The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines were the first messenger RNA (mRNA)-based vaccines ever approved. These monovalent mRNA vaccines stimulate mRNA to produce the viral spike (S) protein, which then triggers an immune response. COVID-19 vaccines elicit both the innate and adaptive immune responses. In this longitudinal study, authors from Saudi Arabia investigated the changes in cytokine profile in young individuals vaccinated with mRNA-type COVID-19 vaccines at least one year prior.

Previous studies provided clear histological evidence of off-target biodistribution of genetic vaccines, leading to the synthesis of the S proteins and potentially triggering autoimmune and inflammatory responses. The effects in cerebral and myocardial tissues lead to clinically evident pathological damage. Therefore, some authors emphasized the need for biodistribution studies and specific benefit-harm assessment for COVID-19 genetic vaccines.

About the study

Participants were recruited in November 2020, before the start of the COVID-19 vaccination campaign. Individuals with chronic diseases were excluded from the study. Anthropometric measurements included height, weight, body mass index (BMI), waist and hip

circumferences, and blood pressure.

All subjects in this study received the Pfizer mRNA vaccine. After receiving their second booster dose, adolescents were followed up for an average of 14.1 ± 3.6 months and adults for an average of 13.3 ± 3.0 months. During follow-up, participants underwent routine blood sample collection and anthropometric assessments.

A total of 18 serum cytokines, including epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), interferon-gamma (IFN-γ), interleukin-1 alpha (IL-1α), IL-1β, IL-4, IL-6, IL-7, IL-13, IL-17E, IL-17F, monocyte chemoattractant protein-1 (MCP-1), MCP-3, macrophage colony-stimulating factor (MCSF), platelet-derived growth factor (PDGF-AA), transforming growth factor-alpha (TGF-α), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF)-A were assessed using multiplex assay kits.

Results

84 subjects (36 males and 48 females) participated in this study. The mean age was 27.2 ± 12.3 years. Female participants were significantly older than male participants.

Serum cytokine levels

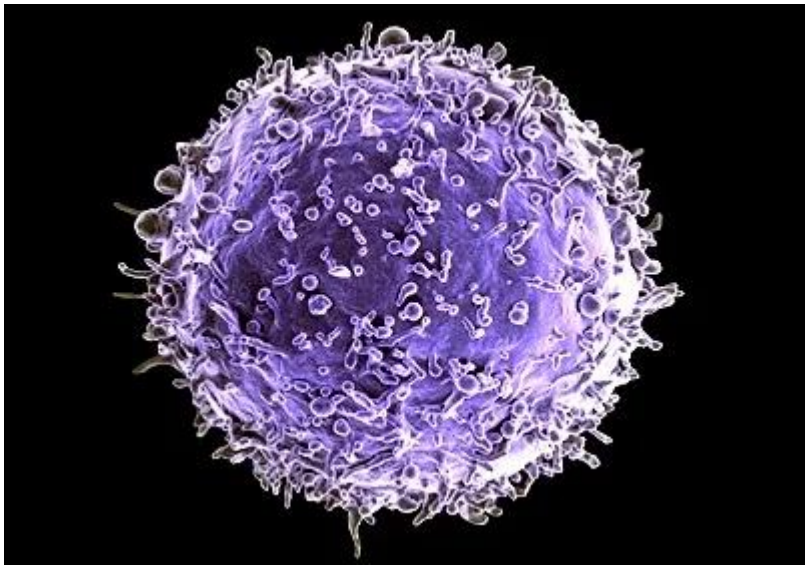
All participants who received the last dose of the Pfizer vaccine within 4 months or less before blood sample collection had a significant increase in serum levels of cytokines, chemokines, and growth factors, including EGF, FGF2, IFN-γ, IL-1β, IL-4, IL-6, IL-7, IL-17E, MCP-1, MCP-3, TNF-α, and VEGF-A. Only MCSF serum levels were reduced. When adjusted for age, EGF, IL-4, IL-6, MCP3, TNF-α, and VEGF-A remained statistically significant.

All participants who received their last dose of the Pfizer vaccine 5 or more months before blood sample collection had significantly elevated serum levels of TNF-α, IL-4, MCP-3, and VEGF-A.

Notably, post-acute sequelae of COVID-19 (PASC) syndrome has been associated with a triad of IL-1β, IL-6, and TNF-α.

The cytokines found to persist for months after COVID-19 vaccination have different roles in immune response and inflammation. EGF and FGF2 are involved in cellular proliferation and wound healing, contributing to tissue repair. IFN-γ and TNF-α are key players in promoting Th1 immune responses, enhancing the activation of macrophages and cytotoxic

T-cells. IL-6 and IL-1β are associated with inflammation, and IL-4 and IL-13 are crucial for Th2 immune responses. MCPs facilitate the recruitment of immune cells to sites of inflammation, while MCSF supports the survival and proliferation of macrophages.



Age and gender differences

A gender-specific analysis showed a more pronounced increase in pro-inflammatory cytokines, including IL-4, IL-6, and TNF-α, in men than in women.

Age-specific analysis showed that older adults experienced a more pronounced increase in EGF, IL-6, MCP1, and TNF-α.

Adolescents showed a greater increase only in VEGF-A, which induces the proliferation and migration of vascular endothelial cells and is essential for physiological and pathological angiogenesis. Previous data revealed that the SARS-CoV-2 S protein can bind to neuropilin (NRP)-1, which normally functions as a coreceptor for VEGF-A. By antagonizing the docking of VEGF-A to NRP-1, the S protein could disrupt physiological pathways involved in angiogenesis and nociception. One consequence could be an increase in unbound forms of VEGF-A that could bind to other receptors and be responsible for diffuse microvascular and neurological damage. (Talotta, R. Impaired VEGF-A-Mediated Neurovascular Crosstalk Induced by SARS-CoV-2 Spike Protein: A Potential Hypothesis Explaining Long COVID-19 Symptoms and COVID-19 Vaccine Side Effects? *Microorganisms* 2022, *10*, 2452.

https://www.mdpi.com/2076-2607/10/12/2452)

Interestingly, a study investigating cytokine responses to heterologous pathogens, Toll-like receptor agonists, and SARS-CoV-2 antigens in children aged 5 to 11 years vaccinated with two doses of the BNT162b2 mRNA COVID-19 vaccine, found an increase in *in vitro* VEGF response after stimulation with the SARS-CoV-2 S1 and S2 proteins one and six months after the second BNT162b2 vaccination. https://discovermednews.com/mrna-covid19-vaccine-decreases-responses-to-heterologous-pathogens-in-children/ Additionally, a study conducted in patients with long COVID found increased levels of VEGF-A and von Willebrand factor (VWF) that were associated with persistent CT findings of pulmonary lesions and impaired diffusing capacity for carbon monoxide (DLCO). (Philippe A et al. VEGF-A plasma levels are associated with impaired DLCO and radiological sequelae in long COVID patients. Angiogenesis 2024; 27, 51–66. https://doi.org/10.1007/s10456-023-09890-9)

Conclusion

This longitudinal study investigated the effects of mRNA COVID-19 vaccination on the cytokine profiles in young adults. The results showed increased cytokine levels even one year after vaccination. Furthermore, the results indicated differences in cytokine levels based on gender and age.

According to the authors, these results found in young individuals vaccinated with mRNA-type COVID-19 vaccines at least one year prior could be related to the persistent production of the spike protein, the highly inflammatory nature of mRNA-LNP, and the persistent stimulation of the immune system.

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Journal Reference

Alghamdi A, Hussain SD, Wani K *et al*. Altered Circulating Cytokine Profile Among mRNA-Vaccinated Young Adults: A Year-Long Follow-Up Study.Immunity, Inflammation and Disease, 2025; 13: e70194. https://doi.org/10.1002/iid3.70194