BIOLOGICAL MECHANISMS OF POLY-L-LACTIC ACID IN COLLAGEN BIOSTIMULATION UNDER CONDITIONS OF LIPOATROPHY ASSOCIATED WITH GLP-1 AGONIST USE

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Abstract

The use of glucagon-like peptide-1 (GLP-1) agonists has become established as an effective therapeutic strategy for the treatment of type 2 diabetes mellitus and obesity, promoting significant weight loss. However, marked reductions in adipose tissue, particularly in facial regions, may cause lipoatrophy characterized by loss of volume, skin laxity, and changes in skin quality. In this context, poly-L-lactic acid (PLLA) stands out as a collagen biostimulator widely used in clinical practice to restore dermal structure and promote facial rejuvenation. This study aims to analyze the biological mechanisms involved in the action of poly-L-lactic acid in collagen biostimulation under conditions of lipoatrophy associated with the use of GLP-1 agonists. This is a narrative literature review based on Brazilian and international scientific articles addressing the interactions among biomaterials, controlled inflammatory responses, tissue remodeling, and skin aging. The findings show that PLLA acts by inducing a subclinical and transient inflammatory response, triggering the activation of macrophages and fibroblasts. This process promotes the release of cytokines and growth factors, such as TGF-β, which stimulate neocollagenesis, particularly of types I and III collagen. Myofibroblasts also participate in the reorganization of the extracellular matrix, contributing to increased dermal firmness and thickness. Under conditions of GLP-1-induced lipoatrophy, which are characterized by a reduction in adipocytes and changes in adipokine signaling, the use of PLLA promotes the structural recovery of the skin, partially compensating for volume loss through the regeneration of connective tissue. It is concluded that poly-L-lactic acid represents an effective and

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safe therapeutic approach to collagen biostimulation in patients with lipoatrophy associated with GLP-1 agonist use, acting through multiple biological pathways related to inflammation, regeneration, and tissue remodeling. Nevertheless, further controlled clinical studies are required to deepen the understanding of its long-term effects and optimize application protocols.

Keywords: Poly-L-lactic acid; Collagen biostimulation; Lipoatrophy; GLP-1; Dermal remodeling.

INTRODUCTION

The contemporary healthcare landscape has been significantly affected by the emergence of glucagon-like peptide-1 (GLP-1) receptor agonist medications, which were initially developed to treat metabolic conditions such as type 2 diabetes mellitus and obesity. However, there has been a substantial increase in the use of these drugs to promote rapid weight loss. This process results in relevant systemic changes, including a reduction in subcutaneous fat compartments and adipose deposits, with evident effects on facial structure (DANESHGARAN; SHAULY; GOULD, 2025). In this context, it is necessary to understand the biological responses of skin tissue to these changes, particularly regarding the structural reorganization of the dermis and the adaptation of soft tissues to volume reduction.

In light of these transformations, the scientific literature has focused on investigating strategies that act on the extracellular matrix, emphasizing the induction of biological processes capable of promoting tissue reorganization. Poly-L-lactic acid (PLLA) is used in this context as a biostimulatory agent whose primary function is related to the induction of collagen synthesis through cellular activation (HADDAD et al., 2017). Accordingly, this study establishes a relationship between the effects of PLLA and the pathophysiological processes associated with the rapid loss of adipose tissue, contributing to an understanding of the mechanisms involved in the dermal response (FISHER et al., 2024).

Based on this framework, the following research question was formulated: What cellular mechanisms are involved in collagen biostimulation induced by poly-L-lactic acid under conditions of lipoatrophy associated with the use of GLP-1 agonists?

The relevance of this question is directly related to the growing use of these medications and the need for a deeper understanding of the biological processes that regulate the tissue response to reductions in adipose tissue. Volume loss causes changes in the cellular dynamics of the dermis, requiring adaptations involving fibroblasts, the extracellular matrix, and signaling pathways responsible for collagen synthesis. In this regard, the study investigated whether PLLA-induced biostimulation can modulate these processes and promote the structural reorganization of skin tissue (DE MOURA et al., 2024).

From this perspective, the study focuses on analyzing cellular mechanisms and tissue responses, moving away from approaches centered on visual outcomes and prioritizing an understanding of the biological processes underlying biostimulation. This focus enables a more in-depth analysis of the interactions between the biomaterial and the dermal microenvironment, including fibroblast activation, collagen deposition, and extracellular matrix remodeling.

The general objective of this study is to analyze the biological mechanisms underlying the action of poly-L-lactic acid in collagen biostimulation in skin tissues.

The content is organized into three main sections. First, it addresses the physiological basis of GLP-1 agonists and the effects of rapid weight loss on body composition, emphasizing the redistribution of adipose deposits. It then discusses the mechanism of action of PLLA as a biostimulator, highlighting its interaction with fibroblasts in the deep dermis and its induction of neocollagenesis (AO; YI; WU, 2024). Finally, it analyzes the development of the tissue response over time, including extracellular matrix reorganization, as well as guidelines regarding the safety and predictability of the biological response (RENDON, 2012).

The specific objectives are to describe the physiological effects of GLP-1 agonists on body composition, explain the cellular mechanisms involved in PLLA-induced biostimulation, and analyze the fibroblast response and the process of neocollagenesis in skin tissues.

The methodology of this study consisted of an exploratory and qualitative narrative review. The data sources included scientific databases such as PubMed and Google Scholar, covering publications from 2012 to 2025. The selection of this methodological design made it possible to integrate evidence from studies conducted at different levels of analysis, including long-term investigations and more recent reports, thereby providing a comprehensive understanding of the biological effects associated with the use of GLP-1 agonists and PLLA biostimulation. The literature analysis facilitated the identification of conceptual patterns and mechanisms shared across studies in dermatology and the biosciences, ensuring scientific rigor and consistency (RITA; SANTOS, 2025).

METHODOLOGY

This study is a qualitative, descriptive, and exploratory narrative literature review developed to understand the biological mechanisms involved in the action of poly-L-lactic acid (PLLA) in collagen biostimulation under conditions of lipoatrophy associated with the use of GLP-1 receptor agonists.

The theoretical framework of the study was developed through a bibliographic search of the PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases, conducted between January and March 2026. The search strategy employed controlled and uncontrolled descriptors in Portuguese and English, combined using the Boolean operators AND and OR, including the terms “poly-L-lactic acid,” “PLLA,” “collagen biostimulation,” “facial lipoatrophy,” “GLP-1 receptor agonists,” “semaglutide,” “tirzepatide,” “extracellular matrix,” “fibroblast activation,” “skin aging,” and “dermal remodeling.”

Scientific articles published between 2012 and 2025, available in full in English or Portuguese, were included when they addressed aspects related to the molecular and cellular mechanisms of PLLA, extracellular matrix remodeling, fibroblast activation, skin aging, dermal changes resulting from adipose tissue loss, and tissue effects associated with weight loss induced by GLP-1 agonists. Classic studies and reviews of recognized scientific relevance were also considered to provide a pathophysiological foundation and contextualize the subject.

The exclusion criteria comprised duplicate studies, articles not aligned with the subject, publications lacking verifiable bibliographic support, conference abstracts, editorials, opinions without a methodological foundation, and studies whose scientific traceability could not be confirmed in the databases consulted.

The selected material was analyzed using an interpretive and integrative approach, prioritizing studies with greater methodological consistency, scientific relevance, and clinical applicability. Although a narrative review allows for broad conceptual discussion and theoretical updating of the subject, the limitations inherent to this method are acknowledged, particularly those related to the absence of a systematic selection protocol, the possibility of interpretive bias, and the heterogeneity of the available evidence.

PHYSIOLOGICAL CHANGES INDUCED BY GLP-1 AGONISTS AND THEIR EFFECTS ON TISSUE STRUCTURE

REDUCTION OF ADIPOSE DEPOSITS AND REORGANIZATION OF SUBCUTANEOUS TISSUE

The use of glucagon-like peptide-1 (GLP-1) agonists has brought about major changes in the treatment of obesity and metabolic diseases associated with excess body weight. Initially developed to control blood glucose in patients with type 2 diabetes mellitus, these medications have become widely used in obesity management because of their high efficacy in reducing body weight. Recent studies show that drugs such as semaglutide, liraglutide, and tirzepatide can promote significant body-weight loss over relatively short periods, directly affecting body composition and adipose tissue distribution (Wilding et al., 2021; Jastreboff et al., 2022). In this context, scientific interest in the structural repercussions of the rapid reduction of adipose deposits, particularly in facial regions, has increased.

GLP-1 agonists act through different physiological mechanisms related to the regulation of energy metabolism. Their primary effects include reduced appetite, increased satiety, delayed gastric emptying, and modulation of the hypothalamic centers responsible for food intake (Müller et al., 2019).

Consequently, daily caloric intake decreases substantially, and the body's lipid stores are intensively mobilized. Although this reduction in adipose tissue is beneficial from metabolic and cardiovascular perspectives, it may cause significant changes in the structure of soft tissues, particularly in anatomical regions that are highly dependent on adipose support, such as the face.

The accelerated loss of subcutaneous fat caused by GLP-1 agonists has frequently been associated with the phenomenon popularly known as "Ozempic face," an expression used to describe facial changes resulting from rapid weight loss induced by semaglutide and similar medications. These changes include skin laxity, deepening folds, loss of facial volume, and an aged facial appearance (Kahan; McGowan, 2023). Although the term originated in the media, its broad discussion in the scientific literature demonstrates growing concern regarding the aesthetic effects associated with the prolonged use of these medications.

From an anatomical standpoint, facial adipose tissue plays a fundamental role in supporting the face and maintaining its aesthetic harmony. Superficial and deep adipose compartments contribute directly to facial contours, volume distribution, and the structural support of soft tissues. Recent studies show that the abrupt loss of these compartments can significantly alter facial architecture, favoring the development of tissue ptosis and a loss of anatomical definition (Cotofana et al., 2020). The malar, temporal, mandibular, and periorbital regions are particularly susceptible to volume changes induced by fat loss.

In addition to reduced adipose volume, substantial structural reorganization of the extracellular matrix occurs. The reduction in adipocytes alters the mechanical tension exerted on collagen and elastic fibers, compromising skin firmness and elasticity. According to Farage et al. (2019), skin aging and volume loss are closely related to the progressive degradation of dermal collagen and the reduced regenerative capacity of tissues. When fat loss occurs rapidly, as is frequently observed in patients using GLP-1 agonists, the skin's compensatory mechanisms become insufficient to maintain adequate tissue support.

The rate of weight loss is a determining factor in the severity of the observed facial changes. Recent clinical studies indicate that substantial weight reductions over a short period impede the physiological adaptation of the skin and underlying tissues, favoring more pronounced laxity and facial hollowing (Rubino et al., 2021). Unlike gradual weight loss, during which tissues have a greater capacity for structural reorganization, accelerated loss causes an imbalance between volume reduction and skin retraction.

Another relevant aspect concerns the uneven redistribution of facial fat. Adipose loss does not occur uniformly across the different anatomical compartments, contributing to disproportionate changes in facial contours. In many patients, marked reductions are observed in the malar and temporal regions, while other areas retain a relative amount of residual volume, resulting in evident aesthetic disharmony (Pessa; Rohrich, 2016). This heterogeneity reinforces the complexity of the facial changes associated with weight loss induced by GLP-1 agonists.

Changes in tissue vascularization are also noteworthy. Adipose tissue performs important metabolic and vascular functions, contributing to the nutrition and homeostasis of adjacent tissues. A significant reduction in adipocytes may partially compromise local microcirculation, interfering with cellular oxygenation, skin regeneration, and the physiological inflammatory response (Trayhurn, 2017). Consequently, some patients may experience deterioration in skin quality, increased dryness, and diminished facial radiance.

At the molecular level, adipose tissue loss directly affects the production of adipokines and inflammatory mediators involved in maintaining tissue homeostasis. Substances such as leptin, adiponectin, and proinflammatory cytokines perform important functions in the metabolic, immune, and structural regulation of the skin (Ouchi et al., 2011). The reduction in these mediators resulting from rapid adipose loss may affect mechanisms related to dermal regeneration and connective tissue integrity.

Facial biomechanics also undergo important changes following the volume loss induced by GLP-1 agonists. Reduced adipose support alters the distribution of mechanical forces during muscular

movement, increasing the visibility of expression lines and facial folds. Contemporary studies of facial anatomy demonstrate that structural facial aging is directly related to the progressive loss of adipose compartments and changes in facial ligament support (Rohrich et al., 2021).

Patient age is another relevant factor in the tissue response to accelerated weight loss. Younger patients tend to have greater skin elasticity and regenerative capacity, which promote more efficient adaptation to volume changes. Conversely, older individuals frequently have lower collagen production, reduced dermal elasticity, and a greater predisposition to facial laxity (Shin et al., 2019). Accordingly, the aesthetic effects of fat loss become more evident in older patients.

Recent literature also highlights the influence of genetic and hormonal factors on body and facial fat distribution. Different metabolic patterns may produce distinct responses to weight loss induced by GLP-1 agonists, explaining the clinical variability observed among patients (Srivastava; Apovian, 2018). Some individuals experience early and severe facial fat loss, whereas others retain a relative degree of facial volume even after substantial reductions in body weight.

In addition to their anatomical and structural repercussions, facial changes associated with rapid weight loss can significantly affect patients' perceptions of their self-image and self-esteem. Although many individuals report satisfaction with their body-weight loss, some experience discomfort with facial changes related to an aged appearance and skin laxity. Recent studies indicate that facial appearance strongly influences the subjective perception of health, youthfulness, and psychological well-being (Dayan et al., 2020).

Given these changes, interest is growing in therapeutic approaches intended to restore structural facial support. Procedures such as hyaluronic acid fillers, collagen biostimulation, microfocused ultrasound, and regenerative technologies have been widely used to minimize the aesthetic effects of facial fat loss (Goldie et al., 2022). These strategies seek to restore lost volume, stimulate collagen production, and improve overall skin quality.

Collagen biostimulation has gained particular prominence in the context of patients who experience accelerated weight loss. Substances such as calcium hydroxyapatite and poly-L-lactic acid stimulate biological mechanisms related to neocollagenesis, progressively improving skin firmness and facial support (Hexsel et al., 2020). These procedures have frequently been associated with the aesthetic management of facial changes resulting from GLP-1 agonist use.

Another important contemporary consideration is the need for interdisciplinary monitoring of these patients. Endocrinologists, dermatologists, nutritionists, and aesthetic medicine professionals should work collaboratively to assess the metabolic and structural repercussions associated with weight loss. This multidisciplinary approach enables the early identification of significant facial changes and the establishment of individualized therapeutic strategies.

An analysis of the changes induced by GLP-1 agonists shows that the reduction in adipose deposits extends beyond the metabolic benefits traditionally associated with weight loss. Although these medications represent major advances in the treatment of obesity, their effects on facial structure demonstrate the complex relationship among metabolism, body composition, and skin aging.

Therefore, the reorganization of subcutaneous tissue resulting from accelerated fat loss is a multifactorial process involving anatomical, histological, biomechanical, and psychological changes. An in-depth understanding of these mechanisms is essential to developing preventive and therapeutic strategies capable of minimizing adverse effects on facial aesthetics and improving the quality of life of patients undergoing treatment with GLP-1 agonists.

TISSUE RESPONSE TO LIPOATROPHY AND ADAPTATION OF THE EXTRACELLULAR MATRIX

Lipoatrophy is characterized by a localized or generalized reduction in subcutaneous adipose tissue, causing significant structural, metabolic, and functional changes in the skin and adjacent tissues. In recent years, this phenomenon has received greater scientific attention because of the marked increase in

cases of accelerated weight loss associated with the use of glucagon-like peptide-1 (GLP-1) agonists, such as semaglutide and tirzepatide. The rapid mobilization of the body's lipid stores causes a significant reduction in facial and body adipose support, triggering a series of adaptive responses in the extracellular matrix (ECM), the structure responsible for the biomechanical support and integrity of the skin (Wilding et al., 2021; Jastreboff et al., 2022).

The extracellular matrix is a complex three-dimensional system composed of collagen fibers, elastic fibers, proteoglycans, adhesive glycoproteins, and hyaluronic acid. It plays an essential role in maintaining skin firmness, elasticity, and hydration. The abrupt reduction of adipose tissue directly alters the dynamics of this microenvironment, causing structural disorganization and compromising the skin's mechanical properties (Theocharis et al., 2016). These changes become particularly evident in regions affected by substantial volume loss, such as the face, where dermal support depends heavily on the interaction between the adipose compartments and the ECM.

The loss of adipose support significantly reduces the mechanical tension exerted on dermal fibroblasts, which are fundamental to collagen synthesis and remodeling. Recent studies show that mechanical stimuli are indispensable for maintaining fibroblast activity and dermal homeostasis. When tissue tension decreases abruptly, the production of types I and III collagen declines, directly compromising skin firmness and strength (Wang et al., 2016). Consequently, the dermis becomes thinner, more lax, and more susceptible to wrinkles and surface irregularities.

In addition to reducing the quantity of collagen fibers, lipoatrophy causes substantial structural disorganization of these fibers. Contemporary research in skin biology demonstrates that accelerated weight loss may induce collagen fiber fragmentation and alter the three-dimensional architecture of the dermal matrix (Quan et al., 2015). This process reduces the skin's ability to distribute mechanical forces evenly, promoting the development of depressions, deep folds, and loss of anatomical facial contours.

Elastic fibers also undergo significant changes during the process of tissue adaptation to lipoatrophy. These fibers are responsible for the skin's elasticity and capacity for retraction, but they

progressively deteriorate because of increased activity by proteolytic enzymes, particularly matrix metalloproteinases (MMPs). According to Shin et al. (2019), excessive activation of these enzymes is associated with accelerated skin aging and the loss of dermal elasticity observed in patients who undergo rapid weight reduction.

MMP activation frequently occurs in response to subclinical inflammatory processes triggered by the intensive remodeling of adipose tissues. During accelerated fat loss, inflammatory mediators are released and may stimulate catabolic pathways responsible for extracellular matrix degradation (Kruglikov; Scherer, 2018). Although ECM remodeling is necessary for tissue adaptation, excessive degradation compromises the skin's structural integrity and promotes significant aesthetic changes.

Another relevant aspect is the reduction in glycosaminoglycans and proteoglycans within the extracellular matrix, particularly hyaluronic acid. These molecules have a high capacity for water retention and play a fundamental role in maintaining skin hydration, viscosity, and turgor. Recent studies show that volume loss associated with lipoatrophy significantly reduces the concentration of these components in the dermis, contributing to a dry, dull, and aged skin appearance (Papakonstantinou et al., 2019).

The skin's adaptive response involves a compensatory attempt to reorganize the ECM through fibroblast activation. Initially, fibroblasts increase their biosynthetic activity in an attempt to partially restore the tissue's structural integrity. However, in cases of severe and prolonged adipose loss, this response tends to become insufficient, particularly in individuals with preexisting skin aging or reduced regenerative capacity (Sriram et al., 2015). Consequently, dermal reorganization remains incomplete and is often disordered.

Communication between adipocytes and fibroblasts represents another important mechanism in the maintenance of tissue homeostasis. Adipose tissue performs relevant endocrine functions through the secretion of adipokines, cytokines, and growth factors involved in dermal regeneration and skin metabolism. During lipoatrophy, the levels of these bioactive substances decrease significantly,

compromising processes related to collagen synthesis, tissue repair, and a balanced inflammatory response (Ghaben; Scherer, 2019).

Vascular changes also play an important role in the tissue response to adipose loss. Adipose tissue is highly vascularized and contributes directly to the maintenance of local microcirculation. A reduction in adipose compartments may partially compromise the dermal blood supply, decreasing the availability of oxygen and essential nutrients to skin cells (Sriram et al., 2015). Consequently, some patients develop changes related to tissue hypoxia, which impair physiological regenerative mechanisms.

Hypoxia induced by reduced vascularization activates molecular factors related to extracellular matrix remodeling, particularly hypoxia-inducible factor 1-alpha (HIF-1α). Although this mechanism participates in cellular adaptation to reduced oxygen availability, its prolonged activation may contribute to fibrotic changes and structural disorganization of the ECM (Zhang et al., 2021). This process demonstrates the complexity of the cellular responses triggered by lipoatrophy.

Extracellular matrix reorganization also produces important changes in the spatial orientation of dermal fibers. Electron microscopy studies show that severe adipose loss alters the normal parallel arrangement of collagen and elastic fibers, making them more irregular and fragmented (Quan; Fisher, 2015). This structural change significantly diminishes the skin's biomechanical capacity, promoting permanent deformities and skin laxity.

Clinically, these changes manifest as a loss of firmness, deepened folds, laxity, and surface irregularities. In patients experiencing rapid weight loss induced by GLP-1 agonists, such changes become especially evident in the facial region, where volume reduction is more readily perceptible. The phenomenon popularly known as "Ozempic face" represents the clinical manifestation of these structural changes associated with ECM reorganization and facial fat loss (Kahan; McGowan, 2023).

Age is a determining factor in the severity of the tissue response to lipoatrophy. Younger patients generally have greater fibroblast activity, better dermal vascularization, and greater regenerative capacity, which promotes more efficient adaptation to volume changes. Conversely, older individuals have a

physiological reduction in collagen synthesis, diminished skin elasticity, and a progressive accumulation of oxidative damage, intensifying the structural effects of adipose loss (Farage et al., 2020).

External factors also directly influence the adaptive capacity of the extracellular matrix. Chronic exposure to ultraviolet radiation, for example, accelerates dermal collagen degradation through metalloproteinase activation and increased oxidative stress. Recent studies indicate that patients with a substantial history of photoaging are more predisposed to laxity and poorer structural recovery after accelerated weight loss (Rittié; Fisher, 2021).

In addition to its structural repercussions, lipoatrophy may have a significant psychological impact on patients. Facial volume loss is frequently associated with the perception of premature aging, fatigue, and physical frailty, directly influencing self-esteem and body satisfaction. Contemporary studies in aesthetic dermatology show that facial changes resulting from rapid weight loss may adversely affect individuals' quality of life and emotional well-being (Dayan et al., 2020).

Given this scenario, interest is growing in therapeutic strategies aimed not only at restoring volume but also at functionally restoring the extracellular matrix. Biostimulatory procedures have been widely used in an attempt to stimulate neocollagenesis, dermal reorganization, and improved skin firmness. Substances such as poly-L-lactic acid and calcium hydroxyapatite have shown promising results in the partial correction of structural changes induced by lipoatrophy (Goldie et al., 2022).

Regenerative technologies involving microfocused ultrasound, radiofrequency, and fractional lasers have also been used as complementary tools in the management of laxity resulting from accelerated adipose loss. These approaches provide controlled thermal stimulation, promoting collagen fiber reorganization and improved dermal quality (Hexsel et al., 2020).

Therefore, the tissue response to lipoatrophy is a multifactorial, complex, and dynamic process involving cellular, biochemical, structural, and functional changes in the extracellular matrix. An in-depth understanding of these mechanisms is essential to developing more effective and individualized

therapeutic strategies that can minimize the aesthetic and functional effects associated with the rapid adipose loss observed in patients treated with GLP-1 agonists.

CELLULAR IMPLICATIONS OF ADIPOSE LOSS FOR FIBROBLASTS AND COLLAGEN SYNTHESIS

The loss of subcutaneous adipose tissue, a central feature of lipoatrophy, produces a series of profound cellular effects within the dermal microenvironment, directly affecting fibroblast activity and, consequently, collagen synthesis. This phenomenon is not limited to a passive structural change; rather, it constitutes a biologically active process in which the absence of adipocytes compromises the complex intercellular signaling network responsible for maintaining skin homeostasis (Kim et al., 2021). Recent studies show that adipose tissue performs important endocrine and paracrine functions, directly influencing dermal regeneration, fibroblast activity, and extracellular matrix organization. Accordingly, the accelerated adipose loss observed in lipoatrophy has significant repercussions for the skin's structural and functional integrity.

Fibroblasts, the principal cells responsible for producing extracellular matrix components, are highly sensitive to mechanical and biochemical changes in the dermal microenvironment. A reduction in adipose tissue entails not only diminished physical support but also the loss of bioactive mediators secreted by adipocytes, which are fundamental to the regulation of fibroblast activity and collagen synthesis (Lee et al., 2022). Contemporary research indicates that communication between adipocytes and fibroblasts plays an essential role in maintaining skin homeostasis, influencing regenerative, inflammatory, and metabolic processes related to skin aging.

The primary mediators involved in this process include adipokines such as leptin, adiponectin, and resistin, which modulate the inflammatory response, cellular proliferation, and tissue remodeling. The reduction in these adipokines under conditions of lipoatrophy significantly compromises fibroblast activation, resulting in decreased collagen synthesis and qualitative changes in the dermal fibers produced

(Savoia et al., 2020). Furthermore, recent studies show that a deficiency of these molecules promotes the development of a proinflammatory and catabolic environment, intensifying degenerative processes in the extracellular matrix.

Another relevant aspect concerns the influence of lipoatrophy on the transforming growth factor-beta (TGF-β) signaling pathway, which is considered one of the primary regulatory mechanisms of dermal fibrogenesis. Adequate activation of this pathway is essential for fibroblast differentiation, the synthesis of types I and III collagen, and the maintenance of the structural organization of the extracellular matrix (Wang et al., 2021). In environments characterized by severe adipose loss, TGF-β-mediated signaling is impaired, reducing the expression of genes related to collagen production and the regenerative capacity of skin tissue.

At the same time, recent studies have identified changes in the Wnt/β-catenin pathway, an important regulator of fibroblast proliferation and dermal integrity. Negative modulation of this pathway reduces cellular proliferative capacity and compromises the adequate synthesis of extracellular matrix components, exacerbating the structural effects of lipoatrophy (Humphrey et al., 2023). These changes promote the development of a less dense, less organized, and biomechanically weakened matrix, contributing to laxity, folds, and skin irregularities.

Another important factor is the influence of lipoatrophy on signaling mediated by insulin-like growth factor 1 (IGF-1), whose activity is essential to cell survival and fibroblast metabolism. Recent research shows that reduced IGF-1 activity in the skin microenvironment compromises collagen synthesis, dermal regeneration, and the skin's reparative response (Kapoor et al., 2024). A deficiency of this growth factor is also associated with increased dermal fragility and accelerated skin aging.

The reduction in mechanical stimulation resulting from adipose volume loss also significantly affects fibroblast activity. Mechanotransduction, the process through which mechanical stimuli are converted into cellular biochemical responses, is fundamental to the regulation of collagen synthesis and extracellular matrix organization. Under conditions of lipoatrophy, reduced mechanical tension

diminishes fibroblast activity and the expression of proteins related to cell adhesion and tissue stability (Goldie et al., 2023). This dysfunction compromises the ability of fibroblasts to respond adequately to environmental stimuli and maintain the structural integrity of the dermis.

In addition to structural changes, lipoatrophy is frequently associated with chronic low-grade inflammation characterized by the persistent release of proinflammatory cytokines such as TNF-α and IL-6. These molecules inhibit collagen synthesis and stimulate the production of matrix metalloproteinases (MMPs), enzymes responsible for degrading dermal components (Friedman et al., 2023). Excessive MMP activation creates a catabolic environment in which collagen fiber degradation exceeds the tissue's capacity for replacement, resulting in a progressive loss of skin firmness and elasticity.

Another mechanism widely discussed in contemporary literature concerns the role of oxidative stress in the dermal deterioration associated with lipoatrophy. Increased production of reactive oxygen species (ROS) directly compromises fibroblast function and promotes oxidative damage to proteins, lipids, and cellular DNA (Hexsel et al., 2021). This process contributes to cellular senescence, reducing fibroblast proliferative capacity and exacerbating deficiencies in collagen production and extracellular matrix renewal.

Recent research also indicates that adipose loss may trigger important epigenetic changes in fibroblasts, involving mechanisms such as DNA methylation, microRNA regulation, and histone modifications. These changes directly influence the expression of genes related to collagen synthesis and tissue regeneration (Zhang et al., 2021). Consequently, the skin's reparative capacity becomes progressively impaired, and the structural changes associated with lipoatrophy worsen.

Intercellular communication among fibroblasts, keratinocytes, endothelial cells, and adipocytes also undergoes significant changes in environments characterized by adipose loss. This interaction is essential to coordinating regenerative processes and maintaining dermal homeostasis. Contemporary studies show that interruption of these communication pathways compromises the healing response,

angiogenesis, and extracellular matrix remodeling (Lee et al., 2022). Consequently, the skin becomes structurally more fragile and functionally less efficient.

Functionally, reduced collagen synthesis causes a decrease in dermal thickness, a loss of mechanical strength, and greater susceptibility to permanent deformation. Moreover, collagen produced under conditions of lipoatrophy consists of thinner, disorganized fibers with a reduced capacity to provide structural support (Humphrey et al., 2023). These changes contribute to the folds, skin depressions, and laxity frequently observed in patients who experience substantial weight loss.

The recovery of these processes depends on multiple factors, including age, nutritional status, genetic predisposition, and the presence of appropriate therapeutic interventions. In this context, strategies aimed at dermal biostimulation have gained prominence in contemporary scientific literature. Collagen biostimulators such as poly-L-lactic acid, calcium hydroxyapatite, and polycaprolactone have demonstrated an ability to activate fibroblasts, stimulate neocollagenesis, and promote structural reorganization of the extracellular matrix (Lemos; Moraes, 2020). These therapies contribute significantly to improvements in dermal firmness, elasticity, and quality in patients with facial lipoatrophy.

The cellular implications of adipose loss for fibroblasts and collagen synthesis therefore constitute a complex, multifactorial, and dynamic process involving changes in cellular signaling pathways, oxidative metabolism, intercellular communication, and tissue remodeling. An in-depth understanding of these mechanisms is essential to developing more effective therapeutic strategies capable of minimizing the structural effects of lipoatrophy and promoting greater preservation of dermal integrity and skin quality.

CELLULAR MECHANISMS OF POLY-L-LACTIC ACID IN COLLAGEN BIOSTIMULATION

INTERACTION OF PLLA WITH DERMAL TISSUE AND THE CONTROLLED INFLAMMATORY RESPONSE

Poly-L-lactic acid (PLLA) is a biocompatible and biodegradable synthetic polymer widely used in contemporary regenerative aesthetic medicine, particularly in protocols aimed at collagen biostimulation

and dermal remodeling. Unlike traditional fillers that act exclusively by adding volume, PLLA acts through complex biological mechanisms capable of stimulating progressive and sustained cellular responses in dermal tissue, thereby promoting structural regeneration of the extracellular matrix (Humphrey et al., 2022). Recent studies show that PLLA use is directly associated with gradual increases in skin firmness, improved dermal quality, and prolonged stimulation of neocollagenesis, and it is widely used to treat facial aging and lipoatrophy.

Following its administration into the subcutaneous tissue or deep dermis, PLLA microparticles are recognized by the innate immune system as biodegradable foreign bodies. However, this interaction does not trigger an excessive inflammatory response. Instead, it produces a subclinical, controlled, and physiologically regulated inflammatory process that is essential to activating the regenerative mechanisms responsible for tissue biostimulation (Goldie et al., 2023). This therapeutic inflammatory response constitutes the biological basis of the clinical effects observed after PLLA administration.

The first relevant biological event in this process is the adsorption of plasma proteins onto the surface of the PLLA particles, forming a bioactive layer that promotes cellular recruitment and interaction with immune cells, particularly macrophages and dendritic cells. Recent research shows that this biomaterial-tissue interface plays a fundamental role in modulating the inflammatory response and determining the intensity of dermal biostimulation (Kim et al., 2021). This initial interaction leads to the controlled activation of the regenerative inflammatory cascade.

Macrophages play a central role in this mechanism and are recruited to the administration site through cytokine- and local inflammatory factor-mediated chemotaxis. Contemporary studies indicate that PLLA predominantly favors macrophage polarization toward the M2 phenotype, which is associated with anti-inflammatory, reparative, and proregenerative processes (Lee et al., 2022). The predominance of the M2 profile distinguishes PLLA from potentially proinflammatory materials and contributes to its high biocompatibility and clinical safety.

During this process, activated macrophages release several important biochemical mediators, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). These substances act directly on dermal fibroblasts, stimulating cellular proliferation, collagen synthesis, and extracellular matrix reorganization (Kapoor et al., 2024). Consequently, a microenvironment conducive to the progressive regeneration of dermal tissue is established.

Fibroblast activation represents one of the primary mechanisms involved in PLLA-induced biostimulation. Once stimulated, fibroblasts significantly increase their metabolic activity and initiate the progressive synthesis of types I and III collagen, fibers that are fundamental to dermal support and strength. Unlike conventional fillers, whose effects depend exclusively on the physical presence of the product, PLLA produces a prolonged biological response capable of stimulating neocollagenesis even after its partial degradation (Savoia et al., 2020).

In addition to collagen synthesis, recent studies show that PLLA also promotes the production of elastin, fibronectin, and proteoglycans, which are fundamental to maintaining the skin's elasticity, hydration, and structural integrity (Friedman et al., 2023). This integrated response progressively improves skin firmness, texture, and overall dermal quality, justifying the widespread use of PLLA in facial and body rejuvenation protocols.

Another relevant aspect is the gradual hydrolytic degradation of PLLA. Following administration, the polymer undergoes slow and continuous hydrolysis, releasing lactic acid, a substance naturally metabolized by the body through the Krebs cycle. This progressive degradation maintains a low-level controlled inflammatory stimulus over extended periods, promoting sustained fibroblast activation and continuous collagen production (Humphrey et al., 2022). This mechanism explains the long duration of the clinical results associated with PLLA.

The formation of microscopic fibrous capsules around the PLLA particles is also part of the physiological process of tissue integration. These structures consist predominantly of newly synthesized

collagen, activated fibroblasts, and mononuclear inflammatory cells. Unlike pathological granulomatous reactions, this response represents a physiological mechanism for tissue repair and stabilization of the biomaterial (Goldie et al., 2023).

At the molecular level, the interaction between PLLA and dermal tissue involves the activation of important intracellular signaling pathways, particularly the TGF-β/Smad pathway, which regulates the expression of genes related to fibrogenesis and extracellular matrix remodeling. Activation of this pathway promotes fibroblast differentiation and increases cellular biosynthetic capacity, favoring organized collagen synthesis and the structural strengthening of the dermis (Wang et al., 2021).

At the same time, the activity of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) is modulated in a balanced manner, promoting a physiological equilibrium between collagen degradation and synthesis. Recent studies indicate that PLLA assists dermal reorganization by stimulating controlled extracellular matrix remodeling without causing excessive degradation of structural fibers (Hexsel et al., 2021).

Angiogenesis is also an important component of the regenerative response induced by PLLA. The local release of VEGF during the controlled inflammatory response promotes the formation of new blood vessels, improving the supply of oxygen, nutrients, and growth factors to dermal tissue (Lee et al., 2022). This increase in vascularization directly contributes to metabolic improvement in the tissue and enhances its regenerative mechanisms.

From an immunological perspective, PLLA has low antigenic potential and high biocompatibility, factors that justify its widespread use in minimally invasive aesthetic procedures. Recent research shows low rates of serious adverse reactions when the product is properly diluted and administered in accordance with appropriate protocols (Kapoor et al., 2024). PLLA has therefore become established as an important therapeutic tool in contemporary regenerative aesthetic medicine.

Another relevant aspect is the concept of “therapeutic inflammation,” which has been widely discussed in recent literature on dermal biostimulation. Under this model, controlled immune system

activation is strategically used to stimulate physiological mechanisms of tissue repair and extracellular matrix regeneration (Friedman et al., 2023). PLLA is one of the leading examples of this bioregenerative approach as applied to aesthetic dermatology.

The homogeneous distribution of PLLA particles within the tissue is a fundamental factor in obtaining satisfactory results and preventing complications such as nodules and irregularities. Current studies emphasize the importance of administration technique, proper dilution, and the correct anatomical plane in optimizing the regenerative response and ensuring the clinical safety of the procedure (Goldie et al., 2023).

Moreover, individual factors such as age, immune status, degree of skin aging, and the patient's metabolic characteristics may significantly influence the intensity of the inflammatory response and the biostimulatory capacity of PLLA. Therapeutic individualization is therefore essential to maximizing clinical results and reducing adverse events (Kim et al., 2021).

An in-depth understanding of the cellular, immunological, and molecular mechanisms involved in the interaction between PLLA and dermal tissue enables the continuous refinement of biostimulation techniques and the development of safer and more effective therapeutic protocols. Poly-L-lactic acid therefore acts as an important bioregenerative agent capable of progressively stimulating collagen synthesis, reorganizing the extracellular matrix, and significantly improving skin quality through a carefully regulated subclinical inflammatory response.

FIBROBLAST ACTIVATION AND INDUCTION OF NEOCOLLAGENESIS

Fibroblast activation and the induction of neocollagenesis mediated by poly-L-lactic acid (PLLA) constitute a highly complex biological phenomenon in which cellular, molecular, and biochemical events responsible for the progressive restoration of dermal architecture are intertwined. Far from being limited to a merely volumizing effect, PLLA acts as a modulator of the tissue microenvironment, triggering a

sustained regenerative response based on the functional reprogramming of fibroblasts (SADICK et al., 2019).

Following the establishment of the subclinical inflammatory stimulus described above, a biochemical environment conducive to fibroblast activation develops, characterized by the abundant release of soluble mediators such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). These molecules play a central role in orchestrating the regenerative response by promoting the transition of fibroblasts from a quiescent state to a metabolically active phenotype (CABRAL et al., 2021).

In this context, fibroblasts exhibit a marked increase in their biosynthetic activity, with intensified gene transcription and translation processes directed toward the production of structural proteins. This functional reprogramming results in the substantial synthesis of type III collagen during the initial stages, which serves as a provisional matrix for the subsequent deposition of more robust and organized type I collagen (THEOCHARIS et al., 2019).

The TGF-β/Smad signaling pathway emerges as a fundamental molecular axis governing this process, promoting the activation of genes responsible for fibrogenesis and extracellular matrix organization. The translocation of Smad complexes into the cell nucleus triggers the expression of structural and regulatory proteins, consolidating the process of neocollagenesis (MASSAGUÉ, 2012).

Concurrently, activation of the MAPK/ERK pathway contributes to fibroblast proliferation and amplification of the cellular response, demonstrating the existence of an intricate intracellular signaling network that sustains dermal regeneration. The synergy between these pathways strengthens the magnitude of the PLLA-induced response (SUN et al., 2020).

Another highly relevant event is the differentiation of fibroblasts into myofibroblasts, cells with contractile properties and a high secretory capacity. This phenotypic transition, mediated by mechanical and biochemical stimuli, contributes significantly to collagen deposition and organization within the extracellular matrix (HINZ, 2021).

PLLA-induced neocollagenesis is progressive and cumulative, reflecting the polymer's slow and continuous degradation. This characteristic ensures the persistence of cellular stimuli over time, enabling the formation of a denser, more cohesive, and functionally efficient dermal matrix (LORENC; FAGIEN, 2021).

Extracellular matrix reorganization extends beyond the simple deposition of collagen fibers and involves the spatial reorientation of these structures to restore the appropriate distribution of mechanical forces within the tissue. This structural rearrangement is decisive for restoring the biomechanical integrity of the skin (TRACY et al., 2022).

Within tissue remodeling, the regulation of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) plays a crucial role. The balance between collagen degradation and synthesis ensures orderly matrix renewal, preventing both degeneration and disorganized fibrosis (KAPOOR et al., 2021).

Angiogenesis, stimulated by the release of factors such as VEGF, provides additional support for fibroblast activity. Increased local vascularization promotes the supply of oxygen and nutrients essential to maintaining cellular metabolic activity (GUREVICH et al., 2021).

Furthermore, paracrine interactions between fibroblasts and immune cells perpetuate the regenerative stimulus even after the initial inflammatory response has subsided. This intercellular communication demonstrates the integrated and systemic nature of the neocollagenesis process (RODRIGUES et al., 2019).

Lactic acid, a product of PLLA degradation, also modulates the dermal microenvironment by participating in metabolic pathways that promote fibroblast activation and collagen synthesis. Its action further demonstrates the biochemical complexity of the process (ANDERSON et al., 2020).

From a biomechanical perspective, the progressive deposition of collagen increases dermal thickness and tensile strength, contributing to the restoration of skin firmness and elasticity. These changes are directly reflected in the clinical improvement observed (HEXSEL et al., 2020).

The quality of the synthesized collagen is a determining factor in the durability of the results, with type I collagen being responsible for forming a more organized and resistant matrix. The transition from type III to type I collagen represents an essential stage in tissue maturation (FRANTZ et al., 2021).

However, the fibroblast response to PLLA is not uniform and is modulated by individual variables such as age, metabolic status, and intrinsic regenerative capacity. These factors directly influence the intensity and quality of neocollagenesis (FARAGE et al., 2020).

The PLLA administration technique also plays a determining role in treatment efficacy, as the homogeneous distribution of the product ensures uniform cellular stimulation and prevents structural irregularities (SADICK et al., 2019).

Repeated treatment sessions enhance the fibroblast response, producing a cumulative effect that intensifies collagen deposition and extracellular matrix reorganization (CABRAL et al., 2021).

An in-depth understanding of these mechanisms has driven significant advances in regenerative medicine, enabling the development of increasingly precise and effective therapeutic protocols (GOLDIE et al., 2022).

In this context, PLLA has become established as a biostimulatory agent of considerable clinical relevance because it promotes not only volume restoration but also the functional restructuring of dermal tissue (MORAES et al., 2022).

Fibroblast activation and the induction of neocollagenesis by poly-L-lactic acid constitute a multifaceted process in which signaling pathways, biochemical mediators, and cellular mechanisms interact, culminating in the progressive regeneration of the extracellular matrix and restoration of skin integrity.

LONG-TERM TISSUE REMODELING AND EXTRACELLULAR MATRIX DYNAMICS

Long-term tissue remodeling induced by poly-L-lactic acid (PLLA) is a highly sophisticated biological process in which the progressive degradation of the polymer is intrinsically coordinated with

its replacement by endogenous collagen, culminating in the sustained restructuring of the extracellular matrix (ECM). This phenomenon transcends the immediacy associated with conventional fillers and falls within the field of regenerative medicine because it promotes lasting changes in the architecture and functionality of dermal tissue (LORENC; FAGIEN, 2021).

It should first be emphasized that PLLA, as a semicrystalline aliphatic polymer, undergoes degradation predominantly through the nonenzymatic hydrolysis of its ester bonds, a process that occurs slowly and continuously within the physiological environment. This characteristic gives the material prolonged degradation kinetics, allowing biological stimuli to be maintained for months or even years after implantation (ANDERSON et al., 2020).

PLLA hydrolysis results in the formation of oligomers and, subsequently, lactic acid monomers, which are readily metabolized by the body through the Krebs cycle. This metabolic pathway ensures not only the material's biocompatibility but also the absence of an accumulation of toxic by-products, which is crucial to the clinical safety of the biomaterial (CHRISTENSEN et al., 2020).

As the polymer degrades, PLLA particles are progressively replaced by newly formed connective tissue characterized by the deposition of endogenous collagen. This replacement process lies at the heart of biostimulation because it transforms a temporary exogenous material into an autologous, functional biological structure (SADICK et al., 2019).

Collagen deposition occurs in an organized and sequential manner, beginning with the formation of more immature and reticular type III collagen, followed by its gradual replacement with type I collagen, which is structurally more robust and responsible for the mechanical strength of the dermis. This phenomenon reflects the classic process of extracellular matrix maturation (THEOCHARIS et al., 2019).

In this context, extracellular matrix dynamics are governed by a delicate balance between synthesis and degradation, mediated by the coordinated activity of fibroblasts, matrix metalloproteinases

(MMPs), and their tissue inhibitors (TIMPs). This balance is essential to ensuring orderly remodeling and preventing both excessive degradation and the formation of disorganized fibrosis (KAPOOR et al., 2021).

The persistence of cellular stimuli resulting from the gradual degradation of PLLA maintains fibroblast activity at moderate but constant levels. This sustained activation promotes continuous collagen deposition and the progressive reorganization of the ECM, lending durability to the clinical results (HEXSEL et al., 2020).

Histologically, a denser dermal matrix develops, with thick, well-organized collagen fibers arranged parallel to the skin surface. This structural reorganization contributes significantly to improving the skin's biomechanical properties, including strength, elasticity, and support capacity (TRACY et al., 2022).

The tissue restructuring promoted by PLLA also involves restoring interactions among different extracellular matrix components, such as elastin, fibronectin, and proteoglycans. This functional integration is fundamental to maintaining skin homeostasis and preserving dermal integrity over time (FRANTZ et al., 2021).

Another relevant aspect is the modulation of inflammatory cell activity during the remodeling process. As PLLA is degraded, the inflammatory response gradually diminishes, and an anti-inflammatory and regenerative environment favorable to the stabilization of newly formed tissue becomes predominant (MANTOVANI et al., 2019).

Angiogenesis plays a complementary role in this process by ensuring an adequate supply of oxygen and nutrients to the cells involved in remodeling. The formation of new blood vessels contributes to tissue vitality and the maintenance of fibroblast metabolic activity (GUREVICH et al., 2021).

In the long term, the replacement of PLLA with endogenous collagen results in the formation of tissue that not only reproduces but often improves upon the structural characteristics of the original dermis. This qualitative regeneration distinguishes PLLA from other biomaterials and reinforces its therapeutic relevance (GOLDIE et al., 2022).

The stability of the newly formed collagen is influenced by cross-linking and fibrillar reorganization processes, which confer greater resistance to enzymatic degradation. This structural maturation determines the durability of the observed clinical effects (FRANTZ et al., 2021).

Moreover, extracellular matrix remodeling entails the redistribution of mechanical forces within the tissue, promoting better adaptation to physiological stresses. This biomechanical rearrangement helps prevent deformities and maintain skin contours (TRACY et al., 2022).

However, the tissue response to PLLA is not static and is continuously modulated by intrinsic factors such as aging and cellular metabolism, as well as extrinsic factors such as sun exposure and lifestyle habits. These variables influence the longevity of the results obtained (FARAGE et al., 2020).

The possibility of periodically readministering PLLA allows the effects of tissue remodeling to be maintained and enhanced, serving as a strategy for the continuous stimulation of neocollagenesis and the preservation of dermal quality (SADICK et al., 2019).

Clinically, sustained tissue remodeling translates into progressive improvements in skin firmness, elasticity, and thickness, as well as the attenuation of folds and irregularities. These results reflect the efficacy of PLLA as a long-term biostimulatory agent (HEXSEL et al., 2020).

A thorough understanding of extracellular matrix dynamics in the context of PLLA biostimulation is essential to developing more precise and individualized therapeutic protocols capable of maximizing clinical benefits and minimizing possible complications (GOLDIE et al., 2022).

In this regard, PLLA represents an innovative and sophisticated approach in the field of regenerative aesthetics because it promotes the gradual and sustained transformation of dermal tissue based on fundamental biological principles (MORAES et al., 2022).

Long-term tissue remodeling and extracellular matrix dynamics induced by poly-L-lactic acid therefore constitute a continuous and self-regulated process in which polymer degradation is accompanied by its replacement with endogenous collagen, resulting in the lasting restructuring of the dermis and the

maintenance of its structural and functional integrity.

LIMITATIONS, SAFETY, AND ADVERSE EVENTS

Although poly-L-lactic acid (PLLA) has important applications in regenerative medicine and collagen biostimulation, the observed clinical results depend on multiple factors, including the administration technique, product preparation and dilution, depth of the injection plane, individual anatomical characteristics, and each patient's tissue inflammatory response (HADDAD et al., 2017; HUMPHREY et al., 2022; LORENC; FAGIEN, 2021). Therapeutic predictability may therefore vary significantly among individuals.

The literature shows that PLLA has a satisfactory safety profile when properly indicated and administered by qualified professionals (SADICK et al., 2019; HEXSEL et al., 2020). However, transient and delayed adverse events have been reported, including edema, erythema, local pain, bruising, papule formation, subcutaneous nodules, contour irregularities, and, less frequently, persistent inflammatory granulomas (HUMPHREY et al., 2022; GOLDIE et al., 2023). These complications reinforce the importance of appropriate patient selection, in-depth anatomical knowledge, and continuous clinical follow-up (HADDAD et al., 2017).

In addition, the literature specifically addressing the use of PLLA in patients with facial lipoatrophy associated with GLP-1 receptor agonist use remains significantly limited. Most of the available evidence focuses on physiological skin aging, conventional weight loss, or general aesthetic applications (KAHAN; MCGOWAN, 2023; DANESHGARAN; SHAULY; GOULD, 2025), and there is a scarcity of prospective, standardized, and long-term clinical studies focused on this specific patient population.

In this context, although the biological mechanisms described suggest promising therapeutic potential, further studies are required to establish more robust parameters regarding the clinical efficacy, durability of results, long-term safety, and biological effects of PLLA in patients undergoing weight loss

induced by GLP-1 agonists (AO; YI; WU, 2024; KAPOOR et al., 2024).

Finally, because this is a narrative review, the present study does not possess the methodological rigor characteristic of systematic reviews and meta-analyses and is subject to limitations related to reference selection, interpretation of findings, and the methodological heterogeneity of the studies included (RITA; SANTOS, 2025).

CONCLUSION

The final considerations regarding the biological mechanisms of poly-L-lactic acid (PLLA) in collagen biostimulation, particularly in the context of lipoatrophy associated with GLP-1 agonist use, require an integrative and deeply analytical approach capable of articulating the multiple levels of biological organization involved in tissue regeneration. This is therefore not a phenomenon confined to the aesthetic dimension but a process deeply rooted in cell biology and the adaptive dynamics of the extracellular matrix, whose complexity demonstrates the sophistication of organic responses to metabolically induced volume loss.

Lipoatrophy resulting from the use of GLP-1 agonists constitutes a paradoxical condition: while producing substantial metabolic benefits, it triggers relevant structural changes in skin tissue, particularly because of the abrupt reduction in subcutaneous adipose tissue. This reduction compromises the mechanical support of the dermis, disrupts the extracellular matrix, and weakens paracrine communication between adipocytes and fibroblasts, establishing a biological environment unfavorable to the maintenance of dermal homeostasis.

In this context, PLLA emerges as a biostimulatory agent whose action is based on the controlled induction of a subclinical inflammatory response capable of reactivating cellular pathways inherent to tissue regeneration. Far from being pathological, this response constitutes a physiologically modulated stimulus that mobilizes immune cells and triggers a cascade of biochemical events directed toward tissue repair and reorganization.

Macrophage activation and subsequent polarization toward a regenerative phenotype represent one of the first milestones in this process, promoting the release of mediators that act directly on fibroblasts. These cells, in turn, are brought out of their relatively inactive state and shifted toward a highly biosynthetic profile, restoring their ability to produce collagen and other fundamental components of the extracellular matrix.

PLLA-induced neocollagenesis is not limited to the quantitative production of fibers but involves a qualitative transformation of the dermal matrix. Initially, immature collagen is deposited and progressively develops into more organized and resistant forms, culminating in the formation of a fibrillar network capable of restoring skin firmness and elasticity. This process demonstrates the dynamic and continuous nature of tissue remodeling.

The gradual degradation of PLLA plays a central role in sustaining these mechanisms because it ensures the persistence of cellular stimuli over time. Unlike approaches focused on immediate effects, PLLA acts over an extended biological timeframe, allowing the body to rebuild its own dermal architecture autonomously and progressively.

The replacement of the polymer with endogenous collagen represents one of the most relevant aspects of this process because it marks the transition from temporary exogenous support to an authentic and functional biological structure. This phenomenon not only restores lost volume but also reestablishes the tissue’s biomechanical properties, promoting effective and lasting regeneration.

In addition, extracellular matrix reorganization involves the reorientation of collagen fibers, restoration of interactions among matrix components, and reconstitution of an environment conducive to cellular communication. This integrated restructuring contributes to the appropriate redistribution of mechanical forces, prevents the formation of irregularities, and ensures greater tissue stability.

Angiogenesis, which is frequently observed in this context, acts as a complementary element by ensuring an adequate supply of nutrients and oxygen to the cells involved in regeneration. This increase in

vascularization enhances tissue vitality and sustains the metabolic activity required to maintain neocollagenesis.

Another noteworthy point is PLLA's capacity to modulate the balance between extracellular matrix synthesis and degradation. By promoting more efficient regulation of this balance, the biostimulator prevents both structural loss and the formation of disorganized fibrosis, ensuring harmonious and functional remodeling.

In the long term, the effects of biostimulation are reflected in the formation of thicker, stronger, and more elastically competent tissue capable of responding more efficiently to mechanical and physiological demands. This structural transformation demonstrates the regenerative potential of PLLA as a highly sophisticated therapeutic tool.

It is important to emphasize that the response to PLLA does not occur uniformly among individuals and is modulated by intrinsic factors such as age, metabolism, and regenerative capacity, as well as extrinsic factors such as lifestyle habits and environmental exposure. This variability reinforces the need for individualized approaches to therapeutic planning.

In the specific context of lipoatrophy associated with GLP-1 agonist use, PLLA assumes even greater relevance because it not only compensates for volume loss but also acts directly to restore the quality of skin tissue, which is frequently compromised in these patients.

The regenerative approach provided by PLLA thus represents a paradigm shift in the treatment of changes resulting from adipose loss, redirecting the focus from simple aesthetic correction to the biological reconstruction of tissue. This strategy is consistent with the most contemporary principles of medicine, which center on functional restoration and the use of the body's intrinsic mechanisms.

Moreover, the possibility of maintaining results through periodic stimulation expands the therapeutic potential of PLLA, enabling continuous and progressive interventions that accompany the natural changes associated with aging and metabolic conditions.

From a broader perspective, PLLA use demonstrates the importance of an in-depth understanding of the cellular and molecular mechanisms governing extracellular matrix dynamics, underscoring the need for clinical practice based on solid and continuously updated scientific foundations.

The integration of biological knowledge and therapeutic practice is therefore essential to the effective management of lipoatrophy associated with GLP-1 agonist use, enabling the adoption of safer, more predictable, and longer-lasting strategies.

In this regard, PLLA has become established as a prominent agent in the field of biostimulation, not only because of its clinical efficacy but also because of its ability to induce authentic regenerative processes aligned with tissue physiology.

Finally, it is concluded that the biological mechanisms of poly-L-lactic acid, by promoting fibroblast activation, neocollagenesis, and sustained extracellular matrix remodeling, constitute a robust and promising therapeutic paradigm for the treatment of lipoatrophy, particularly lipoatrophy associated with GLP-1 agonist use, reaffirming the role of regenerative medicine as a central component of contemporary aesthetic approaches.

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