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# The use of calcium hydroxyapatite in aesthetic medicine – properties, mechanism of action, and clinical safety

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**Abstract**
**Background**:
Aesthetic medicine has evolved rapidly in recent decades, with dermal fillers becoming a fundamental tool for facial rejuvenation and contouring. Among biostimulatory fillers, calcium hydroxylapatite (CaHA) is one of the most extensively studied materials, valued for its volumizing capacity, regenerative potential, and long-lasting clinical outcomes.
**Aim**:
This paper aims to provide a comprehensive overview of calcium hydroxylapatite used in aesthetic medicine, including its physicochemical characteristics, biodegradability,

biocompatibility, mechanism of action in soft tissues, clinical applications, recommended injection techniques, and safety profile.
**Methods**:
A review of clinical studies, histologic investigations, in vitro research, and systematic analyses was conducted to evaluate the effects of CaHA on tissue remodeling, collagen production, and treatment outcomes across various anatomical regions.
**Results**:
CaHA consists of uniformly sized microspheres suspended in a carboxymethylcellulose gel, providing immediate volume replacement and a stable scaffold that stimulates neocollagenesis. Evidence from histology and in vitro experiments demonstrates increased production of type I and III collagen, enhanced fibroblast activity, and improvements in extracellular matrix composition, including elastin and proteoglycans. Clinically, CaHA is effective in treating nasolabial folds, marionette lines, midface volume loss, neck and décolleté laxity, hand rejuvenation, and selected scar deformities. Diluted or hyperdiluted CaHA is particularly beneficial in areas with thin skin, such as the neck. The overall safety profile is favorable, with most adverse reactions being mild and temporary; more serious events, including nodules or granulomas, are uncommon and typically related to improper injection depth or technique.
**Conclusions**:
Calcium hydroxylapatite is a versatile biostimulatory filler that provides both immediate structural support and long-term tissue regeneration. Its ability to promote collagen formation and improve skin quality makes it a valuable option for facial and extrafacial rejuvenation. When injected with appropriate technique, CaHA demonstrates predictable outcomes and a low rate of complications, reinforcing its role as an important material in modern aesthetic medicine.

**Key words:** calcium hydroxylapatite, CaHA, aesthetic medicine, dermal fillers, biostimulation, collagen stimulation, neocollagenesis, soft tissue augmentation, skin rejuvenation, facial volumization, tissue regeneration, injectable treatments, clinical efficacy, safety profile, biomaterials in aesthetics

## Introduction

One of the fastest-growing branches of medicine is aesthetic medicine, a field that has undergone dynamic development over the past few decades. The 21st century has brought tremendous opportunities for enhancing our appearance, not only through surgical procedures but also through a wide range of minimally invasive treatments. These methods are increasingly gaining acceptance in society, as they often require little to no recovery time and provide natural-looking results. As public awareness grows, cosmetic procedures are becoming more accessible and are used by a steadily increasing number of people seeking rejuvenation or subtle enhancement of their features. Among the most popular techniques are those involving dermal fillers, which allow for the reduction of wrinkles, improvement of facial volume, and contouring of areas such as the lips, cheeks, jawline, and tear troughs.

Historically, the development of dermal fillers has evolved significantly. One of the first fillers used in the history of aesthetic medicine was autologous fat (Neuber, 1983), which involved harvesting a patient's own adipose tissue and re-injecting it to improve facial volume. Although innovative for its time, the technique presented challenges related to variable fat survival and

technique sensitivity. Soon after, paraffin was introduced as another early filler (Geraunt, 1900). However, its use was associated with numerous serious complications, including granuloma formation, migration of the material, and chronic inflammation. These adverse effects ultimately led to the withdrawal of paraffin and similar substances from medical practice.

At the end of the 20th century, a significant milestone in filler technology was achieved when Knapp introduced a filler based on purified bovine collagen (Knapp, 1977). This material represented a major step forward, offering improved biocompatibility and a more predictable clinical outcome compared to earlier substances. Nevertheless, bovine collagen required allergy testing and had a relatively short duration of effect. Several decades later, the first hyaluronic acid-based products emerged (Kim, 2011), revolutionizing the market with their excellent safety profile, reversibility, and ability to provide immediate, natural results. Along with hyaluronic acid, other biopolymers were introduced, such as calcium hydroxylapatite (Jacovella, 2008), which offered longer-lasting effects and the capacity to stimulate collagen production. These developments paved the way for modern aesthetic medicine, where a wide range of fillers is now available, each tailored to specific therapeutic needs.

The aim of this paper is to provide a detailed analysis of calcium hydroxylapatite (CaHA), including its chemical and physical properties, biodegradability, and biocompatibility. As CaHA has become an important component of contemporary aesthetic practice, understanding its scientific basis is essential for ensuring optimal clinical outcomes. In this context, the mechanism of action of CaHA will be closely examined, with particular emphasis on its ability to serve both as a volumizing filler and a biostimulatory agent promoting neocollagenesis. Furthermore, this paper will discuss the clinical applications of CaHA across different facial and non-facial regions, its overall effectiveness in producing long-term aesthetic improvements, and its safety profile, including potential adverse reactions and best practices for minimizing risks.

## Characteristics of calcium hydroxyapatite (CaHA)

CaHA is a synthetic calcium phosphate compound with the chemical formula $Ca_{10}(PO_4)_6(OH)_2$, used in the form of microspheres (20–60 μm) suspended in a carboxymethylcellulose (CMC) gel. This specific chemical structure closely resembles the mineral component of human bone, which contributes to its excellent biocompatibility and favorable behavior in soft tissues. The uniform size of the microspheres, together with their optimal porosity, ensures predictable distribution within the tissue, while also allowing cells to interact with the material in a controlled and physiological manner. Due to these properties, CaHA demonstrates high stability at the injection site and does not migrate, maintaining the intended aesthetic effect over an extended period (Pavicic, 2015).

The CMC gel in which the microspheres are suspended plays an essential role in providing immediate volumizing effects. It is dense, viscous, and elastic, which allows CaHA to be effectively used for modeling both subcutaneous and deep facial tissues. These rheological properties make the material particularly suitable for contouring areas requiring structural support, such as the jawline, cheeks, and chin. In comparison with hyaluronic acid, CaHA is significantly more stable and less prone to degradation by enzymes and mechanical forces. As a result, it offers greater possibilities for sculpting and long-lasting improvement of facial contours (McCarthy, 2024).

After injection, CaHA induces collagen formation around the microspheres without triggering an inflammatory response. This process, known as biostimulation, results from the capacity of the microspheres to act as a scaffold for fibroblast activity, encouraging the synthesis of new extracellular matrix. MRI studies have shown that 2.5 years after injection, CaHA is fully resorbed, with the volume effect maintained due to the newly formed collagen tissue, indicating that its aesthetic impact extends well beyond the presence of the filler itself. The biodegradation process typically takes between 12 and 30 months (Pavicic, 2015), which positions CaHA among the longest-lasting biodegradable fillers currently used in aesthetic medicine.

Synthetic CaHA is characterized by lower crystallinity and higher solubility compared to bone-derived hydroxyapatite (Marković, 2011), qualities that further enhance its safety and integration with soft tissues. These features allow the material to be broken down gradually and uniformly, reducing the risk of long-term complications. Importantly, CaHA microspheres do not induce inflammation but instead stimulate fibroblasts to produce collagen, offering a dual effect of both volumization and tissue regeneration. This mechanism distinguishes CaHA from naturally occurring hydroxyapatite in bone tissue, which primarily functions as a rigid structural component and does not exhibit the same stimulatory properties within soft tissues (González, 2019).

## Mechanism of action of calcium hydroxyapatite in soft tissues

After injection with hydroxyapatite, we obtain an immediate filling effect, restoring volume and filling defects in the tissue (van Loghem, 2025). This instant correction results from the presence of the CMC gel carrier, which provides initial volumization before being gradually resorbed. Simultaneously, the CaHA microspheres act not only as a physical filler but also as a bioactive scaffold, initiating a sequence of tissue responses. Tissue reactions around the microspheres are also observed, including the activation of resident fibroblasts and the reorganization of the extracellular matrix, which together initiate adaptive processes and sustained tissue remodeling (Holzapfel, 2008). These processes create a dual effect—immediate correction followed by progressive improvement due to neocollagenesis.

In a 2008 study, subdermal injections were performed on 5 volunteers, and a biopsy was carried out after 6 months. Histological evaluation revealed a clear deposition of collagen types I and III around the CaHA microspheres, indicating active remodeling and long-term structural changes. This deposition was well integrated within the surrounding tissue, forming organized collagen bundles that replaced the gradually resorbing filler material. The effect of CaHA injections was also studied using picrosirius red staining and polarized light microscopy, techniques capable of differentiating collagen fiber thickness and maturity. The skin showed a higher proportion of thin, newly formed type III collagen fibers (Zerbinati, 2018), which are typically produced during the early stages of wound healing and tissue regeneration before later maturation into thicker type I fibers.

In addition, a recent in vitro/ex vivo study showed that CaHA microspheres in direct contact with fibroblasts stimulate collagen expression: after 24 hours, COL III increased by ~123%, and after 72 hours, COL I increased by ~124% (Niwag, 2023). These findings provide strong evidence that CaHA's biostimulatory activity does not rely solely on mechanical tension or physical support but is the result of direct cellular interaction with the microsphere surface. Such early increases in collagen gene expression suggest that CaHA initiates molecular signaling pathways that promote fibroblast activation and extracellular matrix synthesis.

A systematic review from 2023 (12 studies) concludes that most studies observed increased collagen production (9/12), cell proliferation (4/12), and, in many cases, an increase in elastic fibers (elastin) or proteoglycans, as well as some signs of angiogenesis (Amiri, 2023). The presence of new elastic fibers is particularly important, as elastin synthesis in adults is extremely limited under normal physiological conditions. The findings therefore indicate that CaHA may contribute not only to volumetric correction but also to true dermal rejuvenation, enhancing skin elasticity and firmness. Increased proteoglycan content further improves tissue hydration and mechanical resilience, while angiogenesis supports better oxygenation and metabolic activity of the skin.

Microspheres also promote fibroblast colonization, ECM production, and stimulate angiogenesis, which may aid skin regeneration. These changes do not elicit an immunological response, indicating adaptive remodeling without severe inflammation or phagocytosis (Zerbinati, 2017). The absence of a significant foreign-body reaction highlights the excellent biocompatibility of CaHA and supports its use as a long-term biostimulatory filler. The observed remodeling corresponds to a physiological response, with controlled collagen deposition and neovascularization occurring without fibrosis or granuloma formation.

In an in vitro study, as mentioned, fibroblasts in contact with CaHA actively increased collagen expression, suggesting that close interaction between the microsphere and the cell is crucial, rather than just the presence of the material in the matrix (Nowag, 2023). This implies that the physical surface characteristics of the microspheres—such as their size, shape, roughness, and charge—play a decisive role in cellular signaling and ECM synthesis. The study underscores that the biostimulatory effect is localized and contact-dependent, which has important implications for injection techniques, as precise placement may maximize collagen induction and optimize clinical outcomes.

## Clinical applications of calcium hydroxyapatite in aesthetic medicine

CaHA has been used effectively for many years to correct nasolabial folds, and its usefulness in this indication is supported by extensive clinical data accumulated over nearly two decades. In a classic study by Narins et al., the durability of the effect was demonstrated for 12 to 18 months, and an increase in collagen content was confirmed in histological studies (Narins, 2008). These findings were particularly important at the time, as they showed not only the volumizing ability of CaHA but also its long-term biostimulatory capacity, which contributes to a gradual and natural improvement in skin structure. In a subsequent study involving patients with higher skin phototypes, the safety and good tolerance of the preparation were confirmed, with no risk of discoloration, hyperpigmentation, or scarring—factors that are especially relevant for darker Fitzpatrick types, in whom post-inflammatory changes are more common (Marmur, 2009).

In the case of marionette lines, the effectiveness of CaHA has also been well documented. Among the most significant studies is a multicenter trial evaluating CaHA(+) with lidocaine, conducted on 207 patients, in which a clinically significant improvement in the contour of the mandible and lower face was observed (Pavicic, 2015). The inclusion of lidocaine in the formula increased patient comfort during treatment, while maintaining the lifting and structural properties of the preparation. The results demonstrated not only a visible softening of marionette lines but also enhancement of jawline definition—an increasingly important indication in modern aesthetic practice.

CaHA is one of the most commonly used materials for so-called structural volumizing, a category of procedures requiring strong, durable support of deep tissues. Its strong lifting properties and stability in tissues have been confirmed in numerous clinical studies that highlight its ability to replace age-related fat atrophy, correct skeletal deficiencies, and restore youthful proportions of the face. A prospective study on midface augmentation showed that CaHA not only increases volume in the cheeks but also improves skin elasticity, hydration, and structure for at least 24 weeks (Hong, 2025). These findings suggest that the benefits of CaHA go beyond simple volumization and extend into broader dermal rejuvenation and improvement of overall skin quality.

Histological studies support these clinical outcomes, demonstrating that CaHA induces the production of type I and III collagen, which plays a key role in the long-term stabilization of facial contouring effects (Berlin, 2008). The new collagen matrix integrates smoothly with the tissue, allowing the results to persist even after the microspheres are resorbed. This shift from filler-dependent volume to collagen-dependent structure is central to the mechanism of CaHA and forms the basis of its success in deep structural lifting.

Calcium hydroxyapatite is also widely used in hand skin rejuvenation, an indication in which restoring soft tissue thickness is crucial for reducing the visibility of tendons, veins, and other subdermal structures. Clinical studies by Goldman et al. and other histological analyses have shown that CaHA leads to skin thickening, increased collagen density, and reduced visibility of anatomical structures. These data correlate with ultrasound assessments and skin elasticity tests, providing strong multi-modal confirmation of its clinical benefits in this area. The hands, being one of the most physiologically exposed areas, particularly benefit from CaHA's ability to improve both volume and dermal quality.

There are numerous reports in the literature on the use of CaHA in scar therapy. Studies by Kim et al. document an improvement in volume and remodeling of connective tissue in depressed scars after CaHA treatment, confirmed by histological tests. The microspheres create a scaffold for fibroblast activity, enhancing the reorganization of fibrotic tissue. Similar observations apply to post-traumatic scars, in which CaHA contributes to softening of the scar, improved elasticity, and smoother texture (Kim, 2011). These effects stem from the combination of mechanical lift and biological stimulation unique to CaHA.

An interesting case report documented the presence of CaHA microspheres at the injection site even 6 years after the procedure, with preservation of structure and minimal inflammatory response, demonstrating its stability, biocompatibility, and the long-term tolerance of the material in human tissue (Shumaker, 2009). Although the majority of modern CaHA formulations are expected to biodegrade within 12–30 months, this case highlights how individual tissue characteristics and injection depth can influence persistence.

Clinical and histological studies show that diluted CaHA increases skin density, improves elasticity, smoothes texture, and stimulates fibroblasts to produce collagen. This more superficial, biostimulatory application—often referred to as hyperdiluted CaHA—is gaining popularity as a tool for treating skin laxity in areas such as the neck, décolletage, upper arms, and abdomen. These phenomena have been confirmed, among others, in an animal model, where 30 and 90 days after CaHA injection, a significant increase in collagen content was found in the skin of rats (Thums, 2024). The animal findings closely mirror human clinical outcomes, reinforcing the biological basis of CaHA-induced dermal remodeling.

## Administration techniques and treatment protocols

CaHA preparations (e.g., Radiesse) can be administered using either a needle or a micro-cannula, and the choice of instrument depends on the specific anatomical area, the desired clinical effect, and the practitioner's level of precision. The literature recommends using a 27-gauge or 28-gauge needle, or a 25–27-gauge cannula, depending on the region and the planned depth of injection. These specifications allow the injector to balance product viscosity, patient comfort, and anatomical safety.

In areas requiring highly controlled placement into deeper layers—such as jawline contouring, zygomatic augmentation, or structural restoration in skeletal support zones—a needle provides superior control of movement and accuracy. A needle enables the practitioner to place the product exactly at the desired depth, which is important when creating definition or projection in the bone-adjacent layers. The more rigid instrument also assists with anchoring the material in strategic points, contributing to a more robust lifting effect.

In contrast, when treating more extensive or delicate areas, or when the product needs to be distributed over a broad region (e.g., neck, décolleté, hands, or when CaHA is used in diluted form as a skin booster), a cannula is often recommended. A cannula minimizes tissue trauma, reduces the likelihood of bruising and swelling, and offers safer passage through vascularized tissues due to its blunt tip. This makes it particularly useful in regions with complex vascular anatomy or areas where multiple linear threads or fanning techniques are required. The ability to treat a wide surface area with fewer entry points also enhances patient comfort and decreases post-treatment downtime.

CaHA is typically used for deep or subcutaneous injections in layers where there is adequate space for microspheres to integrate and where they can form a structural scaffold that promotes collagen production (van Loghem, 2025). Correct depth is crucial: too superficial placement may lead to visibility or palpability of the microspheres, while too deep placement may reduce the biostimulatory effect or impair the desired lifting outcome.

For areas such as the neck, the choice of technique becomes particularly important due to the region's unique anatomical characteristics, including thin skin, minimal subcutaneous fat in some individuals, and proximity to the platysma muscle. For these reasons, many authors recommend subdermal or deep subcutaneous administration or the use of cannula-based techniques. Additionally, dilution of the preparation is frequently advised to reduce the risk of particle aggregation, improve distribution, and enhance safety, especially in thinner or more delicate skin (Yutskovskaya, 2017). Diluted CaHA spreads more evenly and offers a softer, more uniform biostimulatory effect, making it ideal for treating skin laxity and crepiness.

Modern CaHA formulations often already contain lidocaine (e.g., Radiesse + lidocaine), which significantly increases patient comfort during the procedure by reducing injection-related discomfort. Beyond structural volumization, dilution or hyperdilution of CaHA (typically at a ratio of 1:2 to 1:4 or more, depending on skin thickness and treatment area) has become a widely adopted technique for skin stimulation, sometimes referred to as "skin-tightening" or "skin-boosting." This approach is particularly effective for revitalizing the neck, décolleté, hands, and various body areas affected by mild laxity or thinning.

Clinical evidence supports the safety and effectiveness of hyperdiluted CaHA. In a study of 32 patients who received diluted CaHA in the face, neck, and décolleté areas, improvement in sagging skin was observed without serious complications—only temporary swelling, redness, and bruising were reported, all of which resolved spontaneously (Halepas, 2022). The study highlights CaHA's versatility as both a volumizing agent and a powerful dermal biostimulator capable of enhancing skin quality in a minimally invasive manner.

**Safety profile and adverse events**

In a review of 21 articles (2004–2015) covering 5,081 CaHA procedures, 173 adverse events (approximately 3%) were reported ( Kadouch, 2017).

The most common adverse effects were bruising (ecchymosis), swelling, redness, tenderness, and pain, which were mostly transient and self-limiting (Jacovella, 2008).

In areas with thin skin or with superficial injections, visible deposits, skin irregularities, or discoloration are possible, especially if the product is placed too shallowly (van Loghem, 2025).

Complications in the form of nodules and granulomas are described in the literature — their risk increases with incorrect injection technique: too superficial location, too large a volume, improper distribution (Jacovella, 2008).

A systematic review indicates that of all complications associated with CaHA, more than 95% are nodules/papules/persistent deposits (Kadouch,2017).

Inflammatory reactions may occur not only shortly after the procedure, but also with a delay—complications such as chronic papules or granulomas may appear weeks, months, or even years later.

In high-risk areas (close to vessels, surrounding anatomical structures, thin skin) – e.g., the lower eyelid, the eye area – the risk of complications increases significantly (van loghem, 2025).

To minimize the risk of complications when using CaHA, the literature provides the following recommendations. The procedure should be performed by an experienced specialist with a good knowledge of anatomy, especially in areas with a high risk of blood vessels or thin skin. The choice of technique (needle vs. cannula), injection depth, and (optionally) CaHA dilution must be tailored to the anatomical area and the purpose of the procedure (volumetry vs. biostimulation) (Loghem, 2015).

When using diluted CaHA: massage or gentle kneading of the skin after the procedure is recommended to help distribute the microspheres evenly and reduce the risk of lumps. Contraindications: active skin infection, inflammation, tendency to scarring/keloids, coagulation disorders, use of oral retinoids or autoimmune diseases - in accordance with the general rules for fillers.

In risk areas, avoid superficial injections, excessive volume, and over-correcting; use spread-out, layered techniques, with a cannula if necessary, and frequent checks (van Loghem, 2025).

## Conclusion

Thanks to the immediate volumizing effect combined with a long-lasting biostimulatory action, calcium hydroxylapatite represents a significant advancement in the field of aesthetic medicine. Its biocompatibility and biodegradability make it a safe filler used for wrinkle reduction, facial contouring, and tissue regeneration. Its effectiveness has been well documented, particularly in the areas of the jawline and chin (Pavicic, 2015). Compared to other fillers, it provides a long-lasting effect, which is driven by the stimulation of fibroblasts to synthesize collagen.

The use of CaHA has its limitations; due to the higher viscosity of the product, superficial injection in areas of high mobility, such as the lips or tear troughs, is contraindicated because it may lead to the formation of nodules and irregularities (Nassar, 2025). There remains a need for further research on this preparation, especially comparative analyses with other fillers such as hyaluronic acid. It is also worthwhile to expand research on the application of CaHA in tissue engineering, regenerative therapies, and scar remodeling.

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