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# ADVANCED OXIDATIVE STRESS TEST

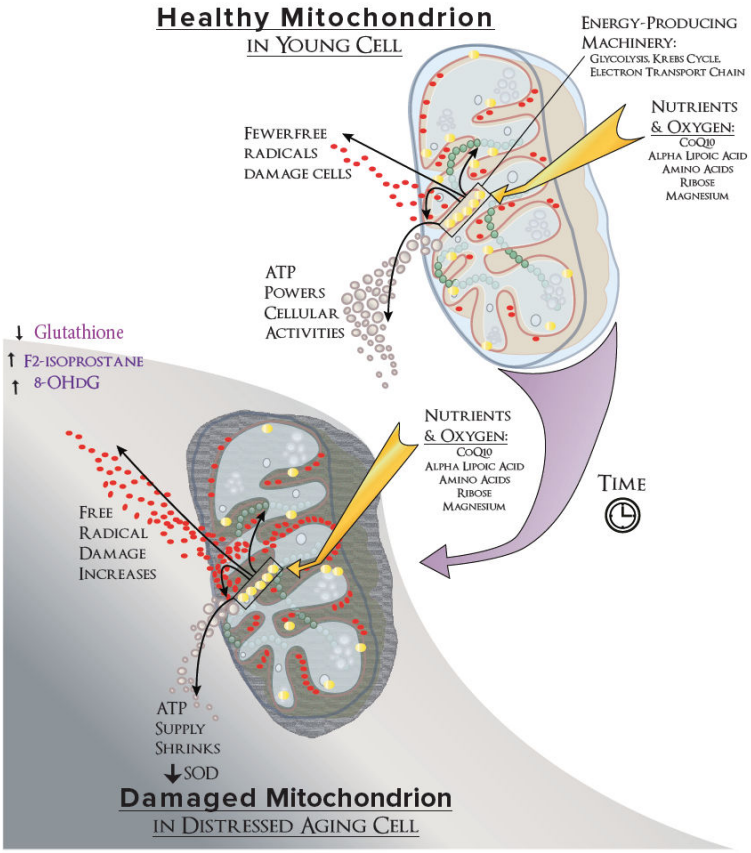
**The Advanced Oxidative Stress test shows how much oxidative stress there is in the body and how effectively antioxidant enzymes remove it. Reactive oxygen species (ROS, also called free radicals) are produced by virtually every metabolic process in the body and are counterbalanced by the action of antioxidants.**

**Mitochondria are the main producers of ROS and the main victims of ROS.[1] Two systems are important for proper removal of ROS. One is intracellular reduced glutathione, the primary antioxidant found within cells. The other is the superoxide dismutase (SOD) family, the main enzymes which remove ROS from the cell and mitochondria. When these antioxidants do not function normally, free radicals accumulate, which leads to cellular damage including DNA, protein and lipid membrane dysfunction.**

**Oxidative stress can increase a person's risk for heart disease,[2] neurologic conditions, [3-6] cancers,[7] or toxicity.[8,9] Oxidative damage to lipids occurs early in the development of ather-osclerosis and can lead to cardiovascular and cerebrovascular disease.[10,11] Oxidative**

**Damage to mitochondria and DNA are hypothesized to be involved in the pathogenesis of Alzheimer's disease.[12] As seen in Table 1, oxidative stress is thought to contribute to Parkinson's disease, cancer,[13] and autoimmune thyroiditis.[14,15]**

**Oxidative damage in the central nervous system has been implicated in neuropathological changes. It has been estimated that 3-10% of the oxygen used by tissues is converted into reactive oxygen species, posing a threat to nearby cells and tissues.[16] The nervous system consumes a high amount of oxygen but does not have high antioxidant defenses, making it susceptible to damage by reactive oxygen species and reactive nitrogen species. Both oxidative and nitrosative stress have been implicated in neurodegenerative and neurological disorders[17] as well as traumatic brain injury.[18]**





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## Glutathione

Glutathione is the most abundant intracellular antioxidant[30] and is critical for defending the cell against oxidative stress. As the name suggests, gamma-L-glutamyl- L-cysteinylglycine (glutathione, GSH) is a tripeptide made from glutamate, cysteine, and glycine. Its sulfur (thiol) group is responsible for its biological activity.

GSH neutralizes free radicals and conjugates toxins for removal from the body, thereby protecting cells from oxidative stress and toxic xenobiotics.[31] GSH is important for mitochondrial function as a redox scavenger.[32] GSH is involved in cell proliferation, apoptosis, auto-phagy, and gene expression. GSH is involved in regulation of Nrf2 (See "Nrf2 Activa-tors" in the Treatment Options section).[30]

## Cellular Antioxidant Defense Systems

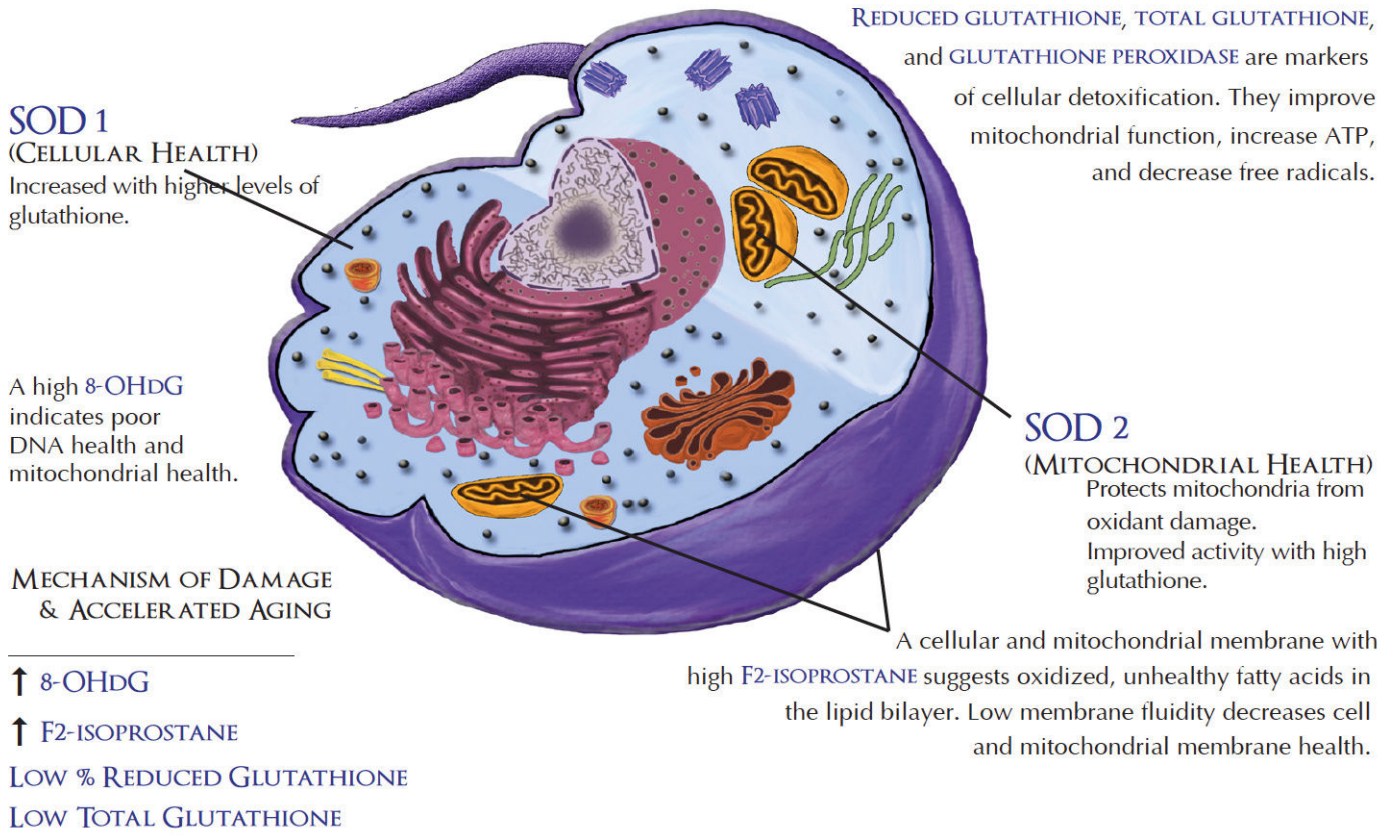


**Figure 2.** High levels of 8-OHdg, F2-isoprostane, with low glutathione and reduced glutathione indicate cell damage and free radical overload.

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## Conditions Associated with Oxidative Stress

| | | |
|---|---|---|
| Alzheimer's disease[19] | Chronic inflammation[6,20] | Premature labor and stillbirth[20] |
| Atherosclerosis[6,20] | Diabetes[6,24] | |
| Autism[21] | Gastrointestinal disorders[25] | Rapid aging[6] |
| Autoimmune disorders[22] | Hormonal imbalance[26,27] | Schizophrenia[23] |
| Bipolar disorder[23] | Major depressive disorder[23,28] | Stroke[6,29] |
| Cancer[20] | Neurodegenerative disorders[6,20,29] | Thyroid dysfunction[14,15] |

## Glutathione

Total glutathione includes both reduced and oxidized glutathione levels. Glutathione is constantly undergoing oxidation and reduction and therefore exists in two forms, reduced and oxidized. The reduced form of glutathione is the radical scavenger (or antioxidant). Oxidized glutathione is the "used up" form of glutathione (Figure 3). Oxidized glutathione has contributed its antioxidant potential and then must be recycled to the reduced form of glutathione to be useful once again. Total glutathione levels can indicate the body's total reserves of glutathione for removing harmful free radicals and toxins. Total glutathione may be low due to genetic variation in enzymes involved in glutathione production, nutritional insufficiency, or exposure to reactive chemicals or medications.[13,33]

**The Advanced Oxidative Stress Test measures these biomarkers from a whole blood and urine specimen:**

- Total glutathione (whole blood)
- Percent reduced glutathione (whole blood)
- F2-isoprostane (urine)
- 8-hydroxy-2'-deoxyguanosine (8-OHdG, urine)

**Disturbed glutathione levels have been seen in these conditions: 13,23,34**

- Aging
- AIDS
- Bipolar disorder
- Cancer
- Cardiovascular disease
- Cystic fibrosis
- Diabetes
- Immune disease
- Inflammatory disease
- Liver disease
- Major depressive disorder
- Metabolic disease
- Neurodegenerative disease
- Schizophrenia

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# Glutathione

**Reduced glutathione** is the active form of glutathione. It is the primary antioxidant needed to remove damaging free radicals from the brain, liver, and lungs. If the levels of reduced glutathione are low, it is difficult for the mitochondria to make cellular energy. Low reduced glutathione indicates poor antioxidant status. Aberrations in glutathione (more oxidized GSH) can lead to hypomethylation because methylation and transsulfuration pathways are interconnected.[35]

***Treatments*** to support glutathione synthesis are amino acids (N-acetylcysteine (NAC), glycine, and glutamate) and selenium. Adjunctive treatments that help raise glutathione levels and support overall detoxification are: taurine, milk thistle, minerals, and the B vitamins (niacin, riboflavin, vitamins B12, B6, and folate). Selenium and alpha-lipoic acid can improve reduced glutathione levels. Remove toxic chemicals or medications that may deplete GSH.

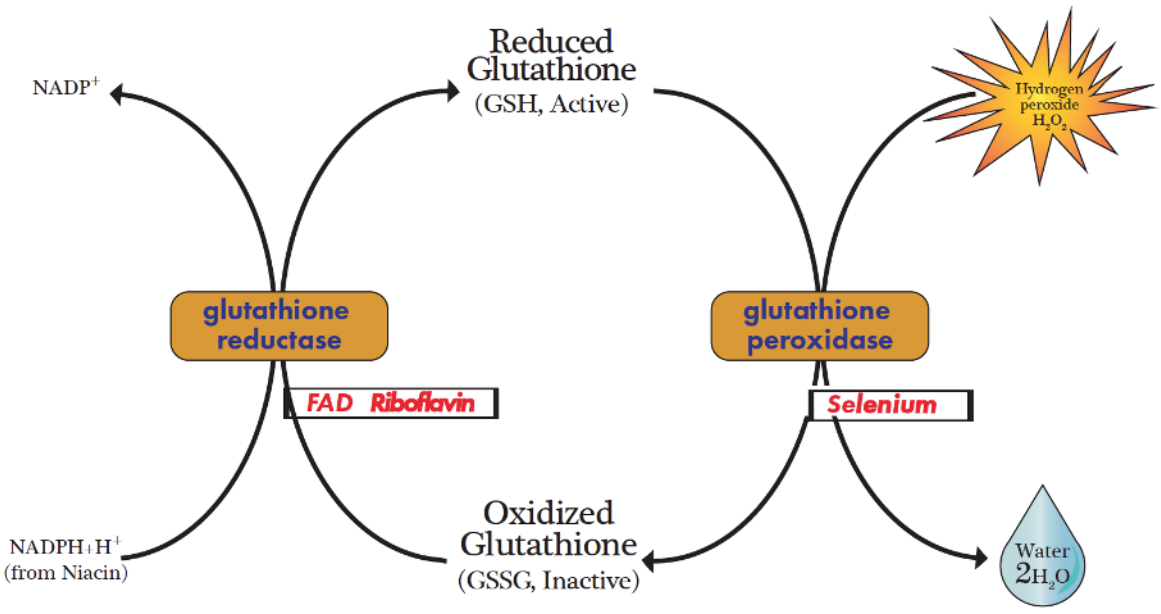


**Figure 3.** The Glutathione Oxidation-Reduction Cycle. Glutathione is constantly undergoing oxidation and reduction and therefore exists in two forms, reduced (GSH) and oxidized (GSSG). The reduced form of glutathione is the antioxidant. The oxidized form of glutathione is the "used up" form which cannot bind free radicals. Glutathione peroxidase uses the cofactor selenium to convert hydrogen peroxide to water. To recycle glutathione and produce the active, reduced form, glutathione reductase, riboflavin, and niacin are needed.

## Low percent reduced glutathione may be associated with: [5,6]

- Anxiety
- Depression
- Fatigue
- Neurological conditions

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# F2-Isoprostane

**F2–isoprostane** (F2-isoprostoglandin, 8-iso-prostoglandin F2α) is the oxidized degradation product of arachidonic acid, a fatty acid with significant inflammatory potential. F2-isoprostane is an oxidized lipid, pro-inflammatory, and a vasoconstrictor.[36] Urinary F2-isoprostane is the gold standard marker of lipid peroxidation in biological specimens[19,37] and has been described as a, "reliable approach to assess oxidative stress."[38]

F2-isoprostane can cause vasoconstriction in the kidneys, lungs, liver, bronchi, blood and lymph vessels, uterus and gastrointestinal tract. F2-isoprostanes are associated with increased perception of pain and are elevated in acutely hyperglycemic diabetics. They are also high in smokers and in autism.

F2-isoprostane has been suggested as an indicator of cardiovascular disease.[2] F2-isoprostanes were higher in patients with coronary artery disease[39] and the levels correlated with the number of lesions as well as the incidence of hypertension.[40] F2-isoprostanes are highly concentrated in atherosclerotic plaques.[41] Plasma F2-isoprostane correlated positively with systolic and diastolic blood pressure, supporting the role of oxidative stress in hypertension.[42]

## High levels of F2-isoprostane may be found in:

- Atherosclerosis[41]
- Attention deficit disorders
- Cancer
- Cardiovascular disease[2]
- Depression[2]
- Generalized pain and inflammation
- Neurodegenerative diseases[3]
  - Alzheimer's disease [4,19]
  - Creutzfeldt-Jakob disease (mad cow)[4]
  - Huntington's disease[4]
  - Multiple sclerosis[4]

**Treatments** to lower F2-isoprostanes, the precursor, arachidonic acid, can be targeted. Clinicians may increase omega-3 fatty acids, decrease dietary arachidonic acid, and increase antioxidants. Lifestyle modifications aimed at decreasing body mass index and smoking cessation can reduce F2-isoprostane.[43] Oral antioxidants lowered isoprostanes in 45% in human intervention studies.[38] Therefore, dietary and supplemental antioxidants should help to lower oxidative stress markers like F2-isoprostane.

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# 8-OHdG

8-OHdG (8-hydroxy-2'-deoxyguanosine) is an oxidized base that has been identified and removed from the DNA, and excreted in the urine. It is the most studied marker of oxidative damage to DNA. DNA damage is a normal part of life, but chronic elevation can be a concern because it signals increased oxidative damage. While 8-OHdG is not a diagnostic marker of cancer, it has been widely used as a marker of oxidative stress, degenerative diseases, and is considered a risk factor for certain cancers.[7] 8-OHdG is of special biological interest because it induces a transversion of DNA bases guanine to thymine, which is a mutation frequently found in cancers.[44]

Oxidative stress as evidenced by high 8-OHdG has been found in depression, fatigue, diabetes, extreme exercise, neurodegenerative disease, toxicity, and other conditions. High urinary 8-OHdG was found in patients with major depression and chronic fatigue syndrome. There was a correlation between 8-OHdG levels and scores for sadness and flulike malaise.[45]

Extreme sports, medications, and environmental toxins, such as arsenic and mercury, can increase 8-OHdG. After four days of antibiotic therapy, urinary 8-OHdG dramatically increased the following: ciprofloxan (100%), tetracycline (230%), kanamycin (400%), and ampicillin (720%).[46] Antibiotic therapy also increased other markers of oxidative damage and decreased ATP production. In-house clinical observations show that chemotherapy increases 8-OHdG as a normal consequence of treatment.

DNA damage has been shown to be involved in the pathogenesis of Alzheimer's disease.[47,48] High 8-OHdG was detected in the cerebrospinal fluid of patients with Alzheimer's and is correlated with the duration of illness.[12] In Alzheimer's patients, astrocytes from the hippocampus and cerebral cortex had increased levels of double-stranded DNA breaks and there was increased 8-OHdG within cerebral tissue.[49,50]

## Elevations of urinary 8-OHdG have been seen in:[8]

- Alzheimer's Disease
- Arsenic Poisoning
- Bladder Cancer
- Cardiomyopathy
- Cigarette Smoking
- Chemical Exposure
- Chronic Obstrutive
- Depression
- Diabetes
- Parkinson's Disease
- Diabetic Nephropathy
- Exposure to Ultraviolet Light
- Extreme Exercise
- Fatigue
- Hemodialysis
- Insomnia
- Neurodegenerative Diseases
- Pulmonary Disease

**Treatments** to decrease urinary 8-OHdG include water-soluble antioxidants, as DNA resides in a water soluble compartment of the cell. Vitamin C and plant-derived antioxidants, such as flavonoids and polyphenols, help to lower 8-OHdG. Other treatments to reduce oxidant stress, avoid toxins and optimize liver function can also decrease 8-OHdG.

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# Oxidant Stress Treatment Options

Oxidative stress can cause high or low levels of an antioxidant enzyme. At the initial onset of oxidative stress, the body produces more of the enzyme to cope with the free radicals. However, with chronic oxidative stress, enzyme levels are depleted and cannot respond properly to the oxidant challenge. Toxins can also deplete antioxidant enzymes. Therefore, treatment options are the same for both high and low levels of GSH. In contrast, F2-isoprostanes and 8-OHdg are elevated in cases of oxidative stress. Generally, treatments include nutritional support for detoxification, stimulation of Nrf2-ARE pathway, antioxidants, minerals, adjunctive nutritional treatments, and elimination of toxins, infection, and environmental sources of oxidative stress. Females may have higher needs for antioxidants.[27]

| Biomarker | Increase Antioxidant Defenses | Reduce Oxidative Stressors |
|---|---|---|
| **Total GSH** | Se, B vitamins, NAC, ALA, amino acids, taurine, GSH, SAG, broccoli seed extract or glucaphoranin, turmeric, green tea, pterostilbene, black pepper, resveratrol | Avoid toxins, infections, and unnecessary medications |
| **Reduced GSH** | ALA, B vitamins, Se, Nrf2 activators, glucaphoranin, SAG, vitamins A, E, D and CoQ10 | Avoid toxins, infections, and unnecessary medications |
| **F2-isoprostane** | Omega-3 fatty acids, SAG, vitamins A, E, D, CoQ10, dietary antioxidants, reduce BMI | Reduce arachidonic acid, stop smoking |
| **8-OHdG** | Vitamin C, flavonoids, water-soluble phytonutrients, green tea, broccoli seed extract or glucaphoranin, turmeric, pterostilbene, black pepper, resveratrol, quercetin | Avoid toxins, infections, and unnecessary medications |

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## Sulfur amino acids and nutritional support for detoxification

Amino acids are necessary for enzyme synthesis, glutathione synthesis and phase II detoxification. Free form amino acids such as cysteine, glycine, and taurine increase glutathione and aid in detoxification. Taurine also aids in detoxification.

S-acetyl glutathione (SAG) can be used to increase glutathione levels (200 to 400 mg, once or twice daily).

N-acety-L-cysteine (NAC) is a derivative of the dietary amino acid, L-cysteine. It is a powerful free radical scavenger and thus supports the body's natural defense system. NAC provides cysteine, the major precursor in the biosynthesis of glutathione.

NAC has the ability to chelate heavy metals[87] and has shown efficacy in treating psychiatric disorders.[88] Two to four grams of NAC each day can provide the building blocks for glutathione.

Medical foods for detoxification, together with a modified elimination diet, help to remove toxins and quench oxidative stress. These typically consist of 21 grams of protein, 2.5 grams of immunoglobulins, 1 gram of arabinogalactan (a prebiotic), and 30 mg of broccoli seed extract (as glucoraphanin) per day.

Milk thistle extract or silymarin from milk thistle (260 – 525 mg) and alpha-lipoic acid (200 to 400 mg) help with liver detoxification. Nutrients to support phase I and phase II detoxification can be taken twice daily: pomegranate extract (75 mg), green tea extract (95 mg), watercress powder (250 mg), methylsulfonylmethane (MSM, 50 mg), and calcium D-glucarate (200 mg/day, especially to detoxify hormones).[89]

## Nrf2 Activators

Nrf2 has been called the "master regulator" of the antioxidant response.[90] Nrf2 is a transcription factor that regulates the expression of antioxidants and anti-inflammatory genes through the human Antioxidant Response Element (ARE). The Nrf2-ARE signaling pathway is the cell's defense against oxidative stress and it is triggered when free radicals increase and/or when there is reduced antioxidant capacity.[91] Activation of the Nrf2-ARE pathway initiates the expression of genes that make proteins involved in glutathione synthesis, Phase II detoxification, drug transport, removal of ROS, reduction of inflammation, and protection from ischemia/reperfusion injury.[90]

The Nrf2-ARE signaling pathway upregulates SOD, GSH, and GPx, among others.[92] For these reasons, targeting the Nrf2- ARE pathway with nutrients is a popular strategy to promote a person's antioxidant defenses. Sulforaphane and curcumin can activate the Nrf2-ARE pathway[90] while sulforaphane increases SOD, GSH, and GPx.[93] Broccoli extract is a source of sulforaphane. Broccoli seed extract or glucoraphanin (also known as sulforaphane glucosinolate or SGS) can increase glutathione levels.

Green tea extract, *trans*-pterostilbene (the primary antioxidant in blueberries), and black pepper extract work together with broccoli extract and turmeric to activate the Nrf2 genetic pathway. These ingredients also activate glutathione- S transferase and down-regulate inflammatory factors such as nuclear factor kappa B (NF-kB). Typical daily doses are: 60 to 120 mg of broccoli extract, 400 to 800 mg of turmeric extract, 400 to 800 mg of green tea extract, 100 to 200 mg of transpterostilbene, and 4 to 8 mg of black pepper extract.

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## Antioxidants

Water-soluble and fat-soluble antioxidants can target both compartments of the cell. Water-soluble antioxidants include vitamin C (1-4 g/d), green tea extract,[94] quercetin (250 to 500 mg/d) and resveratrol (75 to 150 mg/d). A diet high in colorful, organic fruits and vegetables is high in antioxidants, polyphenols and flavonoids. Green tea treatment of diabetic rats with nephropathy reduced oxidative stress markers, including 8-OHdG.[94] Resveratrol, quercetin, and pterostilbene work synergistically to reduce toxicity or infection that elevates MnSOD (SOD2).

ALA helps to neutralize free radicals in both the water-based and lipid-based portion of cells, synthesize glutathione, and recharge important antioxidants. It decreases oxidative stress and increases MnSOD activity and glutathione activity in mitochondria.[95] The commonly given dose of ALA is 300 mg to 600 mg to support antioxidant activity and liver function. Also consider vitamins A, E, D and CoQ10 to deliver antioxidants to the fat-soluble portion of the cell.

## Omega-3 Fatty Acids

Healthy fats are needed when F2-isoprostanes are elevated. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), taken with vitamin E as mixed tocopherols, reduce the rate of lipid peroxide formation in cells. One to two grams of EPA, 600 to 1500 mg of DHA, and 20 – 40 IU of mixed tocopherol vitamin E can be taken one to three times daily for cardiovascular health, nervous system function, and joint tissue health.

## Minerals

Selenium, copper, zinc, manganese, iodine, and iron are the cofactors for many antioxidant enzymes. Selenium protects the thyroid from radical damage, presumably through its role in GPx.63 Copper, manganese, and zinc are important cofactors for SOD enzymes. Selenium is a cofactor for GPx. Chronic use of proton pump inhibitors or a nutritionally poor diet will decrease mineral status. Typical dosages are: selenium (100-200 mcg/d), copper (2-10 mg/d), zinc (15-50 mg/d with food), manganese (5-13 mg/d), iodine (150 mcg-6 mg/d), and iron (15-50 mg/d).

## Lifestyle Modifications

Environmental stresses, such as chemical toxins, endocrine disruptors, heavy metals, and infectious agents can cause oxidative damage. Detoxification of the body is additionally supported with an anti-inflammatory diet free of allergens such as gluten, dairy, eggs, caffeine, nicotine, artificial sugars and flavors, and stimulants. In addition, it is important to foster good mental hygiene with healthy sleeping habits, moderate exercise, and stress reduction techniques to minimize mental and emotional stressors.

### Other testing to consider when a patient shows high oxidative stress:

- Urinary or plasma amino acids: Amino acids are necessary to produce glutathione and are important for phase II detoxification.
- Red cell or urinary minerals: Minerals are important cofactors in antioxidant enzymes.
- Plasma neurotransmitters: Oxidative stress can lead to neurotransmitter imbalances, receptor damage, and ultimately cause neurological disorders.
- Gastrointestinal tract (intestinal permeability, stool testing, food sensitivities): In a patient with chronic oxidative stress, gastrointestinal infection or inflammation may be the underlying cause.
- Serum CoQ10 and serum vitamins A, E, D: CoQ10 and vitamin E are important fat-soluble antioxidants.
- Methylation: Imbalances in glutathione may interfere with methylation pathways.

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