Prevalence, Pathophysiology, and Treatment of Urticaria post-COVID-19 Vaccination: A Systematic Review

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ABSTRACT

Background: Vaccination for COVID-19 has been intensively developed since the end of 2020. Its use must also obtain an Emergency Use Authorization (EUA) permit. Some of the vaccines have been used including Sinovac, Astra Zeneca, Moderna, Pfizer, Johnson & Johnson, and Sinopharm. In fact, there are many effects that have developed after the COVID-19 vaccination administration like local reactions, systemic reactions, and other reactions. In addition, one of them is urticaria. However, the existing literature has focused poorly on urticaria caused by COVID-19 vaccines.

Aims: This research explores the prevalence, pathophysiology, and treatment of urticaria post-COVID-19 vaccination.

Methods: This study conducted a systematic review based on the guideline which is Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched Scopus, ProQuest, Ebsco, and Google Scholar databases from 2020 until 2022 for identifying the data regarding urticaria post-COVID-19 vaccination. In a nutshell, 9 studies were included in the systematic review.

Results: Only 28% of urticarial rashes incident among all cutaneous adverse reactions after post-COVID-19, it was higher among females and people aged 45-49 years old, and people with allergy histories. The most frequent reaction is urticarial following the COVID-19 vaccine administration. This concerns hypersensitivity reaction related to Immunoglobulin E (IgE) mediated, Immunoglobulin G (IgG), and sensitizing excipients in COVID-19 vaccines.

Conclusion: This systematic review raises the concern of hypersensitivity reaction that related to IgE-mediated, IgG, and sensitizing excipients in COVID-19 vaccines. Urticaria is the most frequent reaction after the COVID-19 vaccine administration. Attention to medical history and immunology/allergy consultation might be advantageous to assess the risk of allergy and the guidance of the vaccine.

Keywords: Urticaria, Post-COVID-19 vaccination, mRNA vaccines, Whole inactivated virus, Hypersensitivity reactions.

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1. Introduction

The coronavirus (COVID-19) outbreak spread rapidly throughout the entire world and became a new challenge for controlling the pandemic and reducing its impact. It has affected more than 600 million people worldwide since declaring in March 2020 by the World Health Organization. Vaccination is presently a safe and effective way to control COVID-19. COVID-19 vaccination development started at...
the end of 2020. It holds Emergency Use Authorization (EUA) permit. According to the World Health Organization (WHO), numerous COVID-19 vaccines administered such as viral vectors (Johnson & Johnson's Janssen and AstraZeneca), mRNA (Pfizer and Moderna), and inactivated virus (Sinovac and Sinopharm). Adverse Events Following Immunization (AEFI) are medical events after immunization. Some people might have side effects following COVID-19 vaccination. Common side effects consist of pain or redness at the injection site, fever, headache, muscle aches, and fatigue. Dermatologic reactions after administering COVID-19 vaccinations became reality. Urticaria is a main skin condition that is mast cell-driven disease. It shows angioedema, wheels (hives), or both. The active skin mast cells discharge histamine and other mediators like cytokines and platelet-activating factor (PAF). The signals of mast cell activating in urticaria are various. These include autoantibodies and T-cell-driven cytokines (Zuberbier, et al., 2022). However, this research aims to explore the prevalence, cause, prevention, and treatment of urticaria post-COVID-19 vaccination.

2. Methods
The research was a systematic review using the PRISMA model. The scope of this research includes the prevalence, pathophysiology, and treatment of urticaria after post-COVID-19 vaccination. The keywords that were used are “urticaria” “AND” Cause” “AND” “Prevalence” “AND” “Treatment” “AND” “Covid-19 vaccination”. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart and form the basis for the inclusion or exclusion criteria of the articles. The inclusion criteria were articles related to urticaria post-COVID-19 vaccination that has been published in Scopus, ProQuest, Ebsco, and Google Scholar databases from 2020 until 2022 and open access. The articles should be related to the prevalence, pathophysiology, and treatment of urticaria post-COVID-19. The exclusion criteria were data that had unclear characteristics, review articles, and not full paper articles. The authors initially collected the identified records from four databases source including Scopus, ProQuest, Ebsco, and Google Scholar. We checked for duplicates using STATA and screened the resulting studies based on titles and abstracts afterward. We screened independently the studies based on their full texts and excluded the ineligible studies. The authors independently extracted the data from the eligible studies. These data include the author, title, year, method, and resume. The eligibility criteria of studies included 102 articles out of 430 articles. After reviewing the full-text articles, 93 articles were excluded and only 9 articles were included.

![Figure 1. Search results from various databases](image-url)
### Table 1. Information of the included articles

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Year</th>
<th>Method</th>
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<tbody>
<tr>
<td>Burlando M, Herzum A, Micalizzi C, Cozzani E, Parodi A.</td>
<td>Cutaneous Reactions to COVID-19 Vaccine at the Dermatology Primary Care</td>
<td>2021</td>
<td>The data among patients with skin reactions after COVID-19 administration were collected retrospectively from March 2021 to June 2021 in Dermatology Primary</td>
<td>Only 15% of patients developed cutaneous reactions following COVID-19 administration. Most of them were either mild or moderate. Ten of twenty-one patients developed urticarial reactions following COVID-19 administration. Four of them appeared within 24 hours and the rest after 24 hours.</td>
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<tr>
<td>Grieco T, Ambrosio L, Trovato F, Vitiello M, Demofonte I, Fanto M, et al</td>
<td>Effects of Vaccination against COVID-19 in Chronic Spontaneous and Inducible Urticaria (CSU/CIU) Patients: A Monocentric Study.</td>
<td>2022</td>
<td>From 1 November 2021 until 10 December 2021, only 160 chronic spontaneous and inducible urticaria patients in antihistamine therapy were administered two doses of the Moderna vaccine. Twenty of them got booster vaccines. A web-based questionnaire was collected by phone interview. The questionnaire consists of demographics, adverse event following immunization, medical history, urticaria activity score-7 and cutaneous adverse reactions outcome. Only 17.86% patients developed worsening pre-existing urticaria with average urticaria activity score-7, 3.12. COVID-19 vaccination is secure among chronic spontaneous and inducible urticaria patients. The cases of worsening disease are able to manage by using antihistamines therapies.</td>
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<td>Català A, Muñoz-Santos C, Galván-Casas CR, Riesco MR, Nebreda D, Solá-Truyols A, et al</td>
<td>Cutaneous Reactions After SARS-CoV-2 Vaccination: A Cross-Sectional Spanish Nationwide Study of 405 Cases</td>
<td>2021</td>
<td>This study, a cross-sectional study, was conducted from 16 February until 15 May 2021. The sample of this study is patients who developed cutaneous reactions within 21 days following COVID-19 vaccine administration. An electronic case report form and questionnaire were collected. An online professional survey reported reactions of cutaneous after having a visit with a dermatologist. Clinical images were sent by email. The examiner identified for consensus on clinical patterns and classification. Only 405 patients were with a mean of age of (50.7) (17.6) and 80.2% of them were female. There were 40.2% of the Pfizer administration, 36.3% of the Moderna administration, and 23.5% of the AstraZeneca administration. Cutaneous reactions represented COVID arm (32.1%), urticaria (14.6%), morbilliform (8.9%), papulovesicular (6.4%), pityriasis rosea-like (4.9%) and purpuric (4%) reactions. Varicella zoster and herpes simplex virus reactivations accounted for 13.8% of reactions. Urticaria and/angioedema reactions after Pfizer administration was higher than Moderna and AstraZeneca. Pfizer was 24 patients (40.7%). AstraZeneca was 20 patients (33.9%). Moderna was 15 patients (25.9%). Only 46 patients (78%) of 59 patients with urticaria and/angioedema reactions were female. Mostly its reaction developed after the first dose of COVID-19 vaccines. Cutaneous reactions following the COVID-19 vaccine administration are diverse.</td>
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<td>Pourani MR, Shahidi Dadras M, Salari M, Diab R, Namazi N, Abdollahimajd F.</td>
<td>Cutaneous adverse events related to COVID-19 vaccines: A cross-sectional questionnaire-based study of 867 patients</td>
<td>2022</td>
<td>This study was a descriptive cross-sectional questionnaire study. The online questionnaire was shared from the first of June 2021 to 1 July 2021. The questionnaire was related to COVID-19 vaccine reactions. The questionnaire consists of cutaneous reactions, the onset time, and the persistence duration.</td>
<td>There are 30% of Iran people who developed cutaneous reactions after COVID-19 vaccine administration. The most frequent effects against COVID-19 vaccine were urticaria, focal injection site reaction, and exanthematous rash. There were 25 urticaria cases.</td>
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<td>Bruusgaard-Mouritsen M, Jensen BM, Poulsen LK, Johansen JD, Garvey LH.</td>
<td>Optimizing Investigation of Suspected Allergy to Polyethylene Glycols</td>
<td>2022</td>
<td>The results of the histamine test and the result of the skin prick test were collected from diagnosis time and early allergy assessment.</td>
<td>The positive skin prick test patients and the positive polyethylene glycols 3000/6000 patients reported positive on polyethylene glycols 20000. Three patients had systemic urticaria during the skin prick test. Only 8 patients developed cross-sensitization to poloxamer 407 and 3 to polysorbate 80. All controls tested negative. The skin prick test with rising polyethylene glycols 20000 concentration is able to be diagnostic when the molecular weight of polyethylene glycols is negative. The skin prick test is mandatory.</td>
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<td>Magro C, Nuovo G, Mulvey J, Laurence J, Harp J, Crowson AN.</td>
<td>The skin as a critical window in unveiling the pathophysiologic principles of COVID-19</td>
<td>2021</td>
<td>The dataset of cutaneous caused by COVID-19 vaccine and COVID-19. The data provided by Regional Medical Laboratory and Weill Cornell Medicine and in Tulsa, Oklahoma from March 2020 to June 2021 was reviewed. These included the clinical histories, light microscopic findings, additional immunohistochemical studies, and molecular studies.</td>
<td>After vaccine of COVID-19 administration, the localization of spike glycoprotein was found among cutaneous cases. It binds endothelium in the absence of an intact virus.</td>
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<td>AlMuhizi F, Ton-Leclerc S, Fein M, Tsoukas C, Garvey LH, Lee D, et al.</td>
<td>Successful Desensitization to mRNA COVID-19 Vaccine In A Case Series of Patients with A History of Anaphylaxis to the First Vaccine Dose</td>
<td>2022</td>
<td>Participants chosen from cohort of study related to ongoing reaction of allergic to COVID-19 Vaccine. The clinical evaluation after the first dose of either the Pfizer or the Moderna was hold at the McGill University Health Center (MUHC). The participants undertook skin prick testing. A desensitization protocol applied for the second dose.</td>
<td>Six of 142 patients were chosen with allergic history. All participants were female. Most of them developed urticaria within 30 minutes after the first dose of COVID-19 vaccine. A desensitization protocol applies for the immediate reaction following the first dose of mRNA COVID-19 vaccine.</td>
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<td>Pitlick MM, Joshi AY, Gonzalez Estrada A, Chiarella SE</td>
<td>Delayed Systematic Urticarial Reactions Following mRNA COVID-19 Vaccination</td>
<td>2022</td>
<td>The study was a retrospective case series from 19 January 2021 until 30 April 2021. There were twelve patients referring to Mayo Clinics in Jacksonville, Florida, and Rochester, Minnesota following mRNA COVID-19 administration in order to evaluate delayed systemic urticarial reactions. Each patient reported a history of medical and allergic, demographics, a side effect of the COVID-19 vaccine, and the results of vaccine excipient skin testing.</td>
<td>Eleven patients who developed delayed urticaria after getting the first dose of COVID-19 vaccines. Antihistamines are able to treat delayed systemic urticarial reactions after mRNA COVID-19 vaccine administration.</td>
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<td>Macy E, Pandya S, Sheikh J, Brunette A, M.Shi J, Chung J, et al</td>
<td>Population Based Incidence, Severity, and Risk Factors Associated with Treated Acute-Onset COVID-19 mRNA Vaccination-Associated Hypersensitivity Reactions</td>
<td>2022</td>
<td>This study collected unique individuals with active Kaiser Permanente Southern California (KPSC) health plan coverage. They were administered the COVID-19 mRNA vaccine at the KPSC facility from 16 December 2020 until 11 March 2021. They were also identified, characterized, and along with all treated acute-onset vaccination-associated hypersensitivity events.</td>
<td>The younger females with typical risk factors have more likely treated with acute-onset hypersensitivity events following COVID-19 vaccine. Only 15200 people developed chronic urticaria. 16.3% of patients with treated hypersensitivity reactions had chronic urticarial after first dose reactions and 12.5% of them had it after the second dose reactions.</td>
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### 3. Results

#### a. Prevalence of urticaria post-COVID-19 vaccination

Numerous adverse reactions to the COVID-19 vaccination have been reported (Burlando et al., 2021). Based on Burlando et al (2022), only 21 of 200 patients developed cutaneous reactions following COVID-19 vaccine administration. Fifteen (71%) patients were females with a mean age of 48 years. Ten of twenty-one patients developed urticarial reactions following COVID-19 administration. Four of them appeared it within 24 hours and the rest after 24 hours. AstraZeneca, Moderna, and Pfizer cause acute urticaria, an adverse reaction after getting vaccinated (Brooks et al., 2022). Messenger RNA (mRNA) which encapsulates lipid nanoparticles in the Pfizer vaccine and the Moderna vaccine, encrypt the SARS COV 2 viral spike protein inducing both cell-mediated responses and antibodies. A viral vector needs to synthesize SARS-COV-2 protein S is the AstraZeneca vaccine (Bianchi et al., 2021).

After getting messenger RNA or mRNA vaccination from Moderna and Pfizer, the local reactions were the most frequent cutaneous findings. The immune response shows as rash against spike protein which is similar to morbilliform eruptions that are negative. Like patients with primary COVID-19 infection, their negatives are in viral particles (Burlando et al., 2021). Only 28% of urticarial rashes incident found among all cutaneous adverse reactions. The most common of it in patients are rash and itching after receiving mRNA COVID-19 vaccines (Grieco et al., 2022). The risk of urticaria after administration of the Pfizer mRNA COVID-19 vaccine among healthcare workers was higher among females and people aged 45-49 years old. It rose in people with had previous COVID-19 infections and people with an allergy history (Cugno et al., 2021).
In Spanish, only 21.1% of patients had urticaria after getting AstraZeneca, the COVID-19 vaccine. It was the most frequent reaction after administration (Català et al., 2021). The higher urticarial and angioedema reactions were 40.7% (n= 24) of patients after Pfizer administration. AstraZeneca was 20 patients (33.9%). Moderna was 15 patients (25.9%). Only 46 patients (78%) of 59 patients with urticaria and/or angioedema reactions were female. Mostly its reaction developed after the first dose of COVID-19 vaccines. Based on Brooks et al (2022), chronic spontaneous urticaria triggered by AstraZeneca was reported. The patient with an asthma history and environmental allergies had the first dose of AstraZeneca, the COVID-19 vaccination. In five days, the 60 years old man developed erythema on his palms and cheeks followed by a pruritic rash on his scalp, face, neck, shoulder, and armpit. A Caucasian female who was 48 years old had acute urticaria within 3 hours after the second dose of AstraZeneca (Burlando et al., 2021). A 39 years old man without a history of atopic disorders developed widespread urticaria and swelling of his hands. He got a jab of the second of Astra Zeneca and urticaria showed up in 2 weeks (Suan and Lee, 2022). In Iran, it is reported that 25 cases of urticaria after getting AstraZeneca, Sinopharm, Sputnik V, and Bharat vaccines. However, most of them were vaccinated using AstraZeneca (Pourani et al., 2022). In Thailand, the most common skin allergy reactions from 35,229 injections of vaccination were urticaria after getting AstraZeneca and Sinovac (Rerknimitr et al., 2022).

The previous study reported that urticaria prevalence after the CoronaVac vaccine administration among healthcare workers in Turkey was about 0.8% (Triwatcharikorn et al., 2022). Urticaria was the most frequent reaction among healthcare workers in Turkey after administering with Sinovac/CoronaVac (Durmaž et al., 2022). The study reported a 28 years old patient who was under regular histamine treatment had chronic urticaria after getting the first dose of CoronaVac. Another study recorded a female patient who an allergy history had developed urticaria within 10 minutes of getting CoronaVac (Kaya and Kaya, 2022). Other studies reported that four patients developed symptoms of urticaria after CoronaVac administration. Three of them had it after the first dose of CoronaVac. Another one presented symptoms of urticaria after the second dose of CoronaVac (Akdaş et al., 2022).

b. Pathophysiology of urticaria post-COVID-19 vaccination

The mRNA vaccines use polyethylene glycols (PEGs) as excipients. It contains varied polymers’ molecular weight (Bruusgaard-Mouritsen et al., 2022). The PEG2000 or polyethylene glycols have 2000 molecular weight present as a stabilizer, a solubilizer, and an adjuvant. Being a stabilizer avoids premature degradation of the nanoparticles by the mononuclear phagocytosis system. During the transition of the particles into the intracellular cytosol, the PEG2000 is a solubilizer. Being an adjuvant is for immunogenic potential.

Ethylene oxide makes PEGs by polymerization (Worm et al., 2021). Formaldehyde, neomycin, propylene glycol, and thimerosal are exogenous antigens in vaccine constituents that cause allergic contact dermatitis. Polyethylene glycol moieties and polysorbate-80 have the potential to cause immediate hypersensitivity reactions, as well as delayed hypersensitivity reactions (Magro et al., 2021). Polyethylene glycol (PEG) and structurally-related polysorbate-80 stimulate both non-IgE-mediated reactions and IgE reactions among people with type I allergic reactions after COVID-19 vaccine administration (Grieco et al., 2022). Polyethylene glycol enhances water solubility as an excipient. Alike PEG, polysorbate 80 is an excipient in Johnson & Johnson and the AstraZeneca vaccines against COVID-19. The two mRNA vaccines contain PEG-triggering hypersensitivity reactions. It is caused by previous sensitization to polysorbate 80 and cross-reactivity between polysorbate 80 and PEG (AlMuhizi et al., 2022).

The whole inactivated viruses are the primary element in CoronaVac which is cultured with aluminum hydroxide adjuvant and some mineral salts in Vero cell. Urticaria related to CoronaVac is less likely to be IgE-mediated hypersensitivity. The immune response plays a role in the pathogenesis of CoronaVac. The result of a cross-reactive immune response to the SARS-CoV-2-spike protein present
in previous coronavirus infections causes urticaria for sensitive people (Triwatcharikorn et al., 2022).

Molliform eruptions and urticaria are the main reason for hypersensitivity reactions primarily (Namazi et al., 2022). Three of four patients developed recurrent delayed urticaria after the second dose of the COVID-19 vaccine. These patients thrive a memory T-cell response to the mRNA COVID-19 vaccine. Another reason is the delayed T-cell responses (Pitlick et al., 2022). Either IgE mediated or IgG is the reaction from hypersensitivity after vaccine administration. It is caused by complement-mediated anaphylactic and delayed T-cell-mediated reactions IgE (Namazi et al., 2022).

c. Urticaria treatment post-COVID-19 vaccination

Second-generation H1 antihistamine is the first-line treatment that resulted in half of reduction in the urticaria treatment. Treatment of omalizumab is required to prevent urticaria flares during the vaccination period (Grieco et al., 2022). A recombinant humanized monoclonal anti-IgE antibody, omalizumab, is effective to inhibit hypersensitivity reactions (Smola et al., 2021). Omalizumab is an anti-IgE antibody for the treatment of chronic spontaneous urticaria as well (Bernstein et al., 2020). Dosing does not depend on total serum IgE (Zuberbier et al., 2022). High-dose non-sedating antihistamines like up to 40 mg cetirizine daily are needed to treat urticaria associated with COVID mRNA vaccination. Systemic corticosteroids did not work for acute urticaria or any cause. It causes unsharpened development of effective T-cell-mediated immunity (Macy et al., 2022). Patients with chronic spontaneous urticaria require regular antihistamines for 2 days prior to and after receiving the vaccine. Patients on long-term antihistamines may be advised to increase their usual dose for this period (under clinical supervision) (Bermingham et al., 2021).

4. Discussion

AstraZeneca contains sensitizing excipients namely polysorbate 80. An immediate hypersensitivity type I reaction, urticarial rash, is developed after getting vaccinated of AstraZeneca (Burlando et al., 2021). Pfizer involves polyethylene glycol 2000 which is excipient with sensitizing. Moderna consists of polyethylene glycol 2000 and tromethamine (Bianchi et al., 2021). Polyethylene glycol-2000 (PEG-2000) in some drugs produces hypersensitivity reactions 1 right away and plays a role the urticarial manifestations (Farinazzo et al., 2021).

The main elements in CoronaVac are whole inactivated viruses. These are cultured with aluminum hydroxide adjuvant and some mineral salts in Vero cells. CoronaVac-associated urticaria is less likely to be IgE-mediated hypersensitivity to the vaccine. An immune response to the SARS-CoV-2-spike protein, rather than the vaccine excipients, may play a role in the pathogenesis of CoronaVac-associated urticaria. The result of a cross-reactive immune response to SARS-CoV-2-spike protein present in previous coronavirus infections causes urticaria for sensitive people (Triwatcharikorn et al., 2022).

Urticaria which is immediate hypersensitivity based on Centers for Disease Control and Prevention (CDC) happen within 4 hours after administrating vaccines (Gronbeck and Grant-Kels, 2021). Either IgE mediated or IgG is the reaction from hypersensitivity after vaccine administration. It is caused by complement-mediated anaphylactic and delayed T-cell-mediated reactions IgE (Namazi et al., 2022).

People who developed urticaria less than 30 minutes after the first dose of vaccination had an increased risk of urticaria after the second vaccination (Rerknimitr et al., 2022). A minor subset of cases demonstrated urticarial vasculitis, a morphologic subset of leukocytoclastic vasculitis characteristically triggered by immune complex deposition but other proinflammatory pathways can be implicated. Antibodies bound to an undefined foreign protein introduced by the vaccine could be deposited in microvessels as an immune complex and trigger the classic complement pathway to result in a neutrophil-rich inflammatory reaction (Magro et al., 2021).
5. Conclusion

Urticaria is the most frequent reaction after the COVID-19 vaccine administration. This concerns hypersensitivity reaction which is related to IgE-mediated, IgG, and sensitizing excipients in COVID-19 vaccines. The awareness of healthcare professionals is essential in order to recognize and treat eventual severe reactions from COVID-19 vaccinations. Besides, medical history is required to discover possible risk factors and keep down adverse reaction incidence. Furthermore, immunology/allergy consultation might be advantageous to assess the risk of allergy and the guidance of the vaccine.

Conflict of Interest

The authors declare no conflicts of interest, and no financial support.

References


