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Glutathione Deficiency and Risk of Severe COVID-19

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STORY AT-A-GLANCE

- Glutathione is a crucial antioxidant that plays a role in reducing the severity of COVID-19 illness by acting to reduce the oxidative stress and inflammation that trigger organ failure
- Glutathione deficiency is prominent in many of the comorbidities associated with severe COVID-19 illness including obesity, cardiovascular disease, Type 2 diabetes and aging
- N-acetylcysteine (NAC) is a precursor to glutathione, which one major hospital is studying as a potential "medication" to help fight COVID-19 and potentially prevent ventilation and admission to critical care
- Consider raising your glutathione levels through exercise, certain foods and getting high quality sleep

The symptoms of severe COVID-19 frequently include hypercoagulability, or an increased tendency to produce blood clots. While the pathophysiology is not completely understood,[1] the characteristic changes have been identified.[2] Researchers have found anticoagulant therapy helps improve health outcomes from an illness that can trigger a variety of thromboembolic complications.

Data also show that people who are deficient in glutathione experience some of the more serious symptoms.[3] Interestingly, one study[4] published in Nature in January 2021, evaluated the differences in the prothrombotic potential between COVID-19 and other respiratory viral infections not triggered by a coronavirus. The thrombotic rates were not different between the two groups in mild disease.

However, hypercoagulability in COVID-19 was a dynamic process and the highest risk occurred in severely ill people. The complications of hypercoagulability include the shortness of breath and severe lung complications it triggers.

In one study,[5] patients admitted to Padova University Hospital in Italy for acute respiratory failure showed "markedly hypercoagulable thromboelastometry profiles," which "correlated with a worse outcome."[6]

It appears one of the differences between those who have a mild illness and severe illness is related to the body's ability to reduce the hyperimmune response that leads to a **cytokine storm** and the hypercoagulability that often accompanies it. Glutathione plays a role in the fight against the severe inflammatory response triggered by SARS-CoV-2.[7]

Glutathione Plays a Crucial Role in Severe COVID Illness

Studies published in ACS Infectious Disease[8] and Antioxidants[9] proposed that glutathione plays a crucial role in the body's fight against the severe inflammatory response triggered by the SARS-CoV-2 virus. The research group in the ACS Infectious Disease study called it the "most likely cause of serious manifestations and deaths in COVID-19 patients."

In that study,[10] they theorized the higher infection rate in older individuals and those with comorbidities suggest these groups are sensitive to environmental factors. Certain medical conditions have been identified that increase the risk of severe illness from COVID-19. These include chronic lung disease, **Type 2 diabetes**, heart conditions, **obesity** and smoking.[11]

Specifically, the researchers[12] homed in on an impaired redox homeostasis and concurrent oxidative stress in individuals of advanced age and with comorbidities. Redox homeostasis is a process that helps ensure a proper cellular response to stimuli.

When this is dysregulated, oxidative stress can lead to "cell death and contribute to disease development."[13] Glutathione plays a crucial role in the inflammatory response,

which the researchers theorize is a feasible means in the treatment and prevention of COVID-19. They wrote:[14]

> *"The hypothesis that glutathione deficiency is the most plausible explanation for serious manifestation and death in COVID-19 patients was proposed on the basis of an exhaustive literature analysis and observations.*
>
> *The hypothesis unravels the mysteries of epidemiological data on the risk factors determining serious manifestations of COVID-19 infection and the high risk of death and opens real opportunities for effective treatment and prevention of the disease."*

The paper published in Antioxidants also concluded that a common denominator appeared to be the impaired redox homeostasis system. They proposed glutathione may be "critical in extinguishing the exacerbated inflammation that triggers organ failure in COVID-19."[15]

In the paper, the scientists presented a review of biochemical mechanisms that are counterbalanced by glutathione and the pathways that may explain endogenous glutathione depletion in older people and those with comorbidities known to increase the risk of severe illness.

Glutathione Mediates Reduction in Lung Inflammation

One medical student put this theory to the test when his 48-year-old mother was diagnosed with pneumonia. She was prescribed **hydroxychloroquine** and azithromycin that helped to improve some symptoms but her breathing remained labored. When she had severe respiratory problems, her son contacted Dr. Richard Horowitz, a specialist who was treating his sister for Lyme disease.

He suggested adding glutathione to help reduce the inflammation and protect the lung tissue. The results were dramatic. Within one hour after receiving a 2,000 milligram dose of glutathione, her breathing had improved. She continued taking the glutathione

for five days and did not relapse. Horowitz published two case studies, documenting the results of oral and IV glutathione.[16]

In May 2020, Memorial Sloan-Kettering Cancer Center posted a trial to ClinicalTrials.gov[17] announcing a study using N-acetylcysteine (NAC) in patients with COVID-19. This was first-of-its-kind research.

The team planned to enroll patients with severe disease and evaluate the use of 6 grams of NAC administered intravenously each day in addition to other treatments. The study was last updated in March 2021; the team postulated that:

> *"… a medication called N-acetylcysteine can help fight the COVID-19 virus by boosting a type of cell in your immune system that attacks infections. By helping your immune system fight the virus, the researchers think that the infection will get better, which could allow the patient to be moved out of the critical care unit or go off a ventilator, or prevent them from moving into a critical care unit or going on a ventilator."*

At approximately the same time Memorial Sloan-Kettering announced their study, Dr. Alexi Polonikov from Kursk State Medical University in Russia published papers[18,19,20] proposing glutathione plays a crucial role in the body's ability to respond to a COVID-19 infection. In a short YouTube video, pulmonologist Dr. Roger Seheult[21] explains the science.

In addition to using glutathione during an illness, Polonikov postulates that glutathione may be used as a preventive agent. Based on an exhaustive literature analysis, he later gave an explanation for why he believes **glutathione deficiency** is a plausible reason for serious illness from COVID-19.[22]

> *"(1) oxidative stress contributes to hyper-inflammation of the lung leading to adverse disease outcomes such as acute respiratory distress syndrome, multiorgan failure and death;*
>
> *(2) poor antioxidant defense due to endogenous glutathione deficiency as a result of decreased biosynthesis and/or increased depletion of GSH is the most*

probable cause of increased oxidative damage of the lung, regardless which of the factors aging, chronic disease comorbidity, smoking or some others were responsible for this deficit."

Seheult[23] and Polonikov[24] explain how oxidative damage plays a role in severe illness with COVID-19. In a second video,[25] Seheult explains how COVID-19 sets the stage for significantly increased **oxidative stress** by raising levels of superoxide, a damaging reactive oxygen species (ROS).

Glutathione — A Master Antioxidant

This increase in superoxide occurs in people who have high levels due to chronic diseases that are comorbidities for COVID-19. These include heart disease,[26] Type 2 diabetes[27] and high blood pressure.[28]

When the virus uses the ACE2 enzyme, it generates angiotensin II,[29] which in turn generates superoxide.[30] The ROS can be reduced with glutathione peroxidase[31] as it oxidizes glutathione in the process of reducing H2O2 to water. A deficiency in glutathione creates a buildup of ROS, as Polonikov describes.

The powerful antioxidant function in glutathione has earned it the nickname "master antioxidant."[32] Antioxidants help keep other molecules from oxidizing. Most proteins are constructed from a set of 20 amino acids. The precise arrangement and sequence results in the specific biological activity associated with that protein.[33]

However, glutathione is created from three amino acids — glutamate, glycine and cysteine — to form the glutathione molecule. One function of glutathione is to recycle other antioxidants. This helps increase the effectiveness and recycle the molecules. On the other hand, deficiencies in certain vitamins such as C, E and A can cause a glutathione deficiency.[34,35,36,37]

Comorbid Risk Factors Linked to Glutathione Deficiency

In a review of the literature[38] evaluating the effect of lung disease in COVID-19, researchers wrote that, in 2002, data showed glutathione protected against chronic inflammation during respiratory disease. They postulated that directly increasing glutathione levels in the lungs "would be a logical approach to protection against chronic inflammation and oxidant-mediated injury in lung disease."[39]

In addition to protecting lung tissue, glutathione has been studied in many of the comorbid conditions associated with severe COVID-19. For over a decade, researchers have noted that people with obesity,[40] heart disease[41] and Type 2 diabetes,[42] and who are elderly,[43] have a higher incidence of glutathione deficiency associated with those conditions.

As I reported in "**NAC's Crucial Role in Preventing and Treating COVID-19**," NAC is a precursor to reduced glutathione and has a long history of use for acetaminophen poisoning.[44] It effectively neutralizes the toxin by recharging glutathione and preventing liver damage.

Past studies[45] have also found it can reduce viral replication, including the influenza virus. Importantly, NAC also helps counteract hypercoagulation[46,47] as it has both anticoagulant and platelet inhibiting properties.[48] This is in large part due to the sulfur in NAC that reduces the interchain disulfide bonds by Von Willebrand factors that contribute to clot formation.

Once the Von Willebrand factor sulfur bonds are broken, the clot starts to dissolve, and the blood vessels open allowing for exchange of oxygen and carbon dioxide.

According to the authors of one paper, "NAC is an effective and safe alternative to currently available antithrombotic agents to restore vessel patency after arterial occlusion."[49] Two additional papers[50,51] show the same thing.

Strategies to Support Your Glutathione Levels

As he discusses in the video, Seheult believes there is more to the damage by COVID-19 than oxidative stress.[52] He points out that the clots in patients with confirmed COVID-19

are rich with platelets, indicating another mechanism involving disulfide bonds. He goes on to explain:[53]

> *"And, as we've already talked about N-acetylcysteine and reduced glutathione will break these disulfide bonds and cause them to lyse and potentially relieve the obstruction and the hypoxemia with COVID-19. Again, this is all a hypothesis, but it looks as though it's fitting together."*

Foods that have a positive impact on glutathione production include cruciferous vegetables such as **broccoli**, **green tea**, **curcumin**, rosemary and milk thistle.[54] Getting quality sleep may also help.[55]

Different types of **exercise** can influence your levels as well. In one study,[56] researchers enrolled 80 healthy but sedentary volunteers to measure the type of exercise that may have the greatest effect. They found that aerobic training in combination with circuit weight training showed the greatest benefit.

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