GLUTATHIONE

(N-acetyl-L-cysteine (NAC) + Glycine)

"THE MASTER ANTI-OXIDANT" (and an Anti-Reductant)

Thiols (negative valence sulfur compounds) are the most important systemic and intracellular) antioxidants. In a class by itself is Glutathione, "The Master Antioxidant". Glutathione is critical in defense against Oxidative Stress (OxS) from exogenous assault, but even more essential as it is produced intracellularly to control endogenously-generated oxidative damage.

[Beyond its role as an antioxidant after conversion to Glutathione, negative valence sulfur plays a critical role at the interface between cells and the interstitium. This is the tissue sulfation that NUTRI-SPEC emphasizes so heavily. The resistance to Oxidative Stress (OxS) and nearly any type of exogenous insult (as for example, viral infections) depends upon adequate tissue sulfation. That is why we emphasize saturation with negative valence sulfur via Oxy Tonic as the first step of the NUTRI-SPEC BALANCING PROCEDURE. Oxy Tonic thiol saturation is a key to **LIVE STRONGER LONGER**, and the initial step in Metabolic Therapy for all patients.]

Glycine + NAC (N-Acetyl-Cysteine) supplementation rapidly improves Glutathione deficiency, Oxidative Stress, and free radical oxidation damage.

Enzymes involved in Glutathione biosynthesis and function are completely dependent on ATP and require magnesium as a cofactor. Magnesium supplementation improves mitochondrial function and increases the content of Glutathione in mitochondria. Furthermore, magnesium sulfate is effective as a treatment for preeclampsia, significantly promoting Glutathione production and suppressing ROS (Reactive Oxygen Species) and RNS (Reactive Nitrogen Species) generation. Recent studies show that serum magnesium levels of critically ill patients deserve attention.

Glycine + NAC, when combined intracellularly into Glutathione, stop INFLAM-AGING by reducing the inflammation derived from inflammatory cytokines and prostaglandins, and effectively combats all sources of Immuno-Neuro-Endocrine (INE) Stress.

Here is a list of inflammatory markers (signs of INE Stress leading to INFLAM-AGING) that are improved by Glycine + NAC supplementation as it contributes to the increase of Glutathione:

● prostaglandin inflammation (cyclo-oxygenase pathway of Omega-6 fatty acids from vegetable oils)

● inflammatory cytokines --- including both lymphocytic TH1-and TH2-mediated signs of INE Stress = TNF-α, TGB-β, INF-γ, IL-1, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-17

● Other signs of OxS = elevated Nitric Oxide, peroxide, ROS & RNS, NF-kB

● AGE (Advanced Glycation End-products) --- particularly critical in the INFLAM-AGING of diabetics

● protein carbonyls (an indicator of catabolic tissue breakdown)

● lipid peroxide; lipoxygenase

Even in the elderly, endogenous Glutathione production can be increased to a remarkable level by supplementation with NAC + Glycine. The endogenous production of Glutathione can also be enhanced by other ADAPTAGENS that induce the production of Glutathione. These inducers include particularly ---

- alpha lipoic acid
- carnosine
- quercetin

These three, along with other nutrients that take the anti-oxidant load off Glutathione, such as …

- selenium
- tocopherols and tocotrienols
- taurine
- carnitine
- acetyl-L-carnitine
- propionyl-L-carnitine
- betaine
- CoQ10 ---

are the key to ---

LIVE STRONGER LONGER.

Direct supplementation with Glutathione is nearly worthless. First, very little of it is absorbed from the gut. Even more critically, Glutathione does not efficiently pass through cell membranes. It must be synthesized within the cells. Therefore, your therapeutic target is to induce synthesis of Glutathione, --- either by supplying the precursors Glycine + NAC, or supplying inducers (as per the list above).

Supplementation with Glycine + NAC effectively controls the long list of INFLAM-AGING sources provided above, while supplementation of Glutathione does not. (----- Supplementation of liposomal Glutathione does increase its intestinal absorption, as shown by increased levels in the blood. But the benefits are minimal, since that Glutathione does not efficiently pass into the cells, and is thus largely ineffective clinically.)

Point of Emphasis: only endogenously produced (within the cells) Glutathione results in control of INFLAM-AGING.

NAC is promoted by the health food industry as an antioxidant. It has very little antioxidant activity. In fact, both the amino acid cysteine and NAC are anti-Anaerobic and anti-Anabolic in their Metabolic activity (per the NUTRI-SPEC paradigm of Metabolic Imbalances). As per its anti-Anaerobic benefits, the negative valence sulfur in the cysteine molecule enhances oxidation, minimizes Glycolysis, alters membrane permeability to favor sterols over fatty acids, and reverses excess Tissue Acidosis.

The only special feature of NAC is that it is a more stable form of cysteine to be used in supplements. Cysteine itself is very unstable. (Years ago we had a large amount of cysteine in our Oxygenic A for patients with Anaerobic Metabolic Imbalance. But the cysteine was too unstable, so we removed it from the product.)

So again, NAC has little antioxidant activity. So, why all the hype about NAC as an “anti-oxidant”? The hype solely reflects NAC’s use in production of the body’s most important antioxidant --- GLUTATHIONE. Nearly all antioxidant activity derived from NAC supplementation, and ALL antioxidant activity at the cellular level, results entirely to the extent NAC combines with Glycine to increase Glutathione.

Rushwrth, et al. Existing and potential therapeutic uses for NAC: the need for conversion to intracellular Glutathione for antioxidant benefits. PHARMACOL THER. 2014.

Gibson, et al. Evaluation of the antioxidant properties of NAC in human platelets: prerequisite for bioconversion to Glutathione for antioxidant and anti-platelet activity. J CARDIOVASC PHARMACOL. 2009.

NAC was found to be a weak reducing agent and a poor antioxidant compared with Glutathione. However, platelets treated with NAC showed enhanced antioxidant activity and depression of ROS generation --- but only in association with increases in intraplatelet Glutathione level. NAC supplementation significantly reduced both thrombin-induced and adenosine diphosphate-induced platelet aggregation. It is concluded that NAC should be considered a weak antioxidant that requires prior conversion to Glutathione to convey antioxidant and anti-thrombotic benefit.

The key conclusion of these studies is to reinforce the results of many other studies on the use of NAC as an antioxidant --- that NAC cannot be considered an antioxidant in its own right. Its strength is entirely due to the replenishment of Glutathione in deficient cells (and is ineffective in cells that are not Glutathione deficient).

Why does Glycine + NAC supplementation have such powerful metabolic efficiency and anti-INFLAM-AGING benefits? Most of the benefits derive from intracellular production of Glutathione from Glycine + NAC. But there are at least 2 other factors involved --- the benefits of Glycine and (to a small extent) NAC independent of their roles as Glutathione precursors.

First, consider the many metabolic effects of Glycine alone. ----- Glycine is an important methyl group donor. Methyl groups are abundant in DNA and are important components of multiple cellular reactions. Glycine is also important for normal brain function. Thus, providing Glycine could contribute to multiple benefits shown in the Glutathione studies described above.

Glycine has a hyperpolarizing effect on airway smooth muscle that is broncho-dilatory. Insuring optimal level of magnesium along with Glycine may modestly blunt the stimulatory effect of intracellular free calcium on bronchoconstriction.

To blunt the contribution of OxS to bronchial INFLAM-AGING, use can be made of Glycine + NAC to promote the intracellular synthesis of Glutathione. Glutathione inducers such as lipoic acid, selenium, and zinc are also helpful in this regard. Hydrogen sulfide is also beneficial for bronchial health by several mechanisms. NAC + Taurine may boost hydrogen sulfide synthesis.

When Glycine availability is too low to sustain a normal rate of Glutathione synthesis, there is a consequent rise in gamma-glutamyl cysteine, a metabolic waste product that is further metabolized and then eliminated in the urine. Urinary excretion of this metabolite is elevated in vegetarians and others on low-protein diets --- strongly suggesting that dietary Glycine can be rate-limiting for Glutathione synthesis.

Confirmation of Glycine's fundamental role in Glutathione synthesis is that NAC supplementation without Glycine supplementation does not raise Glutathione as effectively as does combining the two --- and administering Glycine alone, will raise Glutathione intracellularly.

Next, appreciate the role of NAC as a Cysteine donor. Cysteine is critically important in energy metabolism by contributing the sulfhydryl group (negative valence sulfur) (provided by Cysteine) needed for energy generation.

For example, Co-enzyme A is an important component of reactions governing energy generation. It depends on the availability of a sulfhydryl group for its function. Co-enzyme A is an important intermediate in the mitochondrial β-oxidation of fatty acids, and also for pyruvate metabolism in the Krebs' Cycle.

Cysteine is also important in maintaining protein structure, and in iron metabolism as a chelator of toxic iron.

NOTE: The simplest and quite effective source of negative valence sulfur is Oxy Tonic --- a primary component of the NUTRI-SPEC BALANCING PROCEDURE, and an essential ADAPTOGEN and Metabolic Spark for all your patients.)

One "bonus" benefit of Glutathione antioxidant activity comes not directly from the Glutathione itself, but derives from the ability of Glutathione to maintain the reduced state (active form) of vitamins C and E.

In most INFLAM-AGING proceses, OxS appears to have a direct connection with cell senescence. OxS and INFLAM-AGING increase the aging-related phenotype and induce and aggravate the inflammatory response, creating a chronic state of systemic inflammation.

----- OxS very definitely contributes to the states of "dis-ease" that progress as we age. But, these states of disease relate to our Healthspan --- yet do not correlate with Lifespan.

Does this mean there is no connection between OxS and aging? No, it does not. The intracellular portion of the damage from OxS directly feeds into the largely pre-programmed processes of Endogenous Aging (= INFLAM-AGING 'from the inside-out"). (See our article, "ENDOGENOUS INFLAM-AGING".)

Via Exogenous OxS ("from the outside-in"), that Endogenous process of INFLAM-AGING is magnified --- with the production of additional inflammation --- that then feeds right back into the Exogenous process of INFLAM-AGING --- in a vicious cycle.

Picture it this way … Exogenous Aging (which is a major determinant of Healthspan) is driven by external forces --- from the outside-in --- the environmental stresses that elicit OxS:

○ unhealthy microbiota
○ radiation exposure
○ excess UV light exposure
○ excess blue-green light exposure + deficient red-yellow (sun)light
○ emotional stress
○ sleep disturbance
○ nutrient deficiency
○ high sugar diet
○ high vegetable oil diet

But there is one other factor that exacerbates Exogenous Aging --- one that derives from the inside-out --- from one aspect of Endogenous Aging. The mitochondrial-associated functional and structural damage is at the core of both Endogenous Aging and Exogenous Aging.

------- Senescent Cells produce their own Endogenous INFLAM-AGING, independent of OxS-generated Exogenous INFLAM-AGING --- but exacerbated by it. A vicious cycle emerges --- with Exogenous INFLAM-AGING shortening Healthspan --- while provoking an increased Senescent Cell Endogenous INFLAM-AGING attack on Lifespan.

The exogenous OxS inflammation feeds even more endogenous generation of inflammatory cytokines (--- NF-kB, TGF-β) back into the already suffering Lifespan --- which then flows back into ever more exogenous OxS inflammation, and its damage to Healthspan.

This Immuno-Neuro-Endocrine Stress associated with chronic inflammation and leading to INFLAM-AGING is found in cell/tissue processes even in younger individuals. Diabetic patients (both T2D and T1D), by several mechanisms, including particularly elevated Advanced Glycation End products, are particularly susceptible to these premature processes of INFLAM-AGING.

The Oxidative Stress component of aging urgently calls for Glutathione supplementation. To decrease ROS & RNS, decrease free radical oxidative damage, and decrease INFLAM-AGING associated with OxS, supplements must achieve --- one or more of these …

- Synthesize Glutathione
- Induce synthesis of Glutathione
- Preserve Glutathione
- Potentiate the effects of Glutathione

In a study of Glycine + NAC supplementation in Glutathione synthesis, elderly subjects (age 60-75 years) compared to younger subjects (age 30-40 years) showed at baseline:

- higher body mass index
- higher fasting glucose and glycated hemoglobin
- impaired glucose tolerance
- (there were no other differences in blood count, plasma electrolytes, renal function or liver enzymes)
- 55% lower intracellular Glycine
- 24% lower intracellular Cysteine
- 46% lower intracellular Glutathione
- 36% higher oxidized Glutathione
- 155% lower Glutathione to oxidized Glutathione ratio

Since obesity per se and hyperglycemia per se have been linked to decreased antioxidant level and Glutathione synthesis, the data were adjusted to eliminate obesity and higher blood glucose as contributing factors. Even after adjusting for Body Mass Index and blood glucose, Glutathione was even lower --- much lower --- than the young adults --- 229% lower (0.7 compared to 2.3).

The point is that aging itself is the major factor in Glutathione depletion with age. ----- The underlying cause of "aging itself" is Endogenous INFLAM-AGING.

The 2 driving forces are elevated mTORC1, plus excess production of Senescent Cells. (Again, see our article, "ENDOGENOUS INFLAM-AGING".)

The lower rate of Glutathione synthesis in the elderly subjects at baseline was associated with significantly higher markers of oxidative damage (ROS metabolites, F2-isoprostanes, and lipid peroxides).

After only 14 days of supplementation with Glycine + NAC, elderly subjects showed a 50% reduction in lipid peroxides --- and, F2-isoprostane levels even lower than those in the younger control group. Over those 14 days, elderly subjects showed a 95% increase in intracellular Glutathione concentration.

That 14-day study was done on Glycine + NAC supplementation in Type 2 diabetics compared to non-diabetic controls. The ratio of Glycine to NAC supplementation was 1 to 1.

At baseline, T2D participants had 36% lower mitochondrial fat utilization and 106% higher mitochondrial glucose utilization. With 14 days of supplementation, the T2D group experienced a 30% increase in fatty acid oxidation and a 47% decrease in mitochondrial glucose oxidation. The Respiratory Quotient (respiratory exchange ratio) decreased significantly with this improvement in mitochondrial fatty acid oxidation.

At baseline T2D had 103%, 160% and 76% higher concentrations of plasma glucose, insulin, and free fatty acids respectively, and 425% higher insulin resistance. 14 days of supplementation significantly lowered fasting insulin by 19%, FFA by 25%, and insulin resistance by 22%.

The study also showed that the mitochondrial improvements were demonstrated quite well in skeletal muscle. The improved fatty acid oxidation makes muscle function more efficient, and has the additional benefit of weight loss of abdominal adipose.

In a study similar to the one above, supplementation with Glycine + NAC was continued for 12 weeks, and then 24 weeks instead of the 2-week trial described above.

At baseline, the elderly group showed 76% lower Glutathione than the younger adults, while plasma oxidative end-product concentrations were 845% higher and F2-isoprostane concentration 318% higher than the younger group. Glycine + NAC supplementation yielded a 200% increase in cellular concentrations of Glutathione, and decreases in concentrations of OxS end-products of 74%.

This study also measured mitochondrial fuel oxidation. Compared to fasting young adults, older adults had a significantly higher Respiratory Quotient and abnormal mitochondrial fuel oxidation. They showed significant 54% lower mitochondrial fatty acid oxidation and 51% higher mitochondrial glucose oxidation.

Glycine + NAC supplementation entirely corrected mitochondrial fatty acid and glucose oxidation --- and without affecting energy expenditure. The Respiratory Quotient showed much more efficient fat burning, and thus less dependence on sugar metabolism.

Compared to younger subjects, the older adults showed extreme elevation of many pro-inflammatory cytokines at baseline …

- IL-6 was 934% higher (--- !!!)
- TNF-α was 116% higher
- C-reactive protein (CRP) 88% higher
- endothelial function biomarkers of inflammation were as much as 175% higher

It was also shown that elderly subjects had fasting glucose 15% higher and insulin 469% higher, as well as insulin resistance 571% higher than in younger controls. Plasma concentrations of DNA damage markers were higher by 348%.

Glycine + NAC supplementation lowered IL-6 by 77%, TNF-α by 57%, and CRP by 49%, and decreased insulin by 55% and insulin resistance by 59%.

Older adults had significantly impaired cognitive scores, along with lower fasting plasma BDNF (brain-derived neurotrophic factor). Older adults also showed declining physical function --- with slower gate speed, lower grip strength, and decreased performance on the 6-minute rapid walk test.

Glycine + NAC supplementation resulted in significant improvement in both cognitive performance and physical function tests. All measured cognitive functional assessments improved. The slower gate speed improved enough to match the younger control group, and there was significantly improved hand grip strength and 6-minute rapid walk test performance.

With the improvements in Respiratory Quotient (fat burning versus sugar burning in the mitochondria) --- there was a significant reduction in total body fat and in waist circumference --- showing preferred fat loss in the abdomen --- an indication of improved insulin sensitivity.

By what mechanism is there a deficiency of Glycine and Cysteine in aged individuals? This study disproved the theory that these two amino acids, since they are gluconeogenic, are used for increasing mitochondrial use of glucose for energy.

It is falsely theorized that with age there is this steadily increasing defect in mitochondrial fatty acid use, such that amino acids (including Glycine and cysteine, but many others as well) are diverted toward glucose-derived energy generation. (This explanation also accounts for the elevated muscle protein breakdown seen in older adults --- a breakdown that is reversed with Glycine + NAC supplementation.) ----- But …

In this study the supplemented Glycine + NAC was not converted to glucose for mitochondrial energy production, but rather moved energy generation away from glucose utilization, while increasing efficiency of fatty acid use.

The researchers who conducted the study described immediately above did a follow-up on mice to see if Glycine + NAC supplementation could increase Lifespan. It was found that, compared to Placebo, mice supplemented with Glycine + NAC lived 24% longer than control mice, improved/corrected impaired Glutathione synthesis, Glutathione Deficiency, OxS, mitochondrial dysfunction, abnormal mitophagy, nutrient-sensing, and genomic damage.

(Mitophagy is the process of autophagy for mitochondria applied specifically to muscle cells --- both skeletal muscles and the heart muscle. Autophagy is a critical component of all approaches to life extension.)

An essential element in life extension strategies is to improve nutrient sensing in vital organs --- required for proper flow and utilization of nutrients. Glycine + NAC supplementation showed significant improvement in heart, liver, and kidney nutrient sensing. Nutrient sensing is critically important as a regulator of energy metabolism, and is linked to longevity.

The improvement in nutrient sensing from Glycine + NAC supplementation appears to relate to NAD+ (Nicotine Amide Dinucleotide) regulation of muscle energy metabolism. NAD+ is one of the 10 or so drugs and nutrients identified by Gerontologists as clearly beneficial in life extension strategies.

In T2D, there is extensive OxS and Di-carbonyl Stress --- driven by excess accumulation of AGE (Advanced Glycation End-products). The most pathogenically significant Di-carbonyl Stress reflects spontaneous dephosphorylation of glycolytic tricose phosphates, giving rise to highly reactive methylglyoxal. This compound can be converted to a harmless lactate by the sequential activity of enzymes that employ Glutathione as a catalyst.

The field of Geroscience has identified at least 9 hallmark defects of aging that are believed to contribute to the aging process. (See our article on mTOR and Senescent Cells, “Endogenous INFLAM-AGING”.) These hallmark defects of aging include:

- mitochondrial dysfunction,
- dysregulated nutrient sensing (which includes insulin resistance),
- altered intracellular communication, which includes --- inflammation, genomic instability, loss of proteostasis, epigenetic alterations, cellular senescence, telomere attrition, and stem cell exhaustion.

Glycine + NAC supplementation improves the components of 4 aging hallmarks (--- mitochondrial dysfunction, inflammation, insulin resistance and genomic damage).

Leukocyte function is a good marker for health, and is a longevity predictor.

Two groups of women --- a post-menopausal group of healthy women versus a group of healthy women aged 30-43 --- were compared. Measurements included lymphocyte function (adherence, chemotaxis, proliferation, and natural killer cell activity) and neutrophil function (adherence, chemotaxis, phagocytosis, and superoxide) --- as well as cytokine levels (IL-2, TNF-α, and IL-8).

The above parameters scored significantly lower in the post-menopausal women. After daily supplementation of NAC, 600 mg, these levels were rechecked after 2 and 4 months, and then 3 months after the end of supplementation.

The impairment of immune function and increased oxidative markers in post-menopausal women significantly improved after both 2 months and 4 months of supplementation --- bringing their values very close to those of younger women, and thus exerting a modulatory, rather than merely a stimulatory action on the immune system. These beneficial effects persisted for 3 months after the end of supplementation.

The conclusion of this study is that NAC supplementation offers prolonged strengthening of immune defense by increasing the leukocyte Glutathione pool.

The deepest effect of low Glutathione on the immune system is the induction of lymphocyte's apoptotic cascade. The Glutathione deficiency effects on apoptosis and inhibition of T-cell proliferation could explain why CV-19 patients develop lymphopenia, and subsequent failure of the immune system.

----- One way to explain cell death associated with deficient Glutathione is ferroptosis, a unique iron-dependent form of non-apoptotic cell death --- characterized by lipid peroxidation --- with ROS accumulation due to Glutathione inactivation and high levels of Glutathione consumption. Ferroptosis is definitely a causative factor in brain INFLAM-AGING.

Glutathione is essential for appropriate function of all components of the immune system, especially T-lymphocytes, macrophages, and neutrophils. The failure of the immune system combined with the loss of Glutathione protective effect as an antioxidant may explain the progression of viral infections into acute respiratory distress syndrome.

Glutathione in macrophages directly affects the TH1/TH2 cytokine response. More specifically, Glutathione depletion inhibits TH1-associated cytokine production and/or promotes TH2-associated responses.

One of the initial steps in antigen degradation and processing requires Glutathione. Although Glutathione inhibits production of most inflammatory cytokines, it is needed to keep an adequate Interferon Gamma production by dendritic cells essential for intracellular pathogen-host defense. The principal function of endogenous Glutathione is not to limit inflammation but to fine-tune the innate immune response to infection.

Viruses markedly decrease cellular thiols, essentially lowering Glutathione. Glycine + NAC supplementation can restore Glutathione levels.

Glutathione increases activation of cytotoxic T-cells, and adequate functioning of T-lymphocytes and other cells depends upon cellular supplies of cysteine.

Cells acquire cysteine mainly by macrophage and lymphocyte uptake --- impaired immune responses are associated with low Glutathione. Glutathione depletion triggers the lymphocyte's apoptotic cascade --- leading to lymphopenia that affects mostly T-lymphocytes. Lymphopenia is directly associated with severe inflammation response.

Glutathione is of major importance for the appropriate function of the immune system in general, and particularly lymphocytes since low Glutathione inhibits T-lymphocyte proliferation and subsequently inhibits immune response. ----- That decreased immune response can be reversed by Glycine + NAC supplementation.

The liver is an excellent indicator of Glutathione need …

K Q de Andrade, et al. Oxidative Stress and inflammation in hepatic diseases: Therapeutic possibilities of NAC. INT J MOL SCI. 2015.

Oxidative Stress (OxS) associated with excess production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) is a major source of inflammation, and thus INFLAM-AGING. OxS is provoked by …

- continuous exposure to viral, fungal, and bacterial toxins,
- other organic and inorganic toxins,
- alcohol,
- UV light,
- HOHUM PUFAs (Hydrogenated Oxidized, Heated and otherwise Un-Metabolizable Polyunsaturated Fatty Acids),
- Bio-transformed metabolites (caused by Metabolic Imbalances and Inefficiencies --- particularly associated with ingestion of fructose (sugar) and HOHUM PUFAs, and, from abnormal gut microbiota),
- endotoxin (Lipopolysaccharide (LPS)) (abnormal gut microbiota),
- auto-immune diseases,
- drug toxins (both recreational and pharmaceutical) …

More than any other organ or system in the body, the liver must deal with all these sources of OxS. Thus, liver function and liver pathophysiology is one measure of overall oxidative burden.

Liver fibrosis is a wound-healing process, which is reversible, and results from chronic OxS liver burden. Under the load of chronic OxS, the resulting Immuno-Neuro-Endocrine (INE) Stress activates both the innate and the adaptative immune systems --- with polymorphonuclear leukocyte (PMN) infiltration, inducible Nitric Oxide Synthase (iNOS) up-regulation, and recruitment of lymphocytes.

The INE Stress causes both leukocytes and liver Kupffer cells to produce large amounts of Nitric Oxide, inflammatory prostaglandins, and inflammatory cytokines, particularly TGF-β (the potent pro-fibrogenic cytokine) and TNF-α (a potent inflammatory).

Studies of hepatic diseases show that the liver is perfectly representative of all body tissues in defense against OxS. The liver overproduction of ROS and RNS, and, reduction of hepatic Glutathione, are common profiles in not poor liver health, but all organic INFLAM-AGING, regardless of etiology.

Antioxidant defenses are critical throughout the body and their essentiality is particularly demonstrable in hepatic defenses. Research shows that among all antioxidant systems, Glutathione stands out as by far the most abundant cellular antioxidant. Glutathione exhibits numerous and versatile functions in protecting cells against toxicity and all forms of oxidative damage.

Liver fibrosis (liver INFLAM-AGING) is reversible --- so is INFLAM-AGING in all body organs --- by endogenous (--- not plasma) Glutathione.

Glutathione deficiency is a critical factor in cardiovascular health. ----- As the most abundant antioxidant in the heart, Glutathione plays a fundamental role in normalizing a redox homeostatic mechanism that has shifted toward either oxidative or reductive stress. The resulting impaired cellular signaling mechanisms and accumulation of misfolded proteins causes proteotoxicity associated with cardiac INFLAM-AGING.

Oxidative Stress is crucial in atherogenesis. In arteriosclerotic lesions, a higher level of OxS (as evidenced by elevated plasma malondialdehyde and low Glutathione, low α-tocotrienol and low erythrocyte and cardiomyocyte Glutathione peroxidase enzyme activity) --- plays a role in the development of coronary artery INFLAM-AGING. Patients with single, double or triple vessel stenosis, and patients with acute coronary syndrome, show significant decrease in Glutathione.

Excessive homocysteine production (hyperhomocysteinemia) is an independent risk factor for poor heart and vascular health. Elevated homocysteine is particularly significant when Glutathione synthesis is low. Hyperhomocysteinemia decreases Glutathione peroxidase activity --- accelerating both cardiovascular and brain INFLAM-AGING.

Glycine + NAC supplementation supports Glutathione synthesis --- and thus reduces hyperhomocysteinemia, improves Glutathione peroxidase activity, and reduces OxS in the cardiovascular system and in the nervous system. (Supplementation with folic acid and Vitamins B6 and B12 (as found in Activator) is also effective at reducing hyperhomocysteinemia, and may enhance Glutathione activity.)

Atherosclerosis, a chronic manifestation of INFLAM-AGING, may be an ideal environment for the high viral replication capabilities of viruses in human cells --- enhancing hyper-inflammation secondary to immune system dysregulation --- leading to adverse outcomes.

In a vicious cycle, viruses may aggravate the evolution of arteriosclerosis as a result of excess plasma concentration of cytokines. Atherosclerosis progression, as a chronic inflammatory mechanism, is characterized by immune system dysregulation associated with increased pro-inflammatory cytokine production, including IL-6, TNF-α and IL-1β. C-reactive protein (CRP) is an active regulator of host innate immunity and a biomarker of severe INFLAM-AGING --- compromising lung and vascular health.

Macrophage activation may explain the elevated CRP serum levels and contribute to INFLAM-AGING progression. CRP-mediated inflammation in atherosclerosis may be explained by the presence of CRP in the lesions.

Atherosclerosis represents a state of intense OxS characterized by vascular wall lipid and protein oxidation that contributes to chronic inflammation in the endothelium --- in which CRP is a major player. Elevated CRP is an indicator of LDL oxidation in the endothelium --- provoked by activated macrophages releasing excess IL-6.

Enhancing Glutathione synthesis with Glycine + NAC and Lipoic Acid --- while providing adequate selenium and Quercetin and other ADAPTOGENS --- will strengthen the cardiovascular antioxidant defense.

Supplementing with Glutathione precursors NAC + Glycine facilitates the synthesis of Glutathione within every cell of the body --- including the atherosclerotic plaque, thus reducing ROS and LDL oxidation, and mitigating arteriosclerosis.

----- Considering the primary importance of oxidized LDL in the pathogenesis of arteriosclerosis, it is reasonable to elevate the role of antioxidants in the maintenance of cardiovascular health to a higher importance than lipid-lowering or anti-inflammatory therapies.

In the brain, NAC suppresses ischemia-induced neuronal death through promotion of hippocampal Glutathione synthesis. Increased hippocampal Glutathione synthesis neutralizes ROS and RNS and regulates zinc homeostasis in neurons --- promoting neuro-protection after ischemia/ reperfusion.