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Glutathione to Improve Health and Age-Related Degeneration

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STORY AT-A-GLANCE

- Glutathione is a powerful antioxidant composed of three amino acids — cysteine, glycine and glutamic acid
- The lack of glutathione in older adults may be a key element driving the oxidative stress and mitochondrial dysfunction that lead to age-related degeneration
- Researchers looked into supplementation with a combination of glycine and N-acetylcysteine (NAC), two glutathione precursors known as GlyNAC when taken together
- In older adults, GlyNAC supplementation for 24 weeks corrected glutathione deficiency and improved multiple measures of health
- By boosting glutathione, supplementation with GlyNAC led to improvements in oxidative stress, mitochondrial dysfunction, inflammation, endothelial dysfunction, insulin resistance, strength, cognition and more

Glutathione is a powerful antioxidant composed of three amino acids — cysteine, glycine and glutamic acid. In older adults, limited availability of glycine and cysteine may lead to decreased synthesis of glutathione, such that glutathione deficiency is widespread in this population.[1]

The lack of glutathione in older adults may be a key element driving the oxidative stress and mitochondrial dysfunction that lead to age-related degeneration. Meanwhile, a

"practical and effective approach" to lowering oxidative stress as you age may simply involve boosting your glutathione levels.[2]

Boosting Glutathione Improves Strength, Brainpower

Researchers at Baylor College of Medicine looked into supplementation with a combination of glycine and N-acetylcysteine (NAC), two glutathione precursors known as GlyNAC when taken together. They had previously shown that young mice deficient in glutathione had mitochondrial dysfunction, and supplementing with GlyNAC in older mice not only improved glutathione deficiency but also mitochondrial impairment, oxidative stress and insulin resistance.[3]

Additional previous research they conducted in HIV patients[4] also found that GlyNAC supplementation improved "deficits associated with premature aging" in this population.[5] This included improvements to oxidative stress, mitochondrial dysfunction, inflammation, endothelial dysfunction, insulin resistance, genotoxicity, strength and cognition.[6]

A subsequent pilot trial in older humans found similar results, with GlyNAC supplementation for 24 weeks correcting glutathione deficiency and improving multiple measures of health, including:[7]

Mitochondrial dysfunction	Oxidative stress	Inflammation
Endothelial dysfunction	Insulin resistance	Genomic damage
Cognition	Strength	Gait speed
Exercise capacity	Body fat levels	Waist circumference

While the benefits declined after GlyNAC supplementation was discontinued for 12 weeks, the researchers concluded, "Supplementing GlyNAC in aging humans could be a simple and viable method to promote health and warrants additional investigation."[8] In

scientific circles, there are nine hallmarks of aging that lead to most age-related disorders. These include:[9]

Genomic instability	Telomere attrition	Epigenetic alterations
Loss of proteostasis	Deregulated nutrient-sensing (including insulin resistance)	Mitochondrial dysfunction
Cellular senescence	Stem cell exhaustion	Altered intercellular communication (including inflammation)

It's interesting to note that GlyNAC supplementation improved four of these nine defects — mitochondrial dysfunction, inflammation, insulin resistance and genomic damage.[10]

The Power of Three

The study authors believe GlyNAC works by the "power of 3," acting together to bring about beneficial changes, as follows:[11]

1. Correction of glutathione deficiency, which results in correctio of oxidative stress and mitochondrial dysfunction.
2. Glycine, an important methyl-group donor. "Methyl groups are abundant in DNA and are important components of multiple cellular reactions," they noted. "Glycine is also important for normal brain function. Hence providing glycine could improve multiple defects as seen in this trial."
3. NAC, which acts as a cysteine donor. "Cysteine is critically important in energy metabolism by contributing the sulfhydryl (SH) group needed for energy generation … Cysteine and its donated SH groups also play key roles in multiple additional cellular reactions and function."

"We call this the 'Power of 3,'" study author and endocrinologist Dr. Rajagopal Sekhar, associate professor of medicine at Baylor College of Medicine, explained, "because we believe that it takes the combined benefits of glycine, NAC and glutathione to reach this far reaching and widespread improvement." He believes this also the potential to protect brain and muscle health in aging:[12]

> *"I am particularly encouraged by the improvements in cognition and muscle strength. Alzheimer's disease and mild cognitive impairment (MCI) are serious medical conditions affecting memory in older people and leading to dementia, and there are no effective solutions for these disorders.*
>
> *We are exploring the possibility that GlyNAC could help with these conditions by conducting two pilot randomized clinical trials to test whether GlyNAC supplementation could improve defects linked to cognitive decline in Alzheimer's disease and in MCI, and possibly improve cognitive function."*

Glutathione's Link to COVID-19

Due to the significant oxidative stress it causes, a glutathione deficiency may be at the root of severe illness, including from COVID-19. Dr. Alexey Polonikov, from Kursk State Medical University, explained further:[13]

> *"Based on an exhaustive literature analysis and own observations, I proposed a hypothesis that glutathione deficiency is exactly the most plausible explanation for serious manifestation and death in COVID-19 infected patients.*
>
> *The major risk factors established for severe COVID-19 infection and relative glutathione deficiency found in COVID-19 infected patients with moderate-to-severe illness have converged me to two very important conclusions:*
>
> *(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 [glutathione] 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."

Many of the comorbid risk factors that predict severe COVID-19 disease are also tied to glutathione deficiency. In one evaluation of COVID-19 patients from six hospitals in Atlanta, researchers found independent factors that raised the risk of hospitalization. These included smoking, having Type 2 diabetes, being male, being Black, being of advanced age and being obese.[14] Polonikov found evidence that a glutathione deficiency may be implicated in these comorbidities.

In his paper he identified the progressive reduction in endogenous glutathione with aging. This, he believes, makes "the elderly more susceptible to oxidative damage caused by different environmental factors compared to younger individuals."[15] He pointed out that deficiencies in endogenous glutathione are also found in people who have other comorbid conditions.

He proposed these decreased levels with chronic disease could begin a shift toward oxidative stress and exacerbate lung inflammation, ultimately leading "to acute respiratory distress syndrome (ARDS), multiorgan failure and death."

NAC's Role in COVID-19 Treatment and Prevention

NAC, a form of the amino acid cysteine, also plays a crucial role in COVID-19. NAC has a long history of use as a remedy for acetaminophen poisoning. It neutralizes the toxic effects of the drug by recharging glutathione, thereby preventing liver damage. But the idea that NAC can also be helpful against viral infections is not new. Previous research[16] has found it reduces viral replication of certain viruses, including the influenza virus.

In a study published October 2020 in Clinical Immunology, researchers focused on a specific group of patients, namely those with glucose 6-phosphate dehydrogenase

(G6PD) deficiency, which has been shown to facilitate human coronavirus infection due to the fact that G6PD depletes glutathione.[17]

Importantly, NAC may also protect against other problems associated with COVID-19, including the hypercoagulation that can result in stroke and/or blood clots[18] that impair the ability to exchange oxygen in the lungs. Considering many COVID-19 cases involve blood clots in addition to excessive oxidative stress, and NAC effectively addresses both, I believe NAC should be included in standard of care for COVID-19. As noted in the FASEB Journal:[19]

> *"Based on a broad range of antioxidant and anti-inflammatory mechanisms … the oral administration of NAC is likely to attenuate the risk of developing COVID-19, as it was previously demonstrated for influenza and influenza-like illnesses.*
>
> *Moreover, high-dose intravenous NAC may be expected to play an adjuvant role in the treatment of severe COVID-19 cases and in the control of its lethal complications … including pulmonary and cardiovascular adverse events."*

NAC Prevents Strokes and Is Neuroprotective

NAC is most well-known to help increase glutathione and reduce the acetaldehyde toxicity[20] that causes many hangover symptoms. However, it may also prevent strokes in people with hereditary cystatin C amyloid angiopathy (HCCAA), a rare genetic disorder.[21]

People with HCCAA have an average life expectancy of just 30 years, and most die within five years of their first stroke,[22] so reducing their incidence could prove to be essential to increasing survival.

The finding is even more significant because it was conducted by researchers from Children's Hospital of Philadelphia (CHOP), which is notoriously against supplements. NAC appears to work by preventing the formation of amyloid-producing proteins, which promote amyloid deposits linked to strokes.[23] NAC is also sometimes prescribed to break up mucus in the lungs.[24]

NAC is also showing increasing promise as a neuroprotectant. Scientists are investigating NAC as a treatment for Parkinson's disease, which has been linked to glutathione deficiency in the substantia nigra, a region that houses dopamine neurons.[25]

However, because glutathione is poorly absorbed, in many cases it's easier to raise your glutathione by taking NAC instead. It could also have potential for Alzheimer's as, according to the CHOP researchers, the process of protein deposition that occurs in HCCAA is similar to what occurs in Alzheimer's, although at an accelerated pace in HCCAA compared to Alzheimer's, which is why dementia occurs later in life with the latter.

"If the underlying mechanisms of protein deposition and pathogenesis are sufficiently similar, similar or identical treatments may be effective," they said.[26] Another area where NAC shows particular promise is in the treatment of mental health disorders, including post-traumatic stress disorder,[27] depression[28] and substance use disorders.[29]

How to Boost Your Glutathione Levels

Food, supplements and exercise can be used to help optimize your glutathione levels. In addition to NAC and GlyNAC, supplementation with cysteine and glycine has been found to improve glutathione deficiency.[30]

Foods that have a positive impact on glutathione production include cruciferous vegetables such as broccoli, green tea, curcumin, rosemary and milk thistle.[31] Whey protein, which is a rich source of cysteine, may also be beneficial,[32] along with getting quality sleep.[33,34]

Different types of exercise can also influence your levels. In one study researchers enrolled 80 healthy but sedentary volunteers to measure the type of exercise that may have the greatest effect.[35] They found aerobic training in combination with circuit weight training showed the greatest benefit.

You can also use molecular hydrogen to increase your glutathione levels naturally as it will cause your ARE (antioxidant response elements) to go directly to your DNA and have

it transcribe the genes that not only produce glutathione and dozens of other important antioxidants, like catalase and superoxide dismutase. But it will only cause your body to make them, if and only if, your body has excess oxidative stress, which is precisely what you want.

Finally, a commonly overlooked strategy is to increase your melatonin levels by exposing your skin to near infrared. This is because one of the side effects of melatonin is that it causes your body to produce glutathione. The optimal way to get this near infrared exposure is by sun exposure but that is a challenge during the winter months, so near, not far, infrared saunas will work as will photobiomodulation near IR panels.

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