GLUTATHIONE Scientific Research

THE FOLLOWING MEDICAL AND SCIENTIFIC MATERIAL IS FOR CONSUMER INFORMATIONAL AND EDUCATIONAL PURPOSES ONLY-- UNDER SECTION 5 OF DSHEA.

This piece contains scientific articles regarding glutathione and its relationship to various disease conditions. The type of glutathione used in these studies may vary, but these articles will give you an idea of the wide application range and stunning importance of glutathione.

If you go to www.pubmed.gov and search on 'glutathione', over 80,000 articles are listed. The articles mentioned below are followed by their PubMed ID numbers.

Overview: "Glutathione deficiency contributes to oxidative stress, which plays a key role in aging and the pathogenesis of many diseases (including kwashiorkor, seizure, Alzheimer's disease, Parkinson's disease, liver disease, cystic fibrosis, sickle cell anemia, HIV, AIDS, cancer, heart attack, stroke, and diabetes). New knowledge of the nutritional regulation of GSH metabolism is critical for the development of effective strategies to improve health and to treat these diseases." *PMID: 14988435*

ACETAMINOPHIN TOXICITY
Whether accidental or intentional, acetaminophen poisoning is not uncommon; in fact, it is the most common drug- induced cause of liver failure. When hepatic glutathione is depleted, the toxic metabolite NAPQI fails to be conjugated and causes hepatic injury. At risk are chronic alcoholics, binge drinkers, patients taking medications that induce the P-450 isoenzyme system, and those with concomitant liver disease. *PMID: 10223088*

Our findings suggest that acetaminophen administration selectively depletes (within 2 hr) mitochondrial glutathione, and produces local toxicity by altering membrane permeability and decreasing the efficiency of oxidative phosphorylation. This renders mitochondria more susceptible to oxidative damage… *PMID: 8937421*

Toxic doses of paracetamol deplete intracellular GSH and result in cell death by a combination of mechanisms, leading to necrosis and apoptosis, mainly in the liver. In clinical situations characterized by low GSH, the risk of toxicity from therapeutic doses of paracetamol may conceivably be increased. This toxicity has been reported in chronic alcoholics who have low intrahepatic GSH and who may have an induced enzyme system that generates the toxic metabolite of paracetamol. *PMID: 11941382*

ALCOHOLISM
A balanced diet, vitamin supplements, and pharmacological therapy with antioxidants in order to recover depleted glutathione deposits are recommended. *PMID: 18714405*

GSH was statistically decreased in alcohol abusers… *PMID: 17977706*

Specifically, chronic alcohol ingestion decreases the levels of the antioxidant glutathione within the alveolar space by as much as 80-90%, and, as a consequence, impairs alveolar epithelial surfactant production and barrier integrity, decreases alveolar macrophage function, and renders the lung susceptible to oxidant-mediated injury. *PMID: 17220370*

Depletion of mitochondrial GSH by alcohol is believed to contribute to the sensitization of the liver to alcohol-induced injury through tumor necrosis factor (TNF)-mediated hepatocellular death. Through control of mitochondrial electron transport chain-generated oxidants, mitochondrial GSH modulates cell death and hence its regulation may be a key target to influence disease progression and drug-induced cell death. *PMID: 15845418*

ALZHEIMER'S DISEASE

In one study it was shown that the concentration of glutathione was decreased in red blood cells from male Alzheimer's disease patients compared with age- and gender-matched controls. *PMID: 15693022*

It has been observed that Alzheimer's patients show an increased level of plasma TBARS, which indicates a higher free radical oxidation of plasma unsaturated phospholipids, and an increased oxidation of red blood cells glutathione, which indicates oxidative stress in peripheral cells. This latter, glutathione oxidation, was found to correlate statistically with the cognitive status of the patients. *PMID: 15051321*

GSH is the most abundant cellular non-protein thiol, serves as an important antioxidant, and has been proposed to be important in the protection of cerebrum from oxidative damage. GSH has been reported to be decreased in cerebrum of aging rodents and humans, and alterations in GSH metabolism have been described in diseased regions of brain from AD patients. Alterations in peripheral GSH metabolism have also been described in patients with mild cognitive impairment and AD. *PMID: 15857408*

AUTISM

Recent evidence suggests that some autistic children may have reduced detoxification capacity and may be under chronic oxidative stress. Based on reports of abnormal methionine and glutathione metabolism in autistic children, it was of interest to examine the same metabolic profile in the parents. The results indicated that parents share similar metabolic deficits in methylation capacity and glutathione dependent antioxidant/detoxification capacity observed in many autistic children. Studies are underway to determine whether the abnormal profile in parents reflects linked genetic polymorphisms in these pathways or whether it simply reflects the chronic stress of coping with an autistic child. *PMID: 18512136*

This study looked at the metabolism of autistic children. Impairments in the methylation cycle, a very critical part of our body's functioning, were found. Because of this problem in the methylation cycle, autistic children are predisposed to low glutathione which prevents them from detoxifying normally. It was also found that certain co-enzymes, all non-pharmaceutical, support that cycle. *PMID: 15585776*

The induction of NK cell activity by IL-2, IL-15 and glutathione was more pronounced in a subgroup with very low NK cell activity. We conclude that that 45% of a subgroup of children with autism suffers from low NK cell activity, and that low intracellular levels of glutathione, IL-2 and IL-15 may be responsible. *PMID: 18929414*

CANCER & CHEMOTHERAPY

Purpose: We performed a randomized, double-blind, placebo-controlled trial to assess the efficacy of glutathione (GSH) in the prevention of oxaliplatin-induced neurotoxicity. Conclusion: This study provides evidence that GSH is a promising drug for the prevention of oxaliplatin-induced neuropathy, and that it does not reduce the clinical activity of oxaliplatin. *PMID: 12177109*

Background: Early clinical trials have suggested that glutathione (GSH) offers protection from the toxic effects of cisplatin. Conclusions: The results demonstrate that adding GSH to CDDP allows more cycles of CDDP treatment to be administered because less toxicity is observed and the patient's quality of life is improved. *PMID: 9261526*

Here we report that glutathione (GSH) plays a critical role in activation of apoptosis pathways by CD95 (APO-1/Fas) or anticancer drugs. We conclude that dominant apoptosis resistance depends, at least in part, on intracellular GSH levels, which may affect apoptosis signaling at different compartments, for example, the death receptor or mitochondria. *PMID: 15105835*

Glutathione (GSH) is a ubiquitous intracellular peptide with diverse functions that include detoxification, antioxidant defense, maintenance of thiol status, and modulation of cell proliferation. Dysregulation of GSH synthesis is increasingly being recognized as contributing to the pathogenesis of many pathological conditions. These include diabetes mellitus, pulmonary fibrosis, cholestatic liver injury, endotoxemia and drug-resistant tumor cells. Manipulation of the GSH synthetic capacity is an important target in the treatment of many of these disorders. *PMID: 18601945*

CHRONIC FATIGUE SYNDROME

As an antioxidant, glutathione (GSH) is essential for allowing the lymphocyte to express its full potential without being hampered by oxiradical accumulation. It is conceivable that the priority of the immune system for the survival of the host has drawn to this vital area the ever-diminishing GSH precursors, thus depriving the skeletal muscle of adequate GSH precursors to sustain a normal aerobic metabolism resulting in fatigue and eventually myalgia. *PMID: 10608272*

The role of oxidative stress in CFS is an important area for current and future research as it suggests the use of antioxidants in the management of CFS. Specifically, the dietary supplements glutathione, N-acetylcysteine, alpha-lipoic acid... may be beneficial. *PMID: 11703165*

CROHN'S DISEASE

Finally, considering the results that others and we obtained by studies on GSH oral absorption in rat intestine, an oral therapy of GSH in Crohn's disease is suggested. *PMID: 7710773*

The aim of this in vitro study was to evaluate the intracellular redox state and respiratory burst (RB) in neutrophils of patients with Crohn's disease (CD). This study demonstrated a decreased glutathione/glutathione disulfide (GSH/GSSG) ratio index of an increased oxidative state in CD patient neutrophils. *PMID: 16446495*

CYSTIC FIBROSIS

In cystic fibrosis, lung disease is typified by an inflammatory response. This leads to oxidative stress in the lungs. Glutathione is the primary intracellular antioxidant, and provides an important defense in the epithelial lining fluid. *PMID: 10424526*

… GSH system dysfunction may be the trigger for initial depletion of other antioxidants and may also play a role in initiating the over-inflammation characteristic of cystic fibrosis. Proper GSH system functioning also affects immune system competence and mucus viscosity, both of relevance to cystic fibrosis pathophysiology. In a way, cystic fibrosis may be thought of as the first identified disease with GSH system dysfunction. *PMID: 15658882*

Use of a daily GSH regimen appears to be associated in CF patients with significant improvement in lung function and weight, and a significant decline in bacteria cultured in this uncontrolled study. These findings bear further clinical investigation in larger, randomized, controlled studies. *PMID: 18499536*

DIABETES

Analyses of whole blood GSH showed that GSH was significantly lower in diabetic cases… *PMID: 9586798*

An attractive hypothesis is that intracellular excesses of glucose inhibit the antioxidant systems primarily by its ability to cause depletion of the crucial protector GSH. The ultimate effects of such derangement of the protective systems against free radicals may involve vascular and neurological complications. *(J Trace Elem Exp Med. 13:105-111. 2000)*

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HEART DISEASE & STROKE

Background and purpose: Glutathione (GSH) appears to have marked antioxidant activities and therefore may prevent cardiovascular disease (CVD)…. Conclusions: These findings suggest that reduced plasma tGSH levels are a risk factor for CVD, especially for cerebral small vessel disease. *PMID: 15256685*

We present a mechanism based on animal studies, clinical data, and epidemiological data by which protein-energy status in the acute stroke and immediate post injury periods may affect

outcome by regulating reduced glutathione (GSH), a key component of antioxidant defense. *PMID: 12835106*

Blood samples from ten patients with clinically evident manifestations of atherosclerotic disease were used to evaluate in vitro the effects of exogenous glutathione (GSH) on platelet aggregation and on blood filtration and viscosity…. The venous GSH infusion both significantly decreased blood viscosity and increased blood filtration. Partial thromboplastin time was lengthened after GSH infusion even though it remained in the normal range. *PMID: 1308476*

GSH levels were significantly decreased in AMI as compared to control ($p<0.001$). Also, total cholesterol and triglycerides were higher in AMI subjects ($p<0.05$). These finding suggest that depressed GSH levels may be associated with enhanced protective mechanism to oxidative stress in AMI. *PMID: 12944689*

Oxygen free radicals have been shown to cause endothelial vasomotor dysfunction. This study examined the effect of reduced glutathione (GSH), an antioxidant, on human coronary circulation. The results indicate that GSH improved coronary endothelial vasomotor function, particularly in subjects with coronary risk factors, and it potentiated the vasodilator effect of nitroglycerin in human coronary arteries. *PMID: 9639372*

OBJECTIVE: To assess the effects of glutathione on pain-free walking distance (PFWD) and hemodynamic parameters in patients with peripheral artery disease. CONCLUSION: In patients with peripheral artery disease, glutathione prolongs PFWD and shows an improvement of macrocirculatory and microcirculatory parameters. *PMID: 12173710*

HEAVY METAL TOXICITY

Glutathione, as both a carrier of mercury and an antioxidant, has three specific roles in protecting the body from mercury toxicity. First, glutathione, specifically binding with methylmercury, forms a complex that prevents mercury from binding to cellular proteins and causing damage to both enzymes and tissue. Second, glutathione-mercury complexes have been found in the liver, kidney, and brain, and appear to be the primary form in which mercury is transported and eliminated from the body. Third, glutathione increases the antioxidant capacity of the cell, providing a defense against hydrogen peroxide, singlet oxygen, hydroxyl radicals, and lipid peroxides produced by mercury. *PMID: 12495372*

Cells exposed to methylmercury showed a decrease in glutathione peroxidase activity. Simultaneous administration of 10 mM glutathione with 2.5 and 5.0 microM methylmercury dramatically prevented cell injury. *PMID: 2315960*

Glutathione depletion and glutathione supplementation have specific effects on mercury toxicity, both by altering antioxidant status in the body and by directly affecting excretion of mercury and other heavy metals in the bile. *PMID: 12495372*

All forms of mercury have toxic effects in a number of organs, especially in the kidneys. Because of the high bonding affinity between mercury and sulfur, there is particular interest in the interactions that occur between mercuric ions and the thiol group(s) of proteins, peptides and

amino acids. Molecular interactions with sulfhydryl groups in molecules of albumin, metallothionein, glutathione, and cysteine have been implicated in mechanisms involved in the proximal tubular uptake, accumulation, transport, and toxicity of mercuric ions. *PMID: 10699157*

Recent studies have shown that metals, including iron, copper, chromium, and vanadium undergo redox cycling, while cadmium, mercury, and nickel, as well as lead, deplete glutathione and protein-bound sulfhydryl groups, resulting in the production of reactive oxygen species as superoxide ion, hydrogen peroxide, and hydroxyl radical. As a consequence, enhanced lipid peroxidation. DNA damage, and altered calcium and sulfhydryl homeostasis occur. *PMID: 7744317*

HIV

Oxidative stress may contribute to several aspects of HIV disease pathogenesis, including viral replication, inflammatory response, decreased immune cell proliferation, loss of immune function, apoptosis, chronic weight loss, and increased sensitivity to drug toxicities. Glutathione may play a role in these processes, and thus, agents that replete glutathione may offer a promising treatment for HIV-infected patients. *PMID: 7590404*

Clinical studies presented here directly demonstrate that low GSH levels predict poor survival in otherwise indistinguishable HIV-infected subjects. Glutathione is essential for the viability and function of virtually all cells. In vitro studies showing that low GSH levels both promote HIV expression and impair T cell function suggesting a link between GSH depletion and HIV disease progression... the unnecessary or excessive use of acetaminophen, alcohol, or other drugs known to deplete GSH should be avoided by HIV-infected individuals. *PMID: 9050888*

Glutathione supplementation in vitro increases T cell proliferation and suppresses the spontaneous release of tumor necrosis factor–a from peripheral blood mononuclear cells, in HIV-infected patients receiving HAART (highly active antiretroviral therapy). Our findings suggest that therapeutic intervention aimed at normalization of oxidative disturbances in HIV infection could be of interest, in addition to HAART. *PMID: 12854078*

Our data indicate that restoring both GSH concentration and mitochondrial function may hold promise as possible therapeutic strategies for slowing disease progression of dementia in AIDS patients. *PMID: 11582518*

LIVER & KIDNEYS

We prospectively studied the effect of perioperative administration of glutathione on renal function in patients who underwent coronary artery bypass operation. Perioperative glutathione treatment has a salutary effect on perioperative renal function through effects on both renal hemodynamics and tubular mechanism. *PMID: 7952483*

Regardless of the nature of the diet, cirrhotic patients had significantly subnormal values for cysteine, glutathione, and albumin. The data indicate multiple abnormalities in sulfur metabolism in cirrhosis. *PMID: 6468868*

Although the use of non-heart-beating donors (NHBD) is the oldest type of organ transplantation, the results were and still are disappointing. To consider using a liver from NHBD, it is of importance to assess the graft viability. Our aim was to assess the role of reduced liver glutathione (rGSHL) as a potential predictive marker of liver function before transplantation. In conclusion, rGSHL has the potential of becoming an important viability marker, as it could predict survival in autotransplantation NHBD model regardless of the ischemia time. Further investigation to declare reasons for differing rGSHL levels within the liver is required. *PMID: 18975272*

LUNG DISORDERS

Glutathione is present in the epithelial lining fluid of the normal lower respiratory tract, where it is thought to play a major role in providing antioxidant protection to the epithelial cells. A study done on patients with IPF (idiopathic pulmonary fibrosis) showed the lower respiratory tracts to be chronically depleted of glutathione. *PMID: 2913886*

A study of asthmatic children found an inverse correlation between the level of glutathione and the severity of asthma attack. Lowest levels of glutathione were found during acute asthmatic attacks. *PMID: 3189960*

Oxidant/antioxidant imbalance, a major cause of cell damage, is the hallmark for lung inflammation. Glutathione (GSH), a ubiquitous tripeptide thiol, is a vital intra- and extra-cellular protective antioxidant against oxidative stress, which plays a key role in the control of signaling and pro-inflammatory processes in the lungs. *PMID: 16054171*

Glutathione (GSH), a ubiquitous tripeptide thiol, is a vital intra- and extracellular protective antioxidant against oxidative/nitrosative stresses, which plays a key role in the control of pro-inflammatory processes in the lungs. Recent findings have suggested that GSH is important in immune modulation, remodelling of the extracellular matrix, apoptosis and mitochondrial respiration. *PMID: 11028671*

The mechanism of regulation of GSH in the epithelial lining fluid in the lungs of smokers and patients with COPD is not known. Knowledge of the mechanisms of GSH regulation in the lungs could lead to the development of novel therapies based on the pharmacological or genetic manipulation of the production of this important antioxidant in lung inflammation and injury. *PMID: 10600876*

OXIDATIVE STRESS & AGING

Colorectal cancer is associated with oxidative stress, and assessment of oxidative stress and given antioxidants is important for the treatment and prevention of colorectal cancer. *PMID: 18837290*

The significant changes in antioxidant enzyme activity after GSH depletion suggest that thiol status can influence the regulation of other antioxidant enzymes. *PMID: 15947071*

In conclusion, our findings show that the glutathione redox system is affected by age. Oxidative stress increases during the aging process. *PMID: 11835271*

These findings confirm that high blood (glutathione) concentrations and excellent physical and mental health are characteristics of long-lived women. *PMID: 12486409*

These results provide evidence that increased oxidative stress with aging makes chondrocytes more susceptible to oxidant-mediated cell death through the dysregulation of the glutathione antioxidant system. This may represent an important contributing factor to the development of osteoarthritis in older adults. *PMID: 14673993*

A deficiency in GSH puts the cell at risk for oxidative damage. An imbalance in GSH is observed in a wide range of pathologies, such as cancer, neurodegenerative diseases, cystic fibrosis (CF), several viral infections including HIV-1, as well as in aging. *PMID: 18926849*

The reducing compound glutathione (GSH) exists in an unusually high concentration in the lens where it functions as an essential antioxidant vital for maintenance of the tissue's transparency. *PMID: 10803423*

PARKINSON'S DISEASE

Glutathione is an important intracellular antioxidant that protects against a variety of different antioxidant species. An important role for glutathione was proposed for the pathogenesis of Parkinson's disease, because a decrease in total glutathione concentrations in the substantia nigra has been observed in preclinical stages, at a time at which other biochemical changes are not yet detectable. *PMID: 10931172*

Levels of reduced glutathione are decreased in nigra in Parkinson's disease… These data suggest that changes in glutathione function are an early component of the pathological process of Parkinson's disease. *PMID: 1510385*

Rational, integrative management of Parkinson's disease requires, among other things, aggressive repletion of glutathione. *PMID: 11134975*

Past studies have shown that depletion of the naturally occurring antioxidant in the affected area of the brain is one of the earliest signs of PD, but this study shows that glutathione depletion may be a causal factor in the disorder. *PMID: 18094238*

Because of the scavenging activity of glutathione against accumulation of oxygen radicals, its decrease in the brains of Parkinsonion patients has been interpreted as a sign of oxidative stress; however, this change may also result from or lead to mitochondrial damage. It is conceivable therefore that regardless of whether oxidative stress or mitochondrial damage represents the initial insult, these toxic mechanisms may both contribute to neuronal degeneration via changes in glutathione levels. *PMID: 1510368*

Several studies have demonstrated a deficiency in reduced glutathione (GSH) in the nigra of patients with Parkinson's Disease (PD). In particular, the magnitude of reduction in GSH seems to parallel the severity of the disease. GSH was administered intravenous, 600 mg twice daily, for 30 days… All patients improved significantly after GSH therapy, with a 42% decline in disability. *PMID: 8938817*