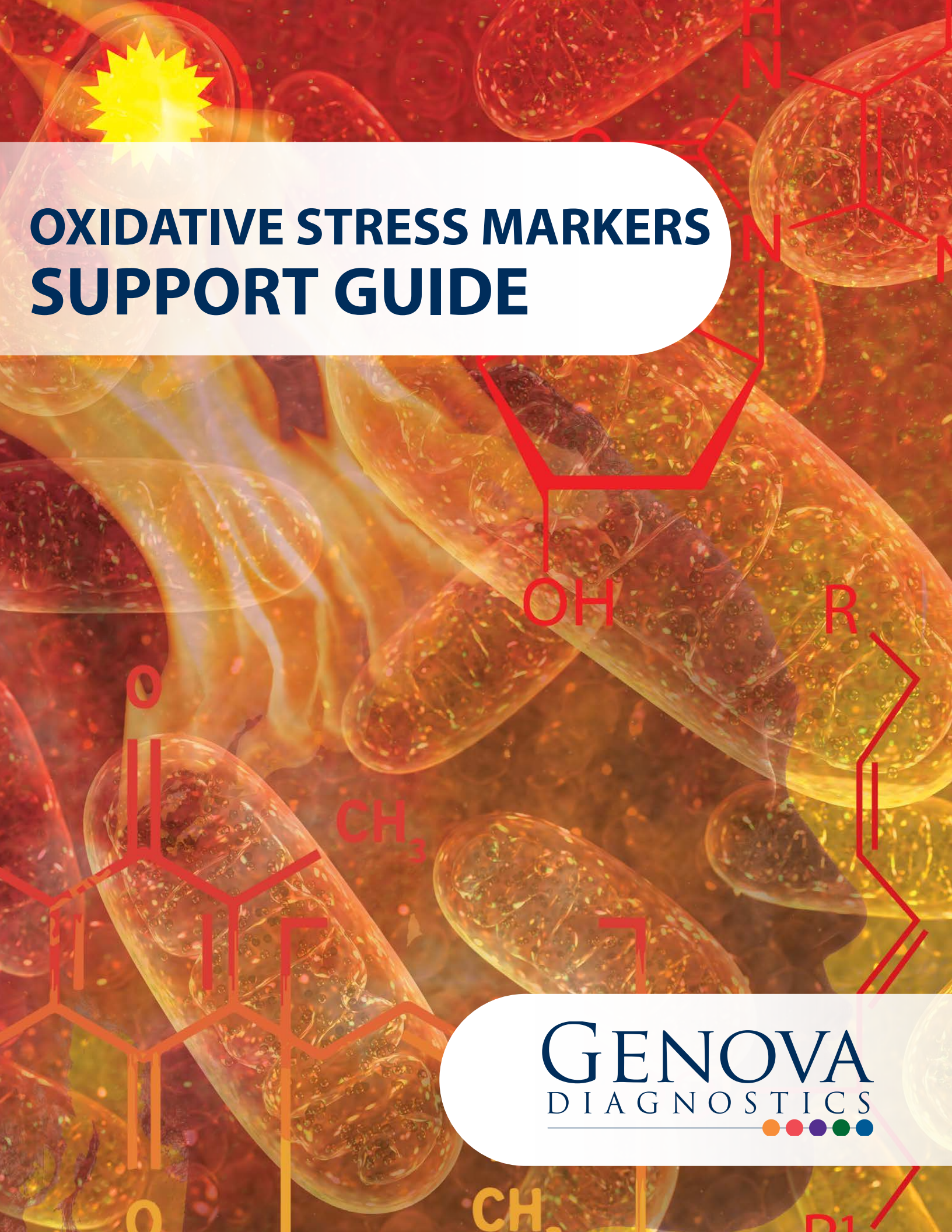
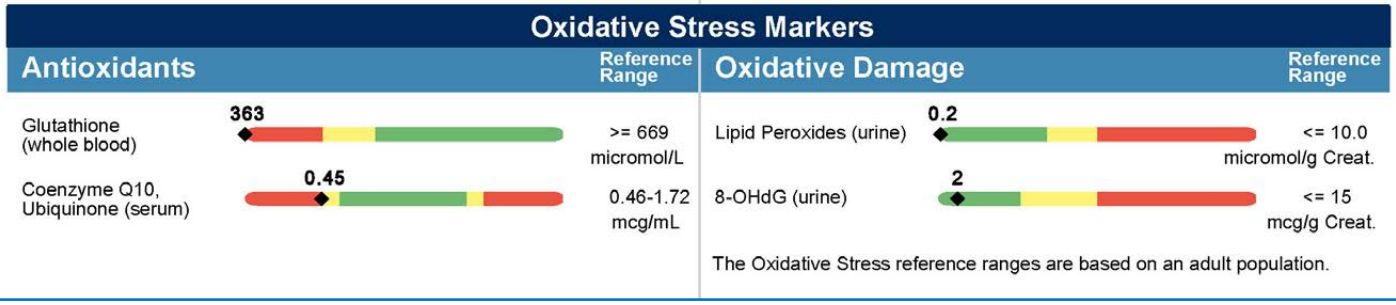
OXIDATIVE STRESS MARKERS
SUPPORT GUIDE



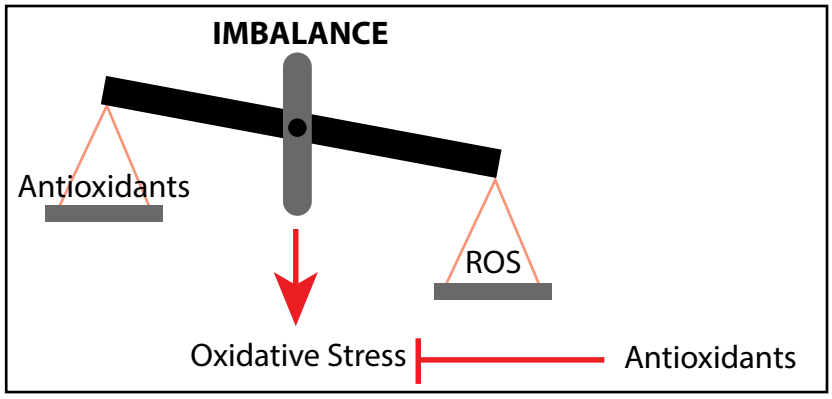
GENOVA
DIAGNOSTICS

OXIDATIVE STRESS MARKERS

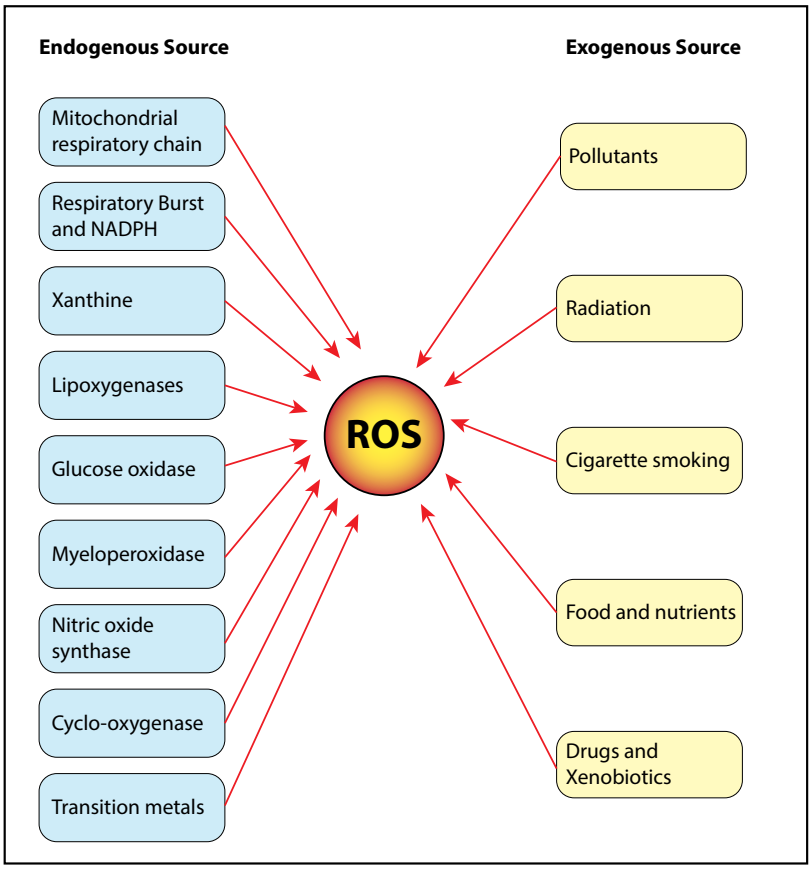


Oxidative Stress Markers

Normal metabolic processes such as cellular respiration, immune system activation, and detoxification result in the production of prooxidative substances including reactive oxygen species (ROS) and reactive nitrogen species. Additionally, external environmental factors such as toxic metal and chemical exposures, smoking, poor diet and certain medications can promote free radical production. Oxidative stress occurs when the production of prooxidative substances outweighs the body's ability to remove them, thus shifting this equilibrium in the direction of oxidation. The instability of free radicals causes them to extract electrons from neighboring molecules in a chain reaction, resulting in cellular damage. Reducing agents, including dietary antioxidants, nutritional supplements, and antioxidant enzymes provide protection against free radical damage. Oxidative stress has an integral relationship with the inflammatory cascade, which produces ROS, and is considered a driving force in the aging process. Oxidative stress has been implicated in a growing list of disorders, including cancer, arthritis, cardiovascular disease, inflammation, diabetes, autoimmune diseases, and neurodegenerative diseases.[1-6]



Sources of oxidative stress



Glutathione (whole blood)

Glutathione (GSH) is a tripeptide comprised of three amino acids (cysteine, glycine, and glutamic acid). Glutathione is the body's most potent intracellular antioxidant. It exists intracellularly in either an oxidized or reduced state.

GSH acts as an antioxidant and detoxifying agent. Excessive formation of reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), is toxic to the cell. Hence, the metabolism of these free radicals are critical, and they are tightly controlled.[7]

Availability of the amino acid cysteine is known to be rate-limiting for glutathione synthesis, and it is widely known that cysteine supplementation (in the form of N-acetylcysteine) can increase GSH levels. Alpha lipoic acid maintains GSH levels via reducing cystine to cysteine as well as inducing de novo GSH synthesis.[8] Recent literature has also suggested that adequate glycine levels are critical in maintaining glutathione levels, and glycine availability may modulate the production of glutathione.[9]

Glutathione's antioxidant function is accomplished largely by GSH peroxidase-catalyzed reactions. GSH neutralizes hydrogen peroxide and lipid peroxide, resulting in water and alcohol. By accepting a free radical electron, GSH is then oxidized. GSH continues to donate and accept electrons, forming a redox cycle to counter free radicals.[10]

Glutathione is also involved in phase II detoxification by conjugating hormones, toxins, and xenobiotics to make them water soluble for excretion.[11]

There are many foods which contain significant GSH sources including, but not limited to, asparagus, avocado, watermelon, ham, and pork.[12]

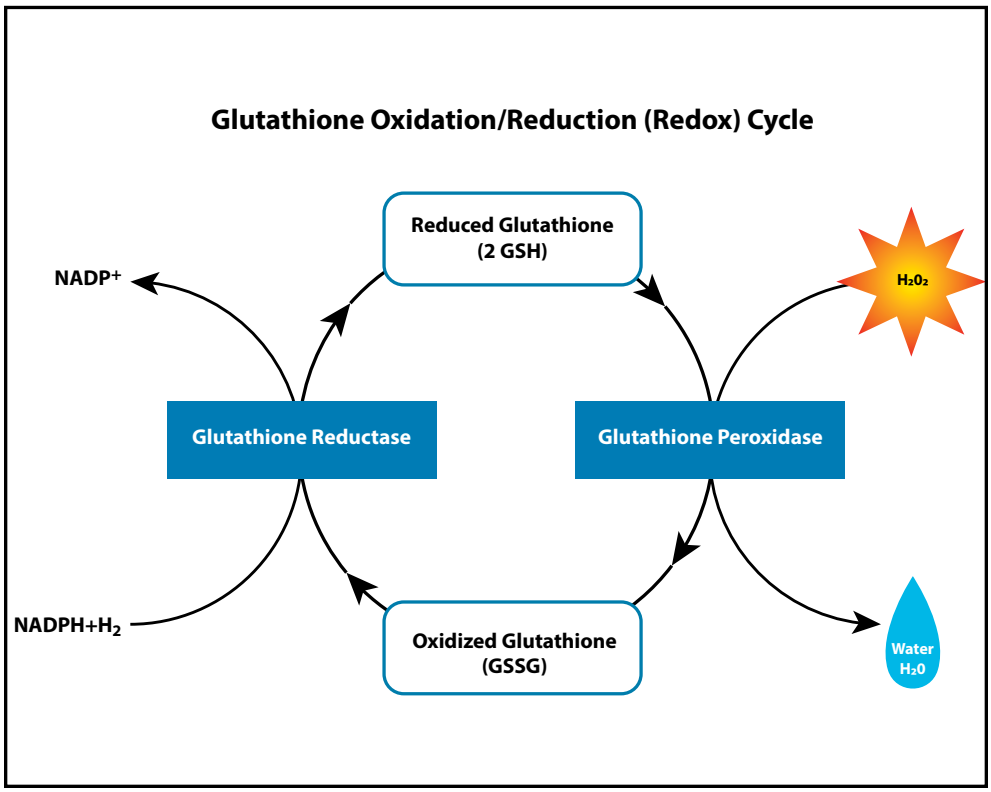
High levels

There is a transient increase in GSH plasma levels after intravenous supplementation and oral GSH ingestion, which may be useful under oxidative stress to counter free radical damage.[13]

Low levels

Nutritional deficiencies in GSH precursors (cysteine, glycine, glutamine) can result in low GSH. Genetic polymorphisms (SNPs) can also affect the production of GSH. Without adequate GSH levels, oxidative stress and free radicals contribute to aging and disease. GSH deficiency and problems with GSH synthesis have been implicated in many diseases such as cancer, neuropsychiatric dysfunction, Parkinson's disease, HIV, liver disease, and cystic fibrosis.[7]

GSH inclusion in oral over-the-counter supplements may be of limited value, since the reduced state will not be maintained when exposed to normal atmospheric conditions and room temperature. Liposomal GSH has been shown to be an excellent alternative to raise GSH levels.[14,15] Additionally, increasing amino acid dietary intake and supplementation with sulfur-containing products (N-acetyl cysteine) and foods (cruciferous vegetables, such as asparagus, broccoli, cauliflower, Brussels sprouts) will support GSH synthesis.[7] The latter requires a healthy gastrointestinal ecosystem.



Lipid peroxides

Lipid peroxides are a class of reactive oxygen species (ROS) that preferentially oxidize polyunsaturated fatty acids (PUFAs) linoleic, arachidonic, and docosahexaenoic acids (omega-6 PUFAs). Lipid peroxides exert their toxic effects via two mechanisms. One is by altering the assembly, composition, structure and dynamics of cell membrane lipid bilayers. The second is by producing more reactive oxygen species or by degrading into reactive compounds capable of damaging DNA and proteins. The central nervous system is particularly prone to lipid peroxidation due to the high quantity of ROS as a byproduct of ATP synthesis in a lipid-enriched environment.[16] Circulating LDLs can be affected by lipid peroxidation and are implicated in diseases including atherosclerosis, metabolic syndrome, and diabetes.[17-19] Genova uses the TBARS (thiobarbituric acid reactive substances) approach for determination of lipid peroxidation; the main indicator of which is malondialdehyde (MDA). MDA is a degradation product of lipid peroxides.

Ferroptosis is an iron-dependent form of cell death that is characterized by the accumulation of lipid peroxides. It is distinct from other cell death modalities, including apoptosis, classic necrosis, autophagy, and others.[20] Synthesis of PUFAs and their incorporation into phospholipid membranes is required for ferroptosis. This process is triggered by the loss of glutathione peroxidase 4 (GPX4), a lipid repair enzyme.[16,21] Depriving cells of cysteine, an amino acid precursor of glutathione can also induce ferroptosis. Clinically, ferroptosis has been associated with degenerative diseases (Alzheimer's, Huntington's, and Parkinson's diseases), carcinogenesis, stroke, intracerebral hemorrhage, traumatic brain injury, ischemia-reperfusion injury, and kidney degeneration.[22]

High levels

Elevated lipid peroxides indicate damage to lipids and lipid membranes. The enzyme glutathione peroxidase is responsible for reducing lipid peroxides and uses glutathione as a cofactor.[16,21] Lower levels of glutathione may contribute to lipid peroxidation.[23,24] Vitamin E mitigates toxicity from lipid peroxides.[16,21] Coenzyme Q10 was shown to reduce lipid peroxides and symptoms in patients with fibromyalgia and headaches.[25] Green tea catechins decreased lipid peroxide concentrations in patients with Alzheimer's disease.[26] Pre-clinical studies demonstrate inhibition of ferroptosis with iron chelators, polyphenols including curcumin, EGCG from green tea, baicalein, and lipophilic antioxidants including vitamin E.[16,27]

8-hydroxydeoxyguanosine (8-OHdG)

8-hydroxy- 2'-deoxyguanosine (8-OHdG) is a byproduct of oxidative damage to guanine bases in DNA.[28] It is used as a biomarker for oxidative stress and carcinogenesis. It has been studied to estimate DNA damage after exposure to carcinogens including tobacco smoke, asbestos fibers, heavy metals, and polycyclic aromatic hydrocarbons.[29] 8-OHdG levels are positively associated with markers of inflammation and evening cortisol, indicating that increased physiological or psychosocial stress is associated with increased oxidative damage.[30,31]

High levels

Elevated 8-OHdG indicates oxidative damage to DNA. Diseases including cardiovascular disease, COPD, cancer, thyroid disease, and diabetes have been associated with excessive concentrations of 8-OHdG.[2,28,32-38] Minimizing exposure to xenobiotics and cigarette smoke, stress management, and increasing antioxidant intake may prevent further oxidative damage.[30,31,39] Increased physical activity is associated with a reduction in urinary 8-OHdG levels.[40] Green tea catechins decreased 8-OHdG concentrations in patients with Alzheimer's disease.[26]

Coenzyme Q10 (CoQ10)

CoQ10 (ubiquinone) is synthesized in almost all cells and membranes. It is vital for electron transfer within the mitochondrial respiratory chain to create energy in the form of ATP. It is an important lipophilic intracellular antioxidant. Endogenous production of CoQ10 decreases with age. Low levels are implicated in age-related and chronic disease due to mitochondrial dysfunction and/or low antioxidant activity.[41]

Supplementation with CoQ10 has been shown to prevent, and provide improvement in, neurologic conditions like Huntington's disease, migraines, and Parkinson's disease. It's been extensively studied and used in metabolic and cardiovascular diseases such as congestive heart failure, hypertension, and diabetes.[41-44] Supplementation is also associated with improved proinflammatory cytokine TNF-α levels.[45]

Coenzyme Q10 decreases with use of statin medications used to lower cholesterol via inhibiting the enzyme HMG-CoA reductase. This enzyme is responsible for cholesterol as well as CoQ10 biosynthesis. This resultant CoQ10 deficiency may contribute to the development of myopathy and muscle symptoms seen commonly with statin use. Treatment with CoQ10 has been found to ameliorate these symptoms and improve well-being and functioning in daily life[41,46]

High levels

In general, elevated CoQ10 is seen in patients who are supplementing, however, there is no known upper level for toxicity. CoQ10 tends to be well-tolerated with a low toxicity profile. Elevated plasma CoQ10 levels have been associated with hypothyroidism.[47]

Low levels

CoQ10 deficiency occurs with age and levels can be depleted with certain medications. Low levels of CoQ10 may prompt a need for supplementation. Decreased circulating levels of CoQ10 have been associated with neurodegenerative diseases, fibromyalgia, diabetes, cancer, mitochondrial diseases, muscular diseases, hyperthyroidism, and heart failure.[42,44,47]

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