Dynamic Chiropractic

NUTRITION / DETOXIFICATION

Glutathione: The Body's Master Detoxifier and Antioxidant

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Glutathione is a tripeptide comprised of the amino acids L-cysteine, L-glutamic and glycine. At the cellular level, glutathione functions as a water-soluble antioxidant and is directly involved in specific detoxification reactions that protect the body against various dangerous substances.[1]

Glutathione, the most abundant cellular thiol, provides the major antioxidant defense mechanism in all mammalian cells by neutralizing toxic peroxides (e.g., hydrogen peroxide formed from oxygen metabolism). Glutathione is known to be consumed more rapidly and depleted upon ingestion of certain medications and environmental toxins. It is also depleted in cases of chronic liver infection and HIV infection. Evidence suggests depletion of liver glutathione stores below a critical threshold is the final event that triggers the conversion of HIV to the more ominous signs, symptoms and complications of AIDS.[2-4]

Unfortunately, for those wishing to boost their glutathione levels, it should be noted that glutathione supplements are not well-absorbed from the intestinal tract.[5] However, supplementation with some standard antioxidants, along with N-acetylcysteine, alpha-lipoic acid, silymarin flavonoid (from milk thistle) and L-glutamine, are proven methods to support and raise serum and tissue levels of glutathione on a daily basis.

Nutritional support to boost glutathione levels should be considered as a useful adjunct in the management of HIV infection, chronic liver conditions, and alcohol- or drug-induced liver damage; to combat exposure to environmental toxins, pollutants, medications, and certain carcinogens; and to help combat the age-related decline in detoxification ability that occurs after age 50.

Antioxidant Function

Glutathione is a premier cellular antioxidant. It exists in reduced (GSH) and oxidized (GSSG) states within our cells. In the reduced state, the thiol group of cysteine is able to quench free radicals by donating a reducing equivalent (H++ e-). This includes quenching various reactive oxygen species (ROS) that are generated during the use of oxygen by our cells in aerobic metabolism. In donating an electron, glutathione itself becomes reactive, but readily reacts with another reactive glutathione to form glutathione disulfide (GSSG). This is possible due to the normally high concentration of glutathione in cells (up to 5 mM in the liver). GSH can be regenerated from GSSG by the enzyme glutathione reductase.

In healthy cells and tissue, more than 90 percent of the total glutathione pool is in the reduced form (GSH) and less than 10 percent exists in the disulfide form (GSSG). An increased GSSG-to-GSH ratio is highly indicative of high levels of oxidative stress (presence of free radicals). As such, the activity of glutathione reductase is used as an indicator for oxidative stress. Glutathione status can be assessed by lab tests using Ellman's reagent or roGFP (redox-sensitive green fluorescent protein).

Glutathione is also a co-factor for the enzyme glutathione peroxidase, which is a critical cellular antioxidant. It also helps to maintain levels of ascorbate and tocopherol by acting as a reducing agent. Conversely, vitamin C and vitamin E supplementation can help to spare glutathione depletion.[1-4, 6-9, 21]

Detoxification Function

Glutathione conjugation is the primary mechanism of eliminating electrophilic (free radical) xenobiotics (some of which are carcinogens) in the liver. Glutathione is required for conjugation reactions and reduction reactions, catalyzed by glutathione S-transferase enzymes in the cytosol, microsomes and mitochondria. The family of glutathione S- transferase enzymes is responsible for the quenching and detoxification of many environmental substances, including free radicals, peroxidized lipids, and xenobiotics (wide variety of environmental toxins, drugs and antibiotics).

In the modern world, the liver's detoxification capacity can be easily overwhelmed, leading to glutathione depletion and an accumulation of toxins and potentially dangerous byproducts of drug and antibiotic metabolism, due to high level of exposure to these man-made compounds.[10-14]

A quick historical review highlights the fact that since World War II, an estimated 85,000 synthetic chemicals have been registered in the U.S. alone. Today's environment now exposes us to various pesticides, herbicides, plastics (e.g., PVC), xenoestogens (e.g., bisphenol A, parabens) and pollutants in our food, water and air. The human body has had very little time to adapt to these new challenges, many of which can overtax our detoxification system, suppress immune function and exert other undesirable health effects. As well, many individuals are prescribed several drugs at one time (polypharmacy), which further depletes glutathione stores. Many experts believe the new chemical environment we live in is a major contributing factor to the high incidence of many degenerative diseases in the modern era.[15]

As an example, glutathione is required for the safe detoxification of acetaminophen (paracetamol). In this instance, it participates in a non-enzymatic conjugation of *N*-acetyl-*p*-benzoquinone imine (NAPQI), the reactive cytochrome P450-metabolite formed by acetaminophen that becomes toxic when GSH is depleted by an overdose or chronic use of acetaminophen.

If NAPQI is permitted to build up in liver cells, it reacts with cellular proteins, killing the cells in the process. As such, chronic use of acetaminophen is known to cause liver damage. This is largely due to the depletion of glutathione. Other drugs have been shown to deplete glutathione as well, rendering liver cells susceptible to damage and death from various drug byproducts.[16-17] As such, health practitioners should ensure that patients employ strategies to guard against drug-induced liver damage from medications by teaching patients how to reconstitute their liver glutathione stores on a daily basis.

Glutathione is also a vital substance that converts fat-soluble toxins into water-soluble forms so they can be safely and efficiently eliminated by the body. This helps prevent the accumulation in the body of various fat-soluble toxins. Glutathione is also needed for the detoxification of methylglyoxal, a toxin produced as a byproduct of metabolism.[1,8]

Immune Function

Glutathione is necessary for maintaining immune-mediated T-cell activation and phagocytosis, in addition to cellular and antibody-mediated cytotoxicity. It is also required to maintain a normal

balance between the T-helper cell 1 (IL-2, IL-12, gamma-interferon) and the T-helper cell 2 (IL-6, IL-4, tumor necrosis factor-alpha, IL-10, IL-1) cytokine response profile.

Plasma glutathione levels in HIV-infected individuals, even in the asymptomatic state, have been found to be depressed as early as three weeks post-infection. Intracellular glutathione levels in both infected CD4 and CD8 lymphocyte subsets are also significantly depressed; levels from 62 percent to 69 percent of normal have been found in the CD4 and CD8 lymphocytes of HIV and AIDS patients.

Depletion of glutathione of 10 percent to 40 percent are capable of completely inhibiting T-cell activation *in vitro*. Research assessing ratios of reduced-to-oxidized glutathione in HIV-positive patients found significantly increased levels of oxidized glutathione compared to HIV-negative controls. These disturbances were greater in patients with more advanced disease. Low serum thiol levels (precursors to glutathione) have been shown in HIV-infected, injecting drug users (IDU) and are associated with an increased risk of mortality: IDU with low serum thiol levels are 5.65 times more likely to experience an accelerated time-to-death.

Glutathione appears to also slow progression of HIV infection by blocking activation of tissue necrosis factor alpha and inhibiting the activity of reverse transcriptase (a major enzyme necessary for HIV replication) by 80 percent to 90 percent in cell cultures. As such, many HIV-infected patients take supplements that are known to raise their cellular and immune levels of glutathione - a factor that is associated with retarding disease progression.[1, 9-14, 18-20]

Restoring and Maintaining Glutathione Stores

Multivitamin: As a first step to preserving glutathione levels, adults should consider taking a high-potency multiple vitamin and mineral containing the following dosages: vitamin C - 1,000 mg; vitamin E succinate - 400 IU; selenium - 100-200 mcg; beta-carotene - 10,000-20,000 IU; and vitamin A - 2,500 IU.[21] In addition, there are several nutrients that are proven to restore and boost glutathione levels to a significant degree, even in HIV-infected patients and other challenging cases. These nutrients include N-acetylcysteine, alpha-lipoic acid, silymarin (from milk thistle) and L-glutamine. I generally recommend that patients take a combination supplement, containing all of these factors at meaningful dosages, to support their glutathione concentrations.

N-acetylcysteine (NAC) has been used successfully to treat hepatic and renal failure caused by glutathione depletion secondary to acetaminophen overdose. It may also help in the treatment of certain pulmonary diseases due to its mucolytic properties. N-acetylcysteine can also act as a heavy-metal chelating agent to rid the body of certain toxic metals, as well as for copper, zinc and boron. It has also been shown to elevate glutathione levels in immune-compromised states when taken as a supplement. Many HIV patients have used N-acetylcysteine as part of their adjunctive nutritional management. N-acetylcysteine has also been shown to slow the progression of chronic kidney disease and may be beneficial to diabetic patients in this regard.

Patients with chronic liver infections (e.g., hepatitis C) have also realized improvement in their condition when NAC was used as part of adjunctive nutritional management.[16-30, 51]

Alpha-lipoic acid is a water- and fat-soluble antioxidant that has been shown to elevate glutathione levels and regenerate vitamin C and vitamin E. Alpha-lipoic acid has successfully raised glutathione levels in HIV patients and been shown to block other steps in the progression of this disease. A clinical trial of 11 AIDS-diagnosed patients taking 450 mg lipoic acid daily for 14 days resulted in increases in plasma ascorbate, total glutathione and total plasma thiols, decreases in lipid peroxide

levels, and a significant elevation in CD4 and CD4-to-CD8 ratios.

Lipoic acid has been shown to help diabetic and prediabetic patients by increasing insulin sensitivity and successfully treating early-stage diabetic neuropathy. Alpha-lipoic acid protects the central nervous system from free-radical damage, which makes it an important nutritional consideration in cases of neuropathy as well as MS, ALS, Parkinson's disease and possibly Alzheimer's disease.[31-38]

Milk thistle contains silymarin, which is a mixture of flavonolignans consisting chiefly of silibinin, silidianin and silicristin. It is essentially the silymarin content of milk thistle extract, which has been shown to provide its medicinal effects, especially in regards to the treatment and prevention of various liver conditions. In 1986, the German Commission E approved an oral extract of milk thistle standardized to 70 percent crude silymarin content as a treatment for liver disease.

Silymarin increases liver glutathione content by more than 35 percent in healthy human subjects and by over 50 percent in rats. As noted previously, glutathione is not only an antioxidant, but also is required for phase I and phase II detoxification function within the liver, facilitating the detoxification of many xenobiotics, drugs and carcinogens. The ability of milk thistle to help restore liver glutathione levels is considered to be a primary means by which silymarin is an effective treatment for various liver diseases.

Silibinin also stimulates RNA polymerase A (also known as polymerase I) and DNA synthesis, which in turn increase the synthesis of ribosome proteins and thus stimulates cell development. This ultimately increases the regenerative capacity of liver cells and results in the production of new liver cells to replace the damaged old ones. As such, silymarin has been shown to aid in the repair of liver cells that have been damaged by various microorgamisms, alcohol and other damaging chemicals.

Moreover, silymarin has been shown to increase the concentrations of superoxide dismutase - a powerful intracellular antioxidant, which quenches the superoxide anion (a very aggressive, damaging and reactive free-radical oxygen species).[39-44]

L-glutamine supplementation has been shown to enhance glutathione stores in conjunction with N-acetylcysteine. It has been shown to help protect the gastrointestinal tract from damage by certain chemotherapy drugs (e.g., fluorouracil) and also prevents the diarrhea that these drugs are known to produce.

Glutamine supplementation has been shown to enhance immune system function and result in a lower level of infection and a shorter stay in hospital following surgery, radiation treatment, bone marrow transplantation, and in patients suffering from injury, compared with patients receiving glutamine-free parenteral nutrition.

L-glutamine is found in the body in higher quantities and concentrations than any other free amino acid. Numerous studies show the benefits of L- glutamine in strengthening the body's immune system when individuals are under stress, including reducing the number of upper respiratory tract infections in athletes who are undergoing high-intensity training.[45-50]

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