



## Monograph

### Glutathione, Reduced (GSH)

#### Introduction

Reduced glutathione, most commonly called glutathione or GSH, is a relatively small molecule ubiquitous in living systems.<sup>1-3</sup> Occurring naturally in all human cells, GSH is a water-phase orthomolecule. Its intracellular depletion ultimately results in cell death and its clinical relevance has been researched for decades.<sup>4</sup>

GSH is the smallest intracellular thiol (-SH) molecule. Its high electron-donating capacity (high negative redox potential) combined with high intracellular concentration (millimolar levels) generate great reducing power.<sup>2</sup> This characteristic underlies its potent antioxidant action and enzyme cofactor properties, and supports a complex thiol-exchange system, which hierarchically regulates cell activity.

GSH levels in human tissues normally range from 0.1 to 10 millimolar (mM), most concentrated in the liver (up to 10 mM) and in the spleen, kidney, lens, erythrocytes, and leukocytes.<sup>5</sup> Plasma

concentration is in the micromolar range (approx. 4.5 μM).<sup>6</sup> Oxidative stressors that can deplete GSH include ultraviolet and other radiation;<sup>7</sup> viral infections;<sup>2,8</sup> environmental toxins, household chemicals, and heavy metals;<sup>2</sup> surgery, inflammation, burns, septic shock;<sup>9,10</sup> and dietary deficiencies of GSH precursors and enzyme cofactors.<sup>11</sup>

#### Biochemistry and Metabolism

Reduced glutathione (GSH) is a linear tripeptide of L-glutamine, L-cysteine, and glycine. Technically N-L-gamma-glutamyl-cysteinyl glycine or L-glutathione, the molecule has a sulfhydryl (-SH) group on the cysteinyl portion, which accounts for its strong electron-donating character. As electrons are lost the molecule becomes oxidized, and two such molecules become linked (dimerized) by a disulfide bridge to form glutathione disulfide or oxidized glutathione (GSSG). This linkage is reversible upon re-reduction. GSH is under tight homeostatic control both intracellularly and extracellularly.<sup>2</sup> A dynamic balance is maintained between GSH synthesis, its recycling from GSSG/oxidized glutathione, and its utilization.

GSH synthesis involves two closely linked, enzymatically controlled reactions that utilize ATP.<sup>12-</sup>

<sup>14</sup> First cysteine and glutamate are combined, by gamma-glutamyl cysteinyl synthetase. Second, GSH synthetase combines gamma-glutamylcysteine with glycine to generate GSH. As GSH levels rise, they

self-limit further GSH synthesis; otherwise, cysteine availability is usually rate-limiting. Fasting,<sup>11</sup> protein-energy malnutrition, or other dietary amino acid deficiencies<sup>15</sup> limit GSH synthesis.

GSH recycling is catalyzed by glutathione disulfide reductase, which uses reducing equivalents from NADPH to reconvert GSSG to 2GSH. The reducing power of ascorbate helps conserve systemic GSH.<sup>16</sup>

GSH is used as a cofactor by (1) multiple peroxidase enzymes, to detoxify peroxides generated from oxygen radical attack on biological molecules; (2) transhydrogenases, to reduce oxidized centers on DNA, proteins, and other biomolecules; and (3) glutathione S-transferases (GST) to conjugate GSH with endogenous substances (e.g., estrogens) and to exogenous electrophiles (e.g., arene oxides, unsaturated carbonyls, organic halides), and diverse xenobiotics. GST underactivity may increase risk for disease<sup>17</sup> but paradoxically, some GSH conjugates can also be toxic.<sup>18,19</sup>

Direct attack by free radical and other oxidative agents can also deplete GSH. The homeostatic glutathione redox cycle attempts to keep GSH repleted as it is being consumed.<sup>21</sup> Amounts available from foods are limited (less than 150 mg/day),<sup>5</sup> and oxidative depletion can outpace synthesis.

The liver is the largest GSH reservoir. The parenchymal cells synthesize GSH for P450 conjugation and numerous other metabolic requirements, then export GSH as a systemic source of –SH/reducing power.<sup>12</sup> GSH is carried in the bile to the intestinal luminal compartment. Epithelial tissues of the kidney tubules, intestinal lining, and lung, have substantial P450 activity and modest capacity to export GSH.<sup>13</sup>

GSH equivalents circulate in the blood predominantly as cystine, the oxidized and more stable form of cysteine. Cells import cystine from the blood, reconvert it to cysteine (likely using ascorbate as cofactor),<sup>16</sup> and from it synthesize GSH. Conversely, inside the cell GSH helps re-reduce oxidized forms of other antioxidants such as ascorbate and alpha-tocopherol.<sup>16</sup>

## Mechanisms of Action

GSH is an extremely important cell protectant. It directly quenches reactive hydroxyl free radicals, other oxygen-centered free radicals, and radical centers on DNA and other biomolecules.<sup>2</sup> GSH is a primary protectant of skin, lens, cornea, and retina against radiation damage, and the biochemical foundation of P450 detoxication in the liver, kidneys, lungs, intestinal epithelia, and other organs.

GSH is the essential cofactor for many enzymes which require thiol-reducing equivalents, and helps keep redox-sensitive active sites on enzymes in the necessary reduced state.<sup>20</sup> Higher-order thiol cell systems – the metallothioneins, thioredoxins, and other redox regulator proteins – are ultimately regulated by GSH levels and the GSH/GSSG redox ratio. GSH/GSSG balance is crucial to homeostasis, stabilizing the cellular biomolecular spectrum, and facilitating cellular performance and survival.<sup>2,20</sup>

GSH and its metabolites also interface with energetics and neurotransmitter syntheses, through several prominent metabolic pathways.<sup>21</sup> GSH availability down-regulates the pro-inflammatory potential of leukotrienes and other eicosanoids. Recently discovered S-nitroso metabolites, generated *in vivo* from GSH and NO (nitric oxide) further diversify GSH's impact on metabolism.

## Clinical Indications: Proven Deficiency States

Glutathione status is a highly sensitive indicator of cell functionality and viability. As intracellular GSH becomes reduced, the cell's functionality is progressively reduced until it dies. In humans, GSH depletion is linked to a number of disease states.<sup>2,3,22</sup>

### ***Inherited Deficiencies***

Individuals with inherited deficiencies of the GSH-synthesizing enzymes exhibit limited or generalized GSH deficiency,<sup>3,14,22</sup> with hemolytic anemia, spinocerebellar degeneration, peripheral neuropathy, myopathy, and aminoaciduria, and often develop severe neurological complications in the fourth decade of life. These conditions are not necessarily lethal because of their incomplete penetrance; in some tissues GSH can attain 50 percent of normal. In addition, some GSH is obtained from the diet. Low erythrocyte GSH also manifests in hereditary nonspherocytic lymphocytic leukemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

### ***HIV Infection/Immunity***

Immune cell functionality and proliferation rely on adequate intracellular GSH,<sup>2,8</sup> and healthy humans with low lymphocyte GSH can have low CD4 counts. HIV infection and sequelae feature systemic GSH depletion.<sup>12</sup> Oxidative stress is elevated at all stages of HIV disease; HIV infection lowers GSH in the plasma, erythrocytes, T-cells and other lymphocytes, and monocytes.<sup>23</sup> Children with HIV also demonstrate low plasma GSH.<sup>8,22</sup> The cachexia and wasting of AIDS may be amenable to GSH repletion.<sup>12</sup> HIV depletion of lung epithelial lining fluid (ELF) glutathione may predispose to opportunistic infections, and the ELF may be repleted using aerosolized GSH.<sup>12</sup>

### ***Liver Cirrhosis, Inflammation***

Plasma and erythrocyte GSH can be low in patients with cirrhosis<sup>6,24</sup> or result from acute or chronic alcohol intake.<sup>22</sup> In nonalcoholic liver disease, liver GSH can be abnormally low and GSSG high.<sup>25</sup> Acetaminophen and other pharmaceutical or environmental xenobiotics can deplete liver GSH. Viral hepatitis can deplete GSH, and in hepatitis C patients monocyte GSH has been found to be depleted.<sup>26</sup>

### ***Pulmonary Disease***

GSH deficiency has been linked to various pulmonary diseases,<sup>3,12,22</sup> including chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), neonatal lung damage, and asthma. The lung is particularly vulnerable to oxidative attack from inhalation of pure oxygen, airborne toxins, and oxygen radical release by lung phagocytes. GSH in lung ELF may be the first line of defense. The GSH content of ELF was found abnormally low in idiopathic pulmonary fibrosis, ARDS, and HIV-positive patients.<sup>23</sup> ARDS patients with sepsis had low GSH and high GSSG in their ELF.<sup>12</sup> GSH repletion can accelerate ARDS patient release from intensive care.<sup>27</sup>

GSH in the ELF can be lifesaving for premature infants. Pulmonary GSH levels have been found to be low in premature infants,<sup>12</sup> and in perinatal hypoxia cases umbilical blood GSH has also been found to be low.<sup>3</sup> Newborns with low GSH in the ELF may be at higher risk of chronic lung disease.<sup>12</sup>

### ***Crohn's Disease, Gastrointestinal Inflammation***

Gastric mucosa of aged subjects can have low GSH,<sup>24</sup> as can patients with gastritis and/or duodenal ulcer linked to *Helicobacter pylori* infection.<sup>22</sup> In Crohn's disease cases the affected ileal zones were found to have low GSH and high GSSG, and GSH enzymes were altered.<sup>28</sup>

### ***Circulation***

Acute myocardial infarction patients<sup>29</sup> and men with familial coronary artery disease<sup>30</sup> exhibit lowered GSH. Glutathione given i.v. prior to cardiopulmonary bypass surgery favorably influenced

postoperative renal function while improving systemic arterial function.<sup>31</sup>

Infusion of GSH into patients with atherosclerosis enhanced microvascular vasodilation in response to acetylcholine, especially in subjects with baseline abnormal vessel wall reactivity.<sup>30</sup> Similar benefits were reported for the epicardial coronary artery system.<sup>32</sup> S-nitrosoglutathione also has platelet anti-aggregation activity in humans, as reviewed in Prasad et al.<sup>30</sup> The mechanism of vasodilation is suspected to be via glutathione's enhancement of nitric oxide.

### ***Metal Storage/Wilson's Disease***

In several copper-overloaded (Wilson's Disease) patients, hepatic GSH was markedly lowered.<sup>2</sup> This preliminary finding correlates with an impressive body of animal data.

### ***Pancreatic Inflammation***

Plasma GSH was significantly lowered in chronic pancreatitis linked to alcohol intake,<sup>33</sup> and patients with acute pancreatitis responded well to glutathione repletion.<sup>2</sup>

### ***Diabetes***

Subjects with impaired glucose tolerance, including early hyperglycemics, had reduced blood GSH.<sup>34</sup> In diabetics, the erythrocytes and platelets can be low in GSH.<sup>22,35</sup> Mild to moderate exercise can help normalize GSH status in diabetics,<sup>22</sup> although strenuous exercise can deplete GSH.<sup>36,37</sup>

### ***Neurodegeneration/Central Nervous System***

A variety of neurodegenerative diseases manifest abnormally low GSH.<sup>2,3,22</sup> In Alzheimer's a decrease in lymphoblast GSH has been reported. In Parkinson's disease the substantia nigra becomes greatly depleted of GSH.

The threshold of GSH depletion, below which the cell will usually die, is 70-80 percent.<sup>2,22</sup> The mitochondria, with their high oxygen radical flux, are particularly vulnerable.<sup>38</sup> Mitochondrial failure has been specifically implicated in retinal degeneration<sup>7</sup> and in Parkinson's disease.<sup>39</sup>

### ***Aging***

The aging process is associated with deterioration of GSH homeostasis. Plasma GSH trends lower while GSSG becomes more elevated.<sup>7</sup> Limited data suggests higher GSH levels correlate with better health, regardless of age, and that subjects with chronic disease have poorer GSH status than those free of disease.<sup>12</sup> Exercise training can strengthen GSH homeostasis.<sup>37</sup> With progressively more disease states manifesting GSH deficiency, repletion is a viable preventive, therapeutic, and anti-aging strategy.

## **Glutathione Repletion Strategies**

### ***Oral/I.V. Glutathione***

Tradition holds that GSH is not systemically bioavailable when given by mouth.<sup>40</sup> However, copious data confirm it is efficiently absorbed across the intestinal epithelium, by a specific uptake system.<sup>41,42</sup> Catabolism of newly-absorbed GSH after it reaches the portal blood intact but prior to its accessing the liver accounts for the paradoxical findings.<sup>43</sup> Such breakdown of circulating GSH does not rule out its oral use for GI conditions such as Crohn's Disease.<sup>28</sup>

Results from two controlled trials seem to suggest oral GSH had no significant benefit, but do not rule out benefit from high-dose GSH to depleted subjects.<sup>4,40</sup> In one trial, the plasma concentration

was high-normal at baseline. In the second, the dose administered (to cirrhosis patients), at 300 mg/day for 28 days, may have been insufficient to replete liver GSH in the context of severe impairment of biosynthesis.<sup>4</sup>

Perlmutter reported case histories indicating success with GSH repletion in various neurodegenerative diseases.<sup>44</sup> He reported marked benefit from its intravenous administration in Parkinson's, and successful oral application of orthomolecular GSH precursors to cases of Alzheimer's, stroke, multiple sclerosis, amyotrophic lateral sclerosis, and post-polio syndrome.

### *N-acetylcysteine*

Cysteine availability most often limits GSH biosynthesis *in vivo*. One orally bioavailable cysteine source is N-acetylcysteine (NAC). NAC is a potent antioxidant with antimutagenic and anticarcinogenic properties, and an established antidote for acetaminophen overdose known to deplete liver GSH. Oral dosing with NAC supplants oral L-cysteine, which is highly unstable and potentially toxic.<sup>45</sup>

Following its intestinal absorption, NAC is converted to circulating cysteine and can effectively replenish GSH in depleted patients.<sup>46</sup> In HIV/AIDS, plasma GSH and cysteine levels are often low. Two clinical trials, one of them double-blind, reported NAC had clinical benefit.<sup>3</sup> Administered intravenously or as an infusion over 15-30 minutes, it can replete glutathione in the ELF and improve lung function in patients with septic shock.<sup>10</sup> In one trial on pulmonary disease, oral NAC at 1800 mg/day failed to increase GSH.<sup>47</sup>

### *alpha-Lipoic Acid*

The antioxidant alpha-lipoic acid (ALA) is another effective GSH repleter. Orally, it raises GSH levels in HIV patients,<sup>48</sup> and is extremely safe and well tolerated.<sup>49</sup> ALA is a broad-spectrum, fat- and water-phase antioxidant with potent electron-donating capacity, and has added biochemical versatility as a Krebs cycle cofactor and transition metal chelator. It is superior to NAC in being recyclable *in vivo* from its oxidized form.

### *Methionine, Ascorbic Acid, Taurine*

Oral L-methionine is a cysteine precursor but can cause nausea and vomiting, whereas its activated counterpart S-adenosylmethione (SAME) is well tolerated. When given i.v. in high doses to cirrhotic patients, SAME repleted erythrocyte GSH.<sup>13</sup> Ascorbate conserves intracellular glutathione and probably is a redox GSH cofactor.<sup>16</sup> Taurine is a sulfur amino acid which, given orally, can raise the platelet aggregation threshold and increase platelet GSH in healthy males.<sup>2</sup>

### *Other Methods of Glutathione Repletion*

One synthetic cysteine delivery agent is L-2-oxothiazolidine-4-carboxylate (OTC, Procysteine), which can be enzymatically converted to cysteine within liver cells. Oral OTC is converted to GSH in humans.<sup>12</sup> Given intravenously to HIV patients, it increased blood GSH levels after six weeks of treatment.<sup>50</sup> In patients with coronary artery disease, oral OTC markedly improved arterial flow-mediated dilation.<sup>51</sup>

Glutathione esters have been heavily researched as potential oral delivery compounds but their long-term safety is in question. Their reported toxicity is perhaps attributable to metal impurities.<sup>3</sup>



## Toxicity/Contraindications

GSH and other thiols tend to be sensitive to redox-active minerals, and care should be taken to omit these from therapeutic preparations.

GSH use in cancer must be approached with caution, since some tumors may utilize it intracellularly to resist chemotherapy drugs.<sup>19</sup>

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