

REVIEW ON GLYCINE AND N-ACETYLCYSTINE (GLYNAC): OVER GLUTATHIONE DEFICIENCY AND ITS COMPLICATIONS

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Abstract: The peptide glutathione is present in both plants and mammals. The liver produces this potent antioxidant to defend the body from free radicals, peroxides, and heavy metals. Cells use glutathione to maintain a healthy level of oxidative stress. In many ways, glycine and N-acetyl cysteine contribute significantly to promoting human health. In this review, it is shown that supplementing with Glycine and N-acetylcysteine (GlyNAC) improves a number of conditions, including glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscle strength, cognition, obesity, tumour, sleep, HIV, COVID-19, male infertility, hypertension, dyslipidemia, hepatotoxicity, schizophrenia through the mechanism of the supplement in cells that are present all over the body. It will be an essential supplement to lead a healthy life for every human being after successful studies as evidence.

Introduction

The peptide glutathione is present in both plants and mammals. The liver produces this potent antioxidant to defend the body from free radicals, peroxides, and heavy metals. Additionally, glutathione rids our bodies of toxins like medicines and pollution.[1] Glutathione keeps the oil filter clean and assists cells in maintaining a healthy level of oxidative stress. GlyNAC aids the cell in producing glutathione.[2] In many ways, glycine and N-acetyl cysteine contribute significantly to promoting human health. Since the amino acids glycine and N-acetyl cysteine are combined to create proteins that are utilised by every cell in the body. In cells, proteins are used for a number of functions. Glutathione insufficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscular strength, and cognition are all improved in older persons who take glycine and N-acetylcysteine (GlyNAC) supplements: Results of a preliminary clinical study.[3] In this review, it is shown that supplementing with Glycine and N-acetylcysteine (GlyNAC) improves a number of conditions, including glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscle strength, cognition, obesity, tumour, sleep, HIV, COVID-19, male infertility, hypertension, dyslipidemia, hepatotoxicity, schizophrenia through the mechanism of the supplement in cells that are present all over the body.

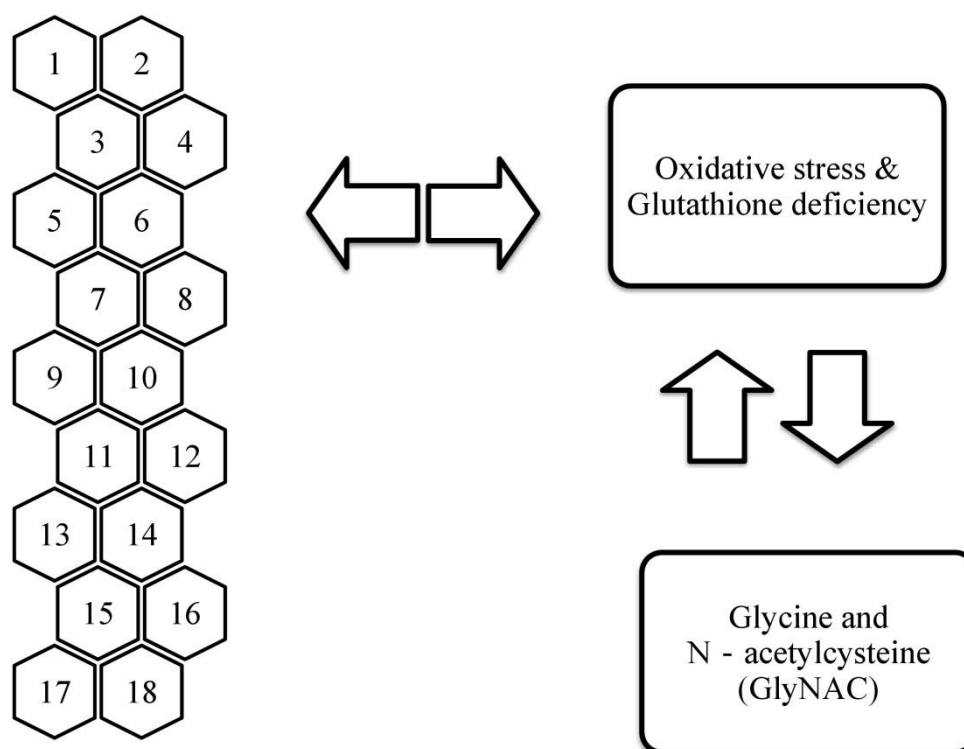


Figure:1 Glycine and N-acetylcysteine (GlyNAC) over Glutathione Deficiency and Oxidative Stress.

1.Mitochondrial Dysfunction; 2.Inflammation; 3.Aging; 4.Endothelial Dysfunction; 5.Insulin Resistance; 6.Muscle Strength; 7.Genotoxicity; 8.Cognition; 9.Dyslipidemia; 10.Obesity; 11.Tumor; 12.Sleep; 13.Hepatotoxicity; 14.Hypertension; 15.Schizophrenia; 16.HIV; 17.Male Infertility; 18.COVID-19.

GlyNAC and Glutathione Deficiency

A condition known as glutathione synthetase shortage limits the formation of glutathione, a crucial chemical. By disarming dangerous chemicals produced during the creation of energy, glutathione assists in preventing damage to cells. Additionally, glutathione aids in the synthesis of DNA, proteins, and other vital cellular components as well as the processing of drugs and cancer-causing substances (carcinogens). Glutathione synthetase is a chemical that aids in the body's production of glutathione and is deficient in people with Glutathione Synthetase Deficiency.[4]

GlyNAC and Oxidative Stress

The aetiology of many illnesses is aided by reactive oxygen species (ROS), which are byproducts of oxidative stress. A significant antioxidant, glutathione, can stop the process by removing ROS. Exogenous glutathione injection can protect RAW 264.7 cells from oxidative damage induced mitochondria-mediated apoptosis and Nrf2/HO-1 signalling pathway activity.[5]

GlyNAC and Mitochondrial Dysfunction

Reactive oxygen species (ROS), the majority of which originate from the mitochondrial respiratory chain, are produced and consumed mostly within mitochondria, which are also the principal intracellular site of oxygen consumption. When it comes to maintaining the proper mitochondrial redox environment to prevent or repair oxidative changes that cause mitochondrial malfunction and cell death, mitochondrial glutathione (mGSH) stands out among the arsenal of antioxidants and detoxification enzymes present in mitochondria. The relevance of mGSH is based on its abundance as well as its adaptability to neutralise xenobiotics, hydrogen peroxide, and lipid hydroperoxides, primarily as a cofactor

of enzymes like glutathione peroxidase and glutathione-S-transferase (GST). Oxidative stress is a result of a variety of death-inducing stimuli interacting with mitochondria; in addition, a variety of diseases are defined by a persistent drop in mGSH levels.[6]

GlyNAC and Inflammation

The imbalance between oxidants and antioxidants is not unique to SARS, but is present in many inflammatory lung disorders where GSH inhibits the activation of redox-sensitive transcription factors like NF- κ B. Reduced glutathione (GSH) inhibits ACE activity, lowers the formation of reactive oxygen species (ROS), and lowers NF- κ B activation to provide anti-inflammatory effects.[7]

GlyNAC and Aging

According to the free-radical hypothesis of ageing, an increase in free-radical-induced oxidative stress is a mediator of age-related functional deterioration. Antioxidants are typically the only source of defence against oxidative stress for cells. Cysteine, glycine, and glutamic acid make up the three amino acids that make up glutathione, the most prevalent endogenous intracellular antioxidant protein that is known to be deficient in older people. Glutathione deficit due to reduced synthesis brought on by a lack of glycine and cysteine and linked to increased oxidative stress. Glycine and cysteine supplements taken orally reduced oxidative stress, stabilised glutathione production rates, and effectively treated intracellular glutathione shortage in elderly people.[8]

GlyNAC and Endothelial Dysfunction

Cellular redox homeostasis and antioxidant defence depend on the generation of glutathione (GSH). The rate-limiting process needs glutamate-cysteine ligase (GCL), which is made up of the catalytic (GCLc) and modulatory (GCLm) subunits. Specific endothelial reduction of GSH production raises baseline and induced ROS levels, decreases eNOS phosphorylation (Ser 1177) and increases eNOS S-glutathionylation (Endothelial nitric-oxide synthase), which prevents endothelium-dependent vasodilation and encourages renal fibrosis after UUO (Unilateral ureteral obstruction).[9]

GlyNAC and Insulin Resistance

In a situation of oxidative stress, glutathione (GSH), an intracellular thiol, eliminates free radicals or lowers the quantity of hydrogen peroxide. Diabetes-related erythrocytes have been shown to have decreased GSH levels and impaired GSH metabolism. The development of oxidative stress as a result of persistent hyperglycemia is a key factor in the genesis of diabetes complications. The rate of NADH/NAD and the activity of the polyol pathway both rise as a result of chronic hyperglycemia. The imbalance in the reduction process is caused by the presence of somewhat accelerated free radical production and sorbitol's partial oxidation to fructose via NAD-related sorbitol dehydrogenase.[10]

GlyNAC and Muscle Strength

The hepatic cells in the body are where glutamate, cysteine, and glycine are combined to form the tripeptide glutathione. In the majority of cells, it is kept in high quantities in an oxidised or reduced state. According to reports, glutathione has a role in the control of several physiological processes, most notably detoxification and antioxidation processes. Due to reduced glutathione's ease of oxidation by reactive oxygen species and subsequent reduction by glutathione reductase, its redox balance has been employed in a variety of contexts as a gauge of antioxidant status. Exercise results in a reduction in glutathione's reduced form and an increase in its oxidised form. Long-term exercise also results in a gradual drop in total plasma and tissue glutathione levels, which raises the possibility that glutathione plays a role in aerobic energy metabolism and muscular contraction maintenance.[11]

GlyNAC and Genotoxicity

One of the most prevalent and harmful lipid aldehydes produced by reactive oxygen species during lipid peroxidation is 4-Hydroxy-trans 2-nonenal (HNE). In human erythroleukemia (K562) cells, we looked at the genotoxic consequences of HNE and how cellular glutathione (GSH) levels affected those effects. According to comet test results, HNE (5–10 M) dramatically enhanced DNA damage in K562 cells by 3- to 5-folds in a time- and dose-dependent manner. GSH replenishment by incubating the cells with GSH-ethyl ester considerably reduced HNE-induced genotoxicity, whereas GSH depletion in cells by L-Buthionine-[S, R]-sulfoximine (BSO) significantly enhanced HNE-induced DNA damage. In addition, over-expression of mGSTA4-4, a GST isozyme that detoxifies HNE, dramatically reduced HNE-induced

DNA damage in cells, whereas siRNA-mediated ablation of GSTA4-4 and aldose reductase increased HNE-induced DNA damage.[12]

GlyNAC and Cognition

In aerobic cells, the tripeptide glutathione and the accompanying enzymes help to maintain oxidant equilibrium. The molecular underpinning of neurodegeneration and brain ageing is oxidative injury to neuronal components. The neuronal plasticity processes that play a part in learning and memory functions involve many biomolecules with redox dependent activity. For the acquisition, but not the consolidation, of spatial memory, the maintenance of normal glutathione levels is crucial. Failures in the hippocampus synaptic plasticity pathways caused by glutathione deficiency may be connected to a loss in spatial memory. According to a number of studies, the modification of antioxidant defence systems mediates the positive effects of neurotrophic therapies.[13]

GlyNAC and Dyslipidemia

Circulating macromolecules like lipoproteins suffer oxidative damage as a result of the persistent loss of extracellular GSH. The rats given buthionine sulfoximine (BSO), a specific GSH inhibitor, had lower plasma levels of vitamin E, ascorbic acid, and glutathione. According to the trinitrobenzene sulfonic acid (TNBS) reactants, the higher mobility of LDL (after in vitro oxidation) extracted from the BSO-treated animals is correlated with a reduction in its amino groups. However, in vivo BSO therapy had no effect on the LDL molecule's mobility. It's interesting to note that in the rats given BSO injections, the modest alteration to LDL does not cause any vascular injury in the dorsal aorta. Animals treated with L-buthionine-SR-sulfoximine (BSO; 4 mmol/kg body weight, twice a day, for 30 days) had their antioxidant status normalised and the minimal changes on LDL were prevented by the administration of glutathione monoester (GME), at a dose of 5 mmol/kg body weight, twice a day, for 30 days. As a result, raising the amount of GSH in cells may have positive benefits against oxidative stress.[14]

GlyNAC and Obesity

The main contributing factor to the onset of metabolic syndrome is obesity. Increased oxidative stress in fat accumulation is a key pathogenic mechanism of the metabolic syndrome linked to obesity. In both people and mice, fat storage and systemic oxidative stress were associated. Obese mice had preferentially higher ROS production in their adipose tissue, along with increased NADPH oxidase expression and reduced antioxidative enzyme expression. Elevated fatty acid levels in cultured adipocytes led to the activation of NADPH oxidase, which in turn increased oxidative stress. Oxidative stress resulted in the dysregulation of the production of adipocytokines (hormones derived from fat), such as adiponectin, plasminogen activator inhibitor-1, IL-6, and monocyte chemotactic protein-1. Finally, NADPH oxidase inhibitor therapy alleviated hyperglycemia, hyperlipidemia, and hepatic steatosis in obese mice by reducing ROS generation in adipose tissue and attenuating adipocytokine dysregulation. The metabolic syndrome is first caused by the increased oxidative stress in accumulated fat, and the redox state of adipose tissue is a possible therapeutic target for the metabolic syndrome linked to obesity.[15]

GlyNAC and Tumor

A variety of cellular functions, such as cell differentiation, proliferation, and apoptosis, depend on glutathione (GSH), and changes in GSH homeostasis are linked to the genesis and development of many human disorders, including cancer. Through redox-sensitive nuclear transcription factors like AP-1, NF-kappaB (NF-kB), and p53, the reversible thiolation of proteins is known to affect a number of metabolic activities, including enzyme function, transport activity, signal transmission, and gene expression. In fact, crucial Cys residues are frequently involved in transcription factors' DNA-binding activity, and it is essential to maintain these residues in a reduced form, at least in the nuclear compartment. The DNA-binding ability of AP-1, a transcription factor linked to tumour promotion, can be reduced if Cys-252 is oxidised. The "guardian of the genome," the tumour suppressor p53, has 12 Cys residues in its amino acid sequence, and some of them become inactive when they are oxidized.[16]

GlyNAC and Sleep

Free radicals and reactive oxygen species are created during the generation of ATP and are regulated by antioxidant molecules in Pathway for redox-methylation. A methylcobalamin cofactor with redox activity can be found in methionine synthase. This cofactor becomes oxidised under oxidative stress, restricting methionine synthase function, and may have an impact on the amounts of global DNA. Methylation in these circumstances, cystathionine and

homocysteine can combine to create cystathionine, which can subsequently be combined with cysteine to facilitate GSH formation. The Excitatory Amino Acid Transport (EAAT3), which is the primary source of cysteine in particular in the neuronal cells, is another source of cysteine. The GSH/GSSG ratio is an indicator of cellular redox status.[17]

GlyNAC and Hepatotoxicity

Glycine significantly reduced the levels of thiobarbituric acid reactive substances (TBARS) and hydroperoxides in the liver and brain when compared to the control after being given at a dose of 0.6 g kg⁻¹ body weight for 30 days. As opposed to alcohol-fed rats that were not supplemented with glycine, the activities of enzymatic and non-enzymatic antioxidants such as reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) in the liver and brain were dramatically increased. On glycine therapy, the levels of blood vitamin E and vitamin C were likewise elevated to nearly normal levels. Microscopic analysis of the alcohol-treated rat liver revealed fatty alterations and inflammatory cell infiltrates, which were reduced by glycine therapy. Rat brains exposed to alcohol showed oedema, which glycine therapy dramatically reduced.[18]

GlyNAC and Hypertension

Triglycerides, non-esterified fatty acids (NEFA), and intra-abdominal fat are all decreased by glycine (IAF). It is yet unclear how glycine affected the reduction of these factors. However, glycine, through its receptor (GlyR), reduces intracellular calcium in the presence of the chloride ion, which serves as a signal for a number of events, including the activation of phospholipase A2 (PLA2) to release arachidonic acid (AA), a precursor to vasoactive compounds like prostaglandin E2 (PGE2). Nitric oxide (NO) availability is decreased and peroxynitrites, a highly reactive species, are produced as a result of calcium activating reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and producing superoxide anions. As a byproduct of the reaction between g-glutamylcysteine and glycine, which is mediated by glutathione synthetase, glutathione removes free radicals that cause vasoconstriction and lower the amount of NO that is available (Nitric oxide). In order to increase the availability of nitric oxide, glycine helps to reduce the production of free radicals, which is the method by which it lowers high blood pressure.[19]

GlyNAC and Schizophrenia

Schizophrenia pathogenesis-related pathways of oxidative stress mechanisms raise the possibility of phenotypic realisation and schizophrenia development. The risk of developing schizophrenia is shown by the red line, while the axes show the distribution of different causative processes. These systems can all be active simultaneously or independently, as well as during various important times. Individuals are more susceptible to oxidative stress due to a variety of hereditary factors. Redox imbalance is caused by genetic predisposition brought on by environmental effects at different key times, which then results in dysregulation of gene expression and redox signalling. These adjustments encourage metabolic imbalances and mitochondrial malfunction. These procedures in turn contribute to improper myelination and faulty neural growth. These elements encourage neurotransmitter abnormalities and parvalbumin-positive interneuron dysfunction. Oxidative imbalance is also a result of immune dysfunction. The culmination of all these mechanisms is the emergence of psychosis and the progression of schizophrenia.[20]

GlyNAC and HIV

In live cells, N-acetyl-L-cysteine, a well-known antioxidant, works to neutralise the effects of reactive oxygen intermediates, preventing H₂O₂ from activating nuclear factor- κ B. Taurine, a protective antioxidant that enables antigen-presenting cells to stimulate T lymphocyte proliferation, is mostly derived from cysteine. The most thoroughly investigated method of raising the cell's GSH pool is to increase cysteine availability for GSH production. The substances put to the test include 2-oxothiazolidine 4-carboxylate, lipoic acid, cysteamine, and N-acetyl-L-cysteine (NAC). The extracellular reduction of cystine to cysteine can also be enhanced by other reducing substances such dithiocarbamate, -mercaptoethanol, and dithiothreitol. GSH and its precursor in individuals with HIV+ who received NAC or Gln supplements.[21]

GlyNAC and Male Infertility

Reactive oxygen species (ROS), which cause oxidative stress in the male germ line, can be produced as a result of a variety of circumstances. A lipid peroxidation cascade in the spermatozoa is sustained by high ROS levels. Acrolein, 4-hydroxynonenal (4HNE), and malondialdehyde are examples of lipid aldehydes that are produced as a result of oxidative stress caused by lipid peroxidation and the generation of free radicals (MDA). The two ways that oxidative

stress can affect sperm function are by damaging the sperm's plasma membrane, which affects sperm motility and its capacity to fuse with the oocyte, or by damaging the sperm's nuclear and mitochondrial DNA (mtDNA), which is linked to shorter telomere length, the formation of the oxidative base adduct 8-hydroxy-deoxyguanine (8-OHdG) and fragmentation of mitochondrial DNA. Due to spermatozoa's poor ability to undertake DNA repair, the impacts of 8-OHdG adducts in sperm DNA are more likely to cause DNA damage. DNA breaks can be single-strand or double-stranded. Oocytes may fail to finish base-excision repair and repair of 8-OHdG lesions due to the high mutagenic load in sperm DNA. As a result, these lesions persist in every cell of the embryo after conception, frequently resulting in hypermutability of the genome, genetic instability, and infertility. Due to ineffective or incorrect DNA repair by the oocyte before S phase, fertilisation of the oocyte (either by in vitro fertilisation or spontaneously) by a sperm cell with a high mutational load may result in the persistence of DNA damage. Increased rates of genetic aberrations in the embryo, including those that cause juvenile malignancies, neuropsychiatric disorders (such as autism and schizophrenia), and illnesses brought on by a dominant genetic mutation, are linked to ROS-induced oxidative stress in the male germ line (such as Apert syndrome and achondroplasia).[22]

GlyNAC and COVID-19

It is possible that biological processes related to ageing and disease make older people and those with comorbidities more susceptible to environmental stress factors, such as infectious agents like coronavirus SARS-CoV-2. The greater incidence of severe sickness and fatalities caused by SARS-CoV-2 (COVID-19) infection among these groups provide evidence. Impairment of redox homeostasis and accompanying oxidative stress, which appear to be important biological processes, may be one explanation for an individual's increased sensitivity to numerous environmental shocks. A thorough literature review and observations led to the idea that glutathione insufficiency is the most likely cause of significant symptoms and mortality in COVID-19 patients. The concept explains the puzzling epidemiological data on the risk variables causing severe COVID-19 infection symptoms and the high risk of mortality, and it creates prospects for the disease's effective treatment and prevention.[23]

Conclusion

This review shows that the glutathione deficiency, oxidative stress and other complications which were caused due to deficiency of glutathione and mitochondrial dysfunction can be rectified by Glycine and N-acetylcysteine (GlyNAC) which was the supplement that helps the cells for the glutathione production and overcome the defects. Many investigations were carried with this GlyNAC supplement to reduce the oxidative stress and to maintain a normal cell function. It will be an essential supplement to lead a healthy life for every human being after successful studies as evidence. In future investigations the advantages and disadvantages of the GlyNAC supplement could be found, which helps to identify the usage of the GlyNAC supplement over human beings in a beneficial ways.

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