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Prospective 3D analysis of facial soft tissue augmentation with calcium hydroxylapatite

Filip Simunovic\textsuperscript{a}, Stefan Schlager\textsuperscript{b}, Michaela Montanari\textsuperscript{c}, and Niklas Iblher\textsuperscript{d}

\textsuperscript{a}Department of Plastic and Hand Surgery, Freiburg University Medical Center, Freiburg, Germany; \textsuperscript{b}Department of Biological Anthropology, University of Freiburg, Freiburg, Germany; \textsuperscript{c}Private Practice for Plastic and Aesthetic Surgery, Bochum, Germany; \textsuperscript{d}Private Practice for Plastic and Aesthetic Surgery, Freiburg, Germany

ABSTRACT

Background: Facial rejuvenation is an expanding field with an increasing number of treatment modalities. Several non-autologous filler materials are available for soft tissue augmentation. Calcium hydroxylapatite (CaOH) is aimed at increasing collagen neosynthesis and thereby producing long-term augmentation effects. Despite a multitude of observational reports, the field is suffering from lack of quantitative morphometric evaluation methods. Objective: The objective of this proof-of-principle study was to investigate whether the effects of facial tissue augmentation with CaOH (RADIESSE™) can be quantified and followed up using 3D surface scanning. Methods: 3 female subjects received augmentation of the mid and lower face with CaOH. The faces were recorded prior, directly after, and two weeks and six months after the injection using standardized photos and 3D scanning. Computational analysis allowed quantifying the change in volume and displacement of the facial surface. Additionally, a patient satisfaction questionnaire was administered. Results: In all subjects, increase in facial volume could be quantified and was present after two weeks and six months. Conclusions: 3D surface scanning is an adequate tool for objective quantification of changes after facial augmentation with filler materials. Persistent volume augmentation after CaOH injections could be quantified after two weeks and six months. Evidence level: IV.

Introduction

Soft tissue fillers are an expanding palette of products offering nonsurgical correction of age-related facial changes. Whereas botulinum toxin injections to the upper face paved the way for nonsurgical facial rejuvenation in the early 2000s, a range of materials aimed at restoring fullness to the middle and lower face followed. While most permanent fillers are prone to complications and thus hyaluronic acid is established as the most widespread facial soft tissue filler, calcium hydroxylapatite (CaHA) is a further substance that has been used increasingly since its Food and Drug Administration approval in the United States in 2006. It is not immunogenic, since CaHA is a normally occurring component of bone and teeth. CaHA microspheres are delivered in a polysaccharide carrier. The augmentative effect of the injection is immediately evident. Following injection, the carrier gel is dissolved, and it is suggested that the remaining microspheres stimulate fibroblast growth and collagen production \cite{1,2}, thus causing a longer-lasting augmentation effect. Eventually, the microspheres dissolve into calcium and phosphate, which are subject to the physiological ion homeostasis of the body.

Several investigations addressed the effects and their persistence after CaHA injections for facial augmentation, showing a low rate of complications and generally high acceptance and satisfaction levels. The duration of effect achieved with CaHA has been reported to last as long as 18 months \cite{3}, 12–24 months \cite{4} or only 6 months \cite{5,6}. In a further study, over 80% of the patients claimed persistence of the results at 12 months after injection \cite{7}. Moers-Carpi et al. compared CaHA to hyaluronic acid for treatment of the nasolabial folds and found better and longer-lasting results with CaHA \cite{8,9}. Another group found that CaHA is superior to human collagen for rejuvenation of the nasolabial folds after an observation period of 6 months \cite{10}.

The above-mentioned studies are contributions to the mounting body of evidence that CaHA is a reliable, long-lasting and safe facial filler. However, these, as well as the majority of studies in the field of facial fillers, are marred by the lack of objective and quantitative morphometrical examination criteria as they mostly rely on patients’ and doctors’ subjective and descriptive evaluations of the results. Whereas there are clearly large intercultural and individual differences between aesthetic standards, it is our opinion that it should be the goal of a scientific outcome evaluation of any medical procedure to develop reproducible and quantifiable measurements to evaluate the achieved results of the intervention. Up to recently, the technological options to evaluate the complex and interacting facial soft tissues were limited to clinical
observation and evaluation of photographs. Gatherwright et al. have evaluated the 3D outcome of CaOH injections in a cadaver model and showed a volume increase and lifting effect (11), yet to this date there is no study evaluating three-dimensional outcome of this filler treatment in living individuals.

To this end, we have previously described the use of three-dimensional surface scanning for quantifying facial soft tissue changes (12). This technology has also been used by other authors to record soft-tissue changes in the face (13–15), but it has not yet gained widespread acceptance. This study was designed to quantify the effects of an intervention (CaOH injection) using this method. Additionally, we aimed at observing the intermediate-term changes after injection over a 6-month period.

Subjects and methods

Four voluntary Caucasian female subjects (ages 60, 56, 65 and 51 years) who presented with a wish for nonsurgical facial rejuvenation were included in this study (Table 1). None of the individuals had a history of prior facial surgery, trauma, notable comorbidity or prior filler injections less than 1 year before the start of the study. All participants signed informed consent forms and paid a symbolic treatment fee, which was refunded after completion of the six-month follow-up. The study medication was supplied by Merz Pharmaceuticals free of charge, as well as a financial support for the 3D calculations.

Prior to injections, the individuals underwent standard photograph series and three-dimensional surface scanning. Scanning was performed using an Artec MHT surface scanner (Artec Group, San Diego, California), which uses structured light technology. A flashing light projects a grid pattern onto the scanned surface, and the distortion of this grid is captured by three cameras from different angles. The subjects were scanned in the sitting and supine position with teeth in occlusion without forced bite, lips closed, eyes opened and with forward gaze and without activation of the mimic musculature. The Frankfort horizontal was used as a reference plane and the head adjusted to align it horizontally and vertically.

All injections of CaHA (RADIESSE™, Merz Pharmaceuticals GmbH, Frankfurt am Main) were performed by a single surgeon (MM). The injections of CaHA in the cheekbone area and the mandibular area were administered with a sharp needle supraperiostally as a single bolus. The other regions were infiltrated with an atraumatic needle in the deep dermal layer. Following the administration, the product was massaged in the different regions in order to prevent irregularities. The volumes injected per region for each patient are given in Table 2.

The measurements were repeated directly following the injections, as well as after 2 weeks and after 6 months. At 2 weeks and 6 months, the participants were additionally asked to fill out a questionnaire assaying their satisfaction and the pain level during the injections, each on a scale from 1 (best) to 6 (worst). They were also questioned whether they would repeat the procedure and whether they would recommend it to their best friend (yes/no). The patient’s weight was recorded at all time points.

Registration

To establish an initial spatial reference between the surface scans, seven landmarks were placed manually on each scan (endocanthion, ectocanthion, pronasale and labial commissures). Based on these references, a generic facial model was aligned rigidly, and subsequently matched onto each of the scans by applying rigid, affine and elastic iterative closest point (ICP) registration algorithms by using the R-package mesheR (https://github.com/zarquon42b/mesheR). As a result, all surface scans can be represented by a surface mesh with quasi-homologuous vertices.

In order to find variation within the cheek region, we defined a T-shaped region on the template (forehead/nose), which was unaffected by the injections (Figure 1A). Based on the correspondence between all vertices, this region was identified in all surface scans and used to register the scans of each patient rigidly onto the corresponding pre-OP state. This allows for an analysis of changes between the aligned surfaces.

ROI

As region of interest (ROI), we defined an area on the left cheek that spanned the treatment area in all patients (Figure 1B). As all vertices are corresponding between scans, the ROI could be extracted consistently for all scans of all patients involved.

<table>
<thead>
<tr>
<th>Table 1. Demographic data and patient satisfaction.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>Age (at treatment)</td>
</tr>
<tr>
<td>Complications (self-reported)</td>
</tr>
<tr>
<td>Swelling and ecchymosis of the pre-jowl area for 1 week</td>
</tr>
<tr>
<td><strong>2 weeks</strong></td>
</tr>
<tr>
<td>Would repeat treatment (yes/no)</td>
</tr>
<tr>
<td>Would recommend to best friend (yes/no)</td>
</tr>
<tr>
<td><strong>Pain (grade)</strong></td>
</tr>
<tr>
<td><strong>6 months</strong></td>
</tr>
<tr>
<td>Would repeat treatment (yes/no)</td>
</tr>
<tr>
<td>Would recommend to best friend (yes/no)</td>
</tr>
<tr>
<td><strong>Pain (grade)</strong></td>
</tr>
</tbody>
</table>

Notes: Grades: 1 – best, 6 – worst.

<table>
<thead>
<tr>
<th>Table 2. Amounts of Radiesse injected per region (amount used on each side in ml, except when otherwise indicated).</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>Infraorbital</td>
</tr>
<tr>
<td>Maxillary</td>
</tr>
<tr>
<td>Nasolabial fold</td>
</tr>
<tr>
<td>Cheek</td>
</tr>
<tr>
<td>Marionette lines</td>
</tr>
<tr>
<td>Jowl region</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
Distance measure

All vertices within the ROI were projected orthogonally, i.e. along their normal vectors, onto from the pre-OP state to the post-OP states. As a metric for changes in distances relating to the pre-OP state, we chose the average distance between the original position of the vertices and these projections.

Volume measurement

To obtain volume changes of an open mesh, we defined the volume between two states as the volume confined by the surfaces of the ROI in the pre-OP state and its orthogonal projection, with the borders simply closed by connecting the border vertices (Figure 1C).

Results

All four patients completed the study without complications. In particular, there were no signs of allergic reaction, nodules or otherwise palpable foreign material. Patient 2 reported swelling and ecchymosis of the pre-jowl area, which resolved spontaneously after 1 week. There were no relevant weight changes (±1 kg) in any of the patients. Unfortunately, patient 4 had to be excluded because of defective pre-injection 3D scans, which did not allow us to perform measurements.
After 2 weeks, satisfaction rates were 3, 1 and 2, and after 6 months 2, 1 and 3, respectively. Participants 1 and 2 stated they would repeat the treatment and recommend it to their best friend, whereas participant 3 would do neither. Pain during treatment was graded as 5, 2–1 and 4 after 2 weeks, and 5, 2 and 6 after 6 months (Table 2).

Figures 2–4 show the results after the injections with CaHA in patients 1, 2 and 3, respectively. In these figures, panels A and E were taken prior to injections, and B and F immediately following the injections. Swelling and ecchymosis are noted in all cases. Panels C and G show the result after 2 weeks, and D and H after 6 months. Panels I, J, K and L represent the displacement of the facial surface vertically to the surface in millimeters comparing pre-injection and directly post-injection (J), pre-injection to 2 weeks post-injection (K) and pre-injection to 6 months (L). Panel I explains the color coding, which ranges from red and yellow (negative = pre-injection inside/less volume than post-injection) to green (0, no change) to shades of blue (positive = pre-injection outward displacement/more volume than post-injection). Time-lapse morphings of the heatmaps are shown as supplemental digital content in videos 1, 2 and 3.

Increase in volume after the injections was documented in all participants. Case 1 exhibited a volume increase of 10.59 ml immediately following the injections, 2.78 ml after 2 weeks and 2.4 ml after 6 months. These values were 3.28, 0.66 and 1.48 ml for case 2 and 14.23, 13.2 and 4.35 ml for case 3, respectively. An alternative method of quantifying the changes in soft tissue volume was to measure the mean surface displacement vertically toward the surface between the baseline and the post-injection time points. Using this method, distances of 2 mm after injection, and 0.54 and 0.46 mm after 2 weeks and 6 months, were measured in case 1. The respective measurements were 0.42, 0.11 and 0.25 mm for case 2 and 2.63, 2.39 and 0.8 mm for case 3 (Figure 5).

Discussion

The field of facial rejuvenation and aesthetic medicine in general is still characterized by a lack of objective methods of result quantification. Since the facial appearance is a highly subjective matter, it is understandable that complete quantification of aesthetic procedures can never be completely achieved by numerical analysis. However, in times of evidence-based medicine, it is our belief that it should be possible to quantify the results of the suggested procedure for a certain aspect of aging-related facial changes (e.g., volume loss). Only when the methods to do so are established, it
will be possible to compare results of different treatment options. This in turn allows the physician and the patient to adopt the best suited treatment approach among the increasingly confusing landscape of products and procedures available.

Descriptive reports of the aging face (16–18) and sound imaging studies of the changes of the facial skeleton (19,20) are numerous. During the recent years, several publications in the field of orthodontics and maxillofacial surgery appeared examining facial soft tissue changes in cleft palate, cleft lip and malocclusion patients (21–25). Certainly, the complexity of the facial soft tissue architecture, with its multiple separate yet interacting compartments, has made this task difficult. Others and our group described three-dimensional surface scanning for this purpose (12,13,15), which has to be seen as the method of choice for quantification of facial soft tissue interventions, yet the technical complexity still limits widespread acceptance.

In this study, it was possible to quantify the effects of CaHA injections for facial rejuvenation by describing the distance of displacement between the skin surface before and after the injections as well as by calculating volume changes in the region of interest. The detection of the facial changes was facilitated by the fact that in two patients, large volumes of CaHA (3.5 and 6.3/8.3 ml per side) were injected. Clinically, the volume restoring effect evidently persisted in cases 1 and 3, yet the changes in subject 2 at 6 months are not clearly evident. However, even when using only 1.5 ml CaHA per side as in patient 2, it was possible to measure the changes using 3D surface scanning technology, suggesting that this method of measurement is precise enough to even detect smaller amounts of a filler material over longer periods, which is simply impossible with simple clinical examination or comparison of 2D photographs. However, it has to be pointed out that although the used scanner has a resolution of 0.5 mm and even minimal changes in the 3D texture can be detected and measured, the technology is not without limitations. Even small alterations in the exact posture of the assessed subject like inclination of the head, activation of masticatory or mimic musculature or coverage with facial hair can lead to variations in the measurements, whose dimensions can possibly exceed those that are meant to be measured. The 2-week and 6-month results of subject 2 might be interpreted in that way (Figure 5), as the observed changes are higher after the longer period of time. The absolute difference is not much, yet the trend that solely relies on...
resorption would be expected to be the other way around as can be shown in the other two subjects. On the other hand, it might be possible that a postulated de novo synthesis of collagen might lead to the observed increase in volume in this case in which the absolute injection volume is lower, and this effect might become more evident. It is essential for studies using high-resolution 3D imaging that exact study protocols are designed and followed to minimize inconsistency in the exact measurements.

Additionally, the post-interventional course over a period of six months could be followed up. It was shown that an augmentation effect is still measurable by this method after a six-month period, which is in line with the literature on the duration of effect of CaHA injections. The measured sustainment of injected volume after 6 months varies from 68 to 99% to 30% in patients 1–3, respectively. It seems to be lower for the higher volume injections. Ideally, in further studies, the duration of the follow-up should be extended until the changes return to the baseline levels. Additionally, a more specific numeric quantification of the resorption process, which might in turn help in prospective treatment planning, requires further studies with more study objects to evaluate individual trends like body fat or individual anatomy, the influence of the filler volume or predictions about specific treatment localizations.

An advantage of the scanning system we use is that it is a fully mobile unit, enabling the researcher to perform the scans in various positions. This is especially important for facial soft tissue, since we previously showed that there is an increased soft tissue mobility between the upright and the supine positions in older individuals (12). Ideally, a rejuvenation procedure should not only increase volume but also reverse the increased soft tissue mobility seen in the older patient, an effect we could not show for CaHA in this study (data not shown), yet the study design allows for such an approach.

Deep CaHA injections were generally tolerated well by the patients. Patient 3 wished a maximal augmentative effect and received 6.3 ml injections to the right, and 8.3 ml to the left side of the face. She consequently complained of pain and reported that because of pain and despite being satisfied with the result, she would not have the procedure again and would not recommend it to her best friend. Possibly, several settings with repeated

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**Figure 5.** Bar charts indicating the changes of volume (A) and the orthogonal distance of displacement of the facial surface (B) relative to the pre-intervention state directly after injection, after two weeks and after six months.
injections would be better suited in these cases, yet our study design did not allow for this approach. Another possibility to improve patient comfort would be to use a mixture of calcium hydroxyapatite dermal filler mixed with local anesthetic, as reported by Rauso et al. (26).

Because of its calcium component, concerns have been raised about the interference of CaHA with bone imaging studies of the face. These have been dissipated by the work of Carruthers et al. showing that the presence of the substance is indeed demonstrated in the soft tissue in plane radiographs and computer tomography images, but its appearance is distinct from the underlying bony structures, which can be diagnostically evaluated (27). In this work, we did not perform diagnostic studies to investigate the presence of the substance.

The purpose of this proof-of-principle study was to use three-dimensional surface scanning to quantify therapy-induced facial soft tissue changes. To the best of our knowledge, this is the first study to achieve this for a facial aesthetic procedure using CaHA. It is worthwhile to design further, larger-scale studies in this fashion to objectively measure the results of aesthetic interventions. It is possible to perform comparative studies, comparing the effect of one procedure against another or longitudinal studies, measuring the effects of a procedure over time. We thus hope that a body of evidence can be accumulated which assists the practitioner in counseling patients based on solid facts, which should be the basis for every treatment modality.

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**Conflict of interest declaration**

Dr Montanari has received allowances for working as clinical instructor for Merz products. All the other authors declare that they have no conflicts of interest to disclose.

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