Clinical Use of Glutathione: More than just Detoxification Support

BY DEBBY HAMILTON, MD, MPH
Glutathione

- Tripeptide: L-y-glutamyl-l-cysteinyl-glycine
  - Reduced form: GSH
  - Oxidized form: GSSG
- Active thiol group: cysteine
- Levels:
  - Intracellular GSH range from 0.5 to 10 mM
  - Extracellular: 1 to 3 times lower
  - Mitochondria GSH: 10 to 15% of intracellular levels
Glutathione Formation

- **Diet:** Minimal intake 100 to 150 mg daily
  - Uncooked, raw, unprocessed, unpasteurized
- **Precursors:** Amino acids: glutamine, glycine, cysteine
- **Cofactors:**
  - Vitamin C, E, B1, B2, B6, B12, Folate, selenium, Mg, Zinc, ALA
Glutathione Formation

- Rate-limiting step: Cysteine
- Anti-oxidant activity of GSH due to presence of sulfur group on cysteine
- Made from methionine
- Genetic SNP in methylation and sulfur pathways influence methionine and cysteine levels
Glutathione
The Super Hero of Antioxidants.
Glutathione Functions:

- **Regulation of cell growth and division**
  
  Glutathione reduces oxides, such as hydrogen peroxide, inside the cell that could prevent cell division and growth.

- **DNA synthesis and repair**
  
  Glutathione protects the DNA from oxidative stress during cell division which allows for DNA synthesis. When the DNA is mutated by a free radical, glutathione repairs the mutated DNA.

  Helps protect mitochondrial function through its antioxidant properties
Glutathione Functions:

- **Protein synthesis**
  glutathione maintains our proteins in their proper form. Its sulfur atom reacts with unnatural sulfur-sulfur bonds in proteins.

- **Amino acid transport**
  glutathione moves substances, such as amino acids, in and out of the cell.

- **Enzyme catalysis**
  glutathione is the catalyst in the chemical reaction between some enzymes.

- **Enzyme activation**
  The highly reactive sulfide bond in glutathione activates enzymes so that they carry out their function.
Detoxification Pathways

**FAT-SOLUBLE TOXINS**
- Phase 1
  - Oxidation
  - Reduction
  - Hydrolysis
  - Hydration
  - Dehalogenation
  
  **(Cytochrome P450 Enzymes)**

**INTERMEDIATE METABOLISM**

**WATER-SOLUBLE WASTE**
- Phase 2
  - Sulfation
  - Glucoronidation
  - Glutathione Conjugation
  - Acetylation
  - Amino Acid Conjugation
  - Methylation

**Nutrients Needed**
- Vitamins B2, B3, B6, B12
- Folic Acid
- Glutathione
- Flavonoids

**Nutrients Needed**
- Methionine
- Cysteine
- Magnesium
- Glutathione
- Vitamin B5, B12
- Vitamin C
- Glycine
- Taurine

**Eliminated via:**
- Urine
- Bile
- Stool

- Glutamine
- Folic Acid
- Choline
Glutathione Functions:

- **Detoxify toxins**
  
  the enzyme glutathione S-transferase takes the sulfur from glutathione and attaches it to toxic molecules, this makes the toxin more water soluble.

- **Chelates heavy metals**
  
  Glutathione binds heavy metals to create compounds that can be eliminated without causing damage to the cell or DNA.
Glutathione Functions:

- **Enhances systemic immune function**

  Glutathione regulates T-cell proliferation by increasing the number of binding cellular receptors.

  Cellular GSH also affects the growth and replication of T-cells through growth stimulating cytokines.

- Increases Natural Killer cell function
Glutathione Functions:

- **Storage and transport of cysteine**
  Glutathione provides and determines the amount and availability of neuronal cysteine.

- **Regulation of homocysteine**
  The methionine cycle and the transulfuration sequence are the mechanisms for homocysteine metabolism. The rapid turnover of glutathione in the liver, kidneys, small intestine and pancreas accounts for the metabolism of homocysteine in these organs.
How do you know if a patient needs glutathione?

- Environmental exposures
- Oxidative stress
- Lifestyle factors
- Chronic disease state
- Genetics
Environmental Chemicals: Depletion of glutathione

- Tylenol
- Acetone/solvents
- Fuel/gasoline
- Heavy Metals
- Pesticides/Herbicides
- Nitrates: Food preservatives
- Artificial sweeteners
- Synthetic food dyes
- Benzopyrenes: tobacco
- Industrial pollutants

- Ethanol
- Household chemicals: detergents, cleaners, bleach
- Plastics
- Non-stick cookware
- Chlorine treated water
- Formaldehydes
- X-rays
- EMF’s
- UV radiation
Depletion of glutathione

- Poor Diet
- Strenuous exercise
- Chronic stress
- Anxiety
- Depression
- Light pollution: suppresses melatonin production so lose an antioxidant
- Aging
As we age, Glutathione levels naturally decrease, resulting in free radical damage and oxidative stress.
Increased oxidative stress

Then:

Increased need for glutathione
One molecule of hydrogen peroxide is reduced to 2 molecules of water while 2 molecules of glutathione (GSH) are oxidized in a reaction catalyzed by the selenoenzyme, glutathione peroxidase. Oxidized glutathione (GSSG) may be reduced by the flavin adenine dinucleotide (FAD)-dependent enzyme, glutathione reductase.
Oxidative Stress

Inflammation

Disease

Oxidative Damage/
Disease Cycle
Diseases with Documented Links to Low Glutathione

**Neuro and Brain**
- Alzheimer’s Disease
- Parkinson’s Disease
- Huntington’s Disease
- Amyotrophic Lateral Sclerosis (ALS, or Lou Gehrig’s Disease)
- Migraines
- Multiple Sclerosis (MS)
- Autism
- ADHD/ADD
- Bipolar Disorder
- Depression

**Immune and Cancer**
- HIV and AIDS
- Cancer (Breast, Lung, Cervical, Colon, Ovarian, Leukemia)
- Lupus
- Viral Infections
- Asthma
- Acne
- Lyme Disease
- Allergies
- Gingivitis
- Rheumatoid Arthritis

**Thyroid and Pancreatic Function**
- Diabetes
- Pancreatitis
- Hyperthyroidism
- Hypothyroidism

**Cardiovascular**
- Atherosclerosis
- Angina
- Erectile Dysfunction
- Hypertension
- Stroke

**Other**
- Inflammatory Skin Conditions
- Accelerated Aging
- Arthritis
- Chronic Fatigue
- Chronic Obstructive Pulmonary Disease (COPD)
- Gout
- Hepatitis of Any Kind
- Cystic Fibrosis
- Infertility
- Eyesight Issues (including Macular Degeneration)
- Gastric Ulcers
Neurodegeneration

- Lewy Body Formation
- Proteasome Inhibition
- Protein Accumulation
- Glutathione Depletion
- Oxidative Stress
- Cellular Death
- Inflammation
Genetic Influence on Glutathione
The methionine cycle involves the remethylation of homocysteine to methionine by either the folate–vitamin B-12–dependent methionine synthase (MS) reaction or the folate–vitamin B-12–independent betaine homocysteine methyltransferase (BHMT) reaction.
Relative to the control children, the children with autism had significantly lower baseline plasma concentrations of methionine, SAM, homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of SAH, adenosine, and oxidized glutathione.

impaired capacity for methylation and increased oxidative stress in children with autism.

Glutathione Enzymes
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Testing for glutathione

- Direct
- Indirect
- Oxidative stress
- Genetic
Glutathione Testing: Direct

- Total glutathione plasma
  - Levels: 3.8-5.5 umol/L

- RBC glutathione: intracellular
  - Levels: 1000-1900 umol/L (goal above 1200)
Glutathione Testing: Indirect Markers

- GGT blood test: Gamma glutamyl transferase
  - If elevated then need for glutathione to transport into cells

- Organic acid test (OAT)
  - Low levels of NAC
  - Elevated 2-hydroxybutyric acid
Glutathione Testing:

- Oxidative damage to DNA/RNA
  - 8-hydroxy-2-deoxyguanosine (8-OHdG)
- Oxidative damage to lipids
  - 8-isoprostane
- Antioxidant reserves/enzymes
  - Cysteine, cystine, SOD, glutathione peroxidase, sulfate, total antioxidant capacity
Glutathione Testing: Genetic

- Genetic SNP’s
  - Glutathione transferases, CBS, methylation markers
  - MTHFR

- Methylation profile
  - Cysteine, cystathionine, homocysteine, methionine, SAM, SAH
Treatment of low glutathione

Glutathione
- Liposomal glutathione
- Acetyl-glutathione
- IV glutathione
- Topical glutathione

Precursors to glutathione
- NAC, cysteine, vitamin C, denatured whey as source of cysteine

Enhance enzyme function: glutathione S-transferase

Improve methylation
GSH was administered intravenously, 600 mg twice daily, for 30 days, in an open label fashion.

All patients improved significantly after GSH therapy, with a 42% decline in disability. Therapeutic effect lasted for 2-4 months.

Our data indicate that in untreated PD patients GSH has symptomatic efficacy and possibly retards the progression of the disease.

**IV Glutathione: Research**

- Randomized, placebo-controlled, double-blind, pilot trial in subjects with PD whose motor symptoms were not adequately controlled with their current medication regimen.

- Intravenous glutathione 1,400 mg or placebo administered three times a week for 4 weeks.

- Over the 4 weeks of study medication administration, UPDRS ADL + motor scores improved by a mean of 2.8 units more in the glutathione group (P = 0.32), and over the subsequent 8 weeks worsened by a mean of 3.5 units more in the glutathione group (P = 0.54).

Concern with N-acetylcysteine

Metabolism of NAC

Oral NAC administration
Rapid absorption

Extensive first-pass metabolism in
liver and intestine

NAC → deacetylation → cysteine + glutamate

GSH + glutamate-cysteine ligase → Glutamylcysteine

3% of NAC excreted in feces
Concern with N-acetylcysteine

- Multiple enzymes needed for conversion from NAC to glutathione
- Genetic SNP’s influence capacity and speed of enzyme
- Extensive first-pass metabolism in liver and intestine
- Inadequate research
- Multiple enzyme pathways for cysteine in addition to formation of glutathione
Glutathione liposomal delivery

**Liposomal technology**

- Common delivery system for poorly absorbed pharmaceutical products
- Using this technology, glutathione is wrapped within microscopic spheres, consisting mainly of phospholipids (liposomes)
- Surface of human cells & liposomes are the same - phospholipids
Liposomal technology (continued)

- Body recognizes the liposome as self
- Absorption begins with membranes vs. going through digestive tract
- Unique liposome structure allows it to combine effectively with the body's natural fluids and penetrate its protective membranes
- Most nutrients require the stomach acids to break them down into smaller molecules so they may be absorbed
- Oral glutathione, not in liposomes, must go through stomach acids, reducing absorption potential
The study was an eight-week, open-label trial using oral lipoceutical glutathione (n=13) or transdermal glutathione (n=13) in children, 3-13 years of age, with a diagnosis of an ASD.

**RESULTS:**

- The oral treatment group showed significant increases in plasma reduced glutathione.
- Both the oral and transdermal treatment groups showed significant increases in plasma sulfate, cysteine, and taurine following supplementation.

Liposomal Glutathione: Research

**METHODS:**

- Fourteen ventilated preterm infants received 1 mg/kg or 10 mg/kg liposomal glutathione intra-tracheally and bronchoalveolar lavage fluid was collected prior to treatment, 12 and 24 h after dosing for glutathione and malondialdehyde estimation.

**RESULTS:**

- Mean glutathione was initially 12.2 micromol/l, increasing to 52.8 micromol/l at 12 h (p = 0.006). Mean malondialdehyde was initially 265.6 nmol/l decreasing to 11.2 nmol/l at 12 h (p = 0.018).

**CONCLUSIONS:**

- Intra-tracheal liposomal glutathione instillation offers a feasible method of raising pulmonary glutathione in preterm infants and shows biochemical antioxidant effects.

Tri-Fortify™
clinical research – human study

- First randomized human study on healthy individuals

- Primary study markers:
  - Glutathione levels in red blood cells
  - Oxidative stress
  - Natural Killer Cell Cytotoxicity

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.
Tri-Fortify™
clinical research summary

- We demonstrate for the first time that liposomal GSH (in humans):
  - increases intracellular GSH
  - inhibits oxidative stress
  - enhances GSH-related immune functions
  - oral liposomal GSH supplementation may be an effective intervention to promote healthy detoxification & immune function

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GLUTATHIONE LEVELS

Increase in Red Blood Cell Levels
(Erythrocytes)

%Improvement*

0%  23%  28%

Baseline  Week 1  Week 2

Weeks of Tri-Fortify™ Supplementation

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Tri-Fortify™
clinical research summary

OXIDATIVE STRESS MARKERS

Oxidized / Reduced GSH

-20% -15% -10% -5% 0%
Baseline Week 1 Week 2

% Decrease* *P<0.05

Weeks of Tri-Fortify™ Supplementation

Lipid Peroxidation

-40% -30% -20% -10% 0%
Baseline Week 1 Week 2

% Decrease* *P<0.05

Weeks of Tri-Fortify™ Supplementation

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Tri-Fortify™
clinical research summary

IMMUNE FUNCTION

Natural Killer Cell Activity

Weeks of Tri-Fortify™ Supplementation

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- Disease state
- Environmental exposure including diet
- Genetics of methylation, sulfation, glutathione detoxification
  - Ability to use nutrients because of genetics
- Assessment of Oxidative stress
- Therapeutic options depending on patient needs
- Dosing depending on patient needs
What Does Glutathione Do?

- There are over a trillion cells in our bodies, and glutathione is found in every one of them. It is especially prevalent in major organs such as our brain, lungs, eyes, and liver. Glutathione is the body's primary, multifunctional protector of cells. Just look at some of its many benefits:

- **Chemical Detoxifier**
  There are over 80,000 harmful chemicals that we routinely encounter in our air, food, and water. Many of them enter our cells and must be purged regularly in order to maintain proper cellular function. Glutathione is our body's first line of defense against the chemicals and impurities in the world around us.

- **Heavy Metal Chelator**
  Similar to its role in expelling chemicals from our bodies, glutathione cleans cells of harmful heavy metals through a process called 'chelation.' Glutathione forms strong bonds ("chelates") with the metal atoms that makes them heavier and easier to filter. In this way, glutathione is the human body's primary chelating agent.

- **Free Radical Neutralizer**
  Glutathione is the body's first and best antioxidant for neutralizing a wide variety of harmful free radicals. It is the only antioxidant that can efficiently recycle itself and recycle itself again to keep our systems clean.

- **Mitochondrial DNA Protector**
  The breaking down of mitochondrial DNA has been long associated with aging and cell death. Glutathione protects mitochondrial DNA, so keeping glutathione at optimum levels in the body is key to protecting our DNA.

- **Cellular Anti-Inflammatory Agent**
  All inflammation starts at the cellular level. Inflammation of the cells and organs is also a sign of dysfunction within those cells and organs. Inflammation has been linked to low glutathione levels.

- **Oxidative Stress Reducer**
  Oxidative stress refers to when our systems are overwhelmed by certain types of oxygen-containing molecules, and so cannot fix the damage those molecules cause quickly enough. It represents a failure on a very basic, biochemical level, and has been linked to cellular abnormalities such as cancer, Alzheimer's, Parkinson's, and sickle cell anemia. Proper glutathione levels help reduce the oxidative stress that can lead to these problems.

- **Hemoglobin Enhancer**
  Hemoglobin carries oxygen to every cell. Unfortunately, when hemoglobin is oxidized, it can no longer carry oxygen molecules and must be reduced. Unsurprisingly, given its role in protecting all other vital functions, glutathione also protects hemoglobin from these harmful oxidizing agents.
Dr. Debby Hamilton, MD, MPH
Researched Nutritionals®

dhamilton@researchednutritionals.com

www.researchednutritionals.com
Tri-Fortify™

liposomal glutathione

- Available in two natural flavors:
  - Watermelon
  - Orange
- 450 mg of glutathione per serving
- 50 mg of vitamin C
- Proven Heat Stable
  - 3rd party lab tested
  - 104°F/40°C / 75% humidity – 90 days
  - Result: exceed label claim
- GMO-free (3rd party lab tested)

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# Supplement Facts

**Serving Size:** 1 teaspoon (5 mL)  
**Servings per Container:** Approx. 48

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<tr>
<th>Nutrient</th>
<th>Amount Per Serving</th>
<th>% Daily Value †</th>
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<tr>
<td>Calories</td>
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<tr>
<td>Total Fat</td>
<td>1 g</td>
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<tr>
<td>Vitamin C (Ascorbic Acid)</td>
<td>50 mg</td>
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<tr>
<td>Glutathione</td>
<td>450 mg</td>
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**Daily Value not established.**  
† Percent Daily Value based on a 2,000 calorie diet

**OTHER INGREDIENTS:** Glycerin, Medium Chain Triglycerides, Phospholipids (soy), Natural Flavor.

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