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The State of Glutathione Research

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Introduction

Glutathione is the primary antioxidant in the body and therefore has a significant role in controlling oxidative stress in the body. It is formed primarily within cells from three amino acids including cysteine, glycine, and glutamic acid.[1] Because it is an antioxidant, it is available in a reduced active form of glutathione (GSH) that neutralizes free radicals and transforms into the oxidized glutathione disulfide form (GSSH). The oxidized form GSSH is then recycled back to the reduced form GSH.

Benefits of Glutathione

While glutathione plays a key role in managing oxidative stress in the body, it also serves multiple other functions. It helps recycle other antioxidants such as vitamin C and vitamin E. Oxidative stress can contribute to damage of tissues and cells down to the level of the mitochondria.

Mitochondria are critical for energy production in the body. Glutathione is essential for protecting the mitochondria and therefore protecting energy formation.[2]

Detoxification is another critical function served by glutathione, including both environmental toxins and endogenous metabolic toxins.[3] With its critical role in detoxification, high levels of glutathione are found in the liver and other detoxification organs such as the kidney and lungs.[4,5] Levels of glutathione can be depleted with ongoing exposure to toxins.

Glutathione serves a key role in immune function. It is involved in increasing natural killer cells and enhancing T cell function.[6-8] By increasing multiple types of immune cells, it supports both the innate and adaptive immune systems. Research studies have shown increases in natural killer cell function with the supplementation of liposomal glutathione.[7,9]

Conditions with Increased Glutathione Needs

As the major antioxidant in the body, glutathione is essential for human health. With chronic disease, there is an increase in inflammation and oxidative stress leading to an increased need for

glutathione. Aging is associated with lower levels of glutathione and increasing levels of oxidative stress.[10] Multiple types of infections have been associated with low levels of glutathione, including viral infections such as COVID-19, influenza, and HIV.[11-13] Chronic infections such as Borrelia infections, which impact an increasing number of people, are associated with low levels of glutathione.[14]

Neuroinflammation is involved in neurodegenerative diseases in adults such as dementia but also in children with autism spectrum disorder. Chronic neuroinflammation leads to depletion of glutathione.[15,16] People with chronic cardiovascular and lung and liver diseases have been shown to have low levels of glutathione, which impact severity of disease.[17-19]

Issues with Glutathione Supplementation

Because glutathione is a critical antioxidant in the body, the question becomes how to best supplement. Glutathione can shift rapidly between the reduced and the oxidized state so when taken in a direct form orally it gets oxidized in the stomach, so the active form is not absorbed. The human gastrointestinal tract contains significant amounts of the enzyme GGT, which recycles GSH precursors. This may decrease GSH absorption significantly from oral glutathione supplementation.[20] To protect glutathione, liposomes, which are lipids surrounding the glutathione, have been developed. Intravenous (IV) glutathione is used by many practitioners in their practice, but because of cost and time it is difficult to do frequently long term. Transdermal, intranasal, and nebulized glutathione are other forms of supplementation but have less research and less availability. Practitioners also use precursors for glutathione such as N-acetylcysteine (NAC). Research on glutathione absorption and clinical outcomes are reviewed below to evaluate efficacy of different glutathione supplementation methods. In vivo studies will be the focus to show practitioners how to best support their patients with glutathione supplementation.

Research on Oral Glutathione

Initial research on supplementing oral glutathione was done with the reduced GSH form without any change in the molecule or added lipids in the form of a liposome. In 1992, researchers gave a single dose of 3 grams of GSH to seven people and did not observe an increase in blood GSH levels.[21] A randomized double-blind placebo-controlled trial was done in 2011 that had 40 participants given 500 mg twice a day for four weeks.[20] Oxidative stress markers were not reduced and there was no increase in total reduced, GSH, oxidized GSSH, or change in ratio of GSH/GSSH.[20] Since there were no changes in glutathione or oxidative stress markers, oral glutathione in its unmodified form was not thought to be an option for glutathione supplementation. From these results, companies developed patented liposomal glutathione preparations. Several of these have been studied for absorption and/or clinical symptom improvement.

One patented form of liposomal glutathione was researched for 6 months in a randomized controlled trial where half of the participants received a low dose 250 mg/day and half received a high dose of 1000 mg/day.[9] Both doses showed increases in glutathione levels with the higher dose showing greater improvements. The high dose of 1000 mg after 6 months showed an increase in GSH (reduced active form) of 30-35% in red blood cells, plasma, and lymphocytes ($P<0.05$).[9] For immune function, natural killer cytotoxicity was measured with a >two-fold increase in the high dose group after 3 months ($P < 0.05$).[9] For oxidative stress evaluation a decrease in oxidized to reduced glutathione ratios in whole blood were seen at the end of the study.

A different patented liposomal glutathione was investigated for absorption and immune function. Participants who had glutathione levels at the low end of normal received either 500 mg or 1000 mg daily for one month.[7] There were no differences observed between dose groups at the end of the study. The maximum increases in glutathione levels were found after 2 weeks with 500 mg daily of 40% in whole blood, 25% in erythrocytes, 28% in plasma and 100% in PBMCs occurring after 2 weeks($P<0.05$).[7] Oxidative stress markers decreased significantly and correlated with the increase in glutathione levels. Immune markers showed improvement also with an increase in natural killer cell cytotoxicity up by 400% in two weeks and an increase in lymphocyte proliferation of 60% in two weeks where both reached statistical significance. ($P<0.05$).[7]

Research on Topical/Transdermal Glutathione

Topical or transdermal glutathione is an easy way to supplement glutathione, but the initial research did not support the efficacy of it. Research compared oral liposomal glutathione versus transdermal glutathione in children with autism spectrum disorder who had low baseline levels of glutathione.[15] The study was conducted over 8 weeks and the doses of both the transdermal and the oral liposomal glutathione began at ¼ recommended dose and increased weekly until the full dose per weight was given at 4 weeks and that dose was maintained throughout the study.[15] The children taking the oral glutathione had significant increases in plasma reduced glutathione along with elevated levels of sulfate, cysteine, and taurine.[15] In the transdermal glutathione group, there were also significant increases in plasma sulfate, cysteine, and taurine levels but not in plasma glutathione levels.[15] The results lead to the concern whether transdermal glutathione was sufficient for raising plasma glutathione levels.

In a comparable manner to altering oral glutathione to increase absorption, a modified version of topical glutathione was developed called glutathione–cyclodextrin nanoparticle complex (GSH-CD). The research studied both absorption levels of the topical GSH-CD along with immune markers for three days when participants were exposed to *Mycobacterium avium*.[22] Topical GSH-CD after three days showed elevated GSH levels in blood mononuclear cells and red blood cells

along with decreased levels of the oxidative stress marker malandialdehyde.[22] Immune elevations in cytokines and an increase in clearance of the *Mycobacterium avium* infection were associated with the topical GSH-CD.[22] The study showed that a modified form of transdermal or topical glutathione could increase blood cell levels of glutathione, which were not found with previous unmodified topical glutathione.

Research on Intravenous Glutathione

Initial research on intravenous (IV) glutathione showed that after an infusion of 2 grams of glutathione the concentration of both total glutathione and cysteine in the plasma increased significantly.[23] Excretion of glutathione in the 90 minutes following infusion increased 300-fold for glutathione and was at a constant rate with a half-life corresponding to 14.1 +/- 9.2 min.[23] Subsequent research on intravenous glutathione has focused more on improvement in clinical symptoms than in vivo absorption studies. Two studies done on Parkinson's patients have shown clinical improvements with IV glutathione given daily for a month, but these clinical improvements returned to baseline after approximately two months without glutathione in both studies.[24,25] Clinical studies have compared IV glutathione to oral N-acetylcysteine (NAC) for

preventing oxidative stress after coronary angiography, which induces oxidative stress damage.[26] IV glutathione prevented the increase in oxidative stress markers as predicted but oral NAC had no effect on the oxidative stress markers.[26] Based on the research, although limited, it appears that IV glutathione is effectively getting into the blood stream. The concern is how long this effect lasts based on the short half-life.

Research on Nebulized and Intranasal Glutathione

Both intranasal and nebulized forms of glutathione are available and used primarily for sinus and lung conditions. Absorption studies are minimal. A safety study on intranasal glutathione found it to be helpful for symptoms in 62% of patients with 12% reporting side effects.[27] Intranasal glutathione is also being researched for neurodegenerative diseases with its close proximity to the nervous system. A study showed high dose intranasal glutathione to improve Parkinsons's symptoms, but the results were not statistically significant.[28]

Efficacy of N-acetylcysteine (NAC) for Glutathione Support

N-acetylcysteine (NAC) is often used as a supplement to increase glutathione levels. Cysteine is the rate-limiting step in glutathione synthesis so the thought is it would lead to an increased production of glutathione. One concern with this is the body's ability to synthesize glutathione from cysteine and other amino acids decreases with age and with certain chronic diseases especially if they involve liver dysfunction.[29] Genetic SNPs, including glutathione building and glutathione recycling enzymes, can also influence the rate of glutathione production from precursors. Studies of NAC have been inconsistent with showing levels of increased glutathione.[29-33] Since the benefits of glutathione include improving immune function and decreasing oxidative stress, NAC has been studied for both functions. Research has shown in specific studies that NAC does not influence immune function.[33] or antioxidant function.[31] Overall, the research on NAC appears to be limited in terms of being a good method for improving glutathione and supporting multiple glutathione functions.

Summary

Glutathione as our primary antioxidant is critical for health. With the toxins in our environment along with high rates of chronic disease and stress, many people are low in this critical nutrient. Because of this, practitioners have searched for ways to elevate glutathione. There is research that shows improvement with targeted forms of oral glutathione in the liposomal form and modified topical glutathione (GSH-CD). Improvements in clinical function have been found with the liposomal oral form. Intravenous glutathione according to research is absorbed and can improve

clinical symptoms, but the concern is the short half-life and the return of symptoms once the IV glutathione has been stopped. Because of cost and needing to be in a clinical setting, IV glutathione is not practical for daily use. Intranasal glutathione and nebulized glutathione as methods for targeted disease states could be helpful but are not adequately researched at this time. Overall, more research needs to be done to understand how to maximize the supplementation of glutathione to benefit patients.

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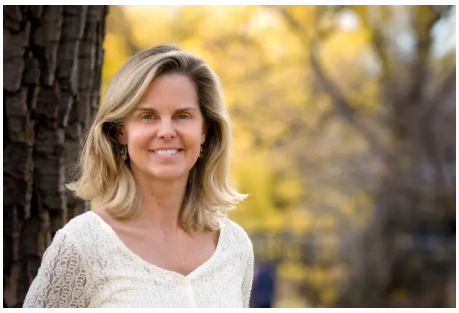

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