THE ROLE OF CALCIUM HYDROXYAPATITE IN STIMULATING COLLAGEN PRODUCTION AND IMPROVING SKIN QUALITY IN AESTHETIC TREATMENTS: AN INTEGRATIVE REVIEW

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ABSTRACT

With the incessant search for different aesthetic procedures to minimize the effects of aging, it becomes necessary to increase research on the effects, improvements, and methods of skin care. Scientific evidence was then sought on the functioning of calcium hydroxyapatite in stimulating collagen production and improving skin quality in the treatments involved. To this end, an integrative review was used, and the search was carried out in the *PubMed* and Virtual Health Library (VHL) databases. The descriptors used were: *calcium hydroxyapatite and dermal filler and collagen*. A total of 61 articles were found, of which 14 met the inclusion criteria in the research. It was noticed that the dual action of the biostimulator, which acts both as an immediate filling agent and as a long-term collagen stimulator, highlights its effectiveness in improving skin quality and obtaining long-lasting and natural results in the context of facial rejuvenation.

Keywords: Calcium hydroxyapatite. Collagen. Dermal fillers.

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INTRODUCTION

The aging process is characterized by a series of physiological changes that affect the structure and function of the skin. Over the years, the production of collagen and elastin decreases, leading to the appearance of wrinkles and sagging. The skin, being the most exposed organ in the human body, constantly suffers from the effects of external factors and natural wear and tear over time, which makes the signs of aging more apparent. With the increase in longevity and the aesthetic pressures of society, the demand for methods to prevent and combat aging is growing, often through aesthetic treatments (Ferraz *et al*., 2021; Silva *et al*., 2022).

As time passes, there are disproportionate changes in soft tissues, the appearance of blemishes and changes in skin texture, as well as the appearance of wrinkles and furrows. Facial aging is related to histological and molecular transformations, such as reduced availability of hyaluronic acid, dermal collagen, and elastin, resulting in progressive thinning of the skin and loss of elasticity. This complex process involves a combination of genetic and biological factors, and external influences (Galvez *et al*., 2023; Muller *et al*., 2024).

Given this scenario, aesthetic interventions have proven to be increasingly relevant, especially considering the increase in demand for non-surgical facial rejuvenation procedures. Calcium Hydroxyapatite (CaHA) emerges as a promising alternative for the treatment of these conditions, not only as a filler, but also as a biostimulator that promotes neocollagenesis. Studies show that the application of CaHA can induce the formation of type I collagen, gradually replacing type III collagen, which contributes to the improvement of skin quality and the restoration of facial volume (Gorbea *et al*., 2021; Neca *et al*., 2022).

The use of collagen biostimulators, such as CaHA, has been shown to be a growing practice, especially in both body and facial harmonization procedures. These products are used to treat flaccidity, improve skin firmness and promote volumization, presenting satisfactory results in several areas, such as the face, abdomen, thighs and buttocks. Unique properties such as a high elastic modulus and viscosity make it a promising option for tissue revolumization and support. In addition, its dual action of stimulating the production of type I collagen and providing immediate apparent results, highlights its importance in the treatment of volume loss associated with aging (Lorenc *et al*., 2018; Gorbea *et al*., 2021; Oliveira *et al*., 2021).

Despite the advances, there is still a lack of robust scientific information on the application of these biostimulators, which highlights the need for studies that consolidate their efficacy and safety. Understanding its action in the aesthetic context is essential to

support therapeutic choices, optimize facial rejuvenation techniques, and ensure the safety and efficacy of procedures (Lorenc *et al*., 2018; Nogueira and Silva, 2022).

Therefore, this work aims to investigate, through an integrative literature review, the efficacy of CaHA, evaluating its role in stimulating collagen production, improving skin quality and its application methods, investigating possible complications, in addition to patient satisfaction results.

METHODOLOGY

Based on the general objective of this research, this study is an integrative literature review, which was structured in 6 stages, namely: elaboration of the research question; literature search; data collection; discussion of the results and presentation of the integrative review, which allowed a triangulation and complete view of the results.

The present study sought to understand in a general way the role of CaHA in stimulating collagen production and improving skin quality in aesthetic treatments. Thus, the integrative review helped in the search and guided the quality of the studies used for research. Data were collected through the search for articles relevant to the proposed objectives. Data collection was carried out in July 2024 with the search for articles in the following electronic databases: *PubMed* and Virtual Health Library (VHL), using original articles in full that covered the years 2008 to 2024.

To carry out the research, controlled descriptors based on Health Sciences Descriptors (DeCS) were used, using the Boolean operator AND to limit it to specific studies. The descriptors used: *calcium hydroxyapatite cosmetic* AND *dermal fillers* AND *collagen* for research in English. Excel was also used to help separate the articles by means of a table to facilitate the analysis.

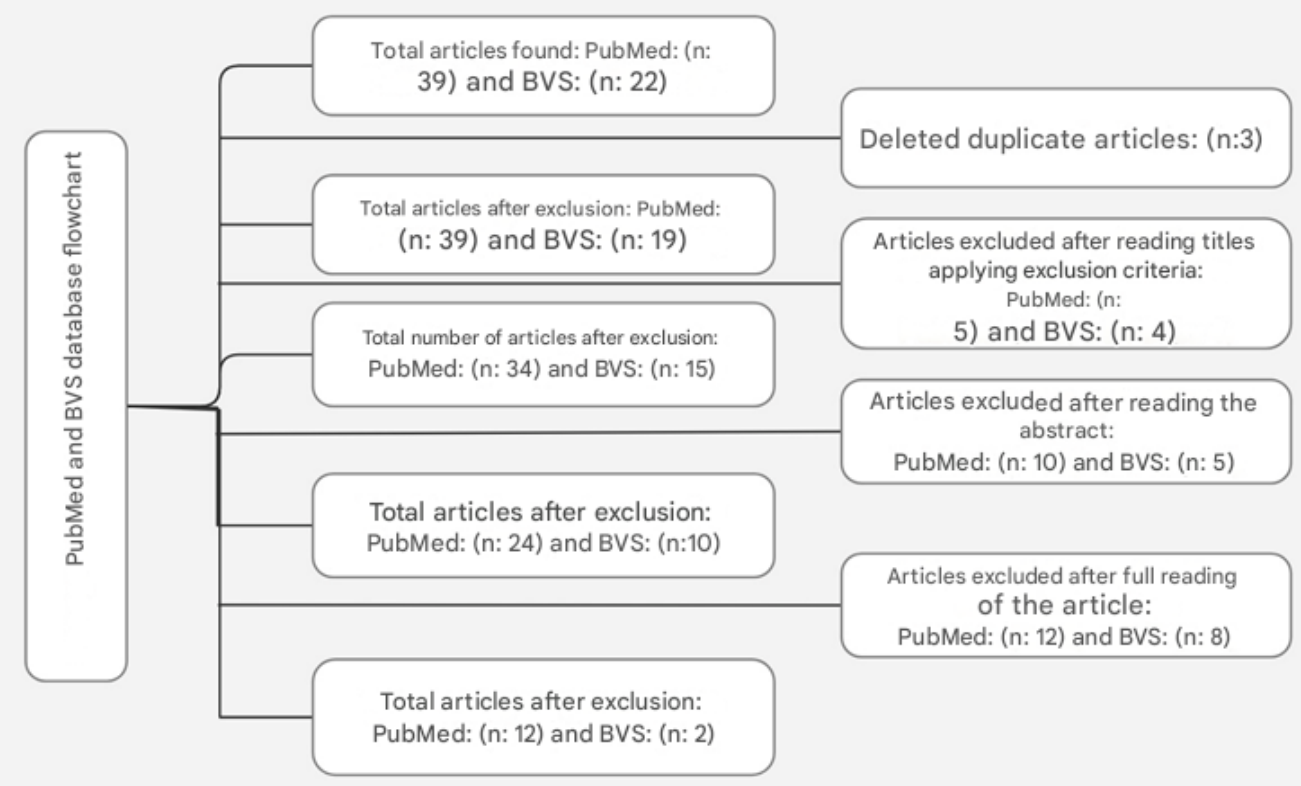
In the selection stage, the following inclusion criteria were adopted: original articles published between 2008 and 2024, available in full in English and addressing CaHA, its applications in aesthetics, associated complications, stimulation of collagen production and improvement of skin quality. The following were excluded from the sample: articles with studies on animals, conference proceedings, theses, dissertations, and technical reports.

Then, the abstracts and titles of the articles were analyzed, applying the inclusion and exclusion criteria to verify the relevance of the research theme. After this initial evaluation, the selected articles were read in full, and those that did not fit the theme or did not meet the criteria required for this integrative review were discarded.

The process of searching for materials was conducted with the help of automated filters in the databases, where the inclusion and exclusion criteria were applied. The

representation of this process can be seen in the adapted PRISMA flow diagram, presented in Figure 1.

Figure 1 - Flowchart of the article selection process.



Source: The authors (2024).

RESULTS

Thus, 14 articles that best addressed the theme were selected, which are shown in Chart 1.

Chart 1 - Selected studies.

Origin	Title	Authors	Year	Considerations
PubMed	*Consensus Recommendations for the Use of Hyperdiluted Calcium Hydroxyapatite (Radiesse) as a Face and Body Biostimulatory Agent*	Almeida *et al.*	2019	Best practices and guidelines for the application of hyperdiluted calcium hydroxyapatite (Radiesse) in aesthetic procedures, emphasizing its versatility and benefits in skin rejuvenation in facial and non-facial areas.
				Go on

PubMed	*Facial rejuvenation with the new hybrid filler HArmonyCa™: Clinical and aesthetic outcomes assessed by 2D and 3D photographs, ultrasound, and elastography*	Galvez *et al.*	2023	Clinical and aesthetic results of the use of the new HArmonyCa™ hybrid filler for facial rejuvenation, evaluating its efficacy and safety through objective methods such as 2D and 3D photographs, ultrasonography and elastography.
PubMed	*Biostimulating fillers and induction of inflammatory pathways: A preclinical investigation of macrophage response to calcium hydroxylapatite and poly-L lactic acid*	Nowag *et al.*	2024	It addresses the initial response of macrophages to biostimulant fillers, such as calcium hydroxapatite and poly-L-lactic acid, and how this response influences collagen regeneration and the organization of the extracellular matrix, highlighting the differences in the inflammatory pathways induced by these materials.
PubMed	*Complications of collagen biostimulators in Brazil: Description of products, treatments, and evolution of 55 cases*	Ianhez *et al.*	2024	It discusses the complications associated with the use of collagen biostimulators in Brazil, presenting a description of the products, treatment methods and the evolution of 55 clinical cases.
PubMed	*Dermal Fillers and Combinations of Fillers for Facial Rejuvenation*	Beer.	2009	Evolution and use of dermal fillers for facial rejuvenation, addressing the combinations of different types of fillers and their characteristics, efficacy and applications in treatments.
PubMed	*Facial Rejuvenation With Fat Grafting and Fillers*	Crowley *et al.*	2021	It evaluates the current trends of fat grafting and fillers in the management of facial rejuvenation, including the cellular changes that occur with aging, the biostimulatory effects.
				Go on
Origin	**Title**	**Authors**	**Anus**	**Considerations**
PubMed	*Introducing aesthetic regenerative scaffolds: An immunological perspective*	Corduff.	2023	Use of injectable biomaterials, called aesthetic regenerative scaffolds, which can direct the body's immune response to promote tissue regeneration in aesthetic treatments, instead of inducing chronic inflammatory processes.

PubMed	*Physiochemical Characteristics of Calcium Hydroxylapatite (CaHA)*	Lorenc *et al.*	2018	It discusses the physiocanemic characteristics of Calcium Hydroxylapatite (CaHA), highlighting its rheological properties, such as modulus of elasticity (G') and viscosity, which contribute to its efficacy in facial volume enhancement treatments and in the stimulation of collagen synthesis.
PubMed	*Histological effects of a combined collagen stimulation procedure consisting of microfocused ultrasound, soft tissue filler, and Ca-HA injections*	Casabona *et al.*	2023	Histological effects of a combined collagen stimulation procedure involving the use of microfocused ultrasound, calcium hydroxyapatite-based fillers, and microneedling, highlighting the efficacy and synergy of these techniques in improving skin laxity.
PubMed	*Nonsurgical Tear Trough Volumization: A Systematic Review of Patient Satisfaction*	Gorbea *et al.*	2021	Non-surgical volumization of the nasolabial fold region, analyzing patient satisfaction and complication rates associated with the use of injectable materials, with the objective of providing guidance for professionals in the field of aesthetic medicine.
				Go on
PubMed	*Calcium hydroxyapatite: a review for efficacy, safety and imaging when used as a filler and as a biostimulator*	Martins *et al.*	2021	Efficacy, safety, and patient satisfaction in the use of calcium hydroxyapatite as a collagen filler and biostimulator, in addition to addressing its visualization in imaging studies.
Origin	**Title**	**Authors**	**Anus**	**Considerations**

PubMed	*Applicability of collagen biostimulators (poly-l-lactic acid and calcium hydroxyapatite) in dermal filler in off-face areas of the body*	Silva *et al.*	2022	Applicability and efficacy of collagen biostimulators, such as Poly-L-Lactic Acid and Calcium Hydroxyapatite, in dermal fillers in off-face areas of the body, presenting clinical evidence and recommendations for their use in body harmonization.
BVS	*Facial Dermal Fillers: Selection of Appropriate Products and Techniques*	Matarasso.	2008	Evolution of facial rejuvenation techniques, highlighting the importance of dermal fillers as effective methods to restore facial volume and contour, in contrast to traditional surgical approaches.
VHL	*Calcium Hydroxylapatite (Radiesse) for Treatment of Nasolabial Folds: Long-Term Safety and Efficacy Results*	Bass *et al*.	2010	Safety and long-term efficacy of Calcium Hydroxylapatite (Radiesse) dermal filler for the correction of facial wrinkles and folds, especially nasolabial folds, based on a comparative study between Radiesse and human collagen.

Source: The authors (2024).

DISCUSSION

Skin aging causes structural, morphological and functional changes in all its layers, mainly due to the significant reduction of fibroblasts. This compromises collagen production, resulting in sagging and other aesthetic dysfunctions. In addition, there are changes in body composition, such as a decrease in lean mass, leading to thinner, wrinkled, dehydrated, fragile skin with a slower healing process, due to the loss of elasticity. Thinning of the skin occurs by reducing components of the extracellular matrix, such as collagen, elastic fibers, and glycosaminoglycans (Silva *et al*., 2022).

Each biostimulator has unique characteristics that lead to its usefulness and specific indications, which increase the opportunities for combined treatments. As a result, CaHA, popularly known as Radiesse®, is a popular dermal filler in aesthetics, widely used to correct wrinkles and replace volume lost over the years. With a proven track record of efficacy and safety of over ten years, it is an attractive choice for professionals and patients alike. In addition to acting as a bulking substitute, it also stimulates collagen production, resulting in long-lasting effects (Beer, 2009).

CaHA has stood out in the aesthetic filler market due to its unique properties that differentiate it from other materials, such as those based on hyaluronic acid. With a high modulus of elasticity, this biostimulator provides a more effective lifting effect. Additionally,

its ability to act as a collagen and elastin biostimulator makes it an attractive option for patients seeking not only immediate results but also long-term benefits. This characteristic is less common among other fillers, which often offer instant results but do not necessarily contribute to skin regeneration (Martins *et al*., 2021).

Thus, studies bring CaHA as an effective and outstanding biostimulatory agent in facial and body aesthetics, promoting not only an increase in volume, but also an improvement in skin quality. It has been shown that its application stimulates neocollagenesis, resulting in a long-lasting and natural rejuvenation effect. Additionally, its biodegradability and favorable safety profile make it an attractive option for patients seeking minimally invasive interventions. The combination of its mechanical and biological properties contribute to skin revitalization, offering satisfactory aesthetic results and a quick recovery, which makes it a popular choice among professionals in the field (Almeida *et al*., 2019).

Recognized for its ability to stimulate the endogenous production of collagen, a crucial factor in maintaining the elasticity and firmness of the skin, when injected, it not only provides an immediate volumizing effect, but also triggers the production of new collagen. Research indicates that even at significant dilutions, Radiesse continues to promote the synthesis of type I collagen and elastin (Almeida *et al*., 2019; Galvez *et al*., 2023).

Contributing to long-lasting results and an improvement in skin elasticity, this biostimulatory property makes CaHA a valuable option, offering sustainable and natural results for patients. In addition, it has a higher modulus of elasticity (G') compared to other fillers, allowing better adaptation and support in areas such as the temporal region and chin. This combination of immediate effects and the continuous stimulation of collagen production make it a preferred choice in facial rejuvenation procedures (Lorenc *et al*., 2018).

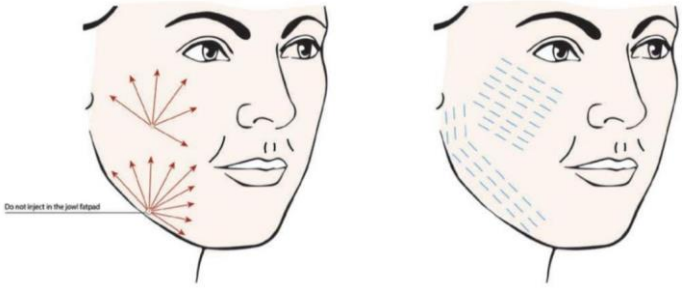
CaHA has been shown to be effective in aesthetic procedures, both in facial areas and in areas of the body, however it is important to note that it is not recommended for lip augmentation, since an unacceptable number of lip nodules has been recorded due to the agglomeration of the product. Its application aims to promote the firmness and elasticity of the skin, being particularly beneficial in regions such as the thighs, abdomen and arms, where sagging is often observed. Studies show that, when injected, it results in gradual improvements in the texture and appearance of the skin (Matarasso, 2008; Silva *et al*., 2022).

For biostimulation and improvement of skin firmness with CaHA, 2 to 3 sessions are usually indicated, with intervals of 1 to 2 months between them. The ideal dilution can vary

according to the area to be treated, the degree of sagging and the thickness of the skin. However, a team of 10 dermatology and plastic surgery specialists, all with extensive experience in facial and body rejuvenation, held a discussion on the best clinical management of this product. The consensus was that the most effective dilution to obtain the best results is 1:1 for facial treatments, 1:2 for the neck region, 1:1 for the buttocks, 1:1 for the inner thighs, 1:1 for the abdomen and 1:2 for the arms. The most recommended technique is fan backinjection using a cannula, with 2 to 5 entry points, depending on the area to be treated (Almeida *et al*., 2019).

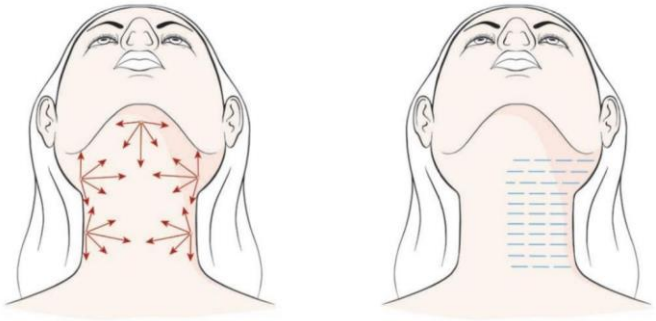
Best practices for application in the most popular regions are illustrated in Figures 2, 3, 4, 5, 6 and 7.

Figure 2 - Facial biostimulation techniques with CaHA.



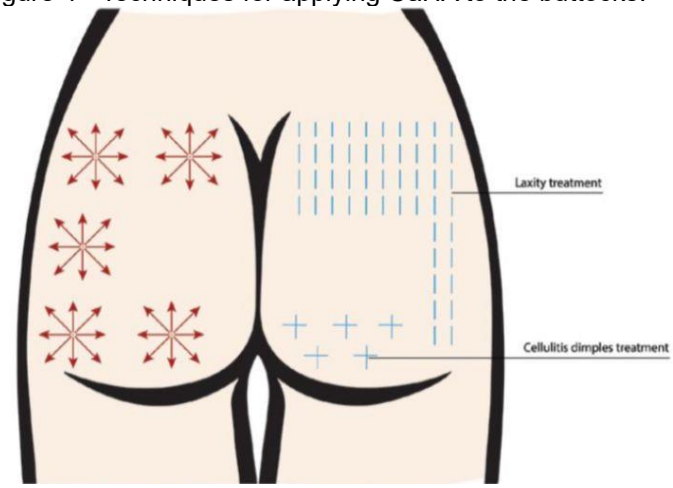
Source: Almeida *et al*. (2019).

Figure 3 - CaHA biostimulation techniques in the neck.



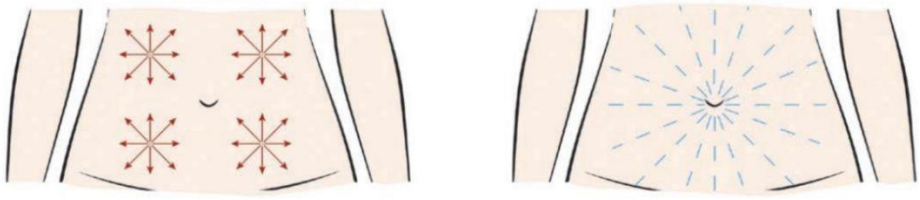
Source: Almeida *et al*. (2019).

Figure 4 - Techniques for applying CaHA to the buttocks.



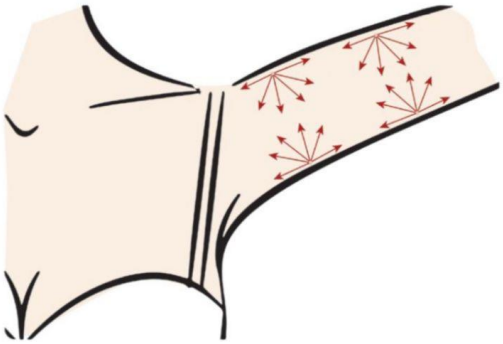
Source: Almeida *et al*. (2019).

Figure 5 - Techniques for applying CaHA to the abdomen.



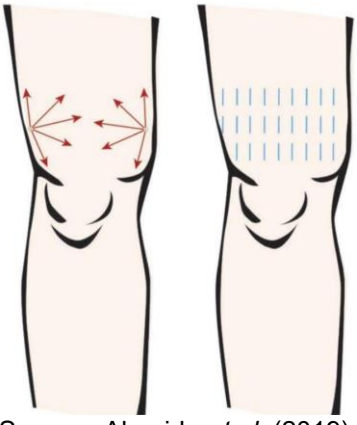
Source: Almeida *et al*. (2019).

Figure 6 - Technique for applying CaHA to the arm.



Source: Almeida *et al.* (2019).

Figure 7 - Techniques for applying CaHA to the inside of the thighs.



Source: Almeida *et al.* (2019).

At the sites where the injection occurs, there is localized trauma to the tissue, resulting in hemorrhage and release of molecular patterns associated with cellular damage. Soon after, the formation of thrombi composed of activated platelets, fibrinogen and fibrin, attracts neutrophils to the area, triggering an inflammatory response. Monocytes from the blood then migrate to the site and differentiate into M1 and M2 macrophages which respond differently to the fillers, with a low inflammatory reaction to CaHA. Differentiating fillers based on immune activity and fibroblast response may have clinical relevance, especially with increasing use in skin tightening treatments in various areas of the body. Understanding how these treatments induce collagen deposition is essential, and more research is needed to clarify these processes and aid in the most effective clinical choice (Corduff, 2023; Nowag *et al*., 2024).

Several hypotheses attempt to explain the unique mechanism of action of CaHA, which seems to differ from the inflammatory response observed with other biostimulators. Among them, the role of CaHA as a calcium reservoir, regulating fibroblasts and stimulating neocollagenesis through direct interactions with its microspheres stands out. Each biostimulatory formulation follows specific immune pathways, resulting in distinct proportions of collagen, elastin, and other components of the extracellular matrix (ECM), which influences the structure and function of the skin. These processes still vary according to genetic factors, age, and health conditions (Nowag *et al*., 2024).

The thrombus resulting from the initial lesion functions as a support for cell adhesion. This thrombus is rapidly covered by plasma proteins such as albumin, fibrinogen, fibronectin, vitronectin, μ-globulin, and complement system components. Over time, these proteins are replaced by others that compete for space on the surface of the thrombus (Corduff, 2023).

Neutrophils are the first cells to arrive at the site, they act by trying to eliminate foreign material through degranulation, phagocytosis and release of extracellular traps, followed soon after by the recruited monocytes. In the absence of bacterial infections, their survival is short, usually 2 to 3 days. The recruited monocytes, on the other hand, are activated and transformed into macrophages, which can differentiate into two types: M1 pro-inflammatory macrophages and M2 macrophages, the latter responsible for reducing inflammation and promoting tissue regeneration. M1 macrophages release inflammatory cytokines, such as TNFα, IL1β, IL-6, and IL-8, creating a feedback loop that attracts more inflammatory cells until the threat is eliminated. When tissue trauma is excessive, the acute inflammatory response is prolonged and intensified (Corduff, 2023; Nowag *et al.,* 2024).

The levels of cytokines in human macrophages of types M1 and M2, after incubation with CaHA, were similar to those of controls, suggesting a non-inflammatory potential of CaHA. In addition to previous histological studies that indicate that CaHA does not trigger an inflammatory response, this study brings additional evidence to support the hypothesis that CaHA's mechanism of action follows a more regenerative pathway, while the others tend to induce a characteristic foreign-body inflammatory response (Nowag *et al*., 2024).

The filler consists of CaHA microspheres, with sizes between 24 and 45 µm, suspended in a sodium carboxymethylcellulose gel. The gel is gradually absorbed, while the microspheres remain, providing a structure for collagen formation. On average, the effect of this filler lasts from 12 to 18 months, but there are reports of lasting more than 30 months in some cases. After about two months of application, it is possible to observe histiocytes and fibroblasts, with dilated endoplasmic reticulum rich in procollagen, around the microspheres. After six months, the deposition of type I collagen occurs, with a lower presence of type III collagen (Crowley *et al*., 2021).

The transitional ECM is remodeled to the ECM of the original tissue, with cells that reflect the function and structure of that tissue. During healing, type III collagen is replaced by type I. In a comparative analysis, CaHA fillers showed higher production of type III collagen at 4 months and type I at 9 months, as well as increased elastin, cell proliferation, and angiogenesis, with no signs of inflammation or granulation tissue. These results suggest that CaHA promotes ECM remodeling in a manner distinct from the fibrous inflammatory response typical of foreign bodies (Corduff, 2023).

It is concluded that the levels of cytokines in human macrophages M1 and M2 after exposure to CaHA were similar to those observed in controls, suggesting a non-inflammatory profile for CaHA. Previous histological data also indicate that CaHA does not trigger an inflammatory response, reinforcing the hypothesis that its mechanism of action is more regenerative, while other biostimulators tend to generate a typical foreign-body inflammatory reaction (Casabona *et al*., 2023; Nowag *et al*., 2024).

A three-fold increase in epidermal and dermal thickness was observed when treating the skin with the proposed treatment, which includes injections of CaHA-based soft tissue fillers. Studies reveal that after three years of follow-up, many patients showed a moderate and sustained aesthetic improvement, and it is also noteworthy that no significant adverse events, such as nodules or granulomas, were recorded during the observation period, which reinforces the safety of the use of this filler in comparison with others available on the market. These findings indicate that Radiesse® is an effective and safe option, providing

long-lasting results without relevant complications (Bass *et al*., 2010; Casabona *et al*., 2023).

In another long-term follow-up, 40% of CaHA-treated folds showed at least a 30-month grade improvement after the last application. Thus, higher patient satisfaction rates and a higher probability of return were obtained compared to other fillers. These results highlight the safety and efficacy of Radiesse® in soft tissue augmentation, indicating that it is as safe as collagen itself (Silva *et al*., 2022).

In another study, elastography images indicated an increase in viscoelasticity in both the reticular dermis and the subcutaneous tissue, suggesting the formation of new collagen fibers. This increase in collagen begins to be noticeable about 60 days after the treatment, reaching its peak between 90 and 180 days after the intervention. With regard to safety, no unexpected or serious treatment-related adverse events were observed. All reported adverse events were mild and completely resolved with topical treatment (Galvez *et al*., 2023).

Among the adverse effects observed with the application of CaHA, in a series of 1748 cases, nodules were most frequently related to complications caused by other biostimulators, while Radiesse® was more frequently associated with edema, a mild redness and inflammation, present in most patients, but resolved spontaneously within the first 48 hours, without the need for additional treatment (Galvez *et al*., 2023; Ianhez *et al*., 2024).

The study by Martins et al. (2021) indicates that patient satisfaction with this material is high, reflecting its effectiveness as both a filler and a biostimulator. Compared to traditional fillers, CaHA not only improves facial contour but also promotes skin firmness, which can be especially beneficial in rejuvenation treatments.

Therefore, CaHA has obtained a great acceptance and satisfaction of patients in relation to other biostimulators, professionals cite the comparatively lower tendency of CaHA of post-injection water absorption, greater moldability and ability to stimulate collagen as additional benefits in relation to the others. They suggest that the injection results in more collagen and elastin production and less inflammation than the injection of the others. In addition, it is also known to have longer-lasting effects, with longevity of up to 2 years, then suffering degradation and natural absorption by the body (Gorbea *et al*., 2021).

Two and a half years after the application of 1.6 mL of the biostimulator, magnetic resonance imaging revealed an increase in tissue volume, with no evidence of remaining CaHA. This suggests a prolonged stimulation of collagen production and its complete biodegradability. They then reported the satisfaction results made with 62 patients who

received CaHa filling: 58 (93.5%) of these patients were satisfied, 3 did not notice any change (4.8%) and only 1 expressed dissatisfaction (1.6%) (Crowley *et al*., 2021; Gorbea *et al*., 2021).

FINAL CONSIDERATIONS

This study found scientific evidence of the applicability of collagen biostimulators, CaHA has been consolidated as an innovative and effective option in aesthetic treatments, especially with regard to facial rejuvenation. In addition to acting as an immediate filler, it stimulates collagen production, promoting a significant improvement in skin quality over time. This duality of action meets the aesthetic needs of patients and contributes to skin health, making it an attractive choice for professionals in the field.

The integrative review conducted in this study revealed that the application of CaHA can induce the formation of type I collagen, gradually replacing type III collagen, which is critical for the restoration of facial volume and skin elasticity. The results obtained in several studies analyzed demonstrate that the biostimulator not only provides immediate aesthetic results, but also promotes long-term benefits, aligning with the expectations of patients who seek less invasive interventions with natural results.

However, despite the advances and growing popularity of CaHA, there is still a pressing need for more research exploring its applications, safety, and efficacy in different clinical settings. The paucity of robust data on its complications and long-term outcomes underscores the need for an ongoing commitment to scientific research. Only through rigorous and well-structured studies will it be possible to establish clear and grounded guidelines for the use of CaHA in aesthetic practice.

Finally, the training and constant updating of health professionals who work in the aesthetic area are essential to ensure the safety and effectiveness of the treatments offered. Awareness of its properties and its implications for aesthetics must be accompanied by an ethical and responsible approach, always prioritizing the well-being of patients. In this way, CaHA is not only a valuable tool in aesthetic medicine, but also as an invitation to reflect on the importance of informed and safe practices in skin care and the search for healthy aging.

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