COVID-19: Dexamethasone discovery carries treatment implications

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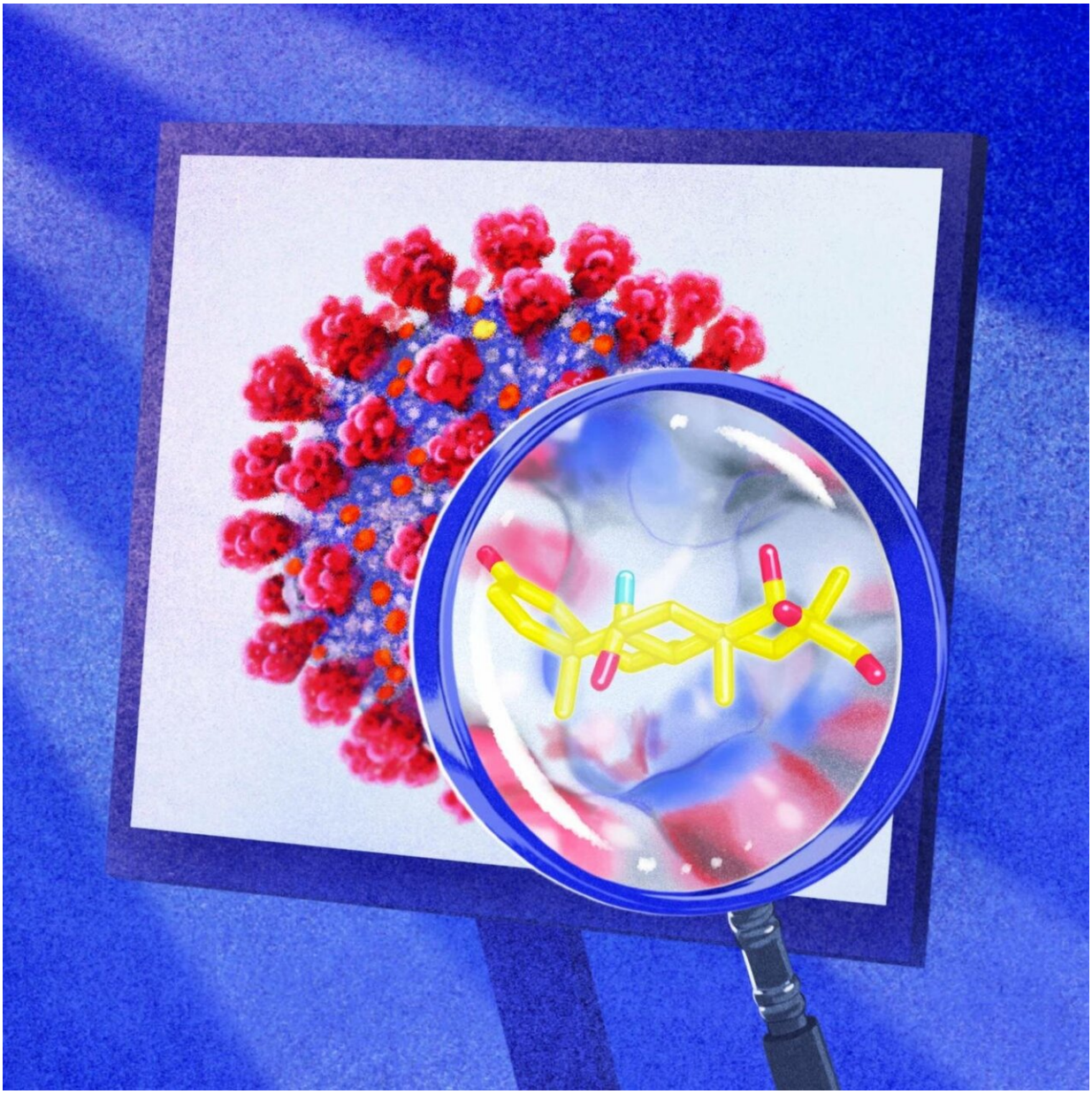

An artist's rendering of the dexamethasone discovery, by Marcin Minor. Credit: Marcin Minor

A new discovery about how the body transports dexamethasone, a drug that can increase the survival chances of patients with severe COVID-19, suggests diabetes and other factors may reduce its potentially lifesaving effectiveness. Based on their findings, the researchers say doctors may need to rethink how they dose the drug for certain groups of patients.

The team of scientists, based at the University of Virginia School of Medicine, the University of South Carolina, and in Poland, has determined how a protein in our blood called serum albumin picks up dexamethasone and takes it where it is needed. Low serum albumin levels are already considered a major risk factor for severe COVID-19, as is diabetes.

The new research suggests diabetes or low albumin levels may make it difficult for patients to get the benefits of dexamethasone, a corticosteroid that calms the hyperactive immune response that can lead to death in severe COVID-19.

Diabetes is associated with high blood sugar levels, which results in a modification of albumin that may alter the binding site for dexamethasone. Other drugs may also compete with dexamethasone for the limited space in serum albumin's cargo holds. Albumin's cargo capacity is also naturally decreased when there is a low albumin level in the blood.

"At this point, we do not have a readily available treatment better than dexamethasone for severe COVID-19 cases, but, like COVID-19 itself, its effectiveness is somewhat unpredictable," said lead researcher

Wladek Minor, Ph.D., of UVA's Department of Molecular Physiology and Biological Physics. "In order to provide a comprehensive picture, this research was conducted in collaboration among structural biologists, computer scientists and clinicians. So, every author of this paper had to step out of the box to combine medical data with structural biology results in order to suggest possible modifications of the treatment that could potentially save more human lives."

Researcher Ivan Shabalin, Ph.D., the first author of a new paper outlining the findings, added: "Working on this interdisciplinary team and seeing how our research in fundamental science may save lives in the current pandemic felt extremely rewarding."

Dexamethasone and COVID-19

For the first time, Minor and his colleagues have demonstrated exactly how serum albumin binds with dexamethasone so that the drug can be distributed through our bodies.

Serum albumin binds with dexamethasone the same way it binds with the hormone testosterone, suggesting that the two could compete with each other, the researchers report. More men die of COVID-19 than women, and low testosterone levels have already been associated with worse outcomes. The authors of the study hypothesized that high dexamethasone levels might affect testosterone transport by competing for the same drug site on albumin.

Serum albumin also uses the same binding dock to pick up several common nonsteroidal anti-inflammatory drugs, so doctors may need to consider the potential for competition in deciding COVID-19 treatment plans, the research suggests.

That said, it's not as simple as increasing the dexamethasone dose for

patients with diabetes or low serum albumin. Too much dexamethasone can be harmful or have unwanted side effects. More research is needed to determine the best dosing in various patient populations, particularly for people with diabetes or low albumin levels, the researchers say.

To better understand serum albumin's role in COVID-19, the researchers analyzed data from 373 patients at a hospital in Wuhan, China, that treated many severe cases of the disease. The scientists found that patients who died had lower albumin levels than those who survived. Those who died also had higher levels of blood sugar. That aligned with the researchers' conclusion that high blood sugar could affect serum albumin's ability to carry its cargo.

"In order to provide rapid response to emerging biomedical challenges and threats like COVID-19, we need to analyze medical data in the context of other *in-vitro* and *in-vivo* results," Minor said. "Five years ago, I wrote in Expert Opinion in Drug Discovery that, 'The use of recent advancements in biochemical, spectroscopy and bioinformatics methods may revolutionize drug discovery, albeit only when these data are combined and analyzed with effective data management systems. Accurate and complete data management is crucial for developing experimental procedures that are robust and reproducible.' This assessment is still valid, and, clearly, not enough progress has been made, because it is mistakenly not recognized as a grand challenge for biomedical sciences."

"Until a vaccine or new drugs are widely available, we have to make the best use of the drugs we know can help fight COVID-19," added team member Dariusz Brzezinski, Ph.D.

More information: Ivan G. Shabalin et al, Molecular determinants of vascular transport of dexamethasone in COVID-19 therapy, *IUCrJ* (2020). DOI: 10.1107/S2052252520012944

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