The effect of a patented nutritional supplement, MaxGXL, on lymphocyte intracellular glutathione levels and parameters of aging

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ABSTRACT

Aim: The primary objective of the study was to evaluate the safety, tolerability and efficacy of a proprietary nutritional supplement (MaxGXL) in promoting lymphocyte intracellular glutathione levels. The supplement, though not containing glutathione itself, is intended to raise intracellular glutathione levels by increasing biosynthesis/recycling and by decreasing glutathione consumption due to inflammatory oxidative stress. The secondary objectives included evaluation of changes in inflammatory markers and quality of life.

Methods: The study was a randomized, double-blinded, placebo-controlled cross-over study with two arms involving 27 persons (9 male, 18 female) ranging from 31 to 72 years old. All participants received either 3 capsules of MaxGXL twice daily or placebo. Subjects were followed for two months, then after a 14-day washout period, cross-over occurred and subjects were followed for an additional 2 months. At the end of the study, subjects were offered 1 month of open-label MaxGXL. Intracellular lymphocyte glutathione was determined using a kinetic enzymatic recycling assay on separated PBMC. Levels of IGF1, DHEA, and TNFα were measured.

Results: Lymphocyte intracellular glutathione levels showed a progressive and significant increase over 2 months relative to baseline in subjects receiving the nutritional supplement. This increase was associated with decreased TNFα and increased levels of age-associated hormones (IGF1 and DHEA). All improvements increased sequentially over duration of study (month 2 > month 1) and no serious adverse events were observed.

Conclusions: MaxGXL, a proprietary nutritional supplement, safely, effectively and significantly increases lymphocyte intracellular glutathione levels. The increases were progressive over the 2 month study period and were associated with decreased inflammation and improved levels of tested age-related hormones.
BACKGROUND

Glutathione
Glutathione (GSH) is a tripeptide composed of cysteine, glutamic acid and glycine. Of these, cysteine is of significant importance as it contains a sulfhydryl (SH) group, meaning that it can be oxidized by donating an electron. GSH is found in all cells and organs, but is particularly high in the liver and the spleen; the latter being composed predominately of T-lymphocytes. Although glutathione has multiple functions, including facilitating the transport of amino acids, detoxifying heavy metals, protecting cellular membrane integrity, regenerating Vitamin C, its major function appears to be anti-oxidation. In fact, it is considered to be the most abundant and important intracellular low molecular weight sulfhydryl-containing peptide in mammalian cells, and one of the most important free radical traps in the human body.

Glutathione exists in two basic forms. The antioxidant form or “reduced glutathione” tripeptide is conventionally called “glutathione” or “γ-L-glutamyl-L-cysteinyl glycine” and abbreviated as “GSH.” The oxidized form is a sulfur-sulfur linked compound known as glutathione disulfide (GSSG). It is ubiquitous in animals, plants and microorganisms and being water-soluble is found mainly in the cell cytosol and other aqueous phases of the living system. Glutathione often attains millimolar levels inside living cells, which makes it one of the most highly concentrated intracellular antioxidants.

Glutathione is homeostatically controlled, both inside the animal cell and outside. Enzyme systems synthesize it, utilize it, and regenerate it per the gamma-glutamyl cycle. It is most concentrated in the mammal liver (10mM), where the P450 Phase II enzymes require it to convert fat-soluble substances into water-soluble GSH conjugates in order to facilitate their excretion. While providing GSH for its efficient metabolic functions, the liver parenchymal cells export GSH to the outside, where it serves as a systemic source of -SH/reducing power.

Glutathione Depletion
Glutathione synthesis occurs within animal cells in two closely linked enzymatically controlled reactions that utilize Adenosine Triphosphate (ATP) and draw on nonessential amino acids as substrates. First, cysteine and glutamate are combined (by the enzyme gamma-glutamylcysteine synthetase), with availability of cysteine usually being the rate-limiting factor. Cysteine is generated from the essential amino acid methionine, from the degradation of dietary protein, or from turnover of endogenous proteins. The buildup of GSH acts to feedback-inhibit this enzyme, thereby helping to ensure homeostatic control over GSH synthesis. The consequences of sustained GSH depletion are fatal. As cellular GSH is depleted, first individual cells die in those areas most affected. Then zones of tissue damage begin to appear. Localized free-radical damage spreads across the tissue in an ever-widening, self-propagating wave.
As with other cell types, the proliferation, growth and differentiation of immune cells are dependent on GSH. Both the T and the B lymphocytes require adequate levels of intracellular GSH to differentiate, and healthy humans with relatively low lymphocyte GSH were found to have significantly lower CD4 counts. Intracellular GSH is also required for the T-cell proliferative response to mitogenic stimulation, for the activation of cytotoxic T “killer” cells, and for many specific T-cell functions, including DNA synthesis for cell replication, as well as for the metabolism of interleukin-2, which is important for the mitogenic response and for the protection against Fas-mediated apoptosis. NrF2 regulates the sensitivity of death reception signals by affecting intracellular glutathione levels. In vitro glutathione supplementation enhances interleukin-2 production and mitogenic response of peripheral blood mononuclear cells from young and old subjects. In summary, it has been demonstrated that decreased levels of glutathione may be a result of various types of prolonged stress, increased free radical formation and hyperactivity of the immune system. These factors in turn compromise the health of mammalian cells.

There is a significant body of literature showing that plasma glutathione levels, as well as intracellular glutathione levels, are directly related to outcome in diseases such as chronic hepatitis, HIV infections, various malignancies and malnutrition to name but a few. In fact, any form of prolonged oxidative stress resulting in increased free radical formation and/or hyperactivity of the immune system results in reduced glutathione levels and resultant immunologic compromise. Despite the apparent importance of maintaining glutathione levels, the literature regarding nutritional supplementation remains controversial and no clear-cut mechanism for increasing plasma and/or intracellular glutathione has emerged.

Plasma levels of glutathione have been demonstrated to be significantly decreased in conditions as diverse as malnutrition, various infections including HIV and Chronic Hepatitis and a wide variety of malignancies (see Figure 1). However, no causal relationship has been proven between the low glutathione levels and disease. Despite this, there is no clear-cut consensus on an efficient and consistent methodology to increase plasma GSH and, more importantly, intracellular GSH by nutritional supplementation. Both intravenous and intrapulmonary installations of GSH have been used to reverse/protect hepatotoxicity in acetaminophen poisoning, but parenteral administration is impractical due to both cost and inconvenience. As a result, the literature is rife with studies of oral supplements. In general, these have involved the use of cysteine (predominantly as N-acetyl cysteine) or the use of oral glutamine. The difficulties attendant with disturbed digestive functions in chronic debilitating conditions and the finding that elevated plasma glutamate levels (which occur in chronic conditions) can both inhibit cysteine uptake by cells as well as directly inhibit GSH synthesis, have limited the utility of oral supplementation in patients with chronic viral infections and malignancies.
Correction of Glutathione Depletion

Studies have demonstrated that oral glutathione is not well absorbed by many of the mammal’s cells and does not replenish losses inside cells where it is most needed. The sulfur-containing amino acid L-cysteine is the precursor that most limits cellular biosynthesis of GSH. When substituted into the diet in place of the total protein

Diseases Associated with Decreased Glutathione

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<th>PULMONARY</th>
<th>NEURO/PSYCH</th>
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1 Adapted from reference 16^
allowance it was effective in raising GSH levels. Glutathione esters are synthetic compounds prepared by linking the glycine end of GSH into ester bonds. These esters do appear to be effective GSH delivery vehicles, but have the disadvantage that they yield alcohols in vivo when their ester bonds are broken, and their safety over the long term has yet to be satisfactorily demonstrated.

Studies suggest that to efficiently raise the levels of glutathione intracellularly, it is necessary to employ several different mechanisms that work simultaneously. First, essential elements needed by the body for manufacture of glutathione must be introduced. Second, gastrointestinal health of the mammal must be able to facilitate nutrient absorption. Third, the liver function must be supported and protected, as the liver is the glutathione “manufacturing and storage house.” Fourthly, it is advantageous to support recycling of existing glutathione and enhancing enzymatic reactions that promote glutathione synthesis. In addition to promoting glutathione synthesis and recycling, another mechanism of improving glutathione concentration is to reduce its ancillary utilization as a free radical trap, thereby preserving it for use as a reluctant for the oxidation reactions which are necessary for the mitochondrial production of ATP in every mammalian cell.

MaxGXL
The present study tested the ability of a complex nutritional supplement, MaxGXL to raise intracellular glutathione levels and counter certain metabolic correlates of aging. This proprietary nutritional supplement represents a novel amalgam of glutathione promoting methodologies. It contains phytocyanins (facilitators of digestive absorption), N-acetyl cysteine (which releases cysteine, the rate-limiting component for glutathione biosynthesis), promoters of glutathione recycling and cordyceps.

Cordycepin, the active ingredient in Cordyceps sinensis (and other species) has many demonstrated functions including anti-tumor, neuroprotective, and hypoglycemic effects. Its functions of import in preserving glutathione are its anti-inflammatory, immunomodulatory, antioxidant and hypolipidemic effects. Cordycepin enhances hepatic metabolism and ATP production, thereby enhancing hepatic glutathione production.

The anti-inflammatory activity of cordyceps is based upon reduction of nuclear factor kappa beta (NFkB) activity in macrophages. Decreased NFkB activity diminishes macrophage activation leading to decreased production of proinflammatory cytokines (including IL1, IL6 and TNFα) and intra and extracellular free radicals. The anti-inflammatory action of cordyceps increases glutathione levels because inflammation produces free radicals, reactive oxygen and reactive nitrogen species which damage cellular components unless they are neutralized by antioxidants, such as glutathione. Glutathione is the most prevalent antioxidant in cells, reaching millimolar concentrations in some tissues such as the liver. In the liver, glutathione can explain nearly 50% of the total reactive antioxidant potential of the tissue.

In quenching reactive species, glutathione becomes oxidized and is exported from the cell, therefore decreasing the intracellular concentration of glutathione. Reduced
Glutathione is crucial because it is required for the regeneration of all other antioxidants. This is important because it is the only natural antioxidant whose oxidation does not produce free radicals. The attenuation of inflammation, therefore, promotes enhanced levels of total and reduced glutathione in cells.

In summary, MaxGXL is expected to increase glutathione concentrations by promoting gastrointestinal absorption of the precursors, facilitating intracellular transport of the requisite components, promoting intracellular glutathione synthesis, and recycling oxidized glutathione. It may protect intra- and extracellular concentrations of glutathione by enhancing hepatic metabolism and reducing ancillary glutathione utilization by reducing macrophage-induced inflammation, the production of proinflammatory cytokines, and ultimately reducing free radical production. In this way, it may preserve glutathione for its role in facilitating increased cellular energy through enhancing mitochondrial ATP production.

**Glutathione and Aging**

Glutathione depletion may also play a significant role in aging, at least in part through its role as a major protector of mitochondrial DNA (MtDNA). Maintenance of normal MtDNA directly correlates with maximum life span, which has been estimated at 122 years in humans. During ATP production in the mitochondria, superoxide free radicals are produced which are converted to hydroxyl and peroxide free radicals. GSH neutralizes hydroxyl free radicals and is an essential component of GSH peroxidase, which neutralizes peroxide free radicals. These free radicals generated within the mitochondria have the potential to damage MtDNA. At age 90 only 5% of normal MtDNA remains when compared to the normal MtDNA level of a 5 year old. GSH levels decrease with age (1% per year) which may account for at least some of the cumulative MtDNA damage.

Promoting high levels of reduced mitochondrial glutathione may counter some of the effects of aging. It has been found that centenarians demonstrate GSH levels similar to 30-50 year old well normals, suggesting that their atypical GSH levels have been pivotal in preserving their health. In support of this notion, it has been found that caloric restriction, which prolongs life, increases both the aging-associated deacetylase Sirtuin1 and GSH levels.

Glutathione may play a significant role in aging. Raising intracellular glutathione levels may reduce the metabolic signs of aging and protect mitochondrial function.

**METHODS**

**Participants**

Recruitment was from patients of the KBK Institute of Advanced Medicine, MaxGXL distributor-derived subjects, and newspaper advertisement. Subjects lacked allergy to any of the ingredients of MaxGXL (including mushrooms, shellfish and Silimarin) and did not use glutathione or glutathione-producing supplements within 2 weeks of baseline, nor
did they participate in any experimental study within 1 month of baseline.

This study was approved by the Independent Institutional Review Board. The purpose, nature, and potential risks of the study were explained to all participants, who gave their written informed consent before participation. The study was conducted in accordance with the U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations) and in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever afforded the greater protection to the subject.

Cordyceps may prolong pro-thrombin time, so subjects on warfarin-like anticoagulants were excluded. All participants had prothrombin time and partial prothrombin time within normal limits. Because vitamin C and alpha lipoic acid can cause mild heartburn, subjects with gastroesophageal reflux disease, severe heartburn, esophageal varices or beta-blocker dependent cirrhosis were excluded. Additionally subjects were free of treatment or diagnosis of congestive heart failure, senile dementia, Alzheimer’s or multi-infarct dementia, peptic ulcer, or end stage renal disease. Subjects were excluded who had diagnosis or treatment of cancer within 6 months of the study, except basal or squamous cell skin cancer. Subjects with diagnosis or treatment for chronic illness without definitive diagnosis were excluded.

The women of childbearing potential were neither pregnant nor lactating. Participants agreed to limit alcoholic beverages to 2 per day for men and 1 per day for women, as well as to abstain from all Tylenol products unless deemed medically necessary. Subjects were substance abuse free for a minimum of 6 months prior to baseline, and those on prescribed narcotics were at steady state for a minimum of 3 months prior to onset of baseline. Participants did not use antibiotics for more than 10 days within 1 month of baseline.

**Study Design**

The study was a randomized, double-blinded, placebo-controlled cross-over study with two treatment arms. A total of 27 subjects (9 males, 18 females) were enrolled (age range 31-72). Subjects were assigned on a random basis to the active treatment arm or to the placebo treatment. Randomization was prepared by the manufacturer which provided MaxGXL and placebo as numerically labeled bottles. All study participants remained blinded to the randomization assignment for the duration of the study. Subjects consumed 3 capsules twice a day. Follow up visits occurred at one and two months. After two months, there was a 14-day washout period before the cross-over. In a double-blinded fashion, subjects previously receiving MaxGXL were issued placebo and subjects previously receiving placebo were issued MaxGXL. Additional follow-up visits occurred at one and two months after the cross-over. At the conclusion of the cross-over period, and at the subject’s sole discretion, all subjects were offered one month of open label MaxGXL. A follow up visit was scheduled after one month. At the final study visit, or in the case of an early discontinuation visit, volunteers were given a final interview.
Blood was obtained at screening, 1 month and 2 months of follow up, and the end of the washout period. After the cross-over, blood was obtained at 1 month, 2 months and at the final study visit. Subjects were asked about any problems which occurred while on the experimental product or comparator and any health problems or changes in their health. Less than 80% compliance by patient report was considered a protocol violation. All laboratory values were compared at initiation and monthly for two months. Safety parameters were noted including clinical laboratory, adverse events, and medical history. Volunteers were asked to promptly report possible side effects, illnesses, infections, medical problems, surgeries, missed doses, lost study products, and other life problems affecting their compliance. Reported side effects were specifically evaluated during the study. Side effects data therefore was not blinded but was collected primarily for safety analysis.

**Supplement**
Both MaxGXL and placebo were obtained from the manufacturer, who provided them in coded bottles. The dosage was 2 daily servings of 3 capsules. Three capsules contain 250 mg vitamin C as Calcium Ascorbate USP, 750 mg L-Glutamine, 375 mg N-Acetyl Cysteine (NAC), 75 mg Alpha Lipoic Acid, and 488 mg of a proprietary GSH Absorption & Recycling Blend consisting of Cordyceps, N-Acetyl D-Glucosamine, Quercetin, Milk Thistle (Silybum marianum) Extract containing 80% Silimarin. Placebo was also administered as 3 capsules BID.

**Laboratory Evaluation**
The following blood tests were performed by LabCorp or KBK Institute of Advanced Medicine; CBC, ESR, Comprehensive Chemistry, PT, PTT, Lymphocyte Glutathione, IL1, IL6, TNF Alpha, Cystatin, Fasting Insulin, Cortisol, DHEA, IGF1, testosterone (men only), progesterone (women only) and estradiol levels. Total lymphocyte intracellular glutathione was determined using a kinetic enzymatic recycling assay kit from Oxford Biomedical Research on separated PBMC. PBMC were separated using Cell Preparation Tubes (Becton Dickinson), and immediate processing within 30 minutes using ice-cold, 5% metaphosphoric acid. Cortisol, estradiol, progesterone and testosterone levels were determined using an Immulite 2000 system.

**Statistical Methods and Data Analysis**
Efficacy as related to lymphocyte glutathione was evaluated at each time point relative to baseline. DHEA, Igf1, and TNF alpha were compared between groups at each time point using a two-tailed t-test. The safety endpoint data was summarized for the study population. Statistical analysis was performed to estimate the treatment effect of MaxGXL and placebo control using participants’ two-tail t-test with significance assigned at a p<0.05 values.

**RESULTS**

**Intracellular lymphocyte glutathione**
Normal subjects receiving the nutritional supplement designed to raise glutathione levels
demonstrated a 121% change from baseline levels in lymphocyte intracellular glutathione over 1 month (p<0.01). The range after 1 month was from 72 to 154 nanograms/10^6 cells. Glutathione levels increased further over 2 months to 276% change (p<0.001). The range after 2 months was from 155 to 310 nanograms/10^6 cells. In contrast, the glutathione level of participants receiving placebo decreased -3% over 1 month (p<0.05) and -7% over 2 months (p<0.05). The ranges were from 1 to 9 nanograms/10^6 cells and from 3 to 15 nanograms/10^6 cells, respectively. Three subjects with chronic insomnia showed the least improvement.

**Figure 2.** Increase in Intracellular Lymphocyte Glutathione Levels using a Patent Pending Oral Glutathione Optimizer.
**Age-associated hormone levels**

Progressive improvements in age-associated hormone levels were observed in normal subjects receiving the glutathione promoting supplement. After 1 month, there was a 16% change from baseline in IGF1 levels (p<0.05). The range was 6 to 41 ng/mL. After the second month of supplementation, there was a 41% change in IGF1 levels (p<0.001). The range was from 14 to 80 ng/mL. The decreases in IGF1 levels in placebo-treated subjects were not statistically significant (-3% at 1 month and -8% at 2 months). The ranges were from 1 to 5 and from 3 to 11 ng/mL, respectively.

Similarly the age-associated hormone DHEA also increased in subjects receiving the glutathione promoting supplement. After 1 month, there was an 18% change from baseline in DHEA levels (p<0.05). The range was 6 to 33 ng/dL. After the second month of supplementation, there was a 46% change in DHEA levels (p<0.001). The range was from 18 to 52 ng/dL. The changes in DHEA levels in placebo treated subjects were not statistically significant (-2 at 1 month and -6 at 2 months). The ranges were from 0 to 5 and from 3 to 11 ng/dL, respectively.

**Figure 3.** Improvement in Age-Associated Hormone Levels using a Patent Pending Oral Glutathione Optimizer.
**Inflammation Marker**

The glutathione-promoting supplement lowered levels of markers of inflammation. The inflammatory cytokine TNFα decreased progressively from baseline at 1 and 2 months (from -41 to -61 % change). These changes were highly significant (p<0.001 and p<0.0001 respectively). The decrements ranged from -14 to -54 pg/ml at 1 month and -27 to -94 pg/mL at 2 months. Of 25 subjects, 19 showed decreased levels of the proinflammatory cytokine. In the placebo controls, in contrast, TNFα levels increased. At 1 month the controls had a nonsignificant 4 % change and at 2 months the percent change was 6 (p<0.05). The increment ranged from 2 to 11 and from 6 to 19 pg/mL. Note that the TNFα assay is only sensitive to 6 pg/ml so the percent change may be underestimated.

**Figure 4.** Improvement in Markers of Inflammation using a Patent Pending Oral Glutathione Optimizer

![Graph showing TNFα levels](image)

**Safety**

Subjects were queried at each visit about health problems or changes in their health. No serious adverse events were reported by the subjects.

**DISCUSSION**

The proprietary nutritional supplement, MaxGXL, safely raised lymphocyte glutathione levels in normal subjects in a placebo-controlled, double-blind study. This supplement does not contain glutathione itself but rather promotes the cellular synthesis of
glutathione and reduces its consumption by decreasing inflammation. The increase in glutathione levels was associated with increases in the hormones IGF1 and DHEA, which normally diminish during the aging process. In concert with these changes, decreases were observed in the marker of inflammation TNFα.

Other benefits of raising the levels of glutathione relate to quality of life. Oxidized glutathione (GSSG) induces sleep. The effects of improved sleep include improved mood, energy, mental focus and decreased pain.

This study is limited by the small number of patients and the short term. Given the progressive nature of the improvements in glutathione, IGF1, DHEA, and TNFα, the question remains whether expanded, longer-term studies would show sequential improvements. The results suggest strongly that such studies are warranted, given the wide variety of diseases associated with decreased glutathione levels.

This research was supported in part by KBK Institute of Advanced Medicine.
REFERENCES


