



HEPATOPROTECTIVE GLUTATHIONE AND ITS NATURAL BOOSTING

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ABSTRACT

Liver is the chief site for intense metabolism and excretion. It is essential organ of our body which performs hundreds of vital functions and produces a number of nutrients. Glutathione is one of such nutrient produced by liver and important for its maintenance. Glutathione is an antioxidant which plays a vital role in reducing oxidative stress maintaining redox balance and enhancing metabolic detoxification. Arising discoveries propose that oral organization of glutathione may build fuse of protein-bound glutathione into liver and diminishing the obsessive discharge of glutathione from liver and is valuable in the treatment of greasy liver illnesses.



Liver diseases are leading cause of metabolic syndrome and death in the world. As a result, altered intracellular glutathione homeostasis has been widely used as an indicator of oxidative stress. The present study reviews the available literature regarding the association of glutathione level and hepatic detoxification and natural way to enhancing glutathione by using selected foods like sulphur rich foods, vitamin C rich foods inclusion, whey protein and life style modification like performing regular yoga and exercises. important cellular components caused by reactive oxygen elements such as free radicles, peroxides, lipid peroxides and heavy metals.

KEYWORDS : AFLD, Antioxidants, Chronic liver diseases, Glutathione, Hepatoprotective activities, NAFLD, NASH, oxidative stress, S- thyolation .

INTRODUCTION

In the modern life style we acquired several life and food habits which are adversely affecting our liver and causing hepatic diseases. It is essential to avoid such habits which are bad for our liver. For caring liver it is also important to eat those things which are particularly nourishing to the liver. One of such thing is Glutathione, this is produced by our body itself. It is one of the body's most important metabolite and the potent antioxidant. Antioxidants are the substances that reduce oxidative stress by combating free radicles in the body. The antioxidant activity which restores the activity of superoxide dismutase, catalases and glutathione peroxidases to normal levels and increases glutathione content and levels of lipid peroxidation and hydroxides in the liver are considered to be hepatoprotective. This powerful antioxidant comprised of three amino acids- cysteine, glutamine and glycine built from elements of carbon, hydrogen, nitrogen, oxygen and sulphur linked together in

following molecular structure $C_{10}H_{17}N_3O_6S$. L-glutathione is called the master antioxidant because of its diverse use and sticky properties. This stuff exists everywhere in our body and protects cells by sticking to toxic molecules like heavy metals, poisonous and cancer causing free radicals. It plays a pivotal role in reducing oxidative stress, maintaining redox balance, enhancing metabolic detoxification and regulating immune system. Various chronic, age related neuro-degeneration, mitochondrial dysfunction and even cancer, have been related to sub optimal or deficient glutathione levels. There is an increasing awareness of its utility in mitigating body toxins load through its ability to enhance hepatic conversion and excretion of compounds such as mercury and persistent organic pollutants (POPs).¹

Glutathione is said to protect against a wide range of health problems, including atherosclerosis, Alzheimer's diseases, chronic fatigue syndrome, colitis, high cholesterol, osteoarthritis, diabetes, glaucoma, heart diseases, hepatitis and liver diseases and Parkinson's diseases². In addition, glutathione is purported to reverse the aging process, prevents cancer, and preserve memory. Maintaining optimal levels of glutathione is essential to our health, because it plays key roles in antioxidant defence, the breakdown of nutrients, and the regulation of the many biological processes including immune response. As our body ages, our natural abilities to produce many compounds like glutathione can slow down and we become weaker. However, we can partially counteract these effects by providing our body's cells with the raw materials needed for vital processes to function in an optimal healthy way; changes in food habits and by certain life style modifications. The glutathione deficiency contributes to oxidative stress, which in turn influences the development of many diseases. According to the limited research, increased glutathione production and through direct administration and promotion through precursors has been found clinically helpful in Parkinson's, cystic fibrosis, emphysema, COPD, lead exposure, non-alcoholic fatty liver disease and exercise induced fatigue among others.²

GLUTATHIONE: ROLE IN HEPATOPROTECTION -

Liquor misuse, greasy liver sicknesses and hepatitis harms the cells of liver. Ongoing liver infections are developing reason for bleakness and mortality. Glutathione is connected to security of liver from such sicknesses. It is an exceptionally solid cancer prevention agent, halfway in light of the fact that this V-L-glutamyl-L-cystenyl-glycine – a tri-peptide present in the each cell of human body in high focus. Despite the fact that its capacities are complicated and stay the subject of examination, glutathione is thought to assume critical part in detoxification and cancer prevention agent frameworks in the cells. Since a decrease of glutathione levels in cells has been found to build the dangers for the illnesses and harming, direct intravenous infusion of glutathione has been utilized to treat patients with constant liver sicknesses and poisoning.^{3,4} Glutathione is combined in cells from glutamic corrosive, cysteine and glycine. Cysteine and glycine are created from methionine and serine individually and glutamic corrosive is orchestrated from α -ketoglutarate, a middle of the road result of glucose digestion. These amino acids are for the most part provided from food. It has been accounted for, an increment in the protein bound type of glutathione in human blood after oral organization, while glutathione in deprotenized division didn't change.⁵ These discoveries propose that oral organization of glutathione may expand the fuse of protein bound glutathione into the liver or abatement the obsessive discharge of glutathione from the liver.

Glutathione plays crucial role in the detoxification and antioxidant system of cells and has been used to treat acute poisoning and chronic liver diseases by intravenous injections. One pilot study examines the therapeutic effects of oral administration of glutathione in the patients with non-alcoholic fatty liver disease (NAFLD). The study was an open level, single arm, multicentre, pilot trial and found that treatment with the glutathione (300mg/day) for 4 months resulted in significant decrease in alanine aminotransferase (ALT) levels. In addition triglycerides, non-esterified fatty acids, and ferritin levels also decreased. This pilot study demonstrates the potential therapeutic effects of the oral administration of glutathione in practical dose for patients.⁶

A study reported that glutathione was most effective when given to the people with fatty liver disease intravenously in high doses. Participants in the study also showed reduction in the malondialdehyde, a maker of cell damage in the liver.⁷ Unfortunately, there are many individuals who are either unwilling or unable, for various reasons to engage in a full lifestyle overhaul and additional therapeutics are often still necessary to address the detrimental chronic presence of NAFLD. The tri-peptide glutathione, V-L- glutamyl-L-glycine, has come to the forefront as a nutritional bioactive with potential use in the management of NAFLD, as it plays a critical role in cellular antioxidant and detoxification system. For year's intravenous glutathione injection have been clinically recognized for their therapeutic value in treating acute poisoning and chronic liver diseases.

More recently oral glutathione has been investigated for its use in the treatment. It has been debated for many years whether oral glutathione supplements translates into increased bioactive levels of glutathione in the body, since many believe that oral glutathione can't be adequately absorbed and therefore, successfully utilized by the body's cells. In the recent years, however, emerging, research has demonstrated that oral glutathione supplementation, particularly in the protein bound forms, may in fact exert a beneficial effect in the cells leading researcher's to considered glutathione supplementation effects in the human body. Including in the treatment of NAFLD.⁸

NAFLD includes a spectrum of liver diseases ranging from simple steatosis (accumulation of triglyceride (TG) inside hepatocytes) to non-alcoholic steatohepatitis (NASH), which is defined as the presence of hepatic steatosis and inflammation along with hepatocytes death; many patients ultimately progress to fibrosis/cirrhosis and liver failure. The prevalence of NAFLD has increased rapidly over the last decades, in parallel with the dramatic rise in obesity and diabetes. Because of its high prevalence in conjunction with obesity, diabetes and insulin resistance. NAFLD has been increasingly appreciated as a hepatic manifestation of metabolic syndrome and is leading cause of death from liver disease in United States.⁹ Hepatic steatosis results from an imbalance between triglycerides synthesis and its disposal. Both 'hepatic' and non-hepatic mechanism contributes to the development of hepatic steatosis. In the liver, although both increased FFA uptake and up regulated *de novo* lipogenesis contribute to the development of hepatic steatosis, accumulating evidence suggest that increased FFA uptake play a predominant role in the development of fatty livers.

NASH is a progressive form of NAFLD, characterized by hepatocytes death and hepatic inflammation. Accumulated evidence suggests that both oxidative stress and pro-inflammatory cytokine tumor necrosis factor α (TNF α) are critical contributors in this progress.

SYNTHESIS OF GLUTATHIONE

Three conditionally essential amino acids, glycine, cysteine and glutamic acid combine to form glutathione in a two-step biochemical reaction. First, cysteine is conjoined with glutamate through the action of glutamate cysteine ligase to produce gamma- glutamylcysteine which proceeds to link with glycine via glutathione synthetase.¹⁰ Glutathione is a tri-peptide that is synthesized from glutamate, cysteine, and glycine through two ATP-consuming reactions. It is the most abundant intracellular antioxidant and exists in both reduced (GSH) and oxidised (GSSG) forms. By donating and reducing equivalents to other unstable molecules, such as ROS, GSH is readily converted to GSSG, which can convert back to GSH by the enzyme glutathione reductase. As a result, altered intracellular glutathione homeostasis has been widely used as indicator of oxidative stress. Although, both dysregulated hepatic glutathione homeostasis and TNF α overproduction are critically involved in the development of NAFLD, whether they can be synergistically implicated in hepatocytes death remains to be clearly defined.

Glutathionylation is a form of S-thiolation where protein cysteine forms a disulphide bond with the cysteine of glutathione. Akin to several well-established post-translational modifications, S-glutathionylation has recently been determined to play an important role in regulating protein function. Although protein S-glutathionylation (a process that generates protein SSG adducts) can be achieved via several different reactions; one well established biochemical event for the formation of protein- SSG is the reaction of GSSG with protein sulfhydryl's. In fact in cells undergoing lethal oxidative stress, cellular

protein-SSG levels show a positive relationship with GSSG levels.¹¹ Researchers have found to take supplement that activate the natural glutathione production in the body. Reducing toxin exposure and increasing intake of healthful foods are also excellent way to naturally increase glutathione level.

HOW TO INCREASE GLUTATHIONE LEVEL?

As our body ages and depending on our natural environment our natural ability to produce many compounds including glutathione decreases. There are number of reasons why our body's glutathione level may become depleted, including poor diet, chronic diseases with age. Maintaining adequate levels of this antioxidant is incredibly important. Since glutamine is a precursor of glutathione, its supplementation in diet can be used to maintain high levels of glutathione and to avoid oxidative stress damage. The foods listed below are where we begin when building a diet to increase glutathione level. Many of foods have numerous other benefits due to their diverse array of nutrients that affects all the system of our bodies.

INCREASING SULPHUR RICH FOODS :

Sulphur is a chemical element found in many amino acids, including those needed to produce glutathione. Allium vegetables, including garlic and onions are rich in sulphur containing compounds that may help increase glutathione production. Cruciferous vegetables contain a compound called sulphoraphane, which has many health benefits. Broccoli, cauliflower, cabbage, kale, and Brussels sprout in particular provide a large amount of sulphoraphane. Studies have shown that sulphoraphane augments and restores blood and cellular glutathione levels.¹² As It has been mentioned above, three conditionally essential amino acids, glycine, cysteine and glutamic acid combine to form glutathione in a two-step biochemical reaction catalysed by enzymes glutamate cysteine ligase and glutathione synthetase. Therefore; the human body requires all three amino acids and adequate enzymatic function to make sufficient quantities of glutathione. Cysteine is sulphur amino acids, which might imply that consuming sulphur rich foods, especially those containing the sulphur amino acids may also support glutathione to link with glycine via glutathione syntheses.¹³

VITAMIN C- RICH FOODS FOR GLUTATHIONE ELEVATION:

In 48 individuals with ascorbate deficiency taking 500mg or 1000mg per day of vitamin C for 13 weeks led to an 18% increase in the lymphocyte glutathione levels compared with placebo. Similarly, in healthy adults following a self-selected vitamin C restricted diet and initial week of placebo supplementation, taking 500mg L- ascorbate per day for weeks four and five in a six-week trial led to an increased levels of glutathione in red blood cells. The lower dose of 500mg daily led to the most prominent rise in glutathione levels.¹⁴ Strawberries, citrus natural products, guava and so on are all illustration of food sources plentiful in nutrient C. Specialists have found that nutrient C might help increment glutathione levels by assaulting free revolutionaries first, subsequently saving glutathione. They likewise found that nutrient C reprocesses glutathione by changing over oxidized glutathione back to its dynamic structure.

Whey Protein:

Consuming foods rich in cysteine, such as whey protein, may promote glutathione synthesis, induce antioxidant defences and reduce inflammation. According to one study, participants who consumed whey protein for five days experienced an increase in serum glutathione levels compared to subjects receiving casein.

Lifestyle Modification:

Research suggests that regular exercise may improve your body's natural antioxidant defence system and boost glutathione levels. According to one study, participants who exercised three times per week for 40minutes had higher glutathione levels than the control group that doesn't exercise.¹⁵

Milk Thistle:

Milk thorn supplements are approach to support glutathione levels normally. This home grown enhancements is separated from milk thorn plant known as silybum marinum. Silymarin found as dynamic compound displayed to increment glutathione levels and forestall consumption in both test cylinder and rat considers.

Add selenium rich foods in the diet:

Selenium is a fundamental mineral and a glutathione cofactor, which means it's a substance required for glutathione action. The absolute best wellsprings of Selenium are chicken, fish, organ meats, curds, earthy colored rice and nuts. By expanding admission of selenium, one might help keep up with or increment body's stock of glutathione. The suggested dietary recompense for selenium for grown-up is 55mcg. This depends on sum expected to expand the creation of glutathione peroxidase.

CONCLUSION

Glutathione is a significant cancer prevention agent that is fundamentally made by the body particularly by our liver and by neurons of CNS however, it is additionally found in dietary sources. Lamentably, the levels of this cell reinforcement can be drained because of many variables, like maturing, a less than stellar eating routine and stationary way of life. One can keep up with fitting glutathione levels by expanding his active work, abstaining from drinking an excess of liquor, getting sufficient sound rest and taking adjusted eating routine. Consideration of milk thorn, whey protein, and sulfur rich eating routine, nutrient C rich food sources in diet and way of life change may likewise help support glutathione levels. This will be useful in detoxifying liver and ensuring hepatic infection.

REFERENCES

1. Yasushi Honda, Takaomi Kessoku et al. Efficacy of glutathione for treatment of non-alcoholic fatty liver disease; an open – label, single arm, multicentre, pilot study. BMC Gastroenterol 2017; 17: 96.
2. Pizzorno J. glutathione Integr Med (Encinitas) 2014; 13(1):8-12,
3. Altomare E, Colonna P, D' Agostino C, et al. high-dose antioxidant therapy during thrombolysis in patients with acute myocardial infarctions. Curr Ther Res Clin Exp.1996; 57: 131-41
4. Allen J, Bradley RD. Effects of oral glutathione supplementation on systematic oxidant stress biomarkers in human volunteers. J Altern complement Med.2011; 17:827-33.
5. Park EY, Simura N, Konishi T, et al. Increase in protein bound form of glutathione in human blood after oral administration of glutathione. J. Agric food chem. 2014; 62: 6183-9.
6. Dentico et al. Glutathione in the treatment of fatty liver diseases: Recentr Prog Med. Jul – Aug1995;(7-8): 290-3.
7. Jones DP, Coates RJ, Flagg EW, et al. Glutathione in foods listed in the national cancer institute's health habits and history food frequency questionnaire. Nutr cancer. 1992; (1): 57-75.
8. Honda Y, Kessoku T, Sumida Y, et al. Efficacy of Glutathione for the treatment of non-alcoholic fatty liver disease: an open-label, single-arm, multicentre, pilot study. BMC Gastroentrol . 2017; Aug 8:17(1):96.
9. James, OF and Day,C.P. Non-alcoholic steatohepatitis (NASH): a disease of emerging identity and importance. J. Hepatol. 29,495-501 (1998) (Google Scholar).
10. Mc Carty M.F.,O Keefe J.H, Dinilolantonio J.J. Dietary glycine is rate limiting for glutathione synthesis and may have broad potential for health protection. Ochsner J. 2018;18:81-87[PMC free article] [Pub Med] [Google Scholar] [Ref List]
11. Piemonte,F. et al. Protein Glutathionylation increases in the patients of liver with non -alcoholic fatty acid disease. J. Gastroenterol. Hepatol. 23, e 457-e468 (2008) CAS [Google Scholar]
12. Jou, J. CHOI, S.S.AND DIEHL, A.M. MECHANISMS OF disease progression in non-alcoholic fatty liver diseases semin . liver dis. 2008, 370- 379 (2008) (google schoholar).
13. Parcel S. Sulphur in Human Nutrition and Application in Medicine. Altrn. Med. Rev.2002; 22-44.

14. Jonston C. S., Mayer C. G., Srilaxmi J. C. Vitamin C elevates red blood cells glutathione in healthy adults. *AM. J. Clin Nutr* 1993:103-105.
15. Elokda A.S., Nielson D. H. Effects of exercise training on the glutathione antioxidant system. *Eur J Cardiovasc Prev Rehabil* 2007 Oct;1 & (5): 630-7 doi: 10.1097/HJR.0bo13e32828622d7.PMID:17925621.