

Delayed-type Hypersensitivity Reaction to Facial Dermal Fillers After COVID-19 Vaccination

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Over the past 1.5 years vaccination has become one of effective measures to combat the novel Coronavirus disease 2019 (COVID-19). Several adverse reactions arising from COVID-19 vaccines have been reported in the literature. These can be categorised into systemic and local adverse reactions – the former often presents with fever, fatigue, and headache, while the latter is frequently associated with pain, erythema, and swelling at the injection site. A recent meta-analysis demonstrated that different relative risks (RR) of systemic reactions depended upon the vaccine type, i.e., 1.13 (95% confidence interval [CI], 0.79 to 1.61), 1.53 (95% CI, 1.08 to 2.16), 1.58 (95% CI, 1.13 to 1.90), 0.72 (95% CI, 0.34 to 1.55), and 1.62 (95% CI, 1.39 to 1.89) for inactivated virus, mRNA, vector, DNA, and protein subunit vaccines, respectively. The RR of local adverse events following immunization with inactivated vaccine, mRNA vaccine, vector vaccine, DNA, and protein subunit vaccine was 2.18 (95% CI, 1.32 to 3.59), 4.96 (95% CI, 4.02 to 6.11), 1.48 (95% CI, 0.88 to 2.50), 1.04 (95% CI, 0.12 to 8.75), and 4.09 (95% CI, 2.63 to 6.35), respectively. However, the vaccine type was not a significant predictor of systemic and local adverse events. In other words, the vaccine safety is “relatively” comparable, in spite of the fact that mRNA vaccines tend to be related to higher adverse effects [1].

Albeit rare, one adverse event of COVID-19 vaccines is linked to hypersensitivity or allergic reaction. Acute allergic reactions following immunisation might be due to vaccine antigen, preservatives, or stabilisers in the vaccine formulation or residual

non-human protein. The incidence of COVID-19 mRNA vaccine-induced anaphylaxis was reported to be ~10 times higher than that reported in previous vaccines, i.e. 1 in every 100,000 immunised persons. Most of such reactions appear to result from IgE-mediated anaphylaxis (type 1 hypersensitivity reaction). However, some people are at a higher risk for non-IgE related mast-cell or complement activation due to certain inactive components or products of the vaccine manufacturing process of the vaccine such as lipid or the polyethylene glycol (PEG)-lipid component. The mRNA vaccines use a lipid-based nanoparticle (LBNP) carrier system that prevents the rapid degradation of *in vivo* mRNA delivery. This carrier system is further stabilised by a PEG-2000 lipid conjugate that supplies a hydrophilic layer which prolongs the vaccine’s half-life [1].

Immediate or type 1 hypersensitivity reactions with an incidence rate of 0.8% for hyaluronic acid (HA) fillers *per se* develop within minutes or hours after the injection. Conversely, delayed-type or type 4 hypersensitivity reactions (DTHR) with an incidence rate of 0.42% may manifest a day, days, weeks, or even years after the injection. As other causes, facial dermal fillers may be complicated by DTHR which results from macrophage and T-cell interactions, and can present as swelling (lumps or nodules), erythema, or granuloma formations at the injection site. Many predisposing or precipitating factors have been found to be associated with DTHR after the filler injection, such as infections, filler properties, trauma, concurrent vaccinations (e.g. for influenza, shingles, COVID-2), and the injection technique [2,3].

Despite a combination of primary studies with low levels of evidence, a recent systematic review included two case series (one of these in the Moderna's document), and three case reports regarding DTHR after the filler injection in persons immunised by COVID-19 vaccines. It was documented that cutaneous reactions were diagnosed in 9 of 414 (or 2.17%) cases after COVID-19 vaccination with Moderna and Pfizer-Biontech. Of those, 8 received Moderna and the other one got Pfizer-Biontech; all were treated with HA fillers. The average time interval from the filler injection to the vaccination was 433.33 ± 323.11 (range, 13 to 1,095) days. The mean time interval between vaccination and the development of DTHR to the filler was 2.67 ± 2.76 (range, 0.75 to 10) days [2].

Amid local infections (e.g. sinusitis, dental infections), low-quality product, and combinations of different fillers, immunobiological factors (e.g. bacterial infection, foreign body 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 [2,3].

After degradation, HA fillers will be cleaved in short-chain and low-molecular-weight (LMW) HA molecules that can trigger the immune response activating CD44 probably when accompanied by other trigger factors such as biofilms [2]. Bacteria inoculated during the injection may form a biofilm. The biofilm surrounding the HA material creates a matrix that can inhibit natural hyaluronidases from degrading the HA. These biofilms can induce a minimal infection with little host response, making them asymptomatic for months or even years. In a microscopic study, nodules developing many years after the HA injection resulted from failure in the degradation process. A subsequent delayed foreign-body tissue reaction to biofilm could have been elicited many months or years following the filler injection [4].

Fillers might also enhance the antigen-specific immune response as adjuvants without triggering one on their own, rather than activating T-cells directly [2]. Adjuvants can trigger the immune system but without having specific antigenic properties themselves. As a result, the innate and adaptive immune systems can be triggered by adjuvants. These adjuvants mimic molecules

such as pathogen-associated molecular patterns (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 antigen-presenting cells specifically dendritic cells (DCs) or macrophages. Certain triggers, such as infections and vaccinations (e.g. SARS-CoV-2 infection and COVID-19 vaccination), may induce adjuvant activity or act as adjuvants themselves [3].

Moreover, allergic reactions to mRNA vaccines might be a response to PEG (that is a particular carrier system of the mRNA vaccine) and/or polysorbate-80 of the viral spike protein (used in adenovirus vector vaccines such as AstraZeneca). Some authors found that patients with human leucocyte antigen subtypes B*08 or DRB1*03 had an increased risk of DTHR associated with dermal fillers [2,3]. Although immunologic reactions appear to be responsible for development of DTHR in this situation, general allergic screening (patch test) and intradermal testing often fail to aid in the diagnosis and prediction [3].

It has been proposed that severe acute respiratory syndrome Coronavirus type 2 (SARS-CoV-2)'s spike protein acts as a triggering factor in developing postvaccination DTHR. The interaction between the spike protein and angiotensin-converting enzyme 2 (ACE2) receptors causes a pro-inflammatory TH1 response and promotes a CD8+ T-cell-mediated reaction, resulting in DTHR formation including lip angio-oedema after the filler injection at the lips. Furthermore, COVID-19 mRNA vaccines have the ability to decrease the conversion of the pro-inflammatory angiotensin-II (ANGII) in the skin. As a result, the accumulation of ANGII provokes an inflammatory and immune response by activating CD8+ and TH1, respectively. Hence, ACE inhibitors (ACEI) may be helpful for treating DTHR associated with COVID-19 vaccines because of its role in the renin-ANG system, which regulates the interstitial fluid volume. It can be hypothesised that the ACEI's reaction is shifted towards an anti-inflammatory reaction that results in an increase in sodium water outflow and subsequently a decrease of the swelling [2,3].

To treat DTHR after the filler injection and COVID-19 vaccination, corticosteroids with 30-60 mg of daily prednisolone for 5 days (coupled with ACE inhibitors such as lisinopril at a daily dose of 10 mg for 3-5 days) appear to provide a superior benefit over antihistamines. In severe and/or persistent cases, hyaluronidase may be used to dissolve the filler in the target tissue [2,3].

Taken all together, long-lasting fillers that may have a higher risk of DTHRs should be avoided as long as the world population still requires COVID-19 vaccination especially Moderna and Pfizer-Biontech [2]. More specifically, patients should be asked about allergies, a history of filler-related adverse events or adverse events towards other types of implants. A 2- to 4-week window between the filler injection and the vaccination as well as 2 months longer for immunocompromised patients (e.g. patients with immunosuppressive medications, chemotherapy, or immunologic disorders) are recommended [3]. Otherwise, blunt-cannula liposuction may be employed to solve facial lump or granulomas following facial dermal filler injections [4]. Further investigations are essential to elucidate the exact pathogenesis, mechanisms, and evidence-based preventive and therapeutic measures regarding COVID-19 vaccine-associated DTHRs after the filler injection.

We refer interested readers to our previous publications regarding head and neck manifestations of COVID-19 and its treatments [5,6] as well as craniomaxillofacial surgery in COVID-19 patients [7-11].

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