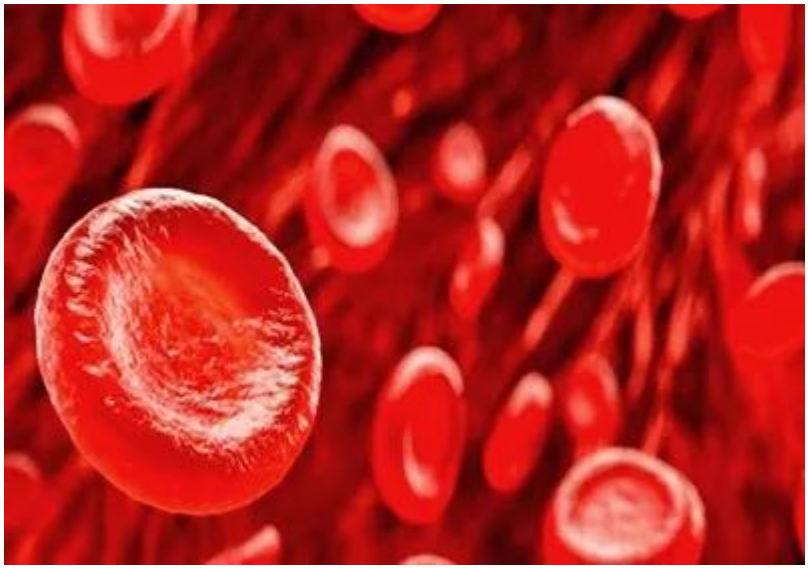
Red blood cells (RBCs) play a key role in microcirculation and tissue oxygenation. As the mechanical properties of RBCs are closely associated with the cell functionality, the alterations in RBCs induced by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may seriously impact microcirculation. In this study, researchers from Germany and Switzerland used a new technique, real-time deformability cytometry (RT-DC), to investigate the morphological and mechanical characteristics of RBCs in children and adolescents infected with SARS-CoV-2 or vaccinated against COVID-19.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins: the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein appears to be a major pathogenic factor in the unique pathogenesis of SARS-CoV-2. The S protein is a glycosylated homotrimer, with each monomer composed of subunits S1 and S2, separated by host cell proteases.

RT-DC is a technique that assesses morphological changes in peripheral blood cells and detects altered mechanical properties associated with specific disease pathologies. Previous studies that used RT-DC to analyze peripheral blood cells from adult COVID-19 patients detected deformed and more heterogeneous RBCs.



***About the Study and** Results*

This study investigated morphological and mechanical changes in the RBCs of 121 children or adolescents, 49 of whom were seronegative for SARS-CoV-2 and 63 seropositive for SARS-CoV-2. The presence of IgG antibodies specific for S1 and S2 subunits of the S protein

defined SARS-CoV-2 seropositivity. The two groups did not differ in terms of age or gender. The mean age of participants was 14.9 years (from 11 to 18).

The study did not include subjects with only one COVID-19 vaccination. Nine participants reported complete COVID-19 vaccination status at the time of blood collection.

Seropositive participants were further categorized based on the time from SARS-CoV-2 infection into two groups: those who tested seropositive more than six months ago ($n = 21$) and those who tested seropositive within the past six months ($n = 18$).

The RT-DC of peripheral blood cells showed significantly increased median deformation of RBCs in participants seropositive for SARS-CoV-2 compared to seronegative. In addition, participants with complete COVID-19 vaccinations had higher median deformation of RBCs than seronegative participants.

However, a higher median deformation of RBCs in seropositive and vaccinated participants has been found only if the SARS-CoV-2-seroconversion had occurred within the past six months. There was no significant difference in the median deformation of RBCs between participants if the SARS-CoV-2-seroconversion occurred more than six months ago.

In both subgroups that tested seropositive (more than six months and within six months of the seroconversion), the RBCs were significantly brighter than in seronegative subjects. The brightness of RBCs did not differ significantly between the two seropositive subgroups. According to the authors, these findings could be caused by various SARS-CoV-2 effects, such as direct infection of RBCs or changes in hemoglobin.

A recent *in vitro* study that investigated whether SARS-CoV-2 binds to and enters human erythrocytes found that SARS-CoV-2 could enter erythrocytes but less efficiently than in SARS-CoV-2 permissive cell lines such as VeroE6. SARS-CoV-2 did not accumulate inside the erythrocytes as observed in VeroE6 cells.
https://discovermednews.com/sars-cov-2-enters-human-erythrocytes-does-not-affect-the-development-plasmodium-falciparum/

The researchers also discussed possible mechanisms that caused a loss of membrane integrity and increased deformation of RBCs, such as the fragmentation of the membrane-bound protein band-3 that coordinates the shape of RBCs, deposition of immune complexes on the membrane of RBCs, mechanical damage of RBCs through capillary shear stress, the release of NO from endothelial cells, and physiological compensatory mechanisms that prevent microthrombosis and hypoxemia during the infection. They speculated that an

increase in median deformation of RBCs observed in seropositive children and adolescents with asymptomatic to mild COVID-19 may represent the maximum capacity of these compensatory mechanisms in young and healthy organisms.

Additionally, since the results demonstrated higher deformation of RBCs in participants with complete COVID-19 vaccination compared to seronegative participants, the authors speculated that increased deformation of RBCs might be a direct consequence of the SARS-CoV-2 S protein presentation and a component of the immune response against SARS-CoV-2. This observation needs to be confirmed further because this study included a small number of participants fully vaccinated against SARS-CoV-2.

Conclusion

This study demonstrated increased deformation of RBCs, measured by the RT-DC, in children and adolescents after SARS-CoV-2 infection and COVID-19 vaccination. Within six months after SARS-CoV-2 infection, the median deformation of RBCs was higher in seropositive and vaccinated participants than in seronegative participants.

This article was published in Scientific Reports.

Journal Reference

Eder J.*et al.* Increased red blood cell deformation in children and adolescents after SARS-CoV-2 infection. Sci Rep 13, 9823 (2023) (Open Access)
https://doi.org/10.1038/s41598-023-35692-6

UNLIMITED DOWNLOADS
VectorStock
ROYALTY FREE VECTOR GRAPHICS