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Review

A systematic review of Radiesse/calcium hydroxylapatite and carboxymethylcellulose: evidence and recommendations for treatment of the face

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Abstract

Radiesse® is a filler composed of calcium hydroxylapatite microspheres suspended in a carboxymethylcellulose gel (CaHA/CMC). It has robust rheological properties that have been associated with its versatility. CaHA/CMC is employed for both on-label indications of filling wrinkles or lines, volumizing, and contouring of areas as well as off-label indications aiming at biostimulation and skin tightening. However, despite the expanding use of CaHA/CMC, overall evidence and recommendations for treatment are currently lacking. This paper aims to provide an up-to-date overview of CaHA/CMC clinical applications, together with a level of evidence of supporting literature, focusing on the face. Based on the data, CaHA/CMC may be considered a safe and effective treatment option for cheeks, jawline, HIV-related facial lipoatrophy, and nasolabial folds. Treatment of marionette lines, chin, pre-jowl, and corner of the mouth also tends to respond with a high degree of efficacy. Despite the recent trend, guidelines, and safety profile of diluted and hyperdiluted Radiesse®, no randomized controlled trials have been published.

Introduction

Skin rejuvenation procedures have become increasingly popular in the field of cosmetic dermatology.[1–4] One form to achieve skin rejuvenation is through the injection of calcium hydroxylapatite (CaHA). CaHA can stimulate fibroblast activity, which leads to the production of collagen.[4] Radiesse® (Merz, Frankfurt, Germany) was approved in 2006 for treating facial folds and wrinkles and facial atrophy associated with HIV. The product has then been employed for the treatment of nasolabial folds, medial and lateral cheek, mid-face, marionette lines, mandibular angle, jawline, chin, and rejuvenation of the dorsal aspect of the hands.[5,6]

Over 100 publications related to Radiesse's efficacy and safety profile have been published. The material is a biocompatible, biodegradable, and resorbable biostimulatory filler composed of 30% smooth regular synthetic microspheres of CaHA (ranging from 25 to 45 μm in diameter) and 70% of carboxymethylcellulose (CMC) gel carrier (CaHA/CMC).[7]

As compared to hyaluronic acid fillers, CaHA/CMC demonstrated higher viscosity and elasticity, and it elicits a biostimulatory effect on fibroblasts, resulting in collagen synthesis, and leading to improvement in skin laxity.[8,9] Due to the reported natural and long-lasting effects, CaHA/CMC seems to fit perfectly in the era of personalized medicine and the trend toward natural beauty.[10,11]

Another important characteristic of CaHA/CMC is its versatility when injected in its unaltered form or diluted/hyperdiluted. The diluted/hyperdiluted CaHA/CMC represents an off-label use of the product, although its use is supported by a global consensus of experts.[12,13]

The level of evidence and recommendations for CaHA/CMC use are currently lacking. Therefore, we aim to provide a systematic review and critically analyze the available literature on

CaHA/CMC applications and evaluate the level of evidence, and offer recommendations to optimize its use in daily practice.

Materials and methods

A comprehensive literature search of MEDLINE (PubMed), Scopus, and Cochrane Library databases on CaHA/CMC applications was performed up to January 2022. The search strategy adopted was similar across the databases and developed using the following keywords: "Radiesse," and "calcium hydroxylapatite." Truncation and synonyms were included in the search process.

Inclusion criteria were any primary clinical studies including retrospective reviews, prospective open-label trials, comparative clinical trials, randomized controlled trials, and systematic reviews concerning Radiesse's use in skin rejuvenation.

Exclusion criteria were non-systematic review articles, non-human studies, non-clinical studies, non-English language studies, case reports, and CaHA other than Radiesse®, combination treatments.

Duplicate findings and inclusion and exclusion criteria were then manually applied to the remaining citations. Additionally, results for lips, perioral area, glabellar lines, frontal area, tear trough-infraorbital area, periocular area, nose, and temples were excluded.[14]

Studies were classified according to specific sites for aesthetic indications and put in chronological order. The level of evidence for each indication was then assessed according to modified criteria published by the Oxford Center of Evidence-Based Medicine.[15]

A practical "Bottom Line," containing a clinical summary and recommendations, is proposed, taking into account the evidence-based approach in combination with the authors' collective clinical experience with CaHA/CMC.

Results

Study selection

A total of 1,515 records were identified through the initial search, of which 92 full texts were assessed for eligibility and 20 studies were included in the qualitative synthesis, regarding face treatment (Figure 1).[10,16–38]

CaHA/CMC has a proven efficacy and safety profile in facial rejuvenation. Five randomized controlled trials (RCT), 10 prospective studies, four retrospective studies, one systematic review, and one meta-analysis have been included in the current study.

Different areas of application have been distinguished: HIV-associated facial lipoatrophy (FLA), nasolabial folds, mid-cheek volume loss, jawline, mixed indications on the face, and dilute/hyperdilute Radiesse®. Some papers reported information regarding the treatment of more than one area. Overall, a summary level of evidence is reported in Table 1.

HIV-associated facial lipoatrophy

A summary of studies included concerning HIV-FLA is reported in Table 2.[16–19] Injections were performed subdermally or supraperiostally with needles or cannulas. Variables assessed included determining improvement in all treated patients, evaluated according to Fontdevila's FLA grade or the global assessment improvement scale (GAIS), without any adverse events. Vallejo et al.[19] performed a comparative study, of CaHA/CMC, poly-L-lactic acid (PLLA), polyacrylamide, and autologous fat, showing statistically significant differences between the initial and final grades of FLA for all products, although performance results related to CaHA/CMC treatment alone are not specified. Of note, one nodule was reported in the PLLA group.

Nasolabial folds

Table 3 reports a summary of studies related to NLFs.[10,20–25] One RCT compared the use of CaHA/CMC with collagen, HA, and NASHA, revealing the superiority of CaHA/CMC in terms of efficacy (NLF correction) over 6–12 months. In parallel, patients' satisfaction scored 4 out of 5, at 3 months posttreatment and remained so for up to 12 months, according to a meta-analysis by Fakhre et al.[25]

A good safety profile was reported with prevalent local and self-limiting adverse events in patients of phototype I-III. Marmur et al.[21] reported the safety profile on 100 patients with phototype IV-VI, exhibiting local and self-limiting adverse events only, while no keloids, hypertrophic scarring, or hypo- or hyperpigmentation were observed. Additionally, lower levels of pain during the injection procedure were reported with Radiesse® + (with integrated 0.3% lidocaine) injected with a needle, as compared to CaHA/CMC without lidocaine or using a cannula ($P<0.0001$).[23,24]

Jawline and marionette lines

Table 4 summarizes studies about the jawline and marionette lines.[26–28] Moradi et al.[26] proved a significant ≥1-point improvement of the Merz jawline assessment scale in patients treated with CaHA/CMC in RCT versus non-treated. In 70% of patients showing improvements at 12 weeks, results were persistent at 48 weeks. Only local and self-limited adverse events were reported. The other two prospective studies supported similar efficacy and safety results[27,28] (Figure 2).

Cheek volume loss

A specific focus on CaHA/CMC employed for treating cheek volume loss has been performed on 116 patients, of which 86 were randomized to a treated arm and 30 untreated,[29] (Table S1). Moers-Carpi et al.[29] presented that midface volumizing with CaHA resulted in high physician and patient satisfaction up to 12 months after treatment and a significant difference in terms of cheek volume on the treated side, as compared to the untreated ($P < 0.05$). For the safety profile in this area, local and self-limiting adverse events were described.

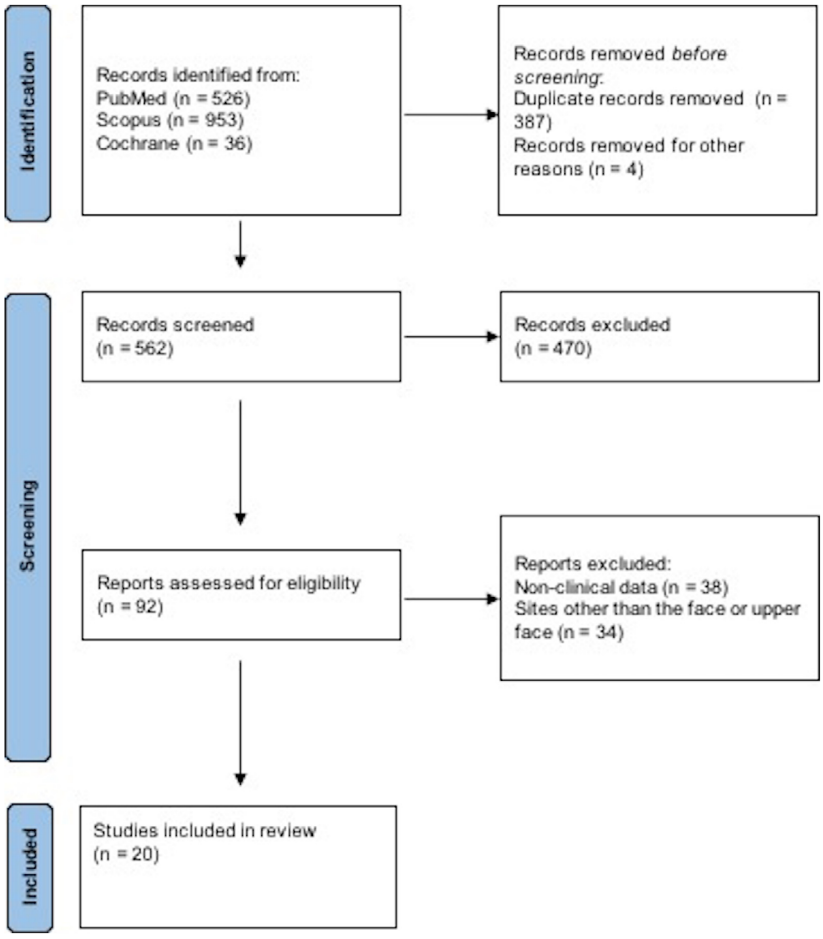

Figure 1 PRISMA flow diagram

Table 1 Level of evidence for Radiesse® use

Level of recommendation: A strong
Jawline: level 1a
Nasolabial folds: level 1a
Cheek volume loss: level 1b
HIV-related facial lipoatrophy: level 1b
Level of evidence and recommendation: B Moderate evidence
Marionette lines, corner of mouth, prejowl: level 2b
Chin, mental crease: level 2b
Level of evidence and recommendation: C Weak evidence
1:1 dilution mid and lower face: level 3b
1:2 hyperdilution mid and lower face: level 3c

Although seven subjects (6.5%) reported lumps or bumps, and three (2.8%) nodules were reported, no long-term sequelae of these adverse events are mentioned in the study, nor the need for a specific treatment. It is worth mentioning that areas treated by Moers-Carpi et al.[29] included the infraorbital area, which was excluded from the current study, and the paper does not specify where the complication occurred. Additionally, injections were performed using a 27G needle, employing a considerable amount of product, up to 10 ml per cheek, with a mean volume of 4.7 ml, which could have contributed to the development of the above adverse events.

Mixed indications on the face

Preferred injection sites were NLFs (38%, $n = 1{,}930$ of 5,081 injections), marionette lines (16%, $n = 815$), and chin and prejowl (Table S1).[30–38] Overall subject satisfaction scores were high regardless of the area treated (87–89%).[36] For more than 4 years, evidence revealed that CaHA has had a favorable safety profile, high patient satisfaction, and good durability.[33] This was further supported by a systematic review by Kadouch.[36] In that review, data from 5,081 treatments registered a total of 3% of adverse events, mainly in the form of nodules. These complications occurred when treating dynamic areas such as the periorbital region and lips, which were excluded from our study.

Diluted/hyperdiluted product

The trend toward the use of CaHA/CMC diluted and hyperdiluted has emerged. These techniques have been described for the face[37,38] (Table S1). Diluted CaHA/CMC is composed of

Table 2 Summary of characteristics of included studies for FLA-HIV

Author, date	Indication	*N*	Females, *n* (%)	Age, mean ± SD (range)	Skin type/ethnicity	Study type	Product	Needle/ cannula	Technique/ depth	Efficacy	Safety
Silvers, 2006[16]	Cheeks, HIV-associated FLA	100	6 (6%)	Mean 48.2 ± 7.2 years (range: 34–69)	Asian (1.0%), Black (18.0%), Caucasian (56.0%), Hispanic (25.0%)	Pro	Pure	25-G needle	Subdermal	7% were very much improved, 86% were much improved, and seven patients 7% were improved	Mainly local and self-limiting adverse events
Carruthers, 2008[18]	HIV-associated FLA – baseline Facial Lipoatrophy Severity Scale (grade 2 or 3)	30	1 (3)	Mean 51	10% I, 73% II, 17% III; 97% Caucasian, 3% Asian	Pro	Pure	–	Subdermal and supramuscular planes	All subjects were rated as improved or better on the GAIS at 3, 6, and 12 months. At 3 months, 80% of subjects had GAIS ratings of very much improved, and 20% were rated as much improved. At 6 months, before touch-up, 59% were rated as very much improved, 31% as much improved, and 10%as improved. At 12 months, before touch-up, 6.9% were rated very much improved, 45% much improved, and 48% improved.	Local and self-limiting adverse events.
Carruthers, 2008[17]	Pronounced NLFs, HIV-related LPA	58	–	–	–	Pro	Pure	25-or 27-G needle	Deep dermis and the subcutaneous tissue or deeper	Plain radiographs showed inconsistencies in detection of CaHA on x-ray films: foreign mass of material was only detected in varying subsets of subjects in each treatment group. In 10% of NLF subjects, a foreign mass was visible prior to injection of CaHA. CT scans, on the other hand, showed consistent visualization in nearly all cases in subjects who were imaged immediately after treatment.	–
Vallejo, 2018[19]	HIV-related FLA Fontdevila FLA grades: *n* = 84 II (moderate), *n* = 63 III (severe). Injection of NLF (*n* = 137), malar region (*n* = 136), zygomatic region (*n* = 14), Bichat bulla (*n* = 5), temporal region (*n* = 4), and supraorbital region (*n* = 1)	147	120 (81.6)	Mean 48 ± 6.9 years (range: 29–71)	–	Pro	Pure/ other fillers	25-G needle or cannula	Radial fanning technique	Surgeon's assessment revealed considerable improvement at months 1 and 2, and a certain degree of deterioration at 12 months, which remained stable afterward. At 24 months, 53% of subjects were rated improved (with none or mild FLA on the Fontdevila scale). Statistically significant differences between the initial and final grades of FLA for each subject were found for all products. Subject self-evaluation showed a general improvement, treatment satisfaction, and reduced impact of FLA on QOL.	Overall, for all products, the following AEs have been reported: pain (*n* = 41), syncope (*n* = 4), swelling (*n* = 2), hematoma (*n* = 2), and infection (*n* = 2). A total of five subjects treated with PLLA developed nodules. Product resorption was confirmed in 31 subjects, especially after the first year. A total of 26 of these 31 subjects were treated with Radiesse Injectable Implant.

CaHA, calcium hydroxylapatite; CT, computerized tomography; FLA, facial lipoatrophy.

Table 3 Summary of characteristics of included studies for nasolabial folds (NLFs)

Author, date	Indication	*N*	Females, *n* (%)	Age, mean ± SD (range)	Skin type/ethnicity	Study type	Product	Needle/ cannula	Technique/depth	Efficacy	Safety
Moers-Carpi, 2007[10]	NLFs (3–4 WSRS)	205	185 (90)	52 (27–80)	–	Pro RCT	Pure vs HA (2 types) vs untreated	27-G needle	Mid to deep dermis	More CaHA gel patients were satisfied or extremely satisfied than each HA tested. At 8 months, significantly more CaHA gel-treated NLFs were improved on the GAIS than any HA, with significantly less product. However, results from the WSRS ratings over time showed no statistical significance for any product over any other one.	No serious adverse events that required intervention were reported at any time points for any injected materials.
Moers-Carpi, 2008[20]	NLFs (3–4 WSRS)	60	52 (87)	50.5 years (range: 34 –67 years)	–	Pro RCT split face	Pure vs NASHA	27-G needle	Mid to deep dermis	GAIS Ratings In summary, at 12 months, GAIS ratings showed 79% of CaHA-treated folds as very much improved, much improved, or improved, compared to 43% of the NASHA-treated folds (*P* 0.001). At 12 months, WSRS ratings showed that 31% of the CaHA-treated folds showed greater improvement than the NASHA-treated folds; only 7% of NASHA-treated folds were rated as greater (*P* 0.001)	Both products were safe and well tolerated, with no serious adverse events reported for either CaHA or NASHA treatment. Four adverse events were reported in this study. These included two hematomas, one nodule, and one extrusion, of 118 folds injected two times each during the course of the study. The hematomas and the nodule appeared on the CaHA-treated fold. The two hematomas resolved in 4 to 5 days, with no further complications; the nodule was treated with 0.2 ml of triamcinolone acetonide and was cleared in 14 days. The extrusion appeared in the NASHA-treated fold; it was treated with antibiotics and resolved without complications.
Marmur, 2009[21]	NLFs	100	94 (94)	52 ± 11 (25 –78)	*n* = 24 IV, *n* = 35 V, *n* = 41 VI; 85% African American, 12% Hispanic, 2% Asian, and 1% as other.	Pro	Pure	25-to 27-G needle	Threading and fanning, subdermally	–	No reports of keloid formation, hypertrophic scarring, hypo- or hyperpigmentation. Local and self-limiting adverse events.

Table 3 Continued

Author, date	Indication	*N*	Females, *n* (%)	Age, mean ± SD (range)	Skin type/ethnicity	Study type	Product	Needle/ cannula	Technique/depth	Efficacy	Safety
Bass, 2010[22]	NLFs	102	–	54.7 (31–76)	87% Caucasian, 9% Hispanic, 2% Black, the rest other	Pro (RCT split face)	Pure vs collagen	27-G needle CaHA vs 30-or 31-G needle for collagen	CaHA dermal/ subcutaneous junction vs mid-to-deep dermis for collagen	About 50% of the CaHA group required only one injection to achieve optimal correction as compared to 32.5% of the collagen-treated folds. To achieve optimal correction, the CaHA-treated folds required, on average, half of the material required for the collagen-treated NLFs ($P < 0.0001$). At 3 and 6 months, about 80% CaHA-treated had ≥1-point improvement from baseline as compared to 27.4% of the collagen group ($P < 0.0001$).	There were no reports of nodule, granuloma, necrosis, erosion, infection, or any other AE.
Beer, 2014[23]	NLFs (grade 2–4 according to Merz Scale)	20	18 (90)	57 (45–72)	II (55%), III (40%), V (5%)	Pro Split-face needle vs cannula	Pure (+0.02 ml lido)	Needle vs cannula	–	At month 1, both groups showed ≥1-point improvement, that was stable in 95% of patients treated with cannula and 85% of needle-treated.	No serious adverse events for both sides apart from self-limiting local reactions. Slightly more painful the cannula treated side as compared to the needle side.
Schachter, 2016[24]	NLFs (not too severe not to be corrected in one session)	102	87 (85)	48.85 (30–77)	I (6%), II (18%), III (58%), IV (8%), V (5%), VI (5%); Caucasian (86%), African American (8%), and Other (6%)	Pro Multileft double-blind RCT (split face design)	Pure vs +	–	Subdermal	A total of 97% of subjects reported that treatment was less painful on the RADIESSE (+) Lidocaine Injectable Implant side, and this difference was significant. Blinded assessments showed significant aesthetic improvement for both NLFs at weeks 1, 2, and 4 ($P < 0.0001$).	AEs were generally expected, injection-related, mild, and transient. However, two cases of vascular compromise and an associated erosion were reported.
Fakhre, 2009[25]	NLFs	410	–	–	–	Meta-analysis	–	–	–	Patient satisfaction was 4.16 of 5 in 324 patients at 3 to 6 months and 4.15 in 86 patients at 1 year.	–

CaHA, calcium hydroxylapatite; GAIS, global assessment improvement scale; NASHA, non-animal stabilized hyaluronic acid; NLF, nasolabial fold; RCT, randomized controlled trial; WSRS, Wrinkle Severity Rating Scale.

Table 4 Summary of characteristics of included studies for jawline and marionette lines

Author, date	Indication	*N*	Females, *n* (%)	Age, mean ± SD (range)	Skin type/ethnicity	Study type	Product	Needle/cannula	Technique/depth	Efficacy	Safety
Baspeyras, 2017[28]	Jawline and marionette lines	35	35 (100)	57 (42–76)	–	Pro	Pure + lido 0.29 ml	–	Intradermal or subdermal based on injector's choice	A significant improvement in jawline and marionette scores was observed for both the left and right sides of the face, at 6 months, 12 months, and 1-point improvement in jawline scores from baseline of about 90% at 6 months, and about 60% at 12 months. PGAIS was improved and very much improved in all cases at 6 months while it was 81% at month 12 while SGAIS revealed 89% improvement and very much improved at all follow-ups. Interestingly, ≥ 97% reported that they would recommend the use of CaHA for jawline contouring to a friend and ≥93% would repeat treatment with CaHA.	Local and self-limiting adverse events.
Moradi, 2021[27]	Jawline	180	146 (81)	55.3 ± 7.1 (22–65)	I-III = 61%, IV-VI = 39%, Caucasian 81%, Asian 6%, African American 13%	Pro (RCT treated vs untreated/delayed)	+	27-G needle or 27-G (?) cannula	Subdermal or supraperiosteal	Treatment response rate (≥1-point MJAS improvement) was 76% for the treatment group and 9% for the control ($P < 0.0001$) at week 12. About 70% of patients who responded to treatment at 12 weeks demonstrated persistent improvement at 48 weeks.	Local and self-limiting adverse events.
Boen, 2022[29]	Jawline augmentation	10	10 (100)	61.2 (44–69)	II-IV	Pro (RCT split face)	+	Needle and cannula	Subdermal and supraperiosteal location for correction of wrinkles and folds along the jawline using both cannula and needle method in a standardized manner	Significant improvement as compared to the treated and untreated side, with 1-point improvement on the jawline score at 1 and 6 months.	No AEs were reported, and subjects tolerated the procedure well.

CaHA, calcium hydroxylapatite; GAIS, global assessment improvement scale; MJAS, Merz jawline assessment scale; PGAIS, physician global assessment improvement scale; RCT, randomized controlled trial; SGAIS, subject global assessment improvement scale.

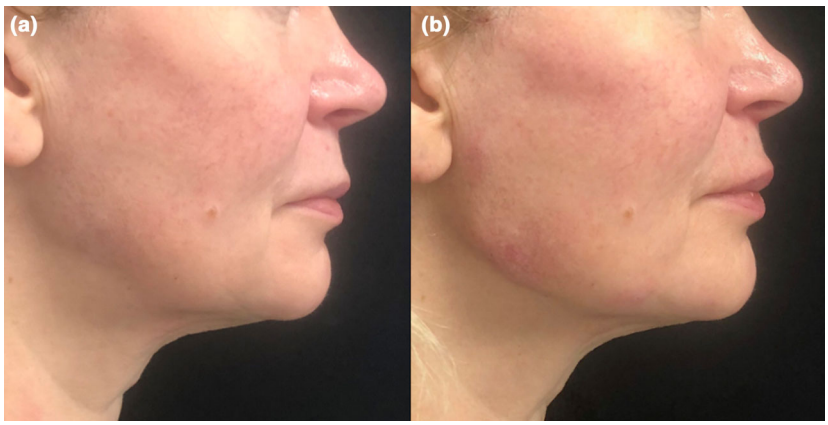

Figure 2 A 57-year-old woman (a) before treatment and (b) immediately after 1.5 ml Radiesse® + treatment injected in the area of zygomatic arc and jawline. An overall effect of contouring as well as an improvement of the jawline can be observed

equal amounts of product and diluent (1 : 1 ratio), while hyperdiluted CaHA/CMC is prepared with at least twice the amount of diluent (≥1 : 2 ratio). Roy et al.[37] reported their retrospective experience with 1 : 1, as well as with 1 : 2 Radiesse® on 75 patients, revealing very good and excellent scores for the subject's and injector's evaluation of the look and feel of the implant, 3 and 6 months after treatment (Figure 3). However, results were not broken down into treatment areas, therefore it is not possible to relate performance results to the different treatment areas.

In a study involving 40 patients, aged between 38 and 72 years, Rovatti et al.[38] reported a ≥1-point reduction in each of the 5-point scale (upper cheek fullness nasolabial fold at rest, marionette lines at rest, oral commissures at rest, and jawline at rest scales) using the 1:2 hyperdiluted technique as evaluated by blinded investigators, showing natural effects, as reported by patients (Figure 4). According to the response, all patients were satisfied and very satisfied with the procedure and the safety profile was in line with previous studies.

Bottom line

Radiesse® is currently cleared by the Food and Drug Administration (FDA) for the treatment of wrinkles and folds of the face and jawline treatment. This is supported by the results of numerous RCT split-face studies.[10,20,22]

The accumulated evidence suggests that CaHA/CMC is a safe and effective treatment with several indications for the face, for both its volumizing characteristics as well as for skin quality improvement. Comparative studies utilizing clinical data suggest that CaHA/CMC may be more effective with less product than HA, with potentially higher GAIS ratings.[10,20]

Histologic data further prove a significant increase of collagen I, angiogenesis, and elastin with CaHA/CMC, as compared to HA, supporting the biostimulatory activity of the filler.[39] Direct contact of CaHA with fibroblasts is a key factor for inducing neocollagenesis.[40] Importantly, current knowledge and scientific observations concerning the effects of CaHA/CMC on the restoration of mechanical properties of the skin, have led to the

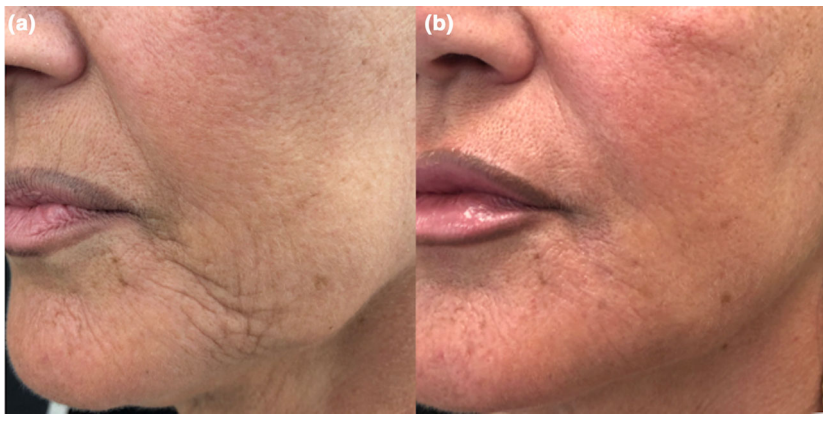

Figure 3 A 55-year-old woman (a) before treatment and (b) 4 months after 2 sessions of 1.5 ml Radiesse® 1 : 1 diluted treatment for mid and lower third of the face. An overall improvement of skin quality can be detected

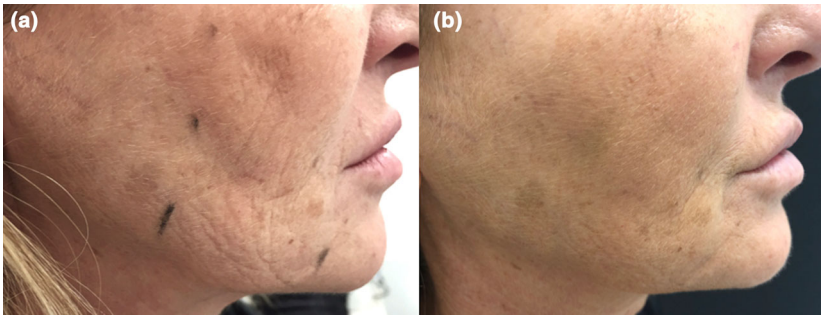

Figure 4 A 62-year-old woman (a) before treatment and (b) 4 months after 2 sessions of 1.5 ml Radiesse® 1 : 2 hyperdiluted treatment for mid and lower third of the face. An overall improvement in skin quality can be detected

concept that this filler has "regenerative" properties and can be included among other regenerative treatments.[41]

Recommendations for the use of CaHA/CMC encompass injection of the product through a cannula with a preferred size of 22G, or 25G, to avoid vascular injections. Beer et al.[23] compared, the efficacy of CaHA/CMC injected with a cannula or needle in an RCT split-face study. Cannula injections provided more stable results but were slightly more painful, as compared to needles.

Based on current knowledge of anatomy and incidence of vascular adverse events, the authors underline that injection of NLFs with a needle should be avoided for safety concerns.[42,43]

Injecting with needles in safe areas such as the zygomatic arch and angle of the mandible may be warranted. Additional caution should be used when injecting CaHA/CMC. These include: limiting the amount of filler and choosing the proper location and layer for the implant, to avoid potential lumps, bumps, and nodules. As a general rule, when non-inflammatory nodules occur within the first 2 weeks after injection, they can be managed with injections of saline solution/sterile water and mechanical massaging of the area. Late nodules can be approached with sterile water corticosteroid injections. Excision should be considered as a last resort.[36,44] In the case of inflammatory nodules, oral antibiotics should be considered.[36] Importantly, in most cases, CaHA nodules are not visible and resolve without any interventions.[6]

Recent consensus studies supported the use of 1 : 1 dilution for the face, employing 1.5–3 ml of CaHA/CMC for each session, scheduled at least 2 or 3 sessions every 1–2 months.[12,13] However, more robust clinical comparative data in the context of RCTs with a focus on dilution/hyperdilution are still needed to further support the material's use in clinical practice, in improving skin quality.

Recommendation

Radiesse may be considered a safe and effective treatment option for HIV-related FLA, NLFs, jawline/marionette lines, and cheeks.

The treatment of marionette lines, chin, pre-jowl, and corner of the mouth also tends to respond with a high degree of safety and efficacy.

Based on published guidelines, the use of dilute and hyperdilute Radiesse for skin tightening via biostimulation may be used.

Clinicians should have adequate training in anatomy, indication for treatment, patient selection, and treatment plans to perform effective treatments and guarantee the best outcomes.

Conclusions

CaHA/CMC has proven to be effective and safe in wrinkles and fold correction of the mid and lower face, providing long-term and natural results. Despite the recent trend, guidelines, and safety profile of diluted and hyperdiluted Radiesse, no RCTs have been performed, suggesting that the role of CaHA/CMC in regenerative medicine needs further investigation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of characteristics of included studies related to mixed indications for the face, cheek volume loss, and dilute/hyperdilute Radiesse®.