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REVIEW ARTICLE

Late inflammatory reactions in patients with soft tissue fillers after SARS-CoV-2 infection and vaccination: A systematic review of the literature

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Abstract

Introduction: Soft tissue fillers are used for cosmetic and reconstructive purposes, and soft tissue filler procedures are among the most common nonsurgical procedures in the USA. Although soft tissue filler procedures are relatively quick and safe, adverse events such as late inflammatory reactions have been reported with every filler product. Infections and vaccinations have been proposed as potential triggers for late inflammatory reactions (LIRs), and it is therefore not surprising that these adverse events have been reported after SARS-CoV-2 infection and vaccination. Therefore, this review aims to give a detailed overview of these cases.

Materials and methods: A literature search was undertaken on LIRs in patients with a history of soft tissue filler use after SARS-CoV-2 infection or vaccination. This systematic review was reported according to the PRISMA guidelines. We searched the electronic database PubMed from January 2020 to August 2021. Data on patient characteristics, filler characteristics, clinical findings, and treatment options were included.

Results: This review included 7 articles with a total of 19 patients with LIRs after SARS-CoV-2 infection or vaccination. Three patients with postinfection LIRs and 16 patients with postvaccination LIRs were reported. These LIRS mainly occurred in females who had HA injections for cosmetic purposes. Three patients with postinfection LIRs had symptoms of facial swelling and/or lip angioedema in a matter of weeks. Sixteen patients reported reactions after SARS-CoV-2 vaccination (13 following Moderna vaccination and 3 after Pfizer vaccination, after both the first and second doses) from 13 hours up to three weeks. These patients presented with similar clinical symptoms as patients with postinfection LIRs. All patients were treated in a conservative manner.

Discussion: This review shows a relationship between LIRs and SARS-CoV-2 infection and vaccination. In the case of vaccination, these adverse events have been reported only after Moderna and Pfizer vaccinations. The reported adverse events are generally minor and self-limiting, and we encourage patients with soft tissue fillers to participate in vaccination programs.

KEYWORDS
adverse events, COVID-19, SARS-CoV-2, soft tissue filler, vaccination

1 | INTRODUCTION

Soft tissue fillers are used for aesthetic purposes as well as to restore aesthetics after trauma or cancer.[1] According to the American Society for Aesthetic Plastic Surgery, the use of soft tissue fillers increased by 59% between 2014 and 2018.[2,3] With almost one million procedures performed annually, soft tissue filler procedures are among the most commonly performed nonsurgical treatments in the United States.[2] The popularity of soft tissue fillers has been attributed to their simple use, quick results, and relative safe use.[4] As a result, the increased use of soft tissue fillers has led to an increase in soft tissue filler products. These products are divided according to their biodegradability into temporary, biostimulatory, or permanent fillers.[5,6] Table 1 shows an overview of soft tissue fillers that have been used in the past and present.

Although the use of contemporarily available soft tissue fillers is considered safe, several studies have shown that complications occur with all filler types.[4,7-13] Late inflammatory reactions (LIRs) are among the most common complications after filler use. However, the etiology of LIRs is unknown; therefore, they are difficult to treat.[13] Examples of LIRs are erythematous lumps, granulomas, edema, or nodules. Several reports have shown that LIRs occur between weeks and years after filler treatment. According to Marusza et al., these complications occur in 0.01%–4.25% of soft tissue filler procedures.[14,15] Thus far, the etiopathogenesis of LIRs is still not known. Several hypotheses have been proposed, such as bacterial contamination, foreign body reaction, delayed-type hypersensitivity reaction, and adjuvant-based filler reactions due to triggers such as infection, trauma, or vaccination.[12,14,16-25]

It is therefore not surprising that in the current COVID-19 pandemic, LIRs have been reported after SARS-CoV-2 infection and vaccination. The first results of the Food and Drug Administration (FDA) on the Moderna vaccine showed adverse events in three patients with soft tissue fillers.[26] This concerned patients, who developed facial swelling eight days after the first dose and one and two days after receiving the second dose of the vaccine. Subsequently, several reports on facial swelling after SARS-CoV-2 infection and vaccination were published. As a result, concerns have been raised among patients with soft tissue fillers regarding the association of LIRs and SARS-CoV-2 infection and vaccination. Therefore, we aimed to provide a detailed overview of the reported LIRs after SARS-CoV-2 infection and vaccination to provide recommendations for patients with injected soft tissue fillers in the current COVID-19 pandemic.

2 | METHOD

2.1 | Literature search and selection criteria

In this systematic review, a literature search was performed on soft tissue filler-related LIRs after SARS-CoV-2 infection or vaccination and conducted according to the PRISMA guidelines.[27] A search was performed in the electronic database PubMed with the use of the index term 'filler' (see supplemental data file). Studies from January 2020 to August 2021 were included without language restrictions. Studies on LIRs in soft tissue filler use after SARS-CoV-2 infection or vaccination were identified. We included original patient studies. Here, there was no limitation on the type of filler product or on SARS-CoV-2 vaccinations. The search was executed with the aid of an experienced medical information specialist. Two reviewers considered the eligibility of each article in the subsequent steps: the reviewers inspected the title first and thereafter screened the abstract. In the case of doubt on the eligibility, they reviewed the full text.

2.2 | Data extraction

When a study was included, the extracted data were entered into standardized tables. These data included article, patient, and filler characteristics, such as the date of publication, study design, number of patients, age and sex of patients, type/amount and location sites of the soft tissue fillers, indication for injection, description of

TABLE 1 Overview of the different soft tissue fillers subdivided according to their biodegradability

Biodegradability	Substances	Manufacturer	Estimated duration of effects
Temporary	Collagen (not used anymore), hyaluronic acid	Restylane, Juvéderm, Belotero	6–24 months
Biostimulatory	Polylactic-L-Acid (PLA), calcium hydroxylapatite (CHA), polycaprolactone	Radiesse, Sculptra Ellansé	12–36 months
Permanent	Silicone, polyalkylimide gel (PAIG, Bio-Alcamid), polyacrylamide gel (PAAG, Aquamid), polymethyl-methacrylate (PMMA, Artocoll/ArteFill), HEMA/EMA (DermaLive)	Artefill, Dermalive, Aquamid, Bio-Alcamid	–

complications, vaccine brand, duration between injection and SARS-CoV-2 positivity or vaccination and type of treatment. The level of evidence was based on the Oxford Centre for Evidence-Based Medicine.[28]

3 | RESULTS

3.1 | Article and patient characteristics

Our search identified a total of 1090 articles in PubMed (Figure 1). After screening the title and abstract, 105 and 40 articles, respectively, were included. Finally, 7 articles were included in the analysis (Table 2). These articles contained a total of 19 patients, of whom 3 patients had adverse events after SARS-CoV-2 infection and 16 had adverse events after SARS-CoV-2 vaccination (13 after Moderna vaccination and 3 after Pfizer vaccination). For the 13 patients who had adverse events after Moderna vaccination, in 5 patients the adverse event occurred after the first dose, in 6 it occurred after the second dose, and in 2 first or second dose was not reported. For the 3 patients who had adverse events after Pfizer vaccination, in one the adverse event occurred after the first dose and in it occurred after the second dose. None of the studies mentioned whether any of the patients who experienced adverse events after SARS-CoV-2 vaccination had previously tested positive for SARS-CoV-2 infection. On the basis of the details reported, the adverse events occurred in females who had hyaluronic acid (HA) injections for cosmetic purposes.

3.2 | LIRs after SARS-CoV-2 infection

The first reports on adverse events in patients with soft tissue fillers following a SARS-CoV-2 infection emerged in January 2021 and were soon followed by several other reports (Table S1a).

Munavalli et al. reported on a 50-year-old woman with a history of HA injections up to 15 days prior to a SARS-CoV-2 infection.[29] Two weeks after her positive PCR test for SARS-CoV-2, she developed lip burning and swelling followed by cheeks and tear trough swelling. The patient's symptoms seemed to worsen over the following days. She was primarily treated with Hylenex (hyaluronidase; unknown manufacturer) injections and showed a transient improvement followed by cheek edema. In the weeks that followed, she received prednisone, doxycycline, Hylenex, microneedling combined with clarithromycin and prednisone, intralesional triamcinolone acetamide and Hylenex, which altogether resulted in a slight improvement. At the last visit, the patient continued to report intermittent mild edema under the eyes.[29]

In another case report, a young patient had HA filler treatment in the nose area 5 months prior to SARS-CoV-2 infection.[30] Three weeks after her infection, she developed edema, induration, and erythema around the radix of the nose. Her symptoms resolved in six days without any medical treatment. Likewise, Shome et al. presented the case of a young woman who was rejuvenated using soft tissue fillers at multiple sites on her face.[31] She presented one month after SARS-CoV-2 infection with swelling around the periocular area. After treatment with anti-inflammatory drugs, the swelling subsided.

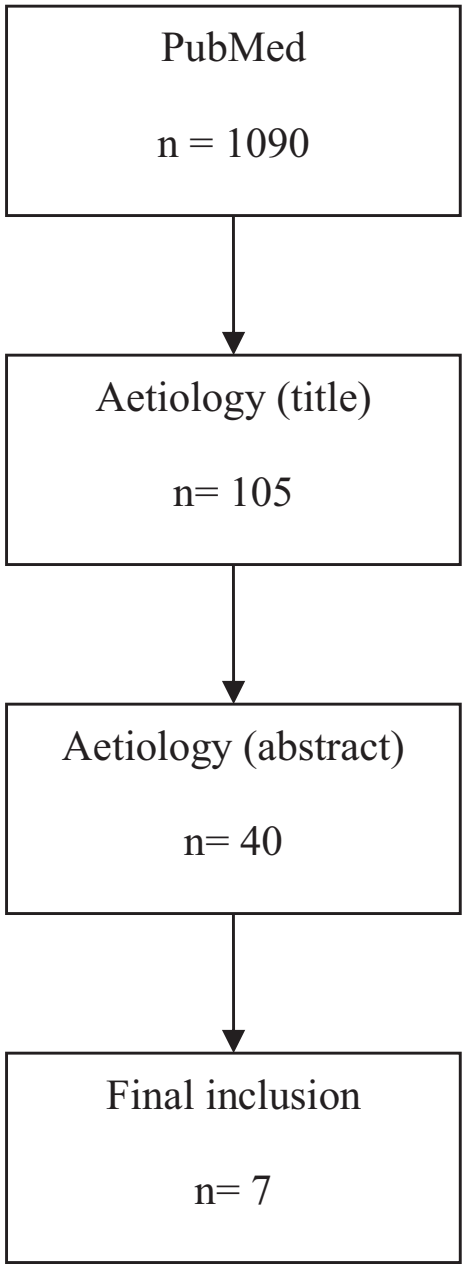

FIGURE 1 Study selection flow chart

Naouri et al. performed a prospective clinical study in patients receiving hyaluronic acid during the COVID-19 pandemic.[32] Fourteen dermatologists in three countries evaluated 1093 patients who received facial HA injections. Patients were then contacted at the 1- and 3-month follow-ups and asked for side effects. Nineteen side effects, such as erythema, edema, and temporary discomfort, were reported. However, none of these patients had a positive SARS-CoV-2 PCR test or COVID-19 symptoms. The authors

TABLE 2 Characteristics of included studies

Author	Publication year	Study design	N Patients (total investigated)	Type of filler	Amount of injected filler	Injection site	Main focus	Level of evidence
FDA briefing on the Moderna vaccine[24,27]	2020	Phase III pivotal clinical trial of investigational vaccine	3	2 unknown 1 Hyaluronic acid	Unknown	Two facial (not further specified), one lips	Postvaccination adverse events	II
Munavalli et al.[27,31]	2021	Case series	4	Hyaluronic acid	Unknown	Various	Postvaccination adverse events	IV
Munavalli et al.[27]	2021	Case report	1	Hyaluronic acid	Unknown	Various	Postinfection adverse events/ Postvaccination adverse events	IV
Rowland-Warmann et al.[28]	2021	Case report	1	Hyaluronic acid	0.9 mL	Nose	Postinfection adverse events	IV
Shome et al.[29]	2021	Case report	1	Unknown	Unknown	Various	Postinfection adverse events	IV
Naouri et al.[30]	2021	Prospective clinical study	0 (1093)	Hyaluronic acid	Unknown	Various	Postinfection adverse events	II
McMahon[32]	2021	International registry of cutaneous manifestation of SARS-CoV-2	9 (414)	Unknown	Unknown	Unknown	Postvaccination adverse events	III

Abbreviations: N, number; mL, milliliter.

therefore suggest an excellent tolerance of HA injections during the COVID-19 pandemic.[32]

3.3 | LIRs after SARS-CoV-2 vaccination

The first adverse events following SARS-CoV-2 vaccination were reported in the preliminary FDA results for the Moderna vaccine (Table S1b),[26] which showed adverse events in three patients. Two patients with recent filler injections (6 months and five weeks) prior to vaccination had facial swelling postvaccination. In a third patient with an unknown time after filler injection, there was lip angioedema two days after vaccination. Her medical history reported a similar reaction after influenza vaccination. In all three patients, the reactions resolved. One of these patients (a 51-year-old woman) was then further analyzed in a case series by Munavilla et al..[29] The patient had several HA injections at various sites and was enrolled in the Moderna study five weeks after receiving her last filler injection. Eight days after receiving the first dose, she presented with progressive facial edema, erythema, and periorbital area and malar cheek tenderness.[29,33] In the following weeks, she received a (combination of) Hylenex, bovine hyaluronidase, antimicrobials, and intralesional 5-fluorouracil. At the final visit, she had hardly any symptoms.

Munavilla et al. also presented another case series of four patients with HA who developed adverse events after vaccination.[33] Two patients received the Moderna vaccine and developed facial swelling and lip angioedema 13 and 24 hours after the second dose, respectively. The other two patients received the Pfizer vaccine and developed inflammatory reactions around the fillers and facial swelling seven days after the first dose and two days after the second. Interestingly, in two of these patients, LIRs occurred after the second dose, while they endured the first dose without any incident. Additionally, two patients (receiving the Moderna and Pfizer vaccines) had a history of facial swelling around the filler treatment areas. In one patient, this was following the treatment of an upper respiratory tract infection. The swelling was eventually treated with antihistamines and oral prednisone. In the second patient, this occurred spontaneously 12 months after injection and responded to hyaluronidase and intralesional corticosteroid combined with 5-fluorouracil. For their current situation, all four patients were treated with lisinopril with a good response.[33]

McMahon et al. reported complications after Moderna and Pfizer vaccination after both doses.[34] They extracted their data from the international registry of cutaneous manifestations of SARS-CoV-2, which was set up at the beginning of 2020. A total of 414 cutaneous reactions were observed, of which 9 cases of facial swelling occurred after cosmetic filler injections.[34] Eight cases of swelling were seen after Moderna vaccination (3 after the first and 5 after the second dose), and one case was seen after the second Pfizer vaccination. Further details about the filler material, clinical presentation, and treatment were not specified.

3.4 | Synthesis

Many concerns have been raised after reports of adverse events in patients with soft tissue fillers after SARS-CoV-2 infection and mostly after SARS-CoV-2 vaccination. The current review aimed to investigate the reported adverse events to provide sufficient advice for patients with soft tissue fillers during the current COVID-19 pandemic.

The current review included 7 articles with a total of 19 patients with adverse events after SARS-CoV-2 infection or vaccination. There were 3 patients with postinfection LIRs and 16 patients with postvaccination LIRs. On the basis of the reports, these events mainly occurred in females who had HA injections for cosmetic purposes. Three patients had a SARS-CoV-2 infection between 15 days and 6 months after filler infection. They developed symptoms in a matter of weeks postinfection (range 3–4 weeks). They presented with facial swelling and/or lip angioedema, which resolved after conservative treatment. Sixteen patients reported reactions after SARS-CoV-2 vaccination. This concerned the Moderna vaccine in 13 patients and the Pfizer vaccine in 3 patients, after both the first and second doses. They reported symptoms from 13 hours up to three weeks postvaccination. These patients presented with similar clinical symptoms as patients with postinfection adverse events. Again, all patients were treated in a conservative manner. Interestingly, a few patients had a history of spontaneous facial swelling after a filler injection, previous vaccination, or after another medical treatment.

It is not the first time that adverse events after filler treatment have been reported after a viral infection. Several case reports reported similar reactions after other viral infections.[35-38] Turkmani et al., for example, described 14 patients with filler-related adverse events after influenza-like illness.[35] It concerned 14 women between 22 and 65 years old who presented with redness and firm, painful swellings of the face at sites of previously injected fillers. These reactions began 3–5 days after patients had influenza-like symptoms (e.g., fever, headache, sore throat, cough, and fatigue). They had a history of multiple fillers over the past four years with the last filler injections between 2 and 10 months prior to their reaction. They had injections with different brands of HA fillers. Most patients had a good response to oral corticosteroids, while a few patients needed hyaluronidase for complete resolution of their symptoms.[35] Another case series by Bhojani-Lync et al. described 4 patients with filler-related adverse events that had influenza-like symptoms a few days prior to their adverse events.[38] All patients had HA fillers in the year before complications emerged. A treatment approach that was similar to that of the previous study was used: oral corticosteroids and additional hyaluronidase in patients with persistent complaints. Again, in all patients, complete resolution of their symptoms was reported.

LIRs may emerge from weeks up to months after soft tissue filler injection. To date, it is unclear which patients will develop these complications, as the etiology of LIRs is not completely clear.[13] It has been proposed that immunobiological factors (e.g., bacterial infection, foreign body reaction, delayed-type hypersensitivity reaction, adjuvant-based filler reactions, and genetic predisposition), chemical properties (e.g., electrical charge, surface irregularities, particle size, hydrophilicity/hydrophobicity, molecular weight, and amount of chemical cross-linking), and injection techniques (e.g., level of implantation, filler volume, and repeated treatments) might play a central role in its development.[12,14,16-25,39–42]

Based on the clinical presentation of the current cases, we suggest that immunobiological factors might play an important role in the etiology of LIRs after SARS-CoV-2 infection and vaccination.

Most authors of the presented studies suggest that these reactions are due to delayed-type hypersensitivity (type IV) reactions initiated by T-lymphocytes and mediated by CD4+ cells.[38] HA is one of the few filler constituents that has proven to evoke a type IV hypersensitivity reaction shown by positive skin testing.[20] However, this concerned only one study. A recent study on patients who experienced LIRs following HA filler injection showed no reaction for general allergic screening (patch test) or intradermal testing.[43]

Munavalli et al. treated their patients with lisinopril, which decreased the clinical symptoms.[29,33] Lisinopril is an angiotensin-converting enzyme inhibitor (ACE-1) that plays a crucial role in SARS-CoV-2 binding properties but is mostly known for its role in the renin-angiotensin system (RAS), which regulates the interstitial fluid volume. The authors therefore propose a novel mechanism of action via ACE-1[29,33]; via several steps, the reaction is shifted toward an anti-inflammatory reaction that results in an increase in sodium water outflow. This results in a decrease of the swelling.[29,33,44]

Another theory is adjuvant-based filler reactions. Alijotas-Reig and colleagues postulate that foreign body materials such as breast implants or dermal fillers might trigger the immune system not as antigens but more like adjuvants.[13,24] By this, they mean that adjuvants can trigger the immune system but without having specific antigenic properties themselves.[25] As a result, the innate and adaptive immune systems can be triggered by adjuvants. These adjuvants mimic molecules such as PAMPs that can trigger the immune system by binding Toll-like receptors (TLRs). This results, for example, in the release of several cytokines and the activation of dendritic cells (DCs) or macrophages.[25] The effects of adjuvants are thought to be mediated by several activities, as described in our former review.[13] Certain triggers, such as infections and vaccinations (e.g., SARS-CoV-2 infection and vaccination), may induce adjuvant activity or act as adjuvants themselves.[24]

Last, it has been suggested that some patients are genetically predisposed to develop LIRs, as a recent study has shown that patients bearing HLA subtypes B*08 and DRB1*03 are at a greater risk of developing these complications.[39] These outcomes suggest that these patients might have a lower threshold to, for example, infections, vaccines, or other factors that trigger the immune system.

3.5 | Recommendations on soft tissue filler use during the COVID-19 pandemic

What we can learn from the cases presented in this review is that adverse reactions toward soft tissue filler do occur after SARS-CoV-2 infection and vaccination. The relationship between these factors seems to be possible, as LIRs occur within a few hours up to several weeks after an infection or vaccination. We believe that these adverse events are generally minor and concern tens of patients. However, to prevent these complications, we can learn from these cases, and we make the following recommendations:

First, we would advise prevaccination counseling in cosmetic patients. More specifically, patients should be asked about allergies, a history of filler-related adverse events or adverse events toward other types of implants. We would also consider a 2- to 4-week window between filler injections and vaccination in general and two months longer for immunocompromised patients (i.e., patients with immunosuppressive medications, chemotherapy, or immunologic disorders). Once filler-related adverse events have occurred, we would advise starting treatment with oral steroids, as most of our patients experience a resolution of their symptoms after their use (Figure 2). In cases of residual complaints, studies have shown that hyaluronidase might be effective. Although not all studies report on the type of filler used, the ones that report do mention HA as the major injected filler in these patients. If patients seek filler treatments in the months prior to vaccination, other filler options (e.g., calcium hydroxyapatite, poly-L-lactic acid, or laser resurfacing) might be prioritized. These recommendations are for HA fillers, as these fillers are the most used worldwide, but for non-HA fillers, more evidence is needed for any future recommendation.

Last, in light of the current pandemic, the risk of becoming infected with SARS-CoV-2 outweighs the risk of developing filler-related adverse events. To date, there have been more than 279 million people infected and almost 5.4 million deaths worldwide. Currently, the only option to reduce the number of infections and deaths is through worldwide SARS-CoV-2 vaccination programs. Therefore, we would advise patients with soft tissue fillers to participate in the current vaccination programs, as filler-related complications seem to be extremely rare and SARS-CoV-2 infections are of great risk.

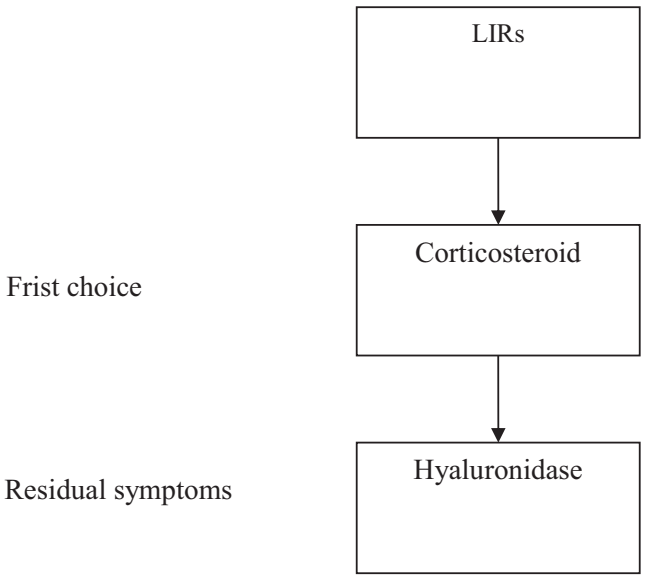

FIGURE 2 Algorithm for treatment of LIRs after SARS-CoV-2 infection or vaccination

4 | CONCLUSIONS AND PERSPECTIVES

Overall, this review shows that LIRs can occur after SARS-CoV-2 infection and vaccination. In the case of vaccination, these adverse events have been reported only after the Moderna and Pfizer vaccines. The reported adverse events are generally minor and self-limiting, and we encourage patients with soft tissue fillers to participate in vaccination programs. We suggest that a patient's medical history should be thoroughly evaluated for soft tissue filler procedures. We also suggest that patients should be asked about filler injection prior to vaccination and that international registries ensure careful reporting of soft tissue adverse events to give a more detailed overview of these complications.

CONFLICT OF INTEREST

No conflict of interest relevant to this article.

AUTHOR CONTRIBUTIONS

Y.B. performed the research, designed the research study, and analyzed the data. Y.B. and J.K. wrote the paper. Y.B., J.K., M.B., and T.R. reviewed the paper.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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REFERENCES

1. Shahrabi-Farahani S, Lerman MA, Noonan V, Kabani S, Woo S-B. Granulomatous foreign body reaction to dermal cosmetic fillers with intraoral migration. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;117(1):105-110.
2. The American Society for Aesthetic Plastic Surgery's Cosmetic Surgery National Data Bank. Statistics 2018. *Aesthet Surg J*. 2019;39(Suppl_4):1-27.
3. Griffin AC. Laser resurfacing procedures in dark-skinned patients. *Aesthet Surg J*. 2005;25(6):625-627.

4. de Vries CG, Geertsma RE. Clinical data on injectable tissue fillers: a review. *Expert Rev Med Devices*. 2013;10(6):835-853.
5. Broder KW, Cohen SR. An overview of permanent and semipermanent fillers. *Plast Reconstr Surg*. 2006;118(3 Suppl):7S-14S.
6. Owosho AA, Bilodeau EA, Vu J, Summersgill KF. Orofacial dermal fillers: foreign body reactions, histopathologic features, and spectrometric studies. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;117(5):617-625.
7. Christensen L, Breiting V, Bjarnsholt T, et al. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. *Clin Infect Dis*. 2013;56(10):1438-1444.
8. Christensen L, Breiting V, Janssen M, Vuust J, Hogdall E. Adverse reactions to injectable soft tissue permanent fillers. *Aesthetic Plast Surg*. 2005;29(1):34-48.
9. Kadouch JA, Kadouch DJ, Fortuin S, et al. Delayed-onset complications of facial soft tissue augmentation with permanent fillers in 85 patients. *Dermatol Surg*. 2013;39(10):1474-1485.
10. Kadouch JA, Tutein Nolthenius CJ, Kadouch DJ, van der Woude H-J, Karim RB, Hoekzema R. Complications after facial injections with permanent fillers: important limitations and considerations of mri evaluation. *Aesthet Surg J*. 2014;34(6):913-923.
11. Kadouch JA, Vos W, Nijhuis EW P, Hoekzema R. Granulomatous foreign-body reactions to permanent fillers: detection of CD123+ plasmacytoid dendritic cells. *Am J Dermatopathol*. 2015;37(2):107-114.
12. de Melo Carpaneda E, Carpaneda CA. Adverse results with PMMA fillers. *Aesthetic Plast Surg*. 2012;36(4):955-963.
13. Bachour Y, Kadouch JA, Niessen FB. The Aetiopathogenesis of Late Inflammatory Reactions (LIRs) after soft tissue filler use: a systematic review of the literature. *Aesthetic Plast Surg*. 2021;45(4):1748.
14. Marusza W, Olszanski R, Sierdzinski J, et al. Treatment of late bacterial infections resulting from soft-tissue filler injections. *Infect Drug Resist*. 2019;12:469-480.
15. Artzi O, Cohen JL, Dover JS, et al. Delayed inflammatory reactions to hyaluronic acid fillers: a literature review and proposed treatment algorithm. *Clin Cosmet Investig Dermatol*. 2020;13:371-378.
16. Alhede M, Er Ö, Eickhardt S, et al. Bacterial biofilm formation and treatment in soft tissue fillers. *Pathog Dis*. 2014;70(3):339-346.
17. Wiest LG, Stolz W, Schroeder JA. Electron microscopic documentation of late changes in permanent fillers and clinical management of granulomas in affected patients. *Dermatol Surg*. 2009;35(Suppl 2):1681-1688.
18. Netsvyetayeva I, Marusza W, Olszanski R, et al. Skin bacterial flora as a potential risk factor predisposing to late bacterial infection after cross-linked hyaluronic acid gel augmentation. *Infect Drug Resist*. 2018;11:213-222.
19. Saththianathan M, Johani K, Taylor A, et al. The role of bacterial biofilm in adverse soft-tissue filler reactions: a combined laboratory and clinical study. *Plast Reconstr Surg*. 2017;139(3):613-621.
20. Micheels P. Human anti-hyaluronic acid antibodies: is it possible? *Dermatol Surg*. 2001;27(2):185-191.
21. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Foreign body granulomas due to injectable aesthetic microimplants. *Am J Surg Pathol*. 1999;23(1):113-117.
22. Alijotas-Reig J, Garcia-Gimenez V, Vilardell-Tarres M. Tacrolimus in the treatment of chronic and refractory late-onset immune-mediated adverse effects related to silicone injections. *Dermatol Surg*. 2012;38(1):38-47.
23. Lombardi T, Samson J, Plantier F, Husson C, Kuffer R. Orofacial granulomas after injection of cosmetic fillers. Histopathologic and clinical study of 11 cases. *J Oral Pathol Med*. 2004;33(2):115-120.
24. Alijotas-Reig J, Garcia-Gimenez V, Llurba E, Vilardell-Tarrés M. Autoimmune/inflammatory syndrome (ASIA) induced by biomaterials injection other than silicone medical grade. *Lupus*. 2012;21(12):1326-1334.
25. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Adjuvants and autoimmunity. *Lupus*. 2009;18(13):1217-1225.
26. Food and Drug Administration. FDA Briefing Document Moderna COVID-19 Vaccine. 2020 May 1, 2021; https://www.fda.gov/media/144434/download
27. Moher D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264–9, W64.
28. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. 2011. http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf
29. Munavalli GG, Guthridge R, Knutsen-Larson S, Brodsky A, Matthew E, Landau M. COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment. *Arch Dermatol Res*. 2022;314(1):1-15.
30. Rowland-Warmann MJ. Hypersensitivity reaction to Hyaluronic Acid Dermal filler following novel Coronavirus infection - a case report. *J Cosmet Dermatol*. 2021;20(5):1557-1562.
31. Shome D, Doshi K, Vadera S, Kapoor R. Delayed hypersensitivity reaction to hyaluronic acid dermal filler post-COVID-19 viral infection. *J Cosmet Dermatol*. 2021;20(5):1549-1550.
32. Naouri M, Dahan S, Le Pillouer Prost A, et al. Good tolerance of hyaluronic acid injections during the period of the COVID-19 pandemic: observing a cohort of 1093 patients in a prospective, observational real-life study. *J Eur Acad Dermatol Venereol*. 2021;35(7):e432-e433.
33. Munavalli GG, Knutsen-Larson S, Lupo MP, Geronemus RG. Oral angiotensin-converting enzyme inhibitors for treatment of delayed inflammatory reaction to dermal hyaluronic acid fillers following COVID-19 vaccination-a model for inhibition of angiotensin II-induced cutaneous inflammation. *JAAD Case Rep*. 2021;10:63-68.
34. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85(1):46-55.
35. Turkmani MG, De Boulle K, Philipp-Dormston WG. Delayed hypersensitivity reaction to hyaluronic acid dermal filler following influenza-like illness. *Clin Cosmet Investig Dermatol*. 2019;12:277-283.
36. Humphrey S, Jones DH, Carruthers JD, et al. Retrospective review of delayed adverse events secondary to treatment with a smooth, cohesive 20-mg/mL hyaluronic acid filler in 4500 patients. *J Am Acad Dermatol*. 2020;83(1):86-95.
37. Beleznay K, Carruthers JDA, Carruthers A, Mummert ME, Humphrey S. Delayed-onset nodules secondary to a smooth cohesive 20 mg/mL hyaluronic acid filler: cause and management. *Dermatol Surg*. 2015;41(8):929-939.
38. Bhojani-Lynch T. Late-onset inflammatory response to hyaluronic acid dermal fillers. *Plast Reconstr Surg Glob Open*. 2017;5(12):e1532.
39. Decates TS, Velthuis PJ, Schelke LW, et al. Increased risk of late-onset, immune-mediated, adverse reactions related to dermal fillers in patients bearing HLA-B*08 and DRB1*03 haplotypes. *Dermatol Ther*. 2021;34(1):e14644.
40. Lemperle G, Gauthier-Hazan N, Wolters M, et al. Foreign body granulomas after all injectable dermal fillers: part 1. *Possible Causes*. *Plast Reconstr Surg*. 2009;123(6):1842-1863.
41. Morhenn VB, Lemperle G, Gallo RL. Phagocytosis of different particulate dermal filler substances by human macrophages and skin cells. *Dermatol Surg*. 2002;28(6):484-490.
42. Tomazic-Jezic VJ, Merritt K, Umbreit TH. Significance of the type and the size of biomaterial particles on phagocytosis and tissue distribution. *J Biomed Mater Res*. 2001;55(4):523-529.
43. Decates T, Kadouch J, Velthuis P, Rustemeyer T. Immediate nor delayed type hypersensitivity plays a role in late inflammatory

reactions after hyaluronic acid filler injections. *Clin Cosmet Investig Dermatol*. 2021;14:581-589.
44. Sloan B. July 2021: Lisinopril for delayed inflammatory responses to hyaluronic acid fillers after COVID-19 vaccinations. *J Am Acad Dermatol*. 2021;85(1):34.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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