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DILUTED AND HYPERDILUTED CALCIUM HYDROXYAPATITE FOR SKIN TIGHTENING

Introduction

Biostimulatory fillers, such as calcium hydroxylapatite (CaHA), have been used for more than a decade for facial volumization and HIV-induced lipoatrophy.¹ Over the last few years, CaHA has also been increasingly utilized to tighten skin and improve skin quality.¹ CaHA is a biodegradable and resorbable filler composed of microspheres suspended in an aqueous carboxymethyl cellulose gel carrier.² The biostimulatory nature of CaHA distinguishes it from other fillers: while the carrier provides initial volume replacement, the particles induce a delayed fibroblast and histiocyte response leading to increased collagen and elastin formation, and ultimately dermal remodelling.²

CaHA reconstitutions can be categorized based on ratios: none/undiluted, dilute (1:1), and hyperdiluted ($\geq 1:2$) (**Table 1**). In hyperdiluted forms, CaHA causes biostimulation without volumization. Overall, this leads to skin tightening and improvement of various skin parameters, such as elasticity, firmness, superficial wrinkles, and overall appearance.¹ The use of diluted and hyperdiluted CaHA for skin tightening is a relatively new technique growing in popularity. It can be used in various areas of the body such as the upper arms, abdomen, and thighs. Hyperdiluted CaHA has also been used to treat cellulite and striae.^{1,4}

This article reviews considerations for diluted and hyperdiluted CaHA and some target areas, including the face, neck and décolletage, and buttocks.

Patient Selection & Education

Appropriate patient selection for hyperdiluted CaHA therapy is the first step in attaining an aesthetically desirable and safe outcome. A proper diagnosis will guide therapy: practitioners must be able to distinguish between volume loss and skin laxity, as only the latter will improve with hyperdiluted CaHA. For the face, diluted CaHA will not improve ptosis due to midface fat pad descent. For treatment of the abdomen or

thighs, hyperdiluted CaHA cannot be used if the apparent laxity is to due excess subcutaneous tissue.⁶

Patient expectations must be evaluated. Patients should be aware that hyperdiluted CaHA for skin tightening is an off-label use. In addition, patients must understand that dermal remodelling is a delayed and long-term process, taking 4 to 6 weeks to appreciate initial effects.⁶ Patients should also be informed that CaHA is radiopaque. It is clearly visible on computerized tomography (CT) scan and may appear on plain x-ray films.

CaHA is contraindicated in patients with known hypersensitivity to CaHA or any of its components.

Reconstitution

Undiluted CaHA is a highly viscous product with immediate volumizing and delayed biostimulatory effects. Dilution of CaHA with saline and/or lidocaine disperses the carboxymethyl cellulose, rendering it less viscous.³ Dilution ratios of 1:1 provide both volumizing and remodelling effects. In contrast, hyperdiluted ratios of $\geq 1:2$ provide biostimulatory effects without

voluminization. For smooth product placement, dilutions can be adjusted based on the skin thickness and degree of laxity. More dilute reconstitutions should be used for thinner skin to reduce the risk of product visibility and palpability.⁴

There are a few considerations for the reconstitution process (**Box 1**). A female transfer adaptor can connect the original CaHA syringe to a LuerLock syringe with the diluent. A minimum of 20 passes between the two syringes should be completed to ensure equal product dispersion. Once homogeneity is achieved, the mixture should be placed into the original syringe for injection. Given that the diluted version tends to separate, the reconstitution process should be completed immediately prior to the treatment.

Anesthesia

Pain management during aesthetic procedures is an important consideration. A reconstitution protocol approved by the U.S. Food and Drug Administration suggests mixing CaHA with lidocaine to a concentration of 0.3%.⁵ Reconstituted mixtures

should not exceed maximum lidocaine doses (3 mg/kg without epinephrine and 7 mg/kg with epinephrine).⁶ Topical anesthesia or injections of local anesthetic at the canula entry point can also be utilized.

Technique Considerations

There are various technique considerations involved with the use of CaHA (**Box 2**). Needles or cannulas can be used to inject CaHA. Researchers have compared precision differences between the two injection modalities in a cadaver study and found that the cannula technique resulted in product placement and confinement to the deep anatomic layers, while needle usage led to product placement in multiple layers. As use of needles can result in superficial placement of CaHA, great caution must be exercised with this approach.³

The plane of injection is critical to treatment success and varies with reconstitutions ratios (**Table 1**). Due to its non-viscous nature, hyperdiluted CaHA can be distributed across a larger surface area and relatively more superficial levels. The aim is to distribute a thin and even layer at

Dilution	Properties: Viscosity and Elasticity	Ideal Plane for Injection	Voluminization Effect	Biostimulation Effect	Overall treatment effect
None	High	Deep-dermal, subdermal, or suprapariosteal	++	+	Voluminization and secondary skin quality improvement
Diluted 1:1 (1.5 mL CaHA + 1.5 mL diluent)	Intermediate	Subdermal	+	+	Volume restoration with easy and even product distribution
Hyperdiluted $\geq 1:2$ (e.g. 1:2 dilution is 1.5 mL CaHA + 3.0 mL diluent)	Low	Dermal-subcutaneous junction	-	+	Skin tightening for large surface areas

Table 1. CaHA Reconstitutions and Properties (Adapted from Lorenzc et al.⁶)

1. Dilution to be performed immediately before injection.
2. Use syringes large enough to hold the desired volume.
3. Use a female adapter to connect the original CaHA syringe and the additional LuerLock syringe.
4. A minimum of 20 passes should be completed to ensure product homogeneity. Considerable force will be required to move the product between the syringes; however, caution must be taken to avoid forcibly pushing the plunger out of the barrel.
5. Transfer the reconstituted mixture into the original syringe for injection.

Box 1. Hyperdiluted CaHA Reconstitution Considerations (Adapted from Goldie et al¹).

1. Treatment aim: distribute a thin and even layer throughout the entire treatment zone, at the dermal-subcutaneous junction.
2. Use 22-25 gauge for canula or 27-30 gauge for needle.
3. For facial treatments, the entry point should be perpendicular to the direction of major arteries.
4. Massage vigorously after treatment.

Box 2. Injection Technique Considerations (Adapted from Goldie et al¹).

the dermal-subcutaneous junction of the entire treatment area. In contrast, undiluted CaHA is viscous and thus must be placed at the deep-dermal, subdermal, or suprapariosteal levels.

For hyperdiluted CaHA injected with a canula, fanning or parallel serial retrograde linear threading injection techniques are recommended.¹ To ensure uniform product distribution, the treatment area should then be vigorously massaged.

Treatment Intervals

CaHA initiates dermal neocollagenesis in which type III is gradually replaced with type I collagen. This process may occur as early as 4 weeks.⁵ Deposition of collagen and elastin starts at 4 months and is completed around 9 months.¹ Various follow-up cycles have been suggested with some indicating 1 follow-up session within 12 months.³ Other protocols recommend follow-up in 3-4 months after the initial treatment, for a total of one to 3 treatments in the first year, followed by annual maintenance sessions.¹

Face

Soft tissue fillers remain a mainstay of facial augmentation and contouring. Diluted and hyperdiluted CaHA provide global treatment as opposed to localized volumization. In these forms, CaHA can be distributed evenly in the immediate subdermal plane to provide general skin tightening.² Hyperdiluted CaHA is not used in the forehead and temples as these areas require volume and contour treatments, or the lips and nasolabial folds due to increased risk of nodule formation.¹ Diluted CaHA with a 1:1 ratio is recommended initially. Hyperdilutions may be utilized for thin skin or areas of greater laxity.¹ Cannulas can be used for even product distribution. Entry points should be perpendicular to the direction of major arteries to reduce the risk of vessel puncture.¹

Neck & Decolletage

Neck restoration procedures are on the rise. Hyperdiluted CaHA is a safe and non-invasive modality for tightening the skin in the neck and decolletage.^{4,8} For this area, patients with mild laxity or

crepey skin will benefit the most from treatment. Patients must understand that excess skin will not disappear; rather, dermal remodelling will make it appear tighter and thus less visible.

The skin in the neck is very thin, increasing the risk of too-superficial product placement and possible subsequent nodule formation. As such, the use of cannulas and hyperdiluted ratios are recommended, as follows: 1:2 to 1:3 for mild skin laxity and/or photoaging, and 1:4 or greater for those with increased photo-induced atrophy.¹ Product can be injected in retrograde fashion with 3-5 entry sites.³ Approximately 0.5-1 syringe is required per session. While results may be visible after one treatment, full rejuvenation may require more sessions, especially if higher dilutions are used.

Buttocks

Patients present with various complaints of the buttocks, such as gluteal sagging or cellulite-associated textural irregularities. Increasing skin tightness and dermal elasticity can address these

patient concerns. Approximately one syringe is required per side.¹ For skin laxity, the dilution ranges from 1:1 to 1:4. Lower ranges of 1:1 or 1:2 can be used for cellulite dimples. CaHA should be injected with a canula in the subdermal layer. A fanning or vertical line technique can be used for contouring the upper and lateral regions, whereas a horizontal cross-hatching technique can be used for the lower region.^{1,2} Three treatment sessions every 4 months are recommended for desired outcomes.¹ Patients with a higher body mass index may not have improvement from CaHA injections alone.⁹

Adverse Effects

In general, CaHA in all its forms is safe. In long-term studies on undiluted CaHA, adverse effects were minor and were mainly injection-related, such as erythema, ecchymosis, and edema.^{10, 11, 12} The development of noninflammatory nodules due to product accumulation has been associated with CaHA injected in the lips, or with superficial placement of product in the nasolabial fold.^{12, 13} In recent studies on diluted or hyperdiluted CaHA, all adverse effects were injection-related and included ecchymoses, swelling, induration and mild pain.^{4, 14, 15}

The most severe complication of soft tissue injectable treatments is vascular compromise in which product is injected into a blood vessel, leading to occlusion and necrosis. To date, no cases of vascular compromise with hyperdiluted CaHA have been reported.¹

Summary

The use of diluted and hyperdiluted CaHA for skin tightening and improvement of skin quality is on the rise. When injected in the subdermal plane in reconstituted forms, CaHA stimulates the production of collagen and elastin, thereby promoting dermal remodelling. Although off-label, it is an efficacious and safe technique used widely.

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