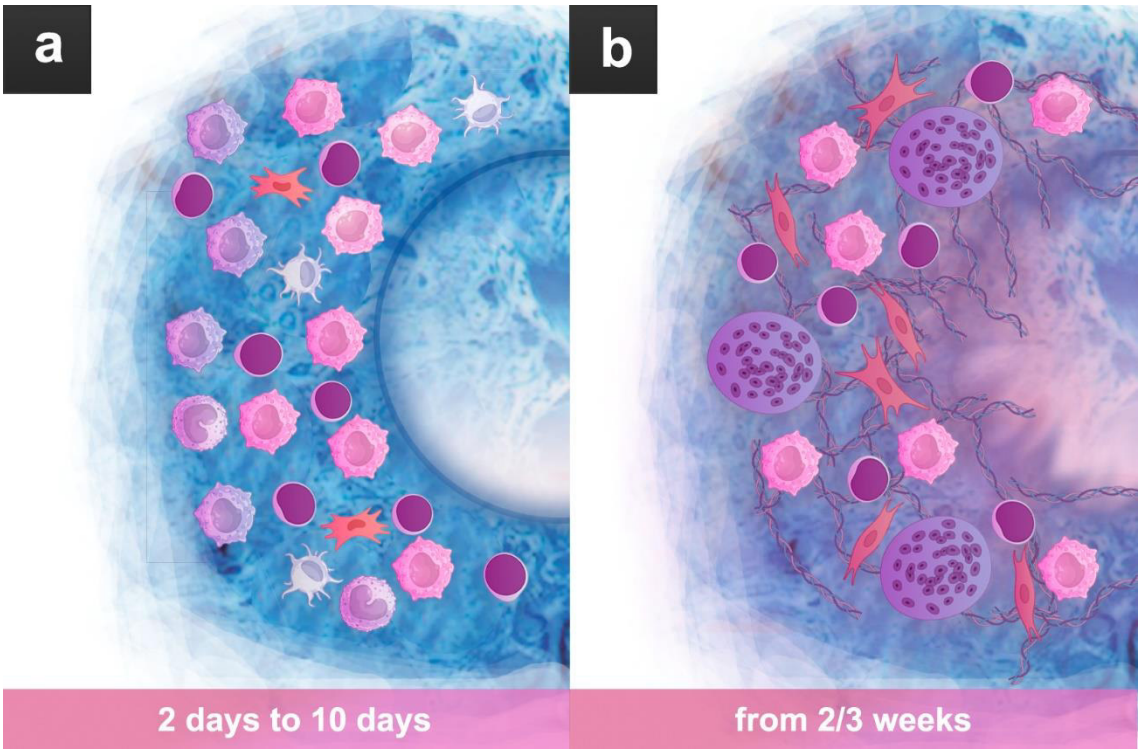
Legend: (a) polarization of immunoregulatory macrophages with release of IL-10, IL-4 and IL-13 with displacement of inflammation to subacute. (b) fibrointegration process characterized by a dense connective tissue modeled with a predominance of type I collagen fibers, with a thin and uniform layer, active fibroblasts, low density of inflammatory cells. Source: elaborated by the authors.

Figure 3. Biomaterial-cell interaction representing the process of tissue integration compatible with healing.



Legend: (a) polarization of pro-inflammatory macrophages with release of TNFα, IL-6, IL-12 and IL-1β with a shift from acute to chronic inflammation. (b) fibrosis process (scarring), with the onset of chronic inflammation, characterized by dense, non-modelled connective tissue with a predominance of type III collagen fibres, presence of excessive type I collagen fibres, with a thick, rigid layer, presence of myofibroblasts, high density of inflammatory cells. Source: elaborated by the authors.

Figure 4. Biomaterial-cell interaction representing the process of tissue integration compatible with the foreign body response.



Legend: (a) polarization of pro-inflammatory macrophages with release of TNFα, IL-6, IL-12 and IL-1β with a shift from acute to chronic inflammation. (b) fibrosis process (foreign body response with presence of fibrous tissue) associated with the absence of biocompatibility, and the immune system aiming to isolate and degrade the foreign body. Source: elaborated by the authors.

It can be understood that PLLA presents a tissue integration process completely opposite to that of CaHA and PCL. PLLA undergoes a fibrointegration process associated with wound healing[18]. This fibrointegration is characterized by the formation of organized fibrous tissue with progressive deposition of type I collagen[7]. Furthermore, it has irregular particles that are flatter and elongated, resembling flakes, which are more compatible with the progression of inflammation[8].

However, these particles, when interacting with the tissue microenvironment, trigger specific cellular responses that ultimately lead to immunoregulation and tissue regeneration. PLLA is capable of stimulating M2 macrophages (immunoregulatory) with the upregulation of IL-4, IL-13, and TGF-β[8-10].

The main paradox of this mechanism of action can be explained by the physicochemical interaction. Although the morphology of the particles does not favor

immunoregulation, the inflammation induced by PLLA creates a microenvironment that subsequently promotes the transition of macrophages to an anti-inflammatory profile.

This process is supported by the release of metabolic byproducts, such as lactic acid, which directly influence cellular phenotype. For example, the controlled biodegradation of PLLA releases lactic acid, which, despite acidifying the environment, also increases the expression of IL-4, IL-13, and TGF-β, acting as a metabolic biomodulator. This favors the polarization of M2 macrophages, and thus the action of PLLA in neocollagenesis occurs indirectly[11-13].

In addition, PLLA interacts with toll-like receptors (TLRs) and scavenger receptors on macrophages, making them susceptible to M1 macrophage polarization, with the release of pro-inflammatory mediators such as IL-1β and TNF-α. Nevertheless, its controlled biodegradation gradually reprograms the tissue microenvironment, inducing M2 macrophage polarization and promoting tissue regeneration. These mediators not only act as immunoregulators but also stimulate neocollagenesis[10-17]. Thus, PLLA performs an immunomodulated fibrointegration process, primarily driven by M2 macrophage polarization, resulting in wound healing[8].

On the other hand, CaHA, being a ceramic material, promotes tissue integration compatible with tissue regeneration and/or repair. This property stems from its chemical composition, similar to the bone mineral matrix, and its ability to interact directly with tissues[27]. Since CaHA exhibits bioactivity, as well as genesis, induction, and conduction activities, it can directly contact fibroblasts to stimulate neocollagenesis and neoelastogenesis[15].

CaHA does not promote fibrointegration but rather a process of integration characterized by its bioactivity and ability to induce neocollagenesis and neoelastogenesis[21]. Its spherical and smooth particles are highly compatible with tissue regeneration, favoring a controlled and temporary inflammatory response, which quickly evolves into an immunoregulatory microenvironment. This controlled inflammatory evolution is essential for the formation of a functional and structurally integrated regenerated tissue[8].

The main mechanism associated with CaHA is related to its chemical composition, which resembles the bone mineral matrix, and the gradual release of

calcium and phosphate ions, which directly stimulate fibroblasts and promote collagen production. This release also induces angiogenesis, promoting the formation of new blood vessels that support the regenerated tissue. This process is accompanied by the release of immunological mediators such as TGF-β, which aids in the transition to M2 macrophages. Moreover, CaHA exhibits limited surface interaction with pro-inflammatory receptors, reducing the release of cytokines like IL-1β and TNF-α, minimizing the risk of exacerbated inflammatory responses[8-15].

Thus, CaHA facilitates a bioactive tissue integration process, sustained by the induction of M2 macrophages and the direct stimulation of fibroblasts. This process not only improves skin quality but also supports safe and efficient tissue regeneration, making it widely used in orofacial harmonization[21].

PCL, in contrast, presents a distinct tissue integration process compared to PLLA and CaHA. PCL promotes integration characterized by its biocompatibility and ability to form a three-dimensional matrix that serves as a scaffold for tissue regeneration[13]. This matrix facilitates fibroblast infiltration, collagen deposition, and vascularization, essential for tissue repair. Its particles exhibit a morphology that favors cellular infiltration and vascularization, creating an environment conducive to tissue repair[23].

The primary mechanism of action of PCL is related to its slow biodegradation, which provides a sustained release of byproducts that modulate the inflammatory response[13]. Although an initial moderate inflammatory response may occur, PCL promotes the polarization of macrophages toward the M2 phenotype, with the upregulation of cytokines such as IL-4, IL-13, and TGF-β[18-24]. This immunological transition fosters a prolonged regenerative environment, allowing long-lasting aesthetic results. This immune modulation not only controls inflammation but also stimulates neocollagenesis and neoangiogenesis, both essential for tissue regeneration[15-24].

In addition, PLLA interacts with toll-like receptors (TLRs) and scavenger receptors on macrophages, initially promoting a pro-inflammatory activation profile characterized by the release of mediators such as IL-1β and TNF-α. As biodegradation progresses, the local tissue microenvironment is gradually modulated toward anti-inflammatory and pro-regenerative macrophage phenotypes within the polarization spectrum, supporting tissue repair. These mediators act both as immunoregulators and as stimulators of

neocollagenesis, contributing to an immunomodulated fibrointegration process that favors wound healing.[15].

The initial inflammatory response is moderate and more controlled due to the morphology of its particles, specifically because they are more spherical, less rough, and more uniform. Consequently, they directly favor M2 macrophage polarization, with the release of inflammatory mediators IL-4, IL-13, and TGF-β, which act as immunoregulators. Despite this, an initial activation of M1 macrophages may occur, but it is rapidly regulated by the byproducts released during PCL biodegradation, promoting an anti-inflammatory environment[8-15-23].

Although these are the main mechanisms of action of the mentioned biostimulators, it is important to highlight that several variables can influence the tissue integration response associated with the application of collagen biostimulators.

Studies have shown that PLLA, CaHA[28], and PCL[29] can promote tissue integration compatible with the healing process, characterized by the presence of granulomas, including foreign body giant cells, lymphocytes, and macrophages, resulting in a fibrointegration process. On the other hand, other studies indicate that the same biostimulators can be applied without evidence of granulomas, suggesting tissue integration more aligned with regeneration or tissue repair[30,31].

Among the included studies, Jeon et al. (2020) reported a late-onset foreign body reaction following PLLA administration, highlighting that collagen biostimulators, while designed to promote tissue regeneration through controlled inflammatory pathways, may in certain cases trigger a persistent low-grade inflammation. This inflammatory process can lead to the formation of foreign body granulomas, a known though infrequent complication. Such findings reinforce the importance of patient selection, injection technique, and follow-up in minimizing adverse outcomes, while preserving the intended bioactive effects. [1]

Thus, various factors can influence the tissue integration performance of collagen biostimulators. Among these, the morphology of the biomaterial particles, such as size, shape, and roughness, stands out. Smaller, spherical particles with smoother surfaces tend to reduce the initial inflammatory response, favoring a more regulated tissue integration aligned with regeneration. In contrast, larger, elongated, or rough-

surfaced particles can intensify the initial inflammation, promoting fibrointegration[8]. The chemical composition of the biomaterial plays a fundamental role, directly influencing biocompatibility and cellular interaction. For example, bioactive materials, such as CaHA, promote direct integration with fibroblasts and other cell types, while more inert materials, such as highly stabilized polymers, rely solely on secondary mediators to stimulate regeneration[3-7-27].

These factors, along with the immune system's response (how it reacts to the properties of the biomaterials) and the patient's systemic conditions (whether their health status is compatible with the biostimulator application), play a crucial role in determining the type of tissue response achieved and the therapeutic success of the intervention.

FINAL CONSIDERATIONS

Collagen biostimulators play a pivotal role in orofacial harmonization, demonstrating significant efficacy in tissue regeneration and aesthetic enhancement. However, their diverse biological responses highlight the need for further research to elucidate the cellular, protein, and molecular mechanisms that influence the type of biological response in the tissue integration process.

Among the three classes of biostimulators discussed, CaHA stands out as the only material capable of directly integrating with cells while encompassing a broader range of interactions and biological activities. Another relevant factor is taking into consideration the material composition, particle size, shape, and topography. Ceramic materials, such as CaHA, generally provide more immediate results but may face limitations in terms of structural application and longevity. In contrast, polymers offer greater flexibility and longer-lasting effects, although their effectiveness relies heavily on immune responses and controlled biodegradation. Thus, more spherical, less flattened and elongated, and smoother particles are more compatible with immunoregulatory responses, while the opposite is also true.

While the clinical distinction between tissue integration and healing may not always be apparent, understanding these processes is essential for establishing a robust scientific foundation within the field of orofacial harmonization. Despite the specific

metabolic activities associated with each type of collagen biostimulator, variations in these responses can arise depending on the biomaterial, the host's immune system, and systemic conditions.

REFERENCES:

1. Bravo BSF, Calvacante T, Nobre CS, Bravo LG, Zafra MC, Elias MC. Exploring the safety and satisfaction of patients injected with collagen biostimulators—a prospective investigation into injectable poly-L-lactic acid (PLLA). J Cosmet Dermatol. 2024; e16723. doi:10.1111/jocd.16723

2. do Nascimento M, Grijó C, Moura JVF, dos Santos Fausto B, Tedesco AD. The functional architecture of the stomatognathic system and orofacial aesthetic repositioning during the aging process. Rev Cient CRO-RJ (Rio J Dent J). 2020;5(1):4-16.

3. Nascimento M. Interação célula-proteína-implante no processo de osseointegração: interação célula-proteína-implante. Braz J Implantol Health Sci [Internet]. 2022 Mar 14 [cited 2025 Jan 6];4(2):44-59. Available from: https://bjihs.emnuvens.com.br/bjihs/article/view/198

4. Nowag B, Casabona G, Kippenberger S, Zöller N, Hengl T. Calcium hydroxylapatite microspheres activate fibroblasts through direct contact to stimulate neocollagenesis. J Cosmet Dermatol. 2022;22(2):426-432.

5. Ray S, Ta HT. Investigating the effect of biomaterials such as poly-(l-lactic acid) particles on collagen synthesis in vitro: method is matter. J Funct Biomater. 2020;11:51.

6. Christen MO, Vercesi F. Polycaprolactone: how a well-known and futuristic polymer has become an innovative collagen-stimulator in esthetics. Clin Cosmet

Investig Dermatol. 2020 Jan 20;13:31-48. doi:10.2147/CCID.S229054. PMID: 32161484; PMCID: PMC7065466.

7. Elias CN, Ribeiro KS, Gomes P de L, Nascimento M do, Souza BM de. Osseointegration, inflammatory process and foreign body reaction of dental titanium implants. OLEL [Internet]. 2024 Dec 5 [cited 2025 Jan 6];22(12):e8087.

8. McCarthy AD, Hartmann C, Durkin A, Shahriar S, Khalifian S, Xie J. A morphological analysis of calcium hydroxylapatite and poly-l-lactic acid biostimulator particles. Skin Res Technol. 2024;30(6):e13764. doi:10.1111/srt.13764. PMID: 38853456; PMCID: PMC11163027.

9. Ao YJ, Yi Y, Wu GH. Application of PLLA (Poly-L-Lactic acid) for rejuvenation and reproduction of facial cutaneous tissue in aesthetics: A review. Medicine (Baltimore). 2024;103(11):e37506. doi:10.1097/MD.0000000000037506. PMID: 38489708; PMCID: PMC10939544.

10. Dong Y, Zhang Y, Yu H, Zhou L, Zhang Y, Wang H, et al. Poly-l-lactic acid microspheres delay aging of epidermal stem cells in rat skin. Front Immunol. 2024;15:1394530. doi:10.3389/fimmu.2024.1394530. PMID: 38881903; PMCID: PMC11177849.

11. Jeon YJ, Koo DW, Lee JS. Late onset foreign body reaction due to poly-L-lactic acid facial injections for cosmetic purpose. Ann Dermatol. 2020;32(6):519-22. doi:10.5021/ad.2020.32.6.519. PMID: 33911797; PMCID: PMC7875245.

12. Lee S, Baek SW, Kim DS, Park SY, Kim JH, Jung JW, et al. Injectable microparticle-containing hydrogel with controlled release of bioactive molecules for facial rejuvenation. Mater Today Bio. 2023;24:100890. doi:10.1016/j.mtbio.2023.100890. PMID: 38162281; PMCID: PMC10755792.

13. Wang M, Chihchieh L, Hou M, Liu S, Zhang Y, Wang H. Polylactic acid-based polymers used for facial rejuvenation: A narrative review. Aesthetic Plast Surg. 2024. doi:10.1007/s00266-024-04543-8. Epub ahead of print. PMID: 39623233.

14. Rittié L. Cellular mechanisms of skin repair in humans and other mammals. J Cell Commun Signal. 2016;10(2):103-20. doi:10.1007/s12079-016-0330-1. PMID: 27170326; PMCID: PMC4882309.

15. Christen MO, Vercesi F. Polycaprolactone: How a well-known and futuristic polymer has become an innovative collagen-stimulator in esthetics. Clin Cosmet Investig Dermatol. 2020;13:31-48. doi:10.2147/CCID.S229054. PMID: 32161484; PMCID: PMC7065466.

16. Corduff N. Introducing aesthetic regenerative scaffolds: An immunological perspective. J Cosmet Dermatol. 2023;22(Suppl 1):8-14. doi:10.1111/jocd.15702. PMID: 36988471.

17. Mathew-Steiner SS, Roy S, Sen CK. Collagen in wound healing. Bioengineering (Basel). 2021;8(5):63. doi:10.3390/bioengineering8050063. PMID: 34064689; PMCID: PMC8151502.

18. Zheng M, Wang X, Chen Y, Yue O, Bai Z, Cui B, et al. A review of recent progress on collagen-based biomaterials. Adv Healthc Mater. 2023;12(16):e2202042. doi:10.1002/adhm.202202042. PMID: 36377336.

19. Moura JVF, Nascimento M, de Souza BM, Posch AT. O processo de angiogênese e integração em implantes osseointegráveis de titânio. Braz J Implantol Health Sci. 2022;4(3):18-32. doi:10.36557/2674-8169.2022v4n3p18-32.

20. Silva NSD, Almeida ACRD, Nascimento MD, Souza BMD, Lourenço TGB, Posch AT. Subgingival microbiota and immune response modulation of osseointegrable implants. RGO - Rev Gaúcha Odontol. 2023. doi:10.1590/1981-86372023004820220070.

21. Neca CSM, Gondim ACL, Rocha CAS, Silva CAP, da Silva FG. O uso de bioestimuladores de colágeno à base de hidroxiapatita de cálcio. E-Acadêmica. 2022;3(2):e7332237.

22. de Oliveira CSFP, da Silva Almeida TJ, de Oliveira Martins L, Sorpreso LATM, Finck NS. Hidroxiapatita de cálcio: uma revisão quanto à eficácia, segurança e imaginologia quando usado como preenchedor e como bioestimulador. Res Soc Dev. 2021;10(14):e05101421689.

23. Nascimento DS, Medeiros LVL, Madureira WF. Bioestimulador de colágeno à base de policaprolactona (PCL-Filler): uma revisão de literatura (odontologia). Repositório Institucional. 2024;3(1).

24. Pereira de Souza M, Serrão da Silva M, Rodrigues Júnior OM. Bioestimuladores de colágeno injetáveis: quanto à ação e eficácia do ácido poli-L-lático, hidroxiapatita de cálcio e policaprolactona, uma revisão integrativa. Rev Foco (Interdisciplinary Studies Journal). 2024;17(8).

25. Lele M, Kapur S, Hargett S, Sureshbabu NM, Gaharwar AK. Global trends in clinical trials involving engineered biomaterials. Sci Adv. 2024;10(29):eabq0997. doi:10.1126/sciadv.abq0997. PMID: 39018412; PMCID: PMC466960.

26. Zhao D, Zhu T, Li J, Cui L, Zhang Z, Zhuang X, Ding J. Poly(lactic-co-glycolic acid)-based composite bone-substitute materials. Bioact Mater. 2020;6(2):346-60. doi:10.1016/j.bioactmat.2020.08.016. PMID: 32954053; PMCID: PMC7475521.

27. Nascimento M, Almeida ARS, Hirata MC, Elzubair A, Rocha DN, Silva MHP. Biomineralization of calcium phosphates functionalized with hydroxyapatite-binding peptide. J Mech Behav Biomed Mater. 2023;146:106082. doi:10.1016/j.jmbbm.2023.106082.

28. Mazzuco R, Evangelista C, Gobbato DO, Almeida LM. Clinical and histological comparative outcomes after injections of poly-L-lactic acid and calcium hydroxyapatite in arms: A split side study. J Cosmet Dermatol. 2022;21:6727–33. doi: 10.1111/jocd.15356.

29. Silva ACB, Payeras MR, Koth VS, Cherubini K, Salum FG. Macroscopic and Histological Effects of Polycaprolactone Dermal Filler in the Orofacial Region: A Study in Rats. Cosmetics. 2024;11:130. doi:10.3390/cosmetics11040130.

30. Kwon T, Han SW, Yeo IK, Kim JH, Kim JM, Hong J, et al. Biostimulatory effects of polydioxanone, poly-d, l lactic acid, and polycaprolactone fillers in mouse model. J Cosmet Dermatol. 2019. doi:10.1111/jocd.12950.

31. Berlin AL, Hussain M, Goldberg DJ. Calcium hydroxylapatite filler for facial rejuvenation: a histologic and immunohistochemical analysis. Dermatol Surg. 2008;34(Suppl 1):S64–S67.