The Health Dividend of Glutathione
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Abstract
Glutathione (GSH) is a naturally occurring chemical used by the human body to protect against chemical and environmental threats. As a consequence of aging, lifestyle, diet, and disease, a gap can develop between the needs and availability of GSH. GSH decreases in association with risk factors for disease and undergoes a diurnal variation with lowest values beginning in the morning and extending through midday. Decreased GSH has been associated with specific diseases, including cardiovascular disease and diabetes, and has been implicated in many others. Abundant biochemical data support a direct causal link between low GSH, impaired defenses, and cellular susceptibility in model systems. Emerging personalized health strategies utilize GSH as a quantitative indicator of health with the expectation that diet selection, GSH supplementation, and lifestyle approaches can be used to manage GSH status, thereby providing a health dividend by protecting against disease development.

Introduction
More than 100 years of research and 81,000 scientific papers have established glutathione (GSH) as one of the most important protective molecules in the human body. The present article provides a brief overview of GSH and its functions in health and disease. Low GSH has been implicated in neuronal, hepatic, renal, pulmonary, cardiac, musculoskeletal, pancreatic, gastrointestinal, visual, auditory, and infectious diseases. Accumulating data have established that poor diet and age-related disease can create a functional disparity between the body's natural GSH defenses and the levels needed for optimal health. The purpose of this article is to provide practical considerations for health professionals concerning the evolving use of GSH as a strategy for maintenance of health.

What is Glutathione?
GSH is a component of defenses for both acute and chronic health challenges. Acute deficiency can be caused by exposure to toxic chemicals and endogenous oxidative reactions. Under acute GSH deficiency, cells cannot maintain normal cell functions, lose ability to divide normally, and can undergo either necrotic or apoptotic cell death (Fig 1A). Under chronic conditions, variations in GSH levels occur due to nutrition, environmental exposures, and activation of the immune system. These variations affect risk of chronic and age-related diseases by limiting protective functions. The protective functions include elimination of cancer-causing chemicals, enhancement of antioxidant defenses, and maintenance of homeostatic conditions of the epithelial barriers (Fig 1B). GSH protects against hundreds of cancer-causing chemicals.[1] GSH is at the apex of a group of protective chemicals, including vitamins C and E, which guard against oxidative damage to tissues.[2] Interorgan transport of GSH is part of a homeostatic control system[3] that maintains a “redox” environment essential for life.[4] The term “redox” refers to chemical reactions involving electron transfer. Adenosine triphosphate (ATP) is obtained from redox reactions in the mitochondria (Fig 2). In this process, most electron transfer occurs with reduction of O2 to water, but a small fraction is reduced to hydrogen peroxide and toxic oxygen radical species. GSH is critical for elimination of these oxidants.
Fig. 1. Protective functions of glutathione (GSH). A) Low GSH can result in acute cell injury and necrotic or apoptotic cell death. Maintenance of high GSH is associated with protection against chronic and age-related diseases, including type 2 diabetes and cardiovascular disease. B. GSH supports multiple protective and metabolic functions.

Fig. 2. Mitochondria produce hydrogen peroxide and other toxic oxidants during the process of formation of ATP.
GSH is a simple molecule, composed of 3 common amino acids: glutamate, cysteine, and glycine, which are also found in protein throughout the body. The amino acids are connected in a unique way so that GSH can be made and broken down independently of the body’s protein. The structure controls the reactivity of a sulfur atom in the cysteine, which is critical for function. GSH reacts with toxic oxygen radicals to form GSH radicals and glutathione disulfide (GSSG), thereby protecting against oxidative damage to DNA and proteins. Living organisms depend on controlled reactions in which chemicals share and transfer electrons to maintain physical and chemical organization. Reactive chemicals with a high affinity for electrons destroy the organization and function because they interfere with the normal processes of sharing and donating electrons. The body is constantly exposed to damaging reactive chemicals, and GSH provides a general biological solution because the electron properties of the sulfur of GSH are ideally suited to protect against such chemicals.

In protection against an imbalance in electron transfer reactions, termed “oxidative stress,”[4] GSH donates electrons to chemicals known as “oxidants.” Oxidants avidly accept electrons, and this disrupts normal electron flow. The electron-donating property of GSH protects against this; in the process, two molecules of GSH are converted to GSSG, an oxidized (disulfide) form. The balance of GSH and GSSG is quantified as the “GSH redox balance,” a measure of the status of the GSH system to protect against such oxidative challenges.[4] In this expression, more reduced (more negative) “redox” values are generally healthy, while more oxidized (more positive) “redox” values are unhealthy. Values measured in blood are a reflection of tissue values because cells have transport systems for both GSH and GSSG. However, oxidation also occurs outside of cells, so under a normal, healthy state, the extracellular balance is oxidized relative to that in cells. Many diseased states have excessively oxidized extracellular GSH redox values.[5]

**Where is GSH found in the body?**

GSH is found in all tissues and body fluids. A healthy balance requires an unequal distribution of GSH and GSSG among these locations,[6] similar to the need for sodium and potassium to differ between plasma and cells. In general, the concentrations of GSH within cells are much higher than outside of cells. Nonetheless, the amounts of GSH in the fluids surrounding cells are important because they provide a chemical-defense barrier to protect the cell surfaces.

The total amount of GSH in the body is about 15 grams, of which the cysteine component represents 5 grams. The organs principally responsible for detoxification (i.e., the liver and kidneys), have the highest amounts, but the 15 grams are distributed among all major organ systems, including brain, heart, skeletal muscle, intestines, lungs, skin, and the immune system. The liver (6% of the body) has about 4 grams of GSH (25% of the body’s total), which is part of an important homeostatic mechanism. Liver GSH varies as a function of diet, time of day, and body needs.[7] The cysteine content of liver GSH is similar to the RDA for sulfur amino acids (methionine plus cysteine), which is 1.4 g for a reference 70 kg individual. Thus, the GSH in the liver is equivalent to a 1-day reserve for the cysteine needed for the body’s protein synthesis.

Homeostatic mechanisms prevent the hepatic GSH content from falling too low.[8] During fasting and starvation, GSH and its precursors are derived from muscle and other tissues. Simple calculations show that the entire human body has no more than a 4-day reserve of GSH so that loss of GSH can become critical in catabolic illness or whenever there is a prolonged period of protein/energy insufficiency. Importantly, GSH declines with age[9,10] (Fig 3A) and has a diurnal variation with lowest values in the morning and early afternoon (Fig 3B).[11] The diurnal variation is linked to cysteine, and cysteine variation increases in individuals over 60 years.[11] Thus, older individuals have increased vulnerability in cell injury due to both a decline in total amount of GSH and a decline in its homeostatic control.
Fig. 3. GSH declines with age and varies with time of day. A. GSH redox balance begins to decline at 45 years old.[9] B. GSH undergoes a diurnal variation with a relative depletion in the morning and early afternoon.[11]

Most research has focused on tissue levels of GSH, but the difference between GSH needs and availability may be equally important in the extracellular fluids, which bathe cells. GSH is found in all extracellular biological fluids, including plasma, interstitial fluid, cerebrospinal fluid, alveolar lining fluid, saliva, bile, pancreatic fluid, tears, sweat, and urine.[12] The concentration of GSH in body fluids can be up to 1,000-fold lower than found in the tissues, yet all cells appear to release GSH, suggesting a universal requirement for extracellular GSH to protect cell surfaces.[12] In addition, specific functions of extracellular GSH are well described. Bile has a high content of GSH to support detoxification of reactive chemicals in the lumen of the small intestines[13] (Fig 4A) and to enhance iron absorption.[14] Lipid peroxides are toxic species in the diet that are eliminated by supplemental GSH.[15] (Fig 4B) GSH in the lining fluid of the lungs eliminates airborne oxidants and helps maintain fluidity of the mucus lining the airways. Elimination of bacteria by pulmonary macrophages in vitro is stimulated by added GSH, but this experiment has not been done in humans in vivo.[16] (Fig 4C) GSH also protects human lung cells (in vitro) from influenza virus (Fig 4D) and protects against influenza in mice.[17] One should note that controlled, double-blind studies of these effects have not been done in vivo in humans.
**Figure 4**

**Fig 4.** GSH directly protects cells and tissues. 
A. GSH is used by the intestines to eliminate reactive chemicals from diet. Redrawn from.[13]  
B. GSH protects against absorption of toxic peroxides derived from dietary fat.[15]  
C. GSH supports clearance of S. aureus by pulmonary macrophages. Redrawn from.[16]  
D. GSH protects against influenza virus production in human small airway epithelial cells. Redrawn from.[17]

**How is GSH Maintained in Tissues and Body Fluids?**

GSH is maintained by a continuous cycle of turnover at a rate equivalent to the entire body pool of GSH being made and degraded daily.[18] GSH is synthesized from the precursor amino acids (i.e., glutamine, glycine, cysteine) in all tissues.[19] Cells in certain organs (i.e., intestines, lung, kidney) can utilize exogenous GSH by a secondary active transport mechanism.[20,21] Supply of GSH from tissue to extracellular fluids occurs through two types of transporters, classified as MRP and OAT transport proteins.[22] The molecular nature of the systems that allow transport in the opposite direction (from extracellular spaces into cells) is not known.[23] The cycle of GSH release, conversion to precursor amino acids, and resynthesis is termed the “GSH cycle.”[3] Although it was earlier proposed that a “γ-glutamyl cycle” functioned in amino acid uptake, this was found to not be an important mechanism. Disulfide forms of GSH include low molecular weight chemicals and protein-bound forms[14]; under many circumstances, the balance between GSH and these disulfide forms (i.e., GSH redox balance) can be more important than the absolute amount of GSH.[24]

GSH is depleted by elimination of reactive chemicals dependent upon abundant GSH transferases.[1] These enzymes increase in response to toxic challenge, and trials have been conducted to determine whether continuous elevation of these enzymes can protect against cancer. In protection against cancer, GSH reacts with cancer-causing chemicals at rates that are faster than the chemical can react with DNA, thereby preventing mutations. To date, however, practical approaches to reduce cancer by increasing GSH transferase have not been established. In addition to cellular activities, GSH transferase is associated with mucus and provides a detoxifying barrier in the small intestines.[13] Animal studies showed that provision of GSH to the GSH transferase associated with the mucus provides a defense mechanism to eliminate ingested toxic chemicals, such as oxidation products from polyunsaturated fatty acids, acrylein, acrylamide, and other reactive chemicals, prior to
absorption by the body. (Fig 4A) This defense depends upon GSH supply outside of the cells, either from the bile, from food, or from a supplement. The finding that oral and pharyngeal cancer is decreased in association with intake of foods high in GSH could reflect the function of this mechanism in protection against cancer-causing chemicals or a better function of the immune system. Studies with human cells in culture further show that added GSH protects cells even in the absence of GSH uptake,[26] apparently due to protection of proteins on the surface of cells. Recent studies show that cell surface thiols function as redox sensors, signaling processes such as platelet activation and early events of atherosclerosis.[27–29] As indicated above, in vitro experiments have demonstrated that addition of GSH to the media improved killing of bacteria by pulmonary macrophages and decreased production of infectious influenza virus by human small airway epithelial cells.

**How Big is the Functional Need for GSH?**

In addition to the age-related decline mentioned above, GSH levels are inversely associated with environmental exposures and disease risk. GSH is decreased in the epithelial lining fluid of human lung in individuals who abuse alcohol.[30] (Fig 5A) This example is illustrative of the hidden risks of low GSH in that these individuals have no apparent lung disease and yet are at considerably increased risk of acute lung injury and death from adult respiratory death syndrome.[31,32] Oxidation of GSH occurs in association with increased carotid intima media thickness (Fig 5B), an indicator of cardiovascular disease risk.[33] GSH redox balance (i.e., the GSH/ GSSG ratio) favors oxidation in cigarette smokers[34] (Fig 5C) and type 2 diabetics.[35] Direct evidence that the decrease and oxidation of GSH occurs due to toxic chemical exposures is available from studies in individuals following chemotherapy.[36] The extensive evidence that GSH status is decreased in association with disease and recognized risk factors for disease implies that maintenance of this protective system could reduce risk of disease development.

**Figure 5**

![Figure 5](image)

**Fig 5.** GSH is decreased and oxidized in association with disease and disease risk factors. A. GSH is decreased in lung epithelial lining fluid of individuals with alcohol abuse.[30] B. GSH is decreased and oxidized in association with carotid media thickness, a risk factor for cardiovascular disease.[33] C. GSH redox balance is oxidized in smokers.[34] D. GSH is oxidized in individuals with type 2 diabetes.[35]
Because of the known functions and increased disease risk with a decline of GSH, systematic efforts are needed to quantify the difference between the available GSH and the amount needed. One approach is to consider how much GSH is present in a natural diet. GSH content has been measured in more than 100 common foods[37] and provides the basis to estimate dietary intake. The best diets contain about 150 milligrams of GSH per day; the worst diets contain as little as 3 milligrams per day.[37] GSH is present in essentially all raw and freshly prepared foods; the best sources are fresh fruits and vegetables, nuts, and whole-cut meats, including poultry and fish. GSH can also be increased by supplements, such as the increase in hepatic GSH following ingestion of silymarin, found in milk thistle. GSH is lost during most food processing procedures, with the exception of fresh-frozen foods. Processed, cured, and canned meat products have essentially no GSH. Similarly, canned or dried fruits and canned vegetables are not good sources. Cereal and grain products are largely deficient, and almost all dairy products, beverages, sweeteners, and condiments lack GSH. Thus, a simple conclusion is that modern processed foods are deficient in GSH compared to natural, freshly prepared foods.[37] In quantitative terms, up to 150 mg of daily intake of GSH can be lost due to food processing.

Many foods also contain reactive chemicals that remove GSH through the GSH transferase reaction associated with the lining of the small intestines. Measurement of a broad range of foods show that milk, prunes, tea, blueberries, and bottled apple juice have high contents of GSH-reactive chemicals.[38] Recently, there has been interest in the potent neurotoxicant acrylamide, because this has been found to be relatively high in French fries.[39] The daily intake of GSH-reactive equivalents can range from almost zero to values exceeding the maximum naturally available 150 milligrams GSH.[38] Thus, the sum of the amount of GSH needed to eliminate reactive chemicals and the amount of GSH lost by food processing can be greater than 300 mg of GSH per day.

The extent to which environmental exposures, alcohol consumption, smoking, inflammation, infection, etc., further increases this dietary GSH gap is not known. Similarly, the magnitude of the GSH gap due to disease is not known. This could be greater than 300 mg – perhaps as high as the GSH equivalent of the RDA for sulfur amino acids (i.e., 3 g/day). The RDA for sulfur amino acids is about 1.1 g/day for women and 1.4 g/day for men; these values are equivalent to 2.7 and 3.3 g/day of GSH. Because the body contains 15 g of GSH, values in this range represent up to 20% of the amount of GSH in the body. There are conditions, such as severe burns, in which the sulfur amino acid requirement is increased. Consequently, there may be conditions in which the functional need for GSH is relatively high, but this upper limit is currently unknown.

GSH Support Strategies: How Can We Improve GSH Status?

GSH is synthesized from amino acid precursors, glutamate, cysteine and glycine. A considerable number of trials have used N-acetylcysteine (NAC) as a cysteine precursor, expecting it to provide a means to increase GSH synthesis. The logic for using NAC is complicated but generally assumes that cysteine is limiting for GSH synthesis. However, the American diet typically has an excess of sulfur amino acids. According to NHANES III, 99% of adult American males and females consume greater than the RDA, 50% consume more than twice the RDA and 1% of people consume more than 4 times the RDA for sulfur amino acids. Consequently, while NAC is likely to benefit individuals with insufficient sulfur amino acid intake, additional approaches are needed to address a functional need for GSH in most Americans. Supplementation with glutamate, cysteine, and glycine provides one alternative, and others include related sources of these amino acids (e.g., whey), supplements to enhance synthesis (e.g., silymarin), as well as the naturally occurring compound itself, GSH.
A common assumption is that dietary or supplemental GSH is not available for use by the human body because the intestines contain an enzyme (i.e., γ-glutamyl transpeptidase; GGT) that degrades GSH. However, a substantial amount of scientific evidence shows that supplemental GSH is bioavailable.[23] As indicated above, added GSH supports detoxification in body fluids such as the lining fluid of the lung and intestines, enhances macrophage function, and decreases influenza virus production. Thus, even for cells that do not absorb GSH, protection can be provided by supplemental GSH.

Different research groups have also shown that GSH is transported across intestinal membranes,[40] across the intestinal epithelium,[41] into human intestinal cells,[42] and from the intestinal lumen into the vascular circulation.[43-45] Orally administered GSH increases GSH in mouse, rat, and human plasma (Fig 6A-C), and the extent of increase is increased by a stress response. (Fig 6B) While studies are not universally consistent, and most organs do not take up GSH, experiments with isotopic tracers, inhibitors of GSH synthesis, inhibitors of GSH transport, and inhibitors of GSH degradation provide detailed evidence for GSH transport in intestines, lung, and kidneys.[21,43,46,47] This subject has been recently reviewed by Lawrence Lash, and this should be consulted for additional details.[23] Animal and human studies further show direct benefit of oral GSH in protection against age-related decline in immune function;[48] enhancement of lymphocyte function;[49] and protection against oxidative injury in newborn lung,[50] influenza viral infection,[17], chemically induced oral cancer,[51,52] and uptake of peroxidized lipids[15] and other toxic chemicals.[53,54]

**Figure 6**

**Fig 6.** Absorption of GSH has been demonstrated in A) mouse, B) rat and C) human studies. In rat, absorption was shown to be dramatically stimulated by phenylephrine, a stress agonist, but this response has not been studied in humans. Measured values after oral GSH are given by filled circles. In B, open circles represent values obtained after rats were given phenylephrine. For each study, controls with an equivalent amount of precursor amino acids did not show increases in plasma GSH. Data from (57), (58) and (59), respectively.

Consequently, the scientific evidence supports the conclusion that the body can utilize exogenously supplied GSH. This characteristic is identical to some vitamins (e.g., niacin), amino acids (e.g., histidine), and amino sugars (e.g., glucosamine), which are utilized from the diet even though they are synthesized within the body. For these, a nutritional deficiency can develop when the amount synthesized is insufficient to fulfill requirements. While GSH is not considered a required nutrient, the same principles apply (i.e., a deficiency can develop when the amount of GSH synthesized is insufficient for detoxification needs).
GSH concentration and GSH/GSSG redox balance can be measured in human plasma, and this provides a means to identify individuals with poor GSH status.[5] Plasma GSH levels decrease with age beginning at about 45 y,[9] undergo a diurnal variation with lowest values at midday[7] and are decreased and oxidized in association with disease risk and disease.[5,55] However, despite the general utility of plasma measurements, deficiencies at barrier surfaces, such as the intestines, lung lining fluid, and immune cells associated with these surfaces, may not be apparent from plasma measurements. This leaves a dilemma in that at least some of the sites most likely to benefit from supplemental GSH are relatively inaccessible for measurement.

The Future: The Health Dividend of GSH

GSH supplementation can be implemented in individuals based upon their known risk factors,[4] but validation that such strategies are effective in humans will require lengthy and costly controlled double-blind studies. In the meantime, validated methods are available to measure GSH and GSSG in body fluids[5] but have not yet been approved by the Food and Drug Administration for clinical use. Availability of such measurements would provide means to evaluate health in individuals and to directly evaluate the efficacy of interventional strategies to normalize GSH and GSH redox balance in individuals with low values. Recent studies show that a related cysteine (Cys) redox balance for plasma cysteine and cystine is more directly related to extracellular oxidative processes and is associated with cardiovascular risk.[55] Analyses of GSH redox and Cys redox have been performed in long-term interventional trials with free radical-scavenging antioxidants (vitamins C, E;)[10] and also zinc[56] in age-related macular degeneration. Results show that GSH redox balance and/or the Cys redox balance is preserved in association with protection against disease progression. Zinc has been found to activate mechanisms for GSH synthesis and also stimulate uptake of cystine. Consequently, combinations of GSH, GSH precursors (including preparations such as whey protein isolates), antioxidants, and inducers of transport and synthesis may provide complementary means to enhance GSH status.

Summary and Conclusions

GSH is one of the most extensively studied chemicals of the human body and its decline with aging and disease risk is well established. GSH is needed both for maintenance of normal metabolism and for defense against a range of disease and toxicity mechanisms. GSH is maintained by continuous processes of GSSG reduction and GSH transport, degradation, and synthesis. GSH concentrations are considerably higher in tissues than in most body fluids, but the fluid concentrations are important because they protect cell surfaces and support protective barrier defenses. Extensive research in model systems establishes that GSH is transported by cells and that added GSH protects against a range of chemical and infectious threats. Although most Americans consume an adequate supply of dietary precursors for GSH synthesis, there is a gap between the amount synthesized and the amount needed (i.e., a decline in GSH is associated with disease risk). Based upon the loss of GSH from food during processing and the measured contents of reactive chemicals in food, this gap can be estimated to be 300 mg/day. However, higher values may be needed to compensate for adverse environmental conditions and disease, but the possible amounts can only be speculated.

Because the American healthcare system is approaching crisis with the ballooning costs of late-stage disease treatment, cost-effective means are needed to preserve health. Available (but not FDA-approved) methods allow prospective assessment of GSH in individuals prior to disease onset, and health maintenance programs are beginning to adopt GSH analysis as part of quantitative health assessment (but not disease treatment). Simple strategies, including supply of GSH, GSH precursors, complementary antioxidants, and zinc, are available to improve GSH status in individuals
with low or oxidized GSH. Such strategies could have considerable personal and societal health and economic impact.

About the Author

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References


