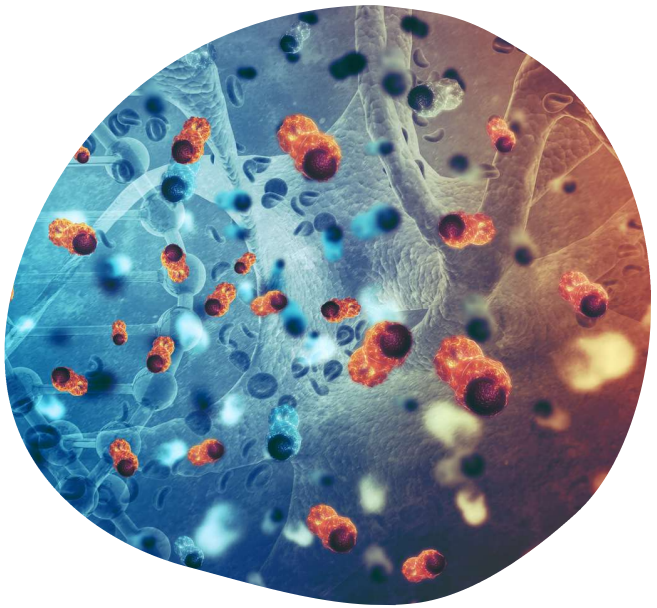
A4M | MEDICINE REDEFINED

Mastering Oxidative Stress:

Blueprint to Longevity

Dr. Kim Bruno, DC, CCN



Introduction & Disclosure

- *17 yrs of clinical practice in functional medicine*
- *Doctor of Chiropractic*
- *Certified Clinical Nutritionist*
- *Colorado native and enjoys spending time outdoors with husband and 2 daughters*

Disclosure:

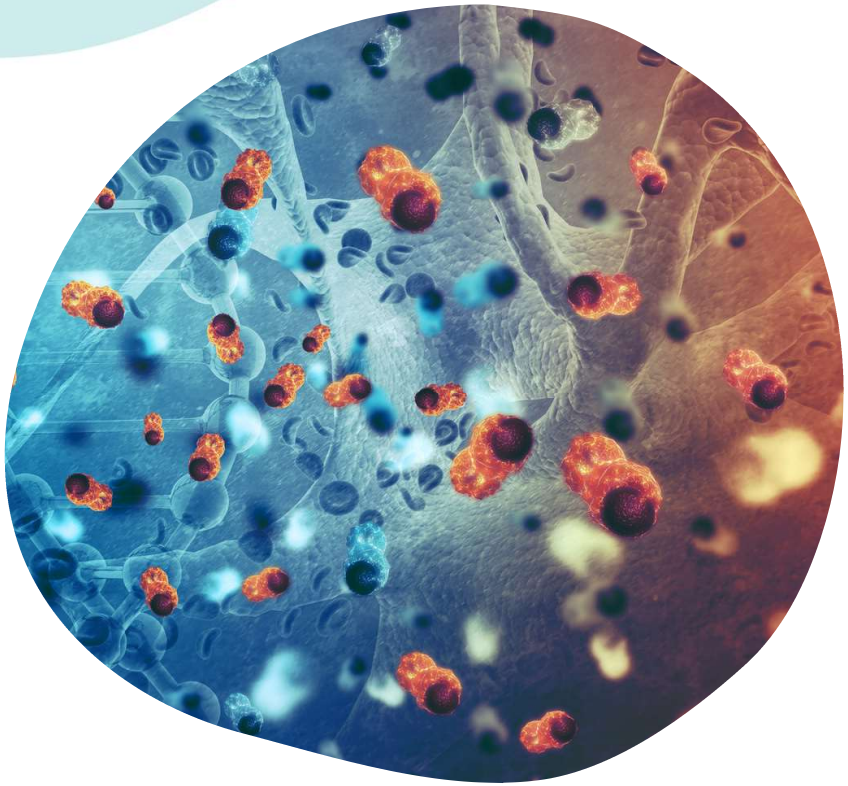
- *Clinical Education Consultant – Vibrant Wellness*

Learning Objectives

1. Review concept of oxidative stress in context of clinical utility and associations of root cause mechanisms to disease
2. Evaluate the production of reactive oxygen species and the protective antioxidant defense system.
3. Review cutting edge lab evaluation combining genetic predispositions with markers of current oxidative damage as a unique, comprehensive insight into individual health, paving the way for personalized wellness strategies.
4. Explore the science supporting antioxidant interventions, focusing on dietary, lifestyle, and supplementation strategies that mitigate oxidative damage.

Oxidative Stress

Clinical Associations



Oxidative Stress As Root Cause To Many Chronic Conditions

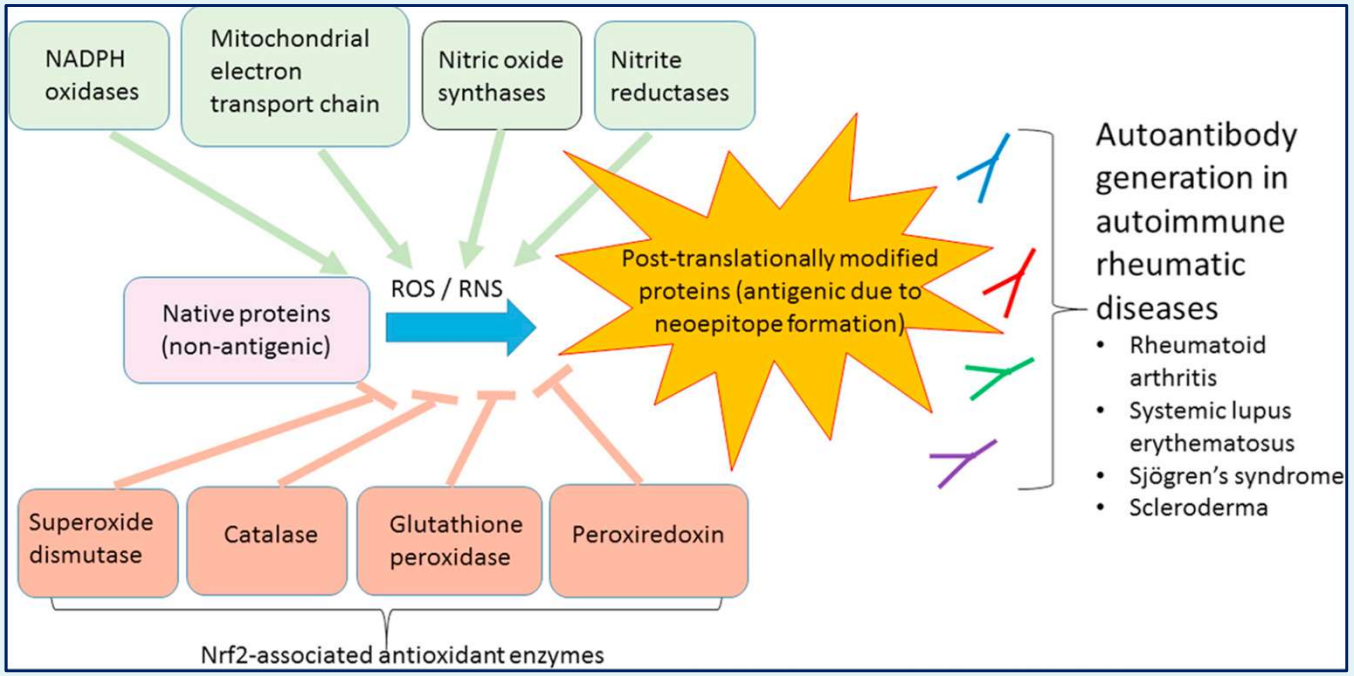
- **Oxidative Stress** increases with age, directly affects tissue function through cellular damage
- **Many conditions associated with aging** have direct relationship with oxidative stress
  - Alzheimer's, cancer, cardiovascular disease, diabetes
- **Imbalance in oxidants** causes cellular damage
  - Specifically thought that the failure of the innate cellular antioxidant defense mechanism is to blame
- **Most of the antioxidant defense** within cells is provided by antioxidant enzymes using their specific substrates to reduce oxidants

Health Conditions
With Strong Evidence of Oxidative Stress

- Aging (sarcopenia, frailty)
- Autoimmune conditions
- Cancer
- Cardiovascular diseases
- Lung disease (chronic pulmonary obstruction, lung cancer)
- Macular degeneration
- Metabolic diseases—diabetes, NAFLD, diabetic retinopathy
- Neurodegenerative disorders (Alzheimer's and Parkinson's diseases)
- Psychiatric diseases (depression, schizophrenia, bipolar disorder)
- Renal disease

Clinical Utility

Mechanisms Of Oxidative Stress In Autoimmune Conditions

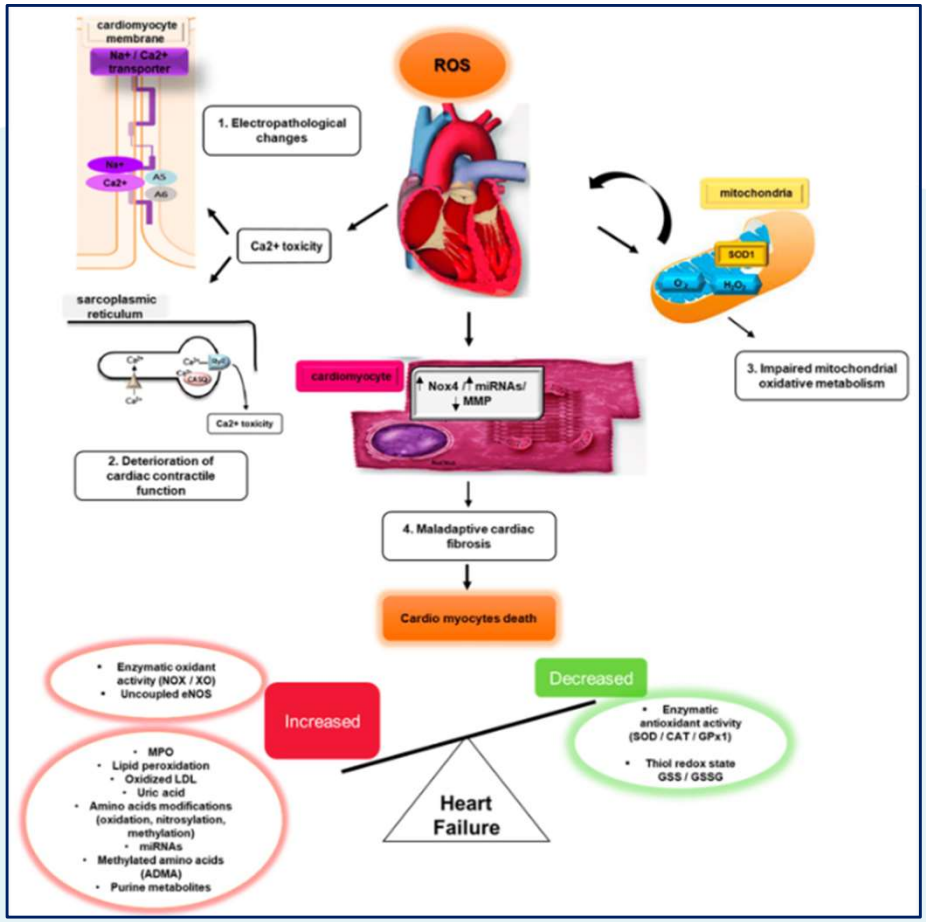


- Oxidative post-translational modifications of proteins, know as protein oxidation
- Protein modifications may give rise to neoepitopes that are recognized as non-self and result in the formation of autoantibodies

Image: https://www.sciencedirect.com/science/article/abs/pii/S0891584918309377.

Clinical Utility

Mechanisms Of Oxidative Stress In Cardiovascular Disease

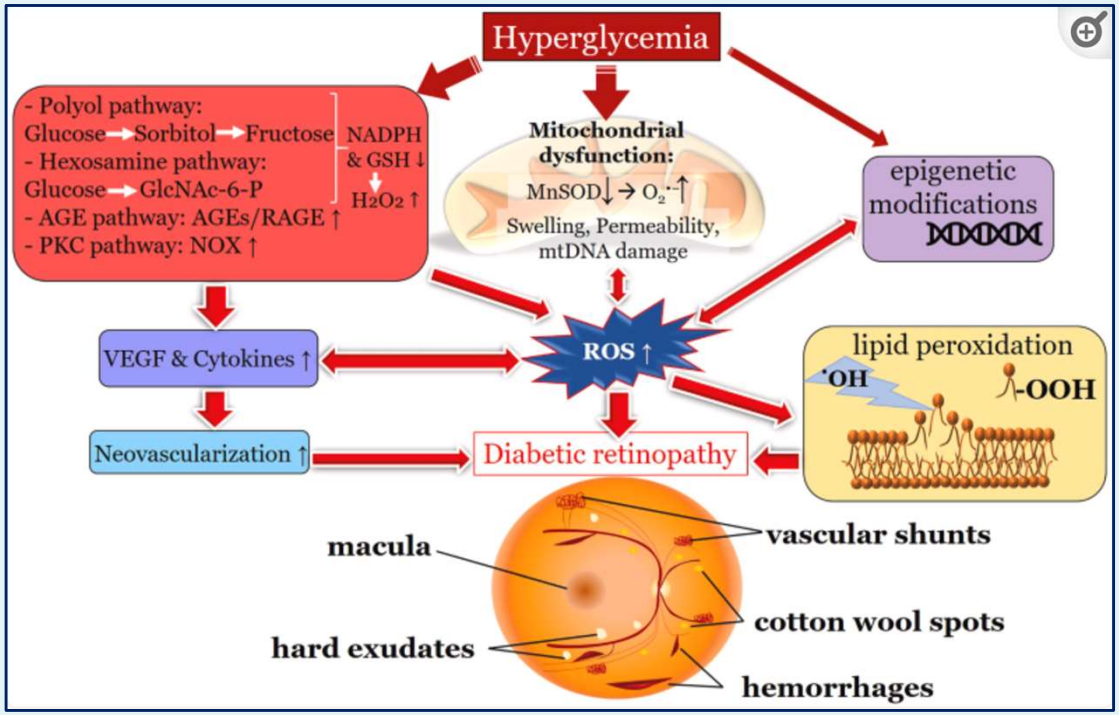


- Oxidative stress triggers endothelial cells proliferation, vascular smooth muscle cells proliferation, and vasoconstriction
- Eventually leading to endothelial dysfunction
- Initiation and progression of atherosclerosis

Image: https://www.mdpi.com/2227-9059/11/3/917

Clinical Utility

Mechanisms Of Oxidative Stress In Diabetic Retinopathy



- Hyperglycemia and epigenetic modifications induce mitochondrial dysfunction and metabolic pathways, such as polyol, hexosamine, PKC pathways and **AGEs (Advanced Glycation End Products)** leading elevated levels of ROS.
- Elevated levels of ROS cause **lipid peroxidation** and neovascularization through elevated VEGF and cytokine levels, finally terminating in diabetic retinopathy.

 Image: https://www.sciencedirect.com/science/article/pii/S2213231723003683.

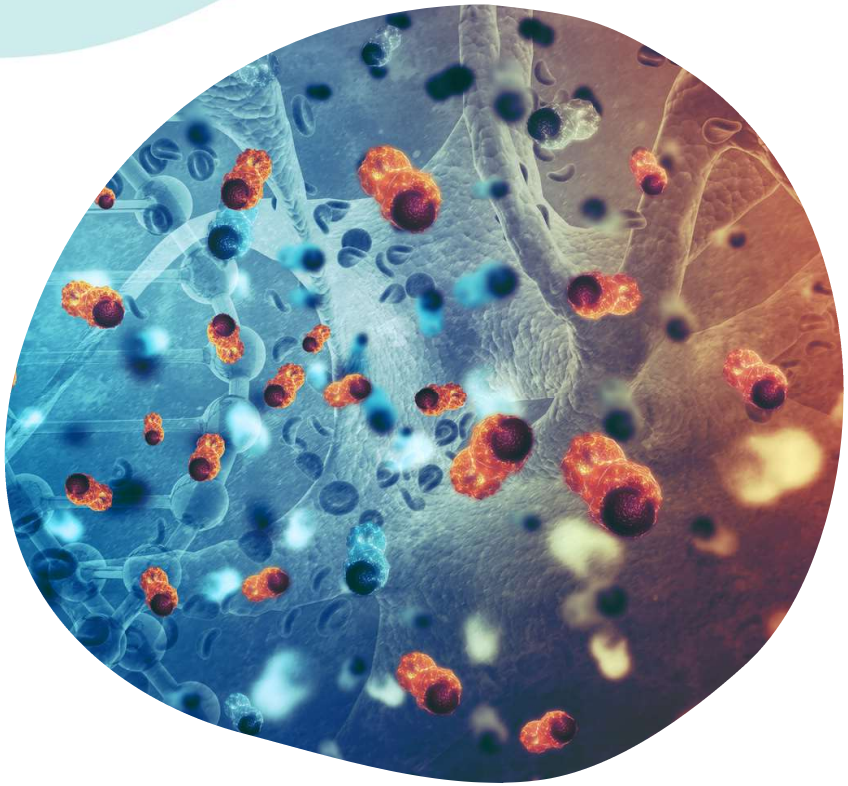
Oxidative Stress & Inflammation

- Consider oxidative stress may be just as important as inflammation
- Inflammatory markers have been more widely available (until now!)
- Clinically, we see many patients with well-established inflammatory disorder presentations whose inflammatory markers are WNL
- Some patients don't respond well (or as expected) to inflammatory targeted treatments
- Chicken or the Egg situation - Treating the root cause of a known inflammatory condition involves treating the cause of sources of ROS, which includes inflammation itself. inflammation which may be driven by oxidative stress, so this involves targeting endogenous and exogenous

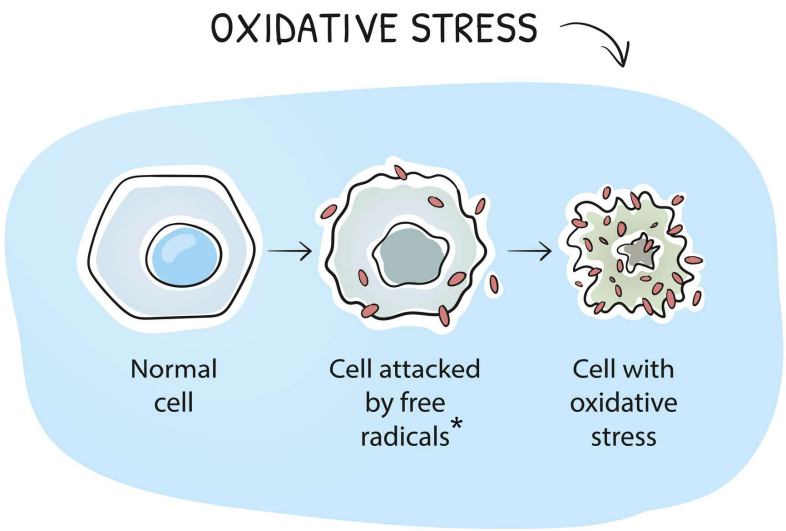
Jomova K, Raptova R, Alomar SY, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Arch Toxicol. 2023 Oct;97(10):2499-2574. doi: 10.1007/s00204-023-03562-9.

Oxidative Stress

Concept Overview



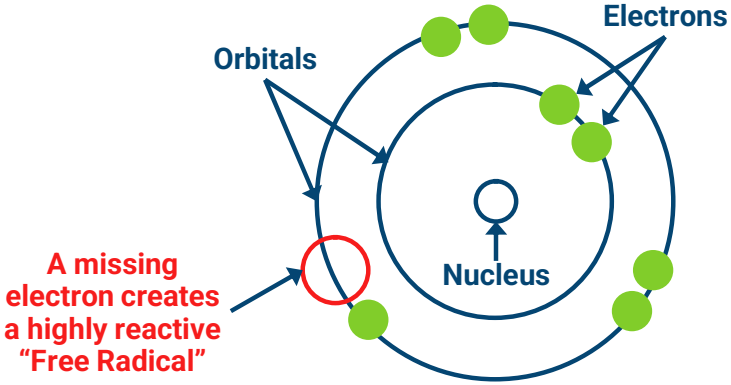
Basic Mechanism of Oxidative Stress



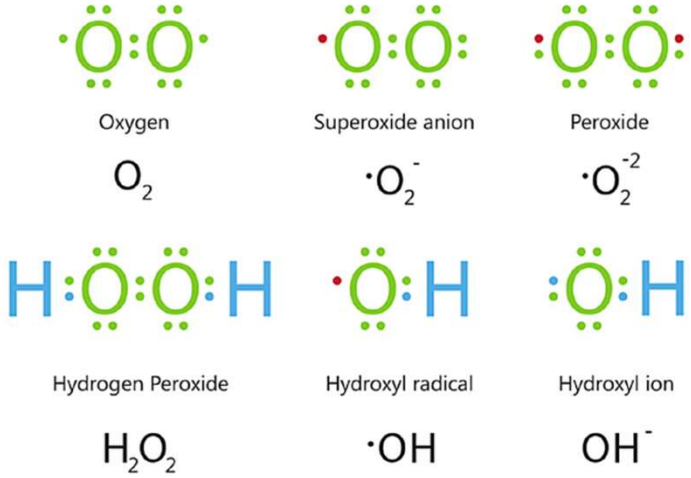
- Cellular Damage ----->
- Tissue Damage --->
- Organ Damage --->
- Altered Function and Organ Death

*such as **reactive oxygen species** (ROS)

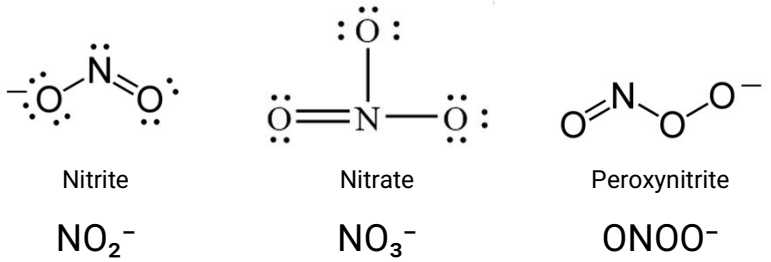
What Are Free Radicals?



Reactive Oxygen Species (ROS)



Reactive Nitrogen Species (RNS)



1.Jakubczyk K, Dec K, Kałduńska J, Kawczuga D, Kochman J, Janda K. Reactive oxygen species - sources, functions, oxidative damage. Pol Merkur Lekarski. 2020 Apr 22;48(284):124-127. PMID: 32352946.
2.Baselet B, Rombouts C, Benotmane AM, Baatout S, Aerts A. Cardiovascular diseases related to ionizing radiation: The risk of low-dose exposure (Review). Int J Mol Med. 2016;38(6):1623-1641. doi: 10.3892/ijmm.2016.2777.

How Are ROS and RNS Formed?

1. Normal Cellular Processes

- Aerobic respiration

2. Inflammatory Processes

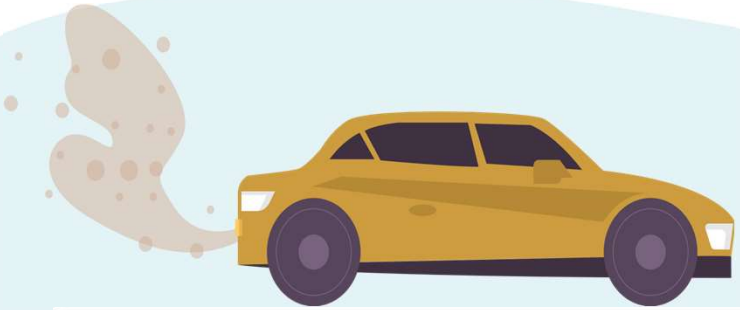
- Macrophages make ROS to kill pathogens

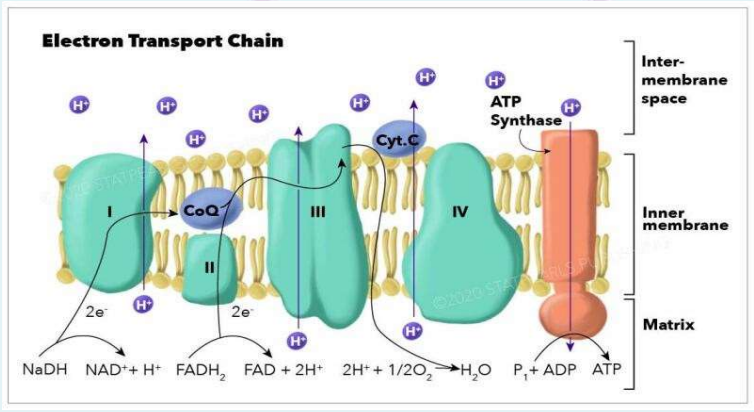
3. Oxidant Exposure

- Diet and lifestyle – *including exposure to heavy metals, environmental toxins, mycotoxins*

1. Muri J, Kopf M. The thioredoxin system: Balancing redox responses in immune cells and tumors. Eur J Immunol. 2023;53(1):e2249948. doi: 10.1002/eji.202249948.
2. Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: A systematic review of observational and intervention studies. Redox Biol. 2021;42:101869. doi: 10.1016/j.redox.2021.101869.
3. Shekhova E. Mitochondrial reactive oxygen species as major effectors of antimicrobial immunity. PLoS Pathog. 2020;16(5):e1008470. doi: 10.1371/journal.ppat.1008470.

1. Normal Cellular Processes Create ROS



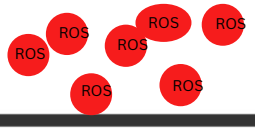


- **Superoxide** (O_2^-) is primarily generated by electrons escaping from ETC
- 0.4-4.0% of oxygen (O_2) consumed is converted into superoxide (O_2^-)
- Producing ~1 kg/year ROS

The consequence is about **100,000 oxidative attacks on mitochondrial DNA per cell per day**

1. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007 Aug;83(1):84-92. Review.
2. National Institutes of Health. Stat Pearls. Electron Transport Chain graphic. Accessed 03.05.2024. https://www.ncbi.nlm.nih.gov/books/NBK526105/figure/article-20982.image.f1/
3. Evans JL, Goldfine ID. Alpha-lipoic acid: a multifunctional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. Diabetes Technol Ther. 2000;2(3):401-413. doi:10.1089/15209150050194279.
4. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci U S A. 1994;91(23):10771-10778. doi:10.1073/pnas.91.23.10771

Free Radicals in Aging



Generation of ROS like superoxide

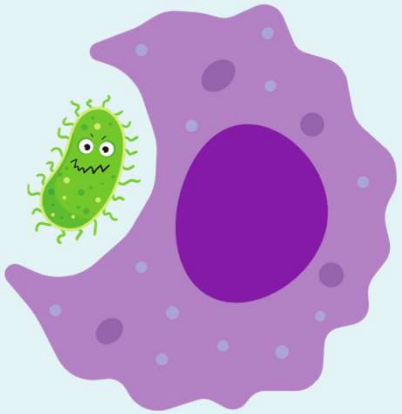
Oxidative damage, mitoDNA mutations

Note: aging causes a decline in mitochondrial function, which amplifies and perpetuates this cycle

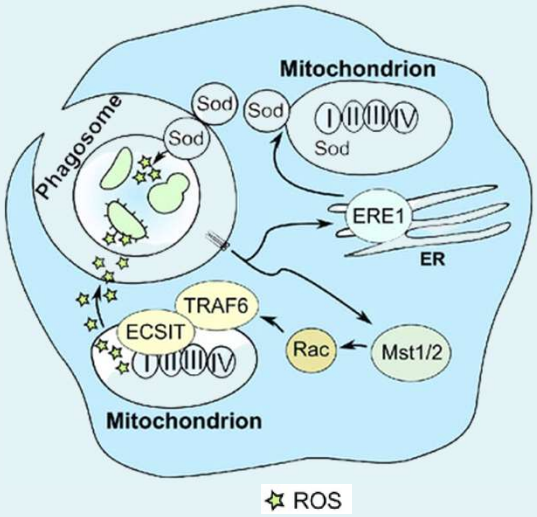
Mitochondrial Dysfunction

2. Inflammatory Processes Create ROS

Innate immune cells produce ROS to kill invading pathogens



Macrophage



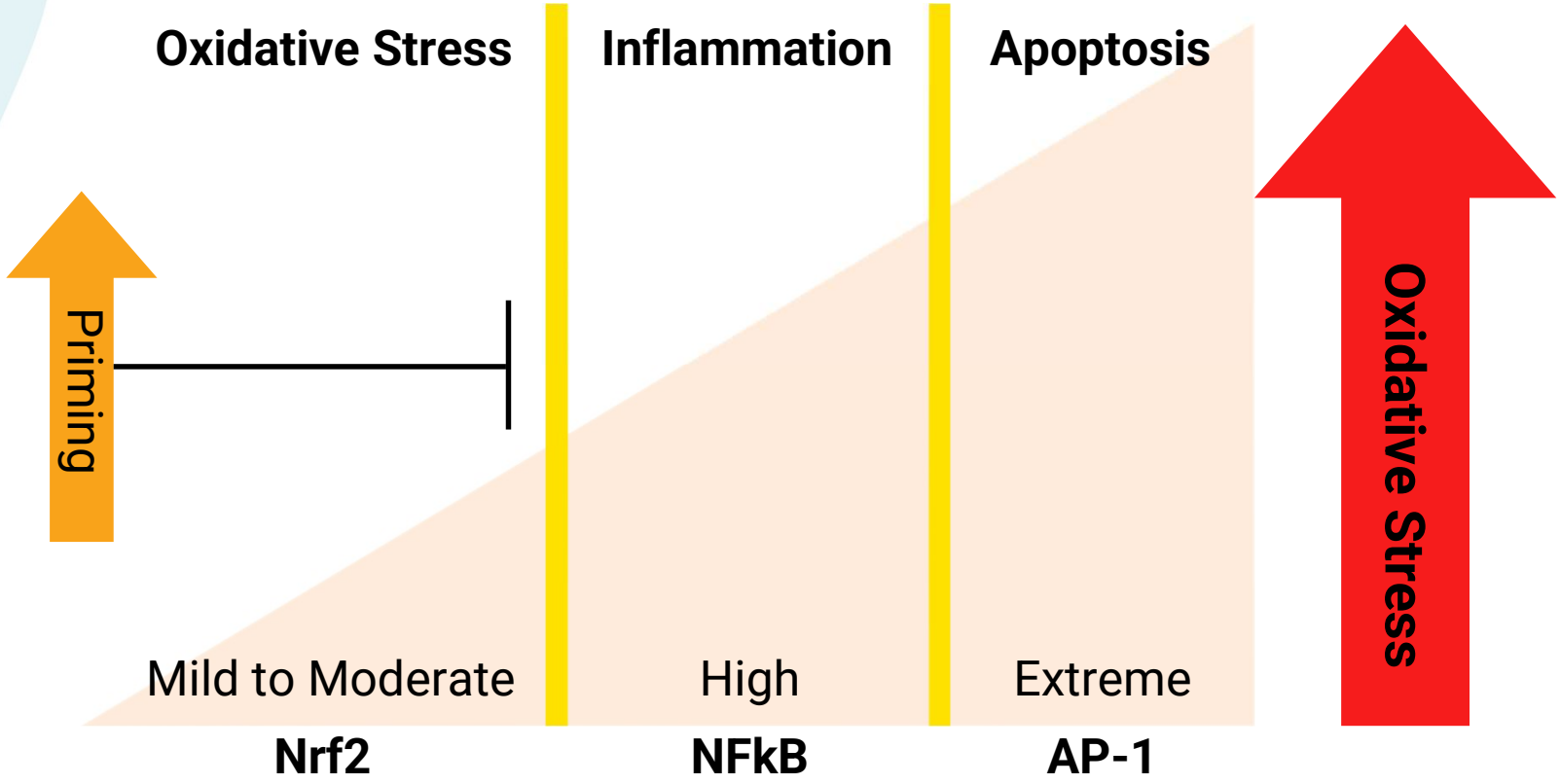
1.Shekhova E. Mitochondrial reactive oxygen species as major effectors of antimicrobial immunity. PLoS Pathog. 2020;16(5):e1008470. doi: 10.1371/journal.ppat.1008470
2.Van der Lugt T, Weseler AR, Gebbink WA, et al. Dietary advanced glycation endproducts induce an inflammatory response in human macrophages in vitro. Nutrients. 2018;10(12):1868.

Are Free Radicals Always Harmful?

- **No.** ROS are essential signaling molecules, required to promote health and longevity
- Turning off mitochondrial ROS signal impairs the lifespan-extending & health-promoting capabilities of reduced calorie uptake, glucose restriction & physical exercise

Ristow M, Zarse K. How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). Exp Gerontol. 2010;45(6):410 8. doi: 10.1016/j.exger.2010.03.014. Review.

Differential Response to Rising Oxidative Stress



3. Dietary & Environmental Oxidants Create ROS

- Too Many Calories
- Hyperglycemia
- Cigarette Smoke
- Alcohol
- UV Radiation
- Ionizing Radiation
- Environmental Toxins
- Heavy Metals
- Mycotoxins

Balance and Protection with **Antioxidants**

- Dietary vitamins & micronutrients
- Plant phytonutrients
- **Endogenous antioxidants!**

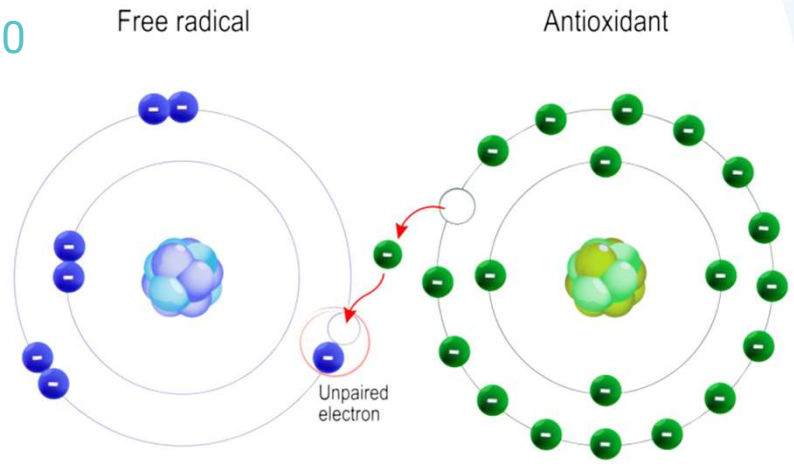
What Are Endogenous Antioxidants?

Enzymatic

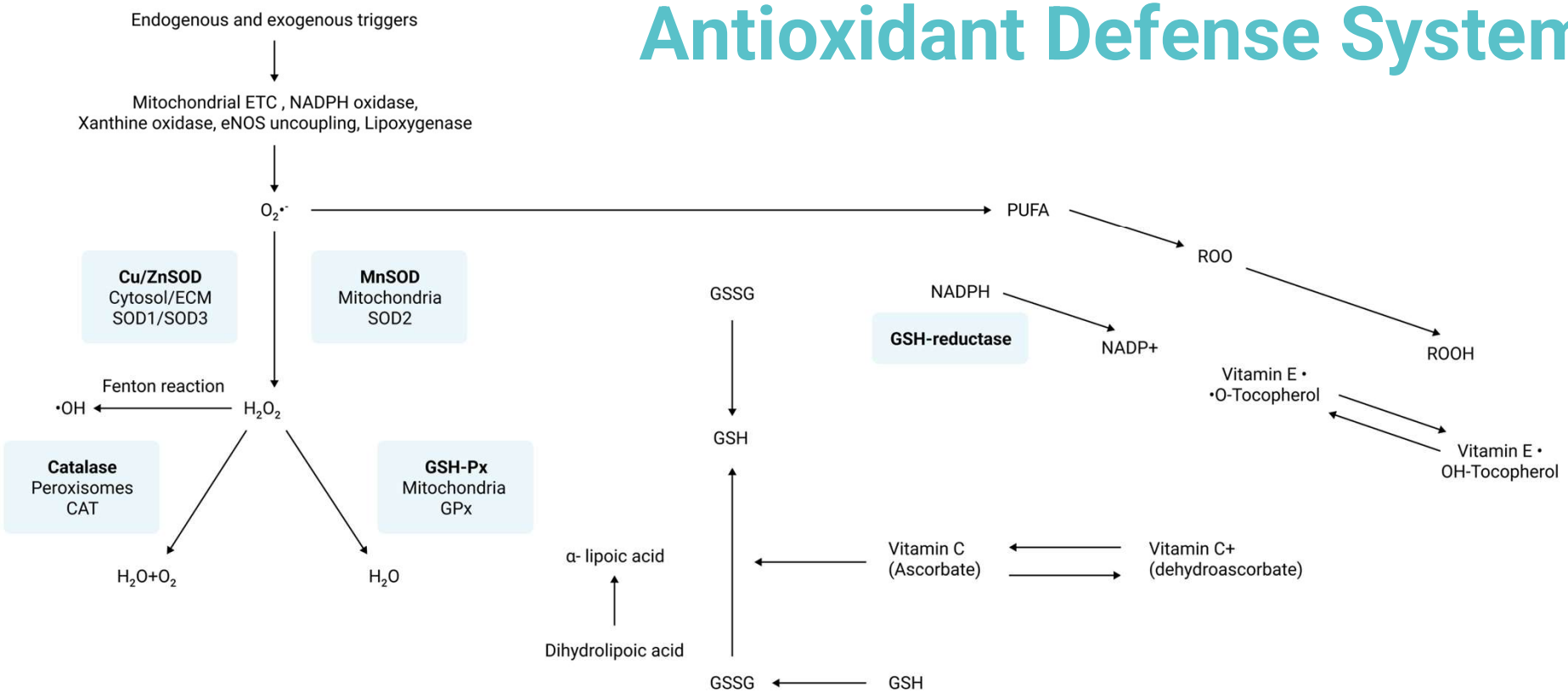
- Catalase (CAT)
- Glutathione Peroxidase (GPx)
- Glutathione S-transferase (GST)
- Super Oxide Dismutase (SOD)
- Thioredoxin (TXN)

Non-Enzymatic

- Albumin
- Alpha-lipoic acid (ALA)
- Bilirubin
- Coenzyme Q10
- Glutathione
- Melatonin
- Uric acid



Built-In Protection:
Antioxidant Defense System



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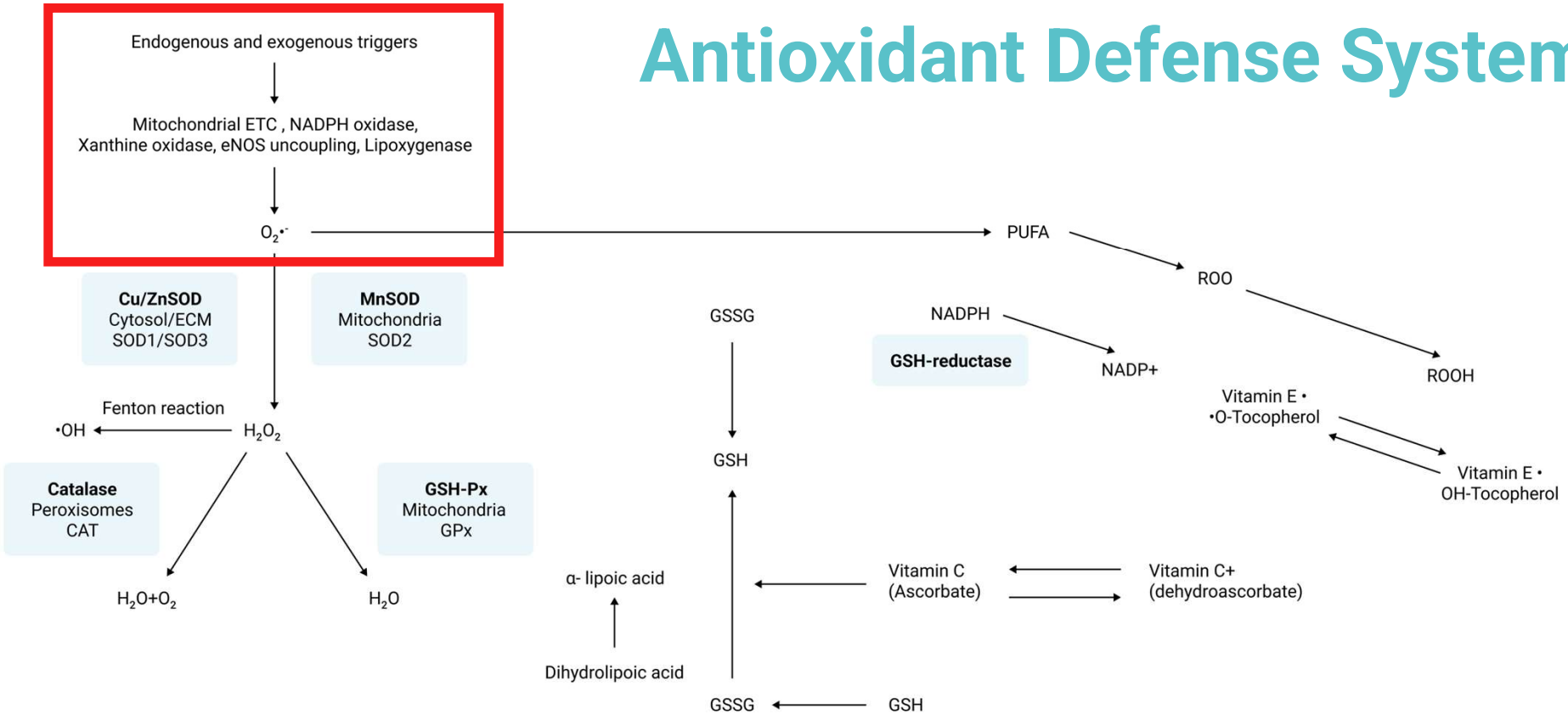

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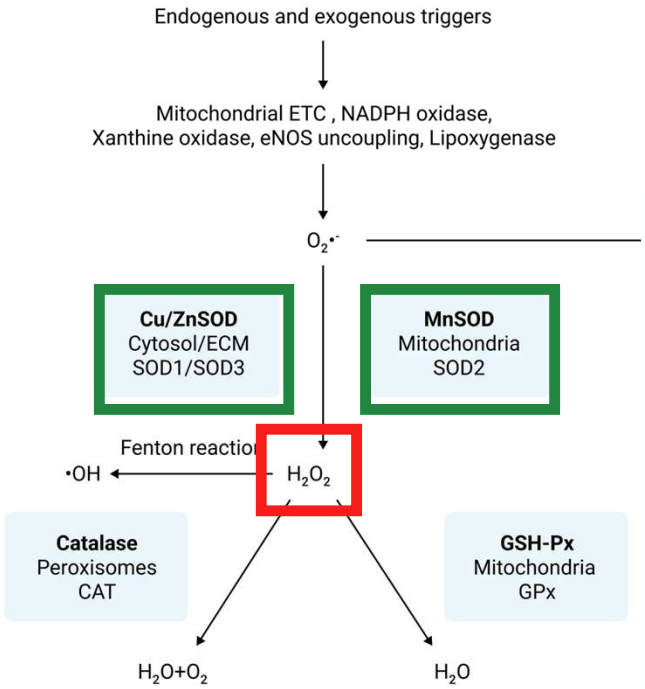

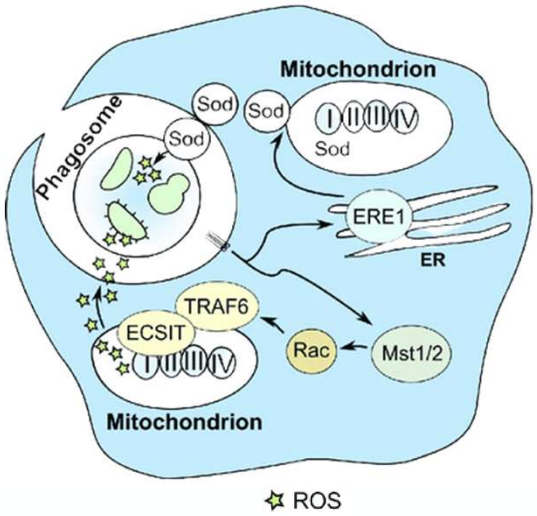

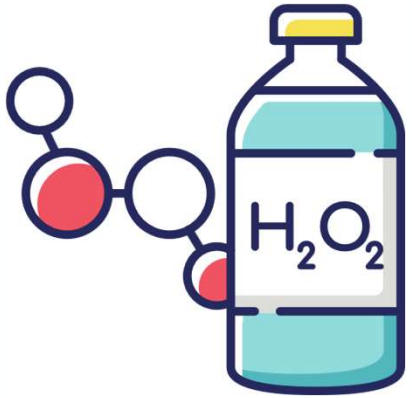

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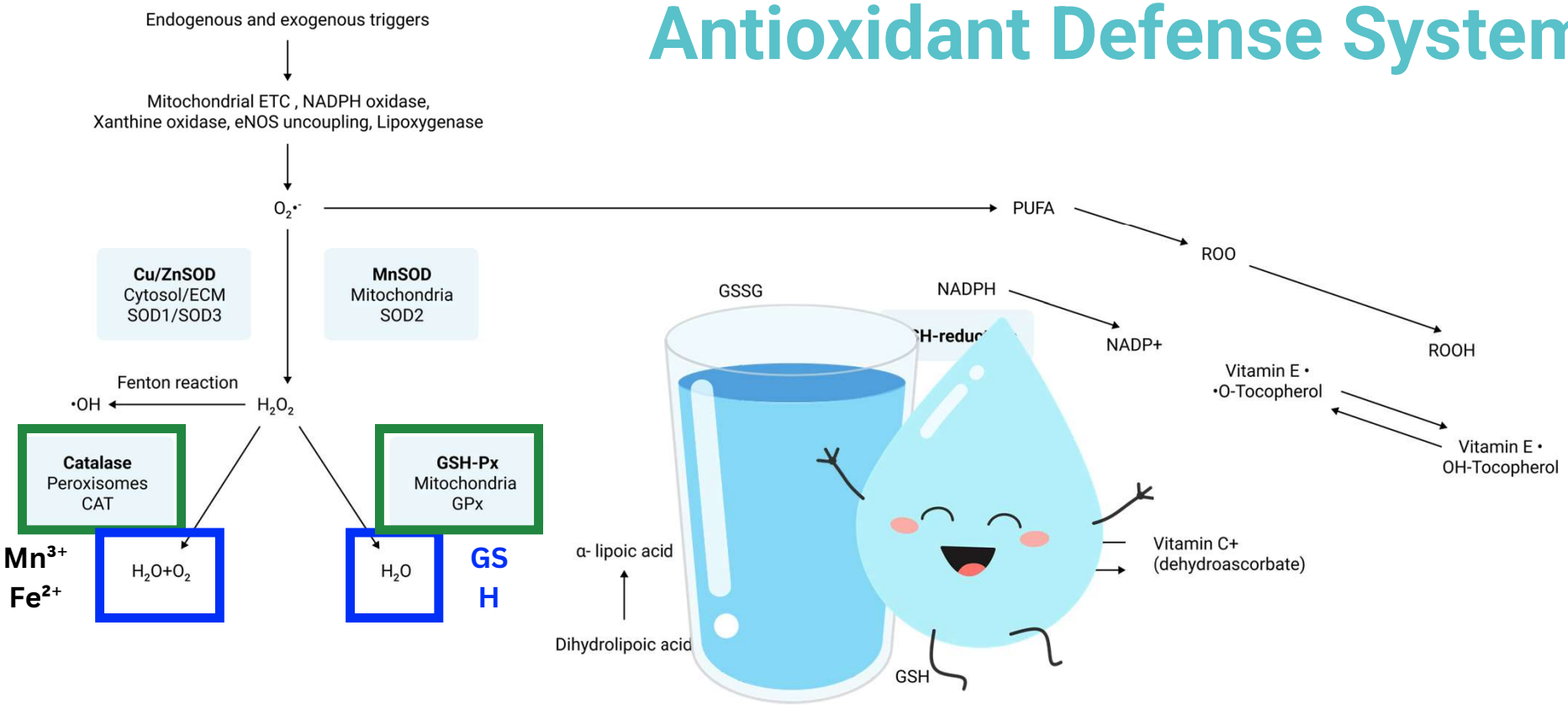

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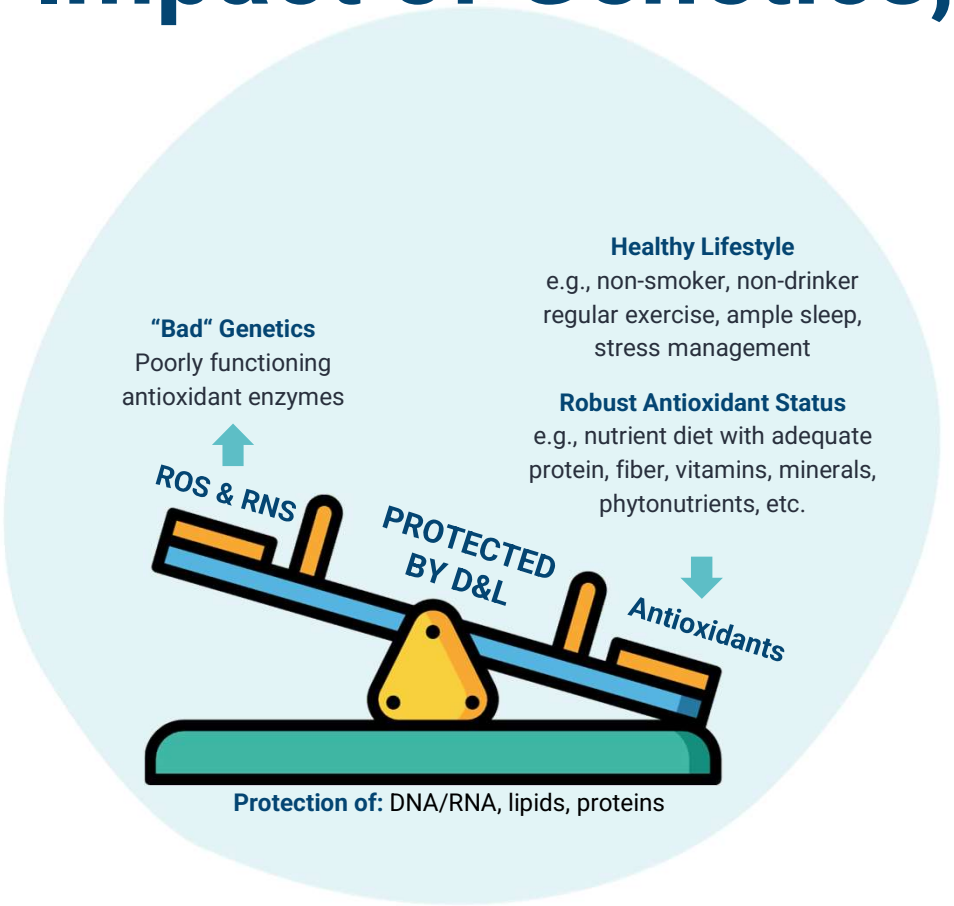
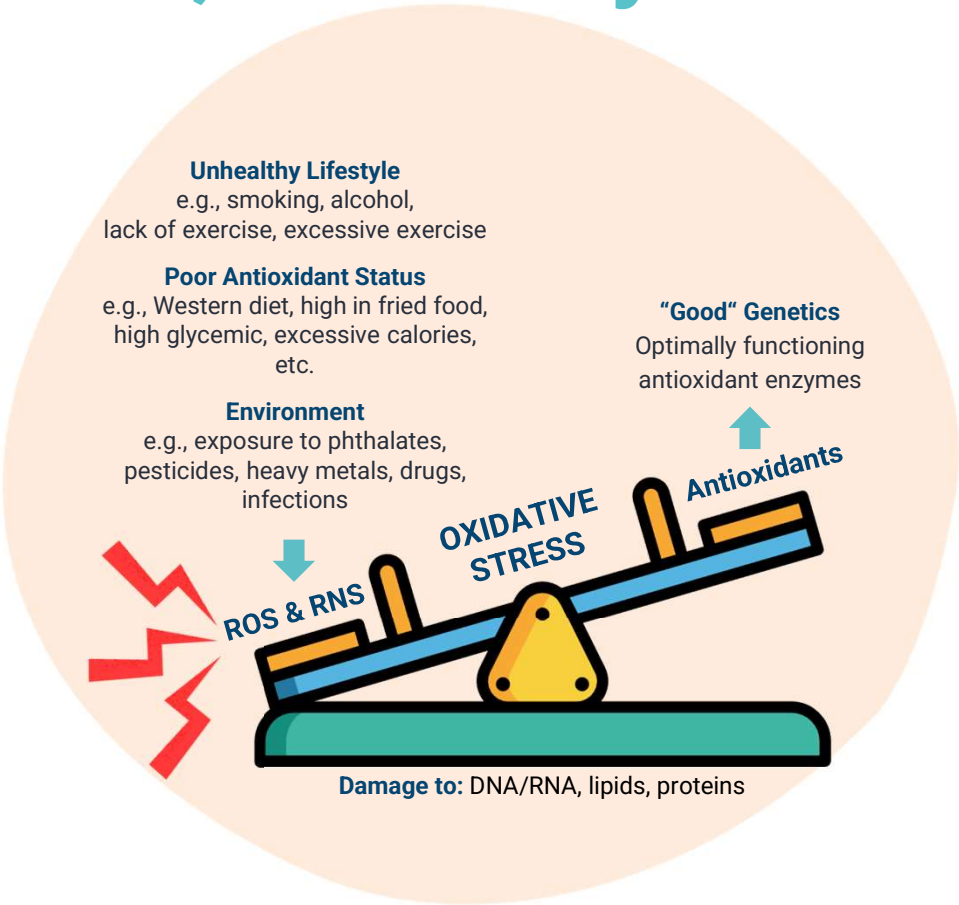
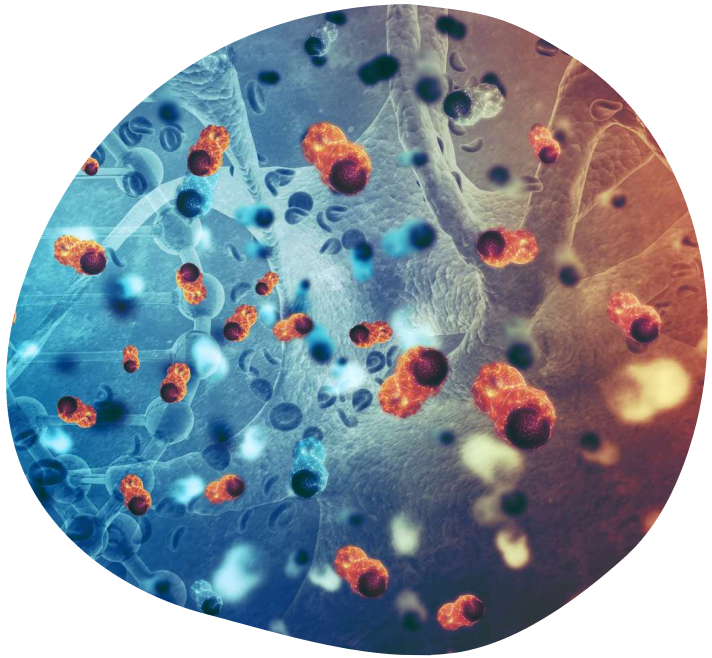
Impact of Genetics, Diet, & Lifestyle



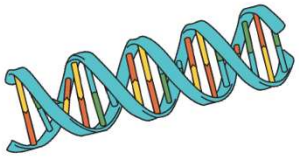


Oxidative Stress Evaluation

- *Oxidative Stress Damage Markers*
- *Genetics of Antioxidant Defense System*



What Is the Best Way To Evaluate Oxidative Stress?



Genetic Predispositions

(Are your antioxidants working?)

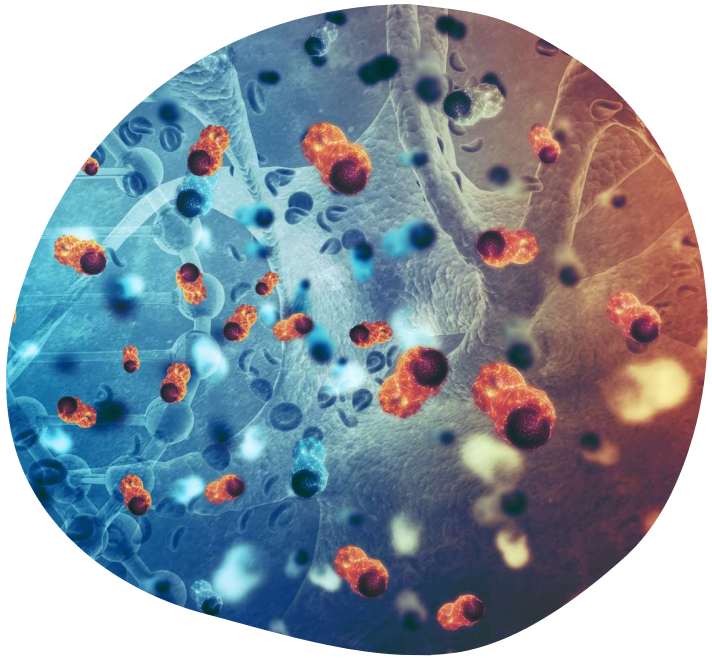
+

Oxidative Damage Markers

(Do you have oxidized lipids, proteins, DNA?)

Genetics in the

Antioxidant Defense System



Antioxidant Genetics: 32 SNPs

AMP-Activated Protein Kinase (AMPK)
- PRKAA2: rs2796498
- PRKAA2: rs10789038

Catalase
- CAT: rs1001179
- CAT: rs7943316
- CAT: rs4756146

Cyclooxygenase-2
- COX-2: -765G

Cytochrome B5 Reductase
- CYB5R3: rs916321

Cytochrome P450
- CYP1A1: rs1048943

Glutamate Ammonia Ligase
- GLUL: rs10911021

Glutathione Peroxidase
- GPX1: rs1050450
- GPX2: rs4902346
- GPX2: rs2071566
- GPX4: rs713041
- GPx1: rs1987628

Glutathione S-transferase
- GSTM1: rs366631
- GSTM5: rs3754446
- GSTP1: rs1695

Glutathione Synthetase
- GSS: rs121909307

Glutathione-Disulfide Reductase
- GSR: rs8190955

Heme Oxygenase
- HMOX1: rs2071746

NADPH Oxidase
- CYBA: C242T
- CYBA: A-930G

Selenoprotein
- SELENOP: rs3877899

Super Oxide Dismutase
- SOD1: rs2234694
- SOD2: rs4880
- SOD3: rs1799895
- SOD3: rs8192287

Thioredoxin System
- TXNRD1: rs7310505
- TXNRD2: rs1548357

Thioredoxin Reductase
- TrxR2: rs4485648

Xanthine Dehydrogenase
- XDH: −337GA
- XDH: 565+64C

SNP Classification: Wild Type vs Mutant

Wild Type

- The most common (a.k.a. **reference** or **ancestral**) allele
- Typically considered “normal”
- Often (but not always) results in **least risk**
- Represented by a (-) sign

Mutant

- The less common (a.k.a. **variant**) allele
- Typically occur **less frequently**
- Often (but not always) results in **elevated risk**
- Represented by a (+) sign

SNP Terminology: Genetic Combinations

Homozygous Wild Type

- Two copies of the most common (a.k.a. **reference** or **ancestral**) allele
- Typically considered "normal"
- Often (but not always) gives the **least risk**

⊖⊖ Homozygous Wild

Heterozygous

- One copy of the wild type allele and one copy of the mutant allele
- Often (but not always) gives **partially elevated risk**

⊕⊖ Heterozygous

Homozygous Mutant

- Two copies of the less common (a.k.a. **variant)** allele
- Typically occur **less frequently**
- Often (but not always) gives **elevated risk**

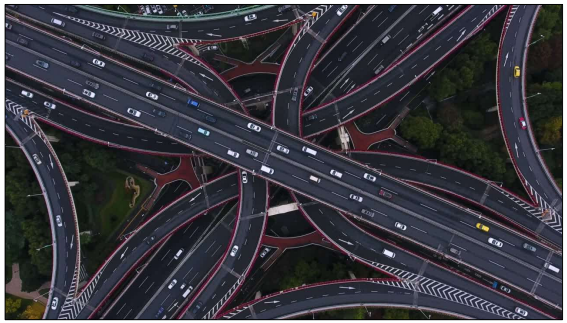
⊕⊕ Homozygous Mutant

**Friendly reminder - our patients may not like to be referred to as mutants* ☺

Highway Analogy: Risk

In Control

Normal



Moderate

Partially Elevated

Risk

Elevated

SNP Information: Genetic Bypass

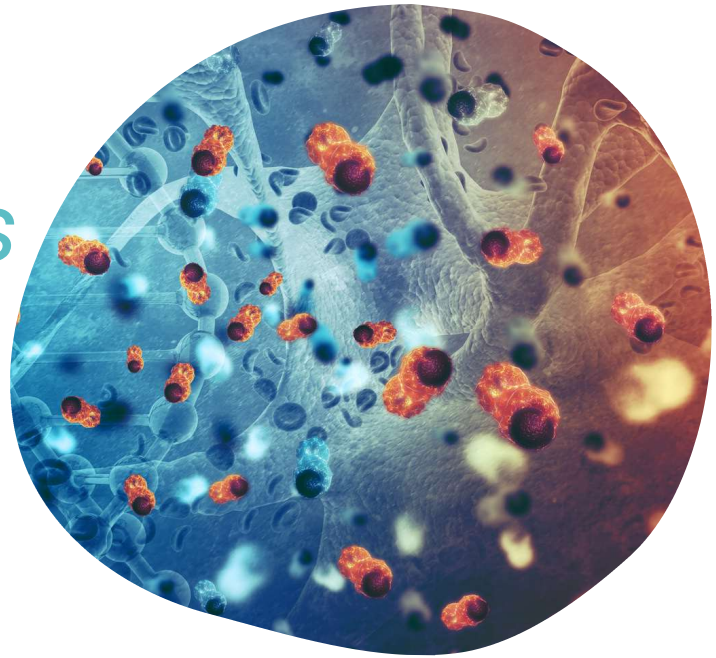
- Is there an alternate highway?
  - Are there affected enzymes/SNP in the alternate pathway
- Evaluate how much traffic is on the highway
  - Especially toxic burden
- What are the enzyme cofactor levels?
  - Consider **Micronutrients**, evaluating intracellular levels of above nutrients

Sample Report: Antioxidant Genetics

Antioxidant Genetics			⊕⊕ Homozygous Mutant	⊕⊖ Heterozygous	⊖⊖ Homozygous Wild
Test Name	**Gene Name**	**Risk Association**	**Your Mutation**	**Your Risk**	**Reference**
rs2234694	SOD1	Increased superoxide levels	⊖⊖A/A	Normal	A/A
rs4880	SOD2	Impaired anti-oxidant activity	⊕⊖C/T	Partially elevated	C/C
rs1799895	SOD3	Elevated ROS production	⊖⊖C/C	Normal	C/C
rs8192287	SOD3	Disrupted EC-SOD activity	⊕⊕T/T	Elevated	G/G
rs1001179	CAT	Mitochondrial dysfunction	⊖⊖C/C	Normal	C/C
rs4756146	CAT	Mitochondrial dysfunction	⊕⊕T/T	Elevated	C/C
rs7943316	CAT	Mitochondrial dysfunction	⊕⊕T/T	Elevated	A/T, A/A

Oxidative Stress

Quantifiable Damage Markers



Oxidative Damage: 16 Markers

Lipid Peroxidation
- Malondialdehyde (MDA)
- Glutathione 4-hydroxynonenal (4-HNE)
- 8-iso-prostaglandin F2α (8-iso-PGF2α)
- 11-β-Prostaglandin F2α
- 15(R)-Prostaglandin F2α

DNA/RNA Damage
- 8-Hydroxy-2-deoxyguanosine (8-OHdG)
- 8-Hydroxyguanine
- 8-Hydroxyguanosine

Protein Oxidation
- Dityrosine
- Bromotyrosine
- Chlorotyrosine

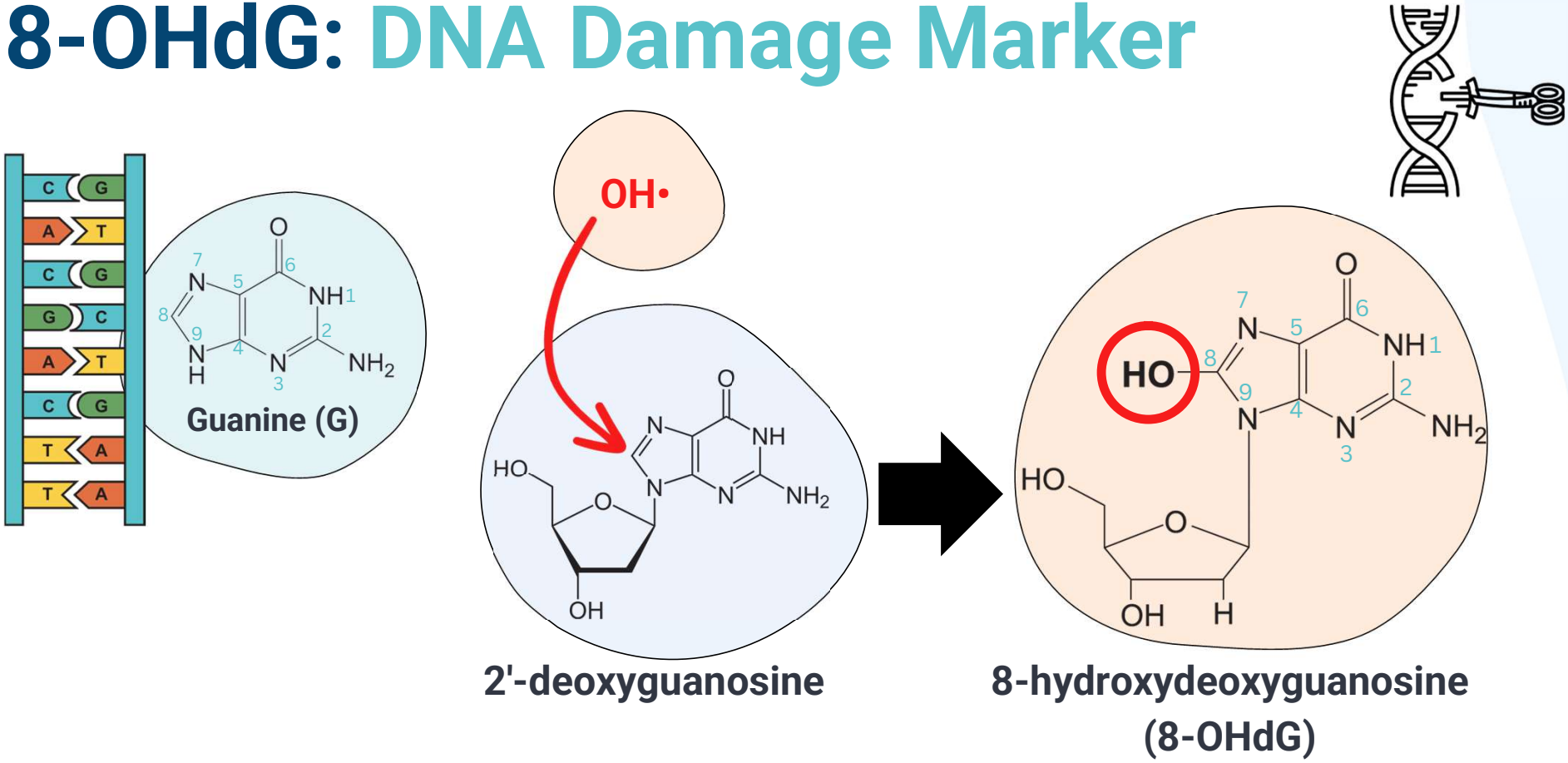
Nitrative Stress Biomarkers
- 8-Nitroguanosine
- 8-Nitroguanine
- Nitrotyrosine

Advanced Glycation Products
- Nε-(carboxymethyl)lysine (CML)
- Nε -carboxyethyllysine (CEL)

Markers of DNA/RNA Damage

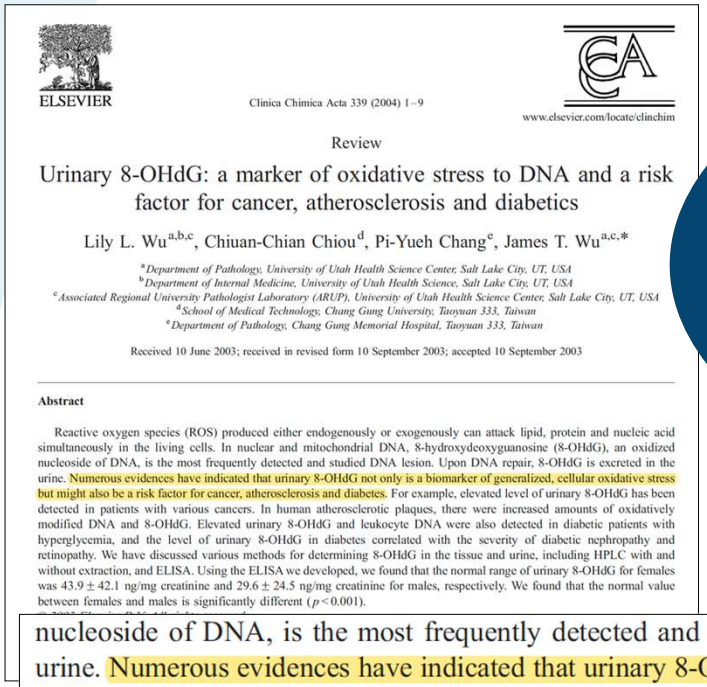
- 8-Hydroxy-2-deoxyguanosine (8-OHdG)
- 8-Hydroxyguanine
- 8-Hydroxyguanosine

8-OHdG: DNA Damage Marker



Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta. 2004;339(1-2):1-9. doi: 10.1016/j.cccn.2003.09.010.

8-OHdG: Biomarker of Early Disease Detection



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Review

Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics

Lily L. Wu[a,b,c], Chiuan-Chian Chiou[d], Pi-Yueh Chang[e], James T. Wu[a,c,*]

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[b] Department of Internal Medicine, University of Utah Health Science, Salt Lake City, UT, USA
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Received 10 June 2003; received in revised form 10 September 2003; accepted 10 September 2003

Abstract

Reactive oxygen species (ROS) produced either endogenously or exogenously can attack lipid, protein and nucleic acid simultaneously in the living cells. In nuclear and mitochondrial DNA, 8-hydroxydeoxyguanosine (8-OHdG), an oxidized nucleoside of DNA, is the most frequently detected and studied DNA lesion. Upon DNA repair, 8-OHdG is excreted in the urine. Numerous evidences have indicated that urinary 8-OHdG not only is a biomarker of generalized, cellular oxidative stress but might also be a risk factor for cancer, atherosclerosis and diabetes. For example, elevated level of urinary 8-OHdG has been detected in patients with various cancers. In human atherosclerotic plaques, there were increased amounts of oxidatively modified DNA and 8-OHdG. Elevated urinary 8-OHdG and leukocyte DNA were also detected in diabetic patients with hyperglycemia, and the level of urinary 8-OHdG in diabetes correlated with the severity of diabetic nephropathy and retinopathy. We have discussed various methods for determining 8-OHdG in the tissue and urine, including HPLC with and without extraction, and ELISA. Using the ELISA we developed, we found that the normal range of urinary 8-OHdG for females was 43.9 ± 42.1 ng/mg creatinine and 29.6 ± 24.5 ng/mg creatinine for males, respectively. We found that the normal value between females and males is significantly different ($p < 0.001$).

nucleoside of DNA, is the most frequently detected and studied DNA lesion. Upon DNA repair, 8-OHdG is excreted in the urine. Numerous evidences have indicated that urinary 8-OHdG not only is a biomarker of generalized, cellular oxidative stress but might also be a risk factor for cancer, atherosclerosis and diabetes. For example, elevated level of urinary 8-OHdG has been detected in patients with various cancers. In human atherosclerotic plaques, there were increased amounts of oxidatively

Discusses urinary (8-OHdG) as a biomarker for **oxidative DNA damage** and its association with increased risk for diseases such as **cancer**, **atherosclerosis**, and **diabetes**.

The study focuses on the mechanisms by which 8-OHdG serves as a signal of oxidative stress and how its elevated levels **can reflect the severity** of these conditions, thus providing a **potential tool for early detection and monitoring of disease progression.**

DNA Damage

Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta. 2004;339(1-2):1-9. doi: 10.1016/j.cccn.2003.09.010.

Markers of Lipid Peroxidation

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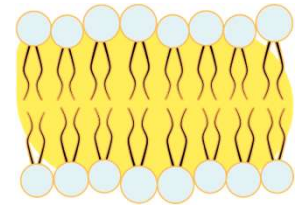
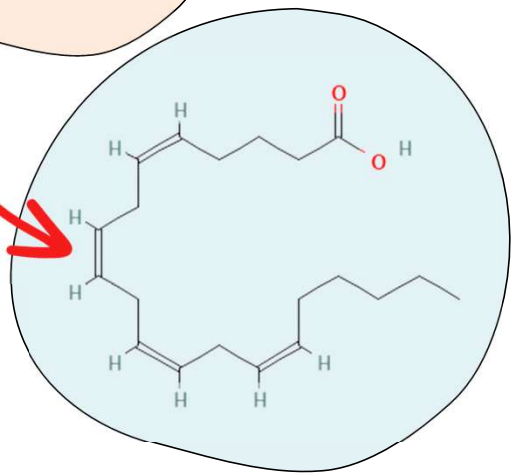
F_2-Isoprostanes: Lipid Peroxidation Markers



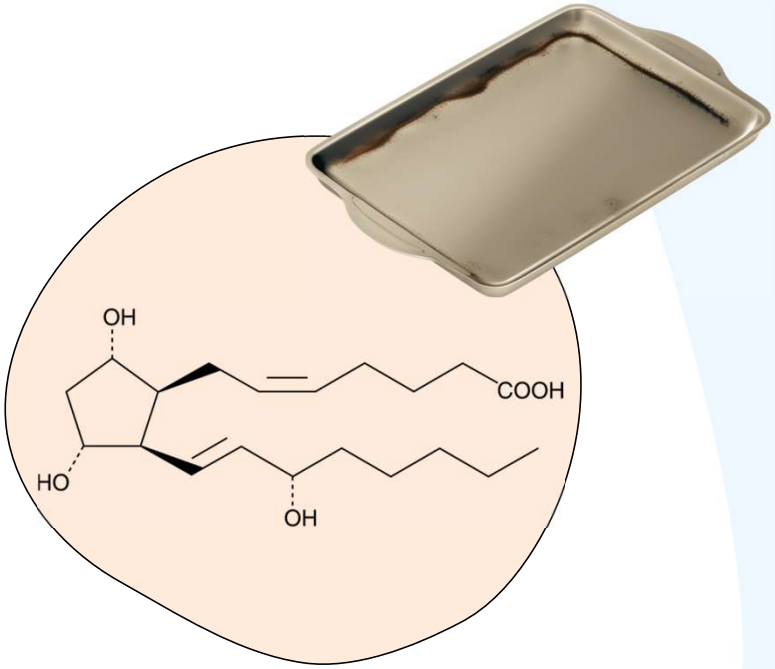
Cell Membranes

Unsaturated fats

Superoxide Free Radical



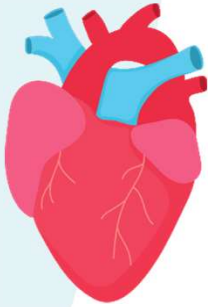
Arachadonic Acid (AA)

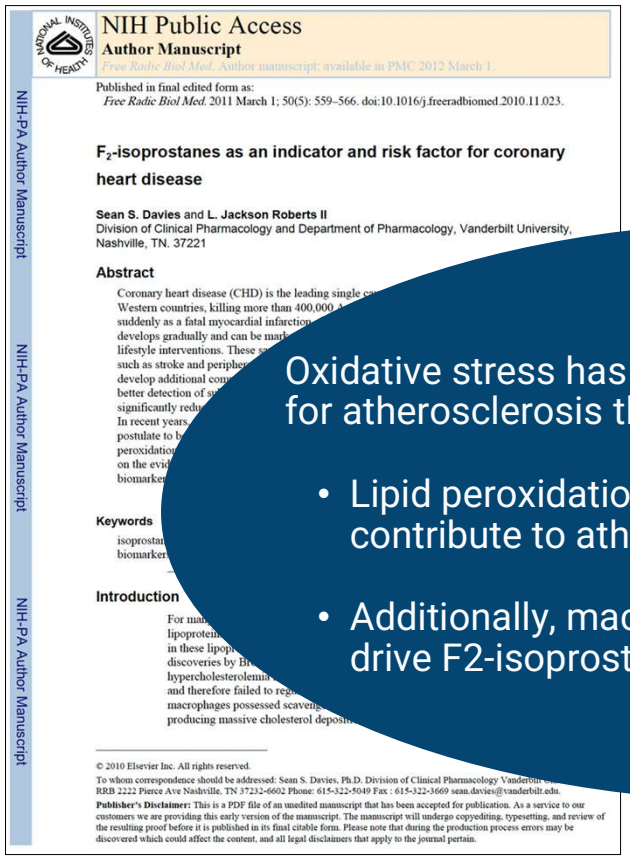


8-iso-prostaglandin $F_2\alpha$

National Institutes of Health. National Library of Medicine. National Center for Biotechnology Information. Arachidonic Acid. Accessed 02.20.2024. https://pubchem.ncbi.nlm.nih.gov/compound/Arachidonic-Acid

F_2-Isoprostane: A Risk Factor for CHD





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Free Radic Biol Med. Author manuscript; available in PMC 2012 March 1.

Published in final edited form as:
Free Radic Biol Med. 2011 March 1; 50(5): 559–566. doi:10.1016/j.freeradbiomed.2010.11.023.

F_2-isoprostanes as an indicator and risk factor for coronary heart disease

Sean S. Davies and **L. Jackson Roberts II**
Division of Clinical Pharmacology and Department of Pharmacology, Vanderbilt University, Nashville, TN. 37221

Abstract

Coronary heart disease (CHD) is the leading single ca
Western countries, killing more than 400,000 A
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develops gradually and can be mark
lifestyle interventions. These s
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Keywords
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biomarker

Introduction

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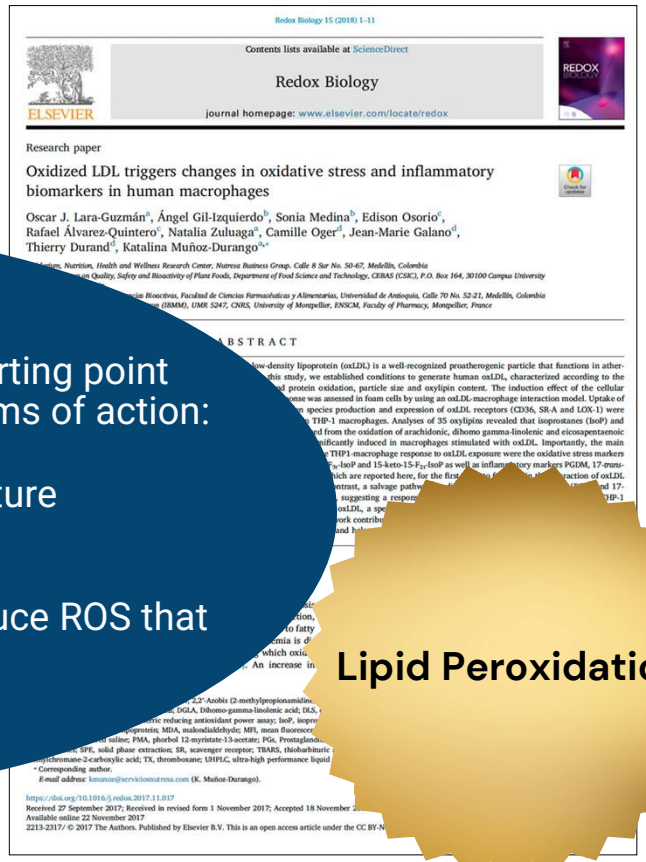
To whom correspondence should be addressed: Sean S. Davies, Ph.D. Division of Clinical Pharmacology Vanderbilt
RRB 2222 Pierce Ave Nashville, TN 37232-6602 Phone: 615-322-5049 Fax : 615-322-3669 sean.davies@vanderbilt.edu.



Redox Biology 15 (2018) 1–11
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Research paper

Oxidized LDL triggers changes in oxidative stress and inflammatory biomarkers in human macrophages

Oscar J. Lara-Guzmán[a], Ángel Gil-Izquierdo[b], Sonia Medina[b], Edison Osorio[c], Rafael Álvarez-Quintero[c], Natalia Zuluaga[a], Camille Oger[d], Jean-Marie Galano[d], Thierry Durand[d], Katalina Muñoz-Durango[b,*]

ABSTRACT

Oxidative stress has been shown to be the starting point for atherosclerosis through various mechanisms of action:

- Lipid peroxidation products in the vasculature contribute to atherogenesis.
- Additionally, macrophage foam cells produce ROS that drive F2-isoprostane production.

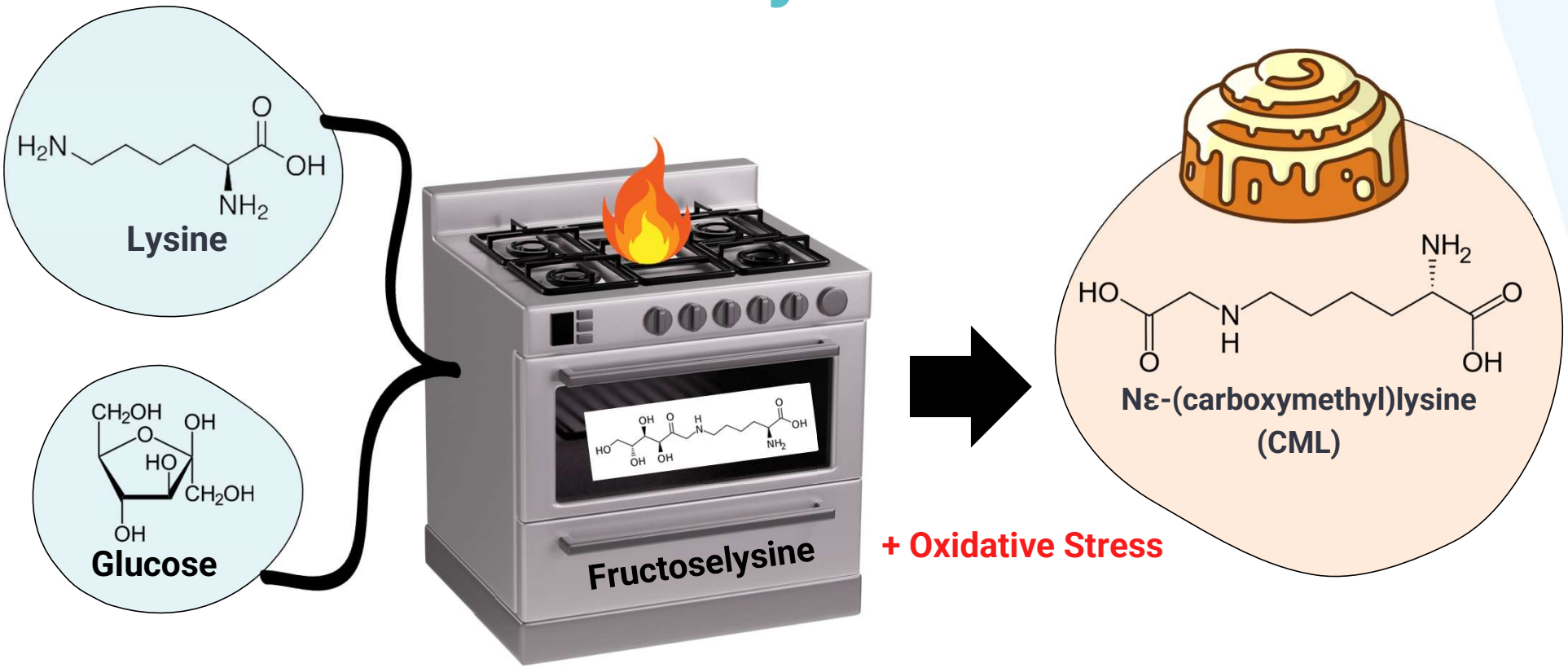
Lipid Peroxidation

1.Davies SS, Roberts LJ 2nd. F2-isoprostanes as an indicator and risk factor for coronary heart disease. Free Radic Biol Med. 2011;50(5):559-66. doi: 10.1016/j.freeradbiomed.2010.11.023.
2.Lara-Guzmán OJ, Gil-Izquierdo Á, Medina S, et al. Oxidized LDL triggers changes in oxidative stress and inflammatory biomarkers in human macrophages. Redox Biol. 2018;15:1-11. doi: 10.1016/j.redox.2017.11.017.

Advanced Glycation Products

- Nε-(carboxymethyl)lysine (CML)
- Nε -carboxyethyllysine (CEL)

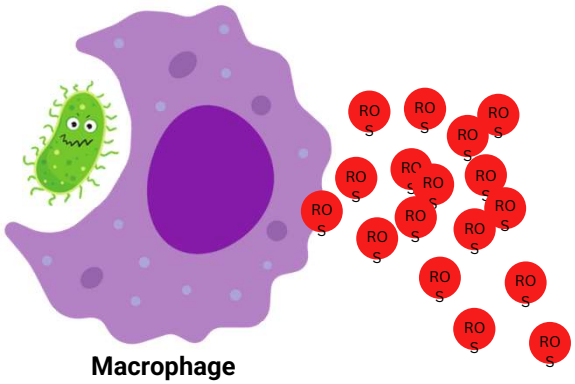
CML: Advanced Glycation Product



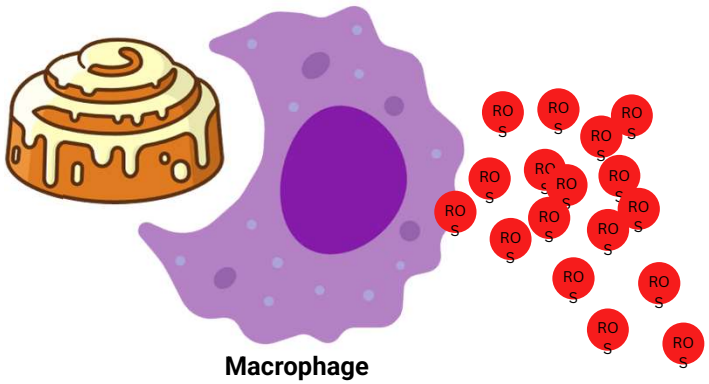
1.Oimomi M, Hatanaka H, Ishikawa K, Kubota S, Yoshimura Y, Baba S. Increased fructose-lysine of nail protein in diabetic patients. Klin Wochenschr. 1984;62(10):477-8. doi: 10.1007/BF01726910. PMID: 6431176.
2.Bui TP, Ritari J, Boeren S, de Waard P, Plugge CM, de Vos WM. Production of butyrate from lysine and the Amadori product fructoselysine by a human gut commensal. Nat Commun. 2015 Dec 1;6:10062. doi: 10.1038/ncomms10062.

Macrophages Create ROS to Perceived Threats

Bacterial & Viral Pathogens



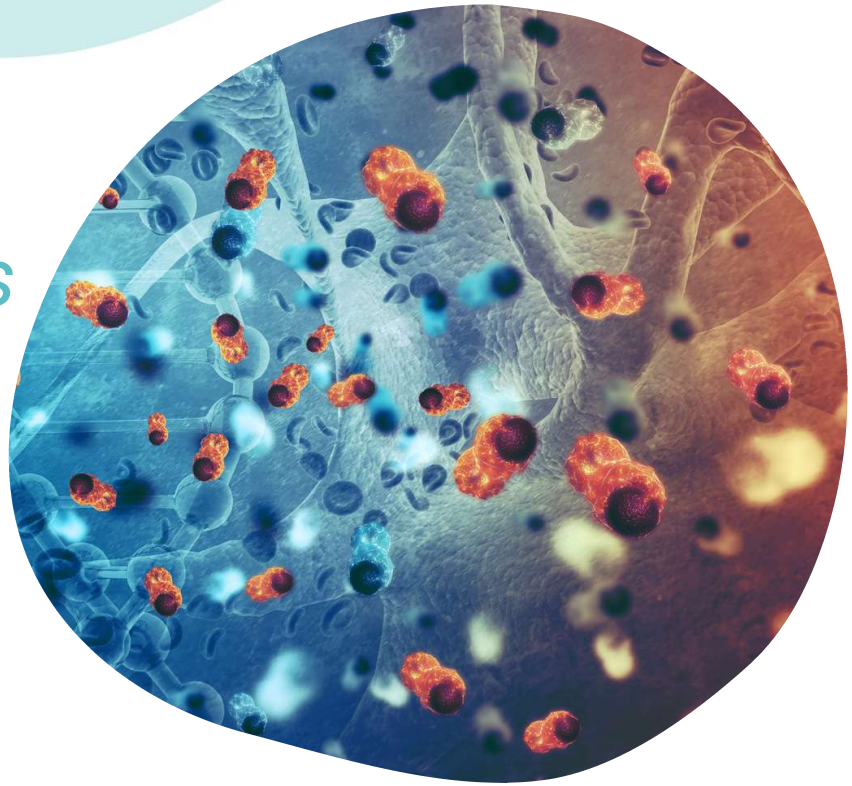
Dietary Advanced Glycation Endproducts



1.Shekhova E. Mitochondrial reactive oxygen species as major effectors of antimicrobial immunity. PLoS Pathog. 2020;16(5):e1008470. doi: 10.1371/journal.ppat.1008470
2.Van der Lugt T, Weseler AR, Gebbink WA, et al. **Dietary advanced glycation endproducts induce an inflammatory response in human macrophages in vitro**. Nutrients. 2018;10(12):1868.

Oxidative Stress

Associated Chronic Conditions
Quantifiable Marker Clusters



Hyperlipidemia:

Elevated F2-Isoprostane and Dityrosine

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F_2-isoprostanes as an indicator and risk factor for coronary heart disease

Sean S. Davies and **L. Jackson Roberts II**
Division of Clinical Pharmacology and Department of Pharmacology, Vanderbilt University, Nashville, TN. 37221

Abstract

Coronary heart disease (CHD) is the leading single cause of death in the United States and most Western countries, killing more than 400,000 Americans per year. Although CHD often manifests suddenly as a fatal myocardial infarction, the atherosclerosis that gives rise to the infarction develops gradually and can be markedly slowed or even reversed through pharmacological and lifestyle interventions. These same atherosclerotic processes also drive related vascular diseases such as stroke and peripheral artery disease, and individuals surviving occlusive events often develop additional complications including ischemic cardiomyopathy and heart failure. Therefore, better detection of subclinical atherosclerosis, along with more effective treatments, could significantly reduce the rate of death from CHD and related vascular diseases in the United States. In recent years, oxidation of polyunsaturated fatty acids (PUFA) in plasma lipoproteins has been postulate to be a critical step in the development atherosclerosis. If so, then monitoring lipid peroxidation should be a useful indicator of disease risk and progression. This review will focus on the evidence that specific PUFA peroxidation products, the F_2-isoprostanes, are useful biomarkers that could potentially be utilized as indicators of CHD.

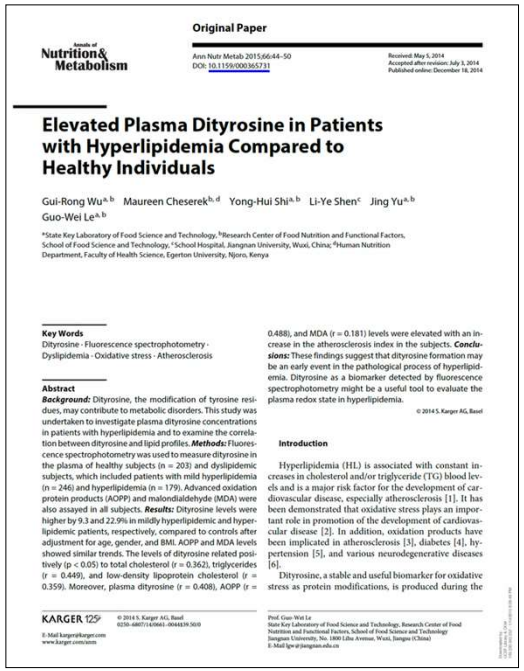
Keywords

isoprostanes; lipid peroxidation; coronary heart disease; cardiovascular disease; oxidative stress; biomarkers; antioxidants; polyunsaturated fatty acids; atherosclerosis

Introduction

For many years, screening and treatment of atherosclerosis focused on cholesterol levels in lipoproteins rather than reducing the peroxidation of the polyunsaturated fatty acid (PUFA) in these lipoproteins. The focus on cholesterol reduction was based on the two seminal discoveries by Brown and Goldstein: the first, in 1974, was that persons with familial hypercholesterolemia lacked the cell surface receptor for low density lipoprotein (LDL) [1] and therefore failed to regulate cholesterol synthesis and the second, in 1979, was that macrophages possessed scavenger receptors that bound and internalized acetylated LDL, producing massive cholesterol deposition similar to those found in the foam cells of

To whom correspondence should be addressed: Sean S. Davies, Ph.D. Division of Clinical Pharmacology Vanderbilt University 506A RRB 2222 Pierce Ave Nashville, TN 37232-6602 Phone: 615-322-5049 Fax.: 615-322-3669 sean.davies@vanderbilt.edu.



Original Paper

Annals of Nutrition & Metabolism

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Accepted after revision: July 3, 2014
Published online: December 18, 2014

Elevated Plasma Dityrosine in Patients with Hyperlipidemia Compared to Healthy Individuals

Gui-Rong Wu[a, b] Maureen Cheserek[b, d] Yong-Hui Shi[a, b] Li-Ye Shen[c] Jing Yu[a, b] Guo-Wei Le[a, b]

[a]State Key Laboratory of Food Science and Technology, [b]Research Center of Food Nutrition and Functional Factors, School of Food Science and Technology, [c]School Hospital, Jiangnan University, Wuxi, China; [d]Human Nutrition Department, Faculty of Health Science, Egerton University, Njoro, Kenya

Key Words

Dityrosine · Fluorescence spectrophotometry · Dyslipidemia · Oxidative stress · Atherosclerosis

Abstract

Background: Dityrosine, the modification of tyrosine residues, may contribute to metabolic disorders. This study was undertaken to investigate plasma dityrosine concentrations in patients with hyperlipidemia and to examine the correlation between dityrosine and lipid profiles. ***Methods:*** Fluorescence spectrophotometry was used to measure dityrosine in the plasma of healthy subjects (n = 203) and dyslipidemic subjects, which included patients with mild hyperlipidemia (n = 246) and hyperlipidemia (n = 179). Advanced oxidation protein products (AOPP) and malondialdehyde (MDA) were also assayed in all subjects. ***Results:*** Dityrosine levels were higher by 9.3 and 22.9% in mildly hyperlipidemic and hyperlipidemic patients, respectively, compared to controls after adjustment for age, gender, and BMI. AOPP and MDA levels showed similar trends. The levels of dityrosine related positively ($p < 0.05$) to total cholesterol ($r = 0.362$), triglycerides ($r = 0.449$), and low-density lipoprotein cholesterol ($r = 0.359$). Moreover, plasma dityrosine ($r = 0.408$), AOPP ($r = 0.488$), and MDA ($r = 0.181$) levels were elevated with an increase in the atherosclerosis index in the subjects. ***Conclusions:*** These findings suggest that dityrosine formation may be an early event in the pathological process of hyperlipidemia. Dityrosine as a biomarker detected by fluorescence spectrophotometry might be a useful tool to evaluate the plasma redox state in hyperlipidemia.

Introduction

Hyperlipidemia (HL) is associated with constant increases in cholesterol and/or triglyceride (TG) blood levels and is a major risk factor for the development of cardiovascular disease, especially atherosclerosis [1]. It has been demonstrated that oxidative stress plays an important role in promotion of the development of cardiovascular disease [2]. In addition, oxidation products have been implicated in atherosclerosis [3], diabetes [4], hypertension [5], and various neurodegenerative diseases [6].

Dityrosine, a stable and useful biomarker for oxidative stress as protein modifications, is produced during the

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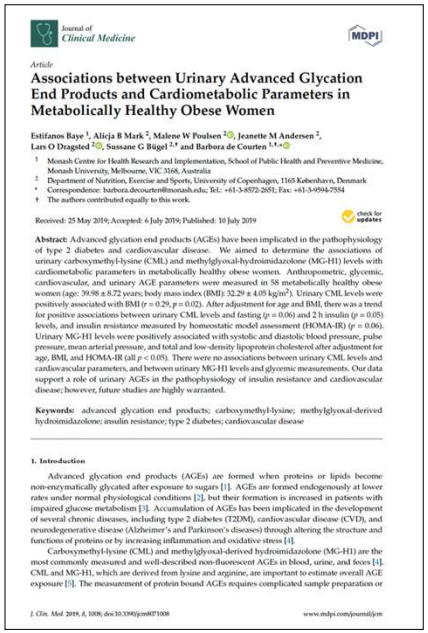
Jiangnan University, No. 1800 Lihu Avenue, Wuxi, Jiangsu (China)
E-Mail lgw@jiangnan.edu.cn

1.Wu GR, Cheserek M, Shi YH, Shen LY, Yu J, Le GW. Elevated plasma dityrosine in patients with hyperlipidemia compared to healthy individuals. Ann Nutr Metab. 2015;66(1):44-50. doi: 10.1159/000365731.
2.Davies SS, Roberts LJ 2nd. F2-isoprostanes as an indicator and risk factor for coronary heart disease. Free Radic Biol Med. 2011;50(5):559-66. doi: 10.1016/j.freeradbiomed.2010.11.023.

Diabetes:

Elevated 8-OHdG, CML, 8-Isoprostane



Journal of Clinical Medicine

MDPI

Article

Associations between Urinary Advanced Glycation End Products and Cardiometabolic Parameters in Metabolically Healthy Obese Women

Estifanos Baye [1], Alicja B Mark [2], Malene W Poulsen [2], Jeanette M Andersen [2], Lars O Dragsted [2], Sussane G Bügel [2,†] and Barbora de Courten [1,*,†]

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[2] Department of Nutrition, Exercise and Sports, University of Copenhagen, 1165 København, Denmark
* Correspondence: barbora.decourten@monash.edu; Tel.: +61-3-8572-2651; Fax: +61-3-9594-7554
† The authors contributed equally to this work.

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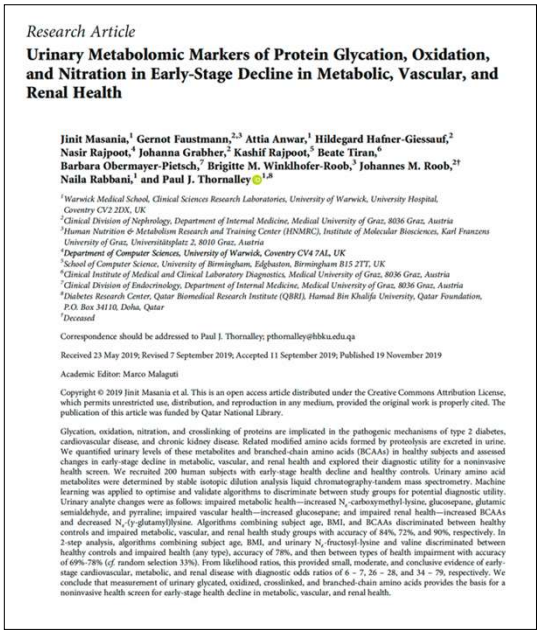
Abstract: Advanced glycation end products (AGEs) have been implicated in the pathophysiology of type 2 diabetes and cardiovascular disease. We aimed to determine the associations of urinary carboxymethyl-lysine (CML) and methylglyoxal-hydroimidazolone (MG-H1) levels with cardiometabolic parameters in metabolically healthy obese women. Anthropometric, glycemic, cardiovascular, and urinary AGE parameters were measured in 58 metabolically healthy obese women (age: 39.98 ± 8.72 years; body mass index (BMI): 32.29 ± 4.05 kg/m^2). Urinary CML levels were positively associated with BMI ($r = 0.29$, $p = 0.02$). After adjustment for age and BMI, there was a trend for positive associations between urinary CML levels and fasting ($p = 0.06$) and 2 h insulin ($p = 0.05$) levels, and insulin resistance measured by homeostatic model assessment (HOMA-IR) ($p = 0.06$). Urinary MG-H1 levels were positively associated with systolic and diastolic blood pressure, pulse pressure, mean arterial pressure, and total and low-density lipoprotein cholesterol after adjustment for age, BMI, and HOMA-IR (all $p < 0.05$). There were no associations between urinary CML levels and cardiovascular parameters, and between urinary MG-H1 levels and glycemic measurements. Our data support a role of urinary AGEs in the pathophysiology of insulin resistance and cardiovascular disease; however, future studies are highly warranted.

Keywords: advanced glycation end products; carboxymethyl-lysine; methylglyoxal-derived hydroimidazolone; insulin resistance; type 2 diabetes; cardiovascular disease

1. Introduction

Advanced glycation end products (AGEs) are formed when proteins or lipids become non-enzymatically glycated after exposure to sugars [1]. AGEs are formed endogenously at lower rates under normal physiological conditions [2], but their formation is increased in patients with impaired glucose metabolism [3]. Accumulation of AGEs has been implicated in the development of several chronic diseases, including type 2 diabetes (T2DM), cardiovascular disease (CVD), and neurodegenerative disease (Alzheimer's and Parkinson's diseases) through altering the structure and functions of proteins or by increasing inflammation and oxidative stress [4].

Carboxymethyl-lysine (CML) and methylglyoxal-derived hydroimidazolone (MG-H1) are the most commonly measured and well-described non-fluorescent AGEs in blood, urine, and feces [4]. CML and MG-H1, which are derived from lysine and arginine, are important to estimate overall AGE exposure [5]. The measurement of protein bound AGEs requires complicated sample preparation or



Research Article

Urinary Metabolomic Markers of Protein Glycation, Oxidation, and Nitration in Early-Stage Decline in Metabolic, Vascular, and Renal Health

Jinit Masania,[1] Gernot Faustmann,[2,3] Attia Anwar,[1] Hildegard Hafner-Giessauf,[2] Nasir Rajpoot,[4] Johanna Grabher,[2] Kashif Rajpoot,[5] Beate Tiran,[6] Barbara Obermayer-Pietsch,[7] Brigitte M. Winklhofer-Roob,[3] Johannes M. Roob,[2†] Naila Rabbani,[1] and Paul J. Thornalley [1,8]

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[8] *Diabetes Research Center, Qatar Biomedical Research Institute (QBRI), Hamad Bin Khalifa University, Qatar Foundation, P.O. Box 34110, Doha, Qatar*
† *Deceased*

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Academic Editor: Marco Malaguti

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Glycation, oxidation, nitration, and crosslinking of proteins are implicated in the pathogenic mechanisms of type 2 diabetes, cardiovascular disease, and chronic kidney disease. Related modified amino acids formed by proteolysis are excreted in urine. We quantified urinary levels of these metabolites and branched-chain amino acids (BCAAs) in healthy subjects and assessed changes in early-stage decline in metabolic, vascular, and renal health and explored their diagnostic utility for a noninvasive health screen. We recruited 200 human subjects with early-stage health decline and healthy controls. Urinary amino acid metabolites were determined by stable isotopic dilution analysis liquid chromatography-tandem mass spectrometry. Machine learning was applied to optimise and validate algorithms to discriminate between study groups for potential diagnostic utility. Urinary analyte changes were as follows: impaired metabolic health—increased N_ε-carboxymethyl-lysine, glucosepane, glutamic semialdehyde, and pyrraline; impaired vascular health—increased glucosepane; and impaired renal health—increased BCAAs and decreased N_ε-(γ-glutamyl)lysine. Algorithms combining subject age, BMI, and BCAAs discriminated between healthy controls and impaired metabolic, vascular, and renal health study groups with accuracy of 84%, 72%, and 90%, respectively. In 2-step analysis, algorithms combining subject age, BMI, and urinary N_ε-fructosyl-lysine and valine discriminated between healthy controls and impaired health (any type), accuracy of 78%, and then between types of health impairment with accuracy of 69%–78% (*cf.* random selection 33%). From likelihood ratios, this provided small, moderate, and conclusive evidence of early-stage cardiovascular, metabolic, and renal disease with diagnostic odds ratios of 6 – 7, 26 – 28, and 34 – 79, respectively. We conclude that measurement of urinary glycated, oxidized, crosslinked, and branched-chain amino acids provides the basis for a noninvasive health screen for early-stage health decline in metabolic, vascular, and renal health.

antioxidants

MDPI

Article

Urinary Oxidative Damage Markers and Their Association with Obesity-Related Metabolic Risk Factors

Salah Gariballa *, Abderrahim Nemmar, Ozaz Elzaki, Nur Elena Zaaba and Javed Yasin

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Abstract: Oxidative damage and inflammation are possible mechanisms linking obesity to diabetes and related complications. This study investigates the levels of oxidative damage markers in the urine of community free-living subjects with increased prevalence of obesity. Methods: Participants were assessed regarding clinical, anthropometric, and physical activity data at baseline and at 6 months. Blood and urine samples were taken for the measurements of oxidative markers in urine (glutathione (GSH), thiobarbituric acid reactive substances (TBARS), pteridine, 8-isoprostane and 8-hydroxy-2′-deoxyguanosine (8-OH-dG)), metabolic and inflammatory markers, and related biochemical variables in the blood. Univariate and multiple regression analyses were used to assess the association between oxidative markers and other clinical prognostic indicators. Results: Overall, 168 participants with a complete 6-month follow-up with a mean (±SD) age of 41 ± 12 (119 (71%) females) were included in the study. In multiple regression analysis, log-transformed urinary pteridine levels were significantly correlated with log-transformed urinary GSH, 8-isoprostane, and TBARS after adjusting for urinary creatinine at both baseline and follow-up. Significant correlations were also found between oxidative damage markers and cardiovascular disease risk factors, including systolic blood pressure, HbA1c, plasma glucose, us-C-reactive proteins, total cholesterol, and HDL. Higher TBARS levels were found in males and diabetic subjects, with lower GSH in diabetic hypertensive and obese subjects, but the latter result did not reach statistical significance. We found nonsignificantly higher TBARS, 8-isoprostane, and pteridine levels in smokers compared to those in nonsmokers. All measured urinary oxidative damage markers levels were higher in obese subjects compared with normal-weight subjects, but results did not reach statistical significance. Conclusion: we found significant associations between urinary oxidative damage and metabolic risk factors, and higher levels of urinary oxidative damage markers in diabetic, hypertensive, smoker, and male subjects.

Keywords: urinary oxidative damage markers; antioxidants; obesity; diabetes; hypertension

1. Introduction

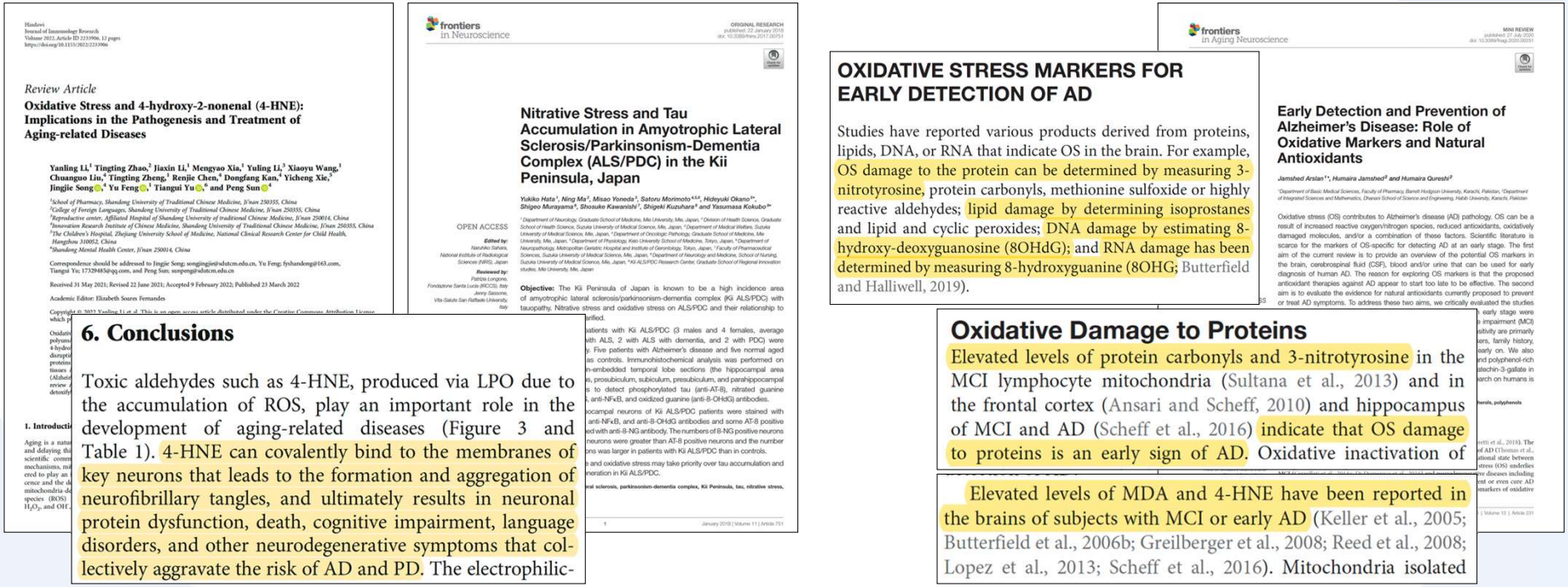
The prevalence of obesity, diabetes, and other cardiovascular disease (CVD) risk factors is increasing rapidly and reaching epidemic levels in Gulf countries, including the United Arab Emirates (UAE) [1–3]. For example, the very recent report of "Diabetes around the world in 2021" revealed that, in the Middle East and North Africa, 1 in 6 adults (73 million) are living with diabetes compared with the global 1 in 10 (537 million adults (20–79 years)). Furthermore, 1 in 3 adults living with diabetes in the Middle East are undiagnosed, and 1 in 7 live births are affected by hyperglycemia in pregnancy [4]. The UAE has one of the highest prevalences of obesity-related diabetes mellitus in the world [3].

Oxidative damage may be causatively linked to obesity-related complications, including insulin resistance and diabetes [5] In addition, oxidative damage may predict the development and progression of diabetes-related complications [5–7]. There is also some evidence that oxidative stress predates the appearance of diabetes complications [8].

1.Baye E, Mark AB, Poulsen MW, Andersen JM, et al. Associations between Urinary Advanced Glycation End Products and Cardiometabolic Parameters in Metabolically Healthy Obese Women. J Clin Med. 2019;8(7):1008. doi: 10.3390/jcm8071008.
2.Masania J, Faustmann G, Anwar A, et al. Urinary Metabolomic Markers of Protein Glycation, Oxidation, and Nitration in Early-Stage Decline in Metabolic, Vascular, and Renal Health. Oxid Med Cell Longev. 2019;2019:4851323. doi: 10.1155/2019/4851323.
3.Gariballa S, Nemmar A, Elzaki O, Zaaba NE, Yasin J. Urinary Oxidative Damage Markers and Their Association with Obesity-Related Metabolic Risk Factors. Antioxidants (Basel). 2022 Apr 26;11(5):844. doi: 10.3390/antiox11050844.

Alzheimer‘s:

Elevated 8-OHdG, 8OHG, 4-HNE, MDA, Isoprostanes, Nitrotyrosine



Review Article

Oxidative Stress and 4-hydroxy-2-nonenal (4-HNE): Implications in the Pathogenesis and Treatment of Aging-related Diseases

Nitrative Stress and Tau Accumulation in Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex (ALS/PDC) in the Kii Peninsula, Japan

OXIDATIVE STRESS MARKERS FOR EARLY DETECTION OF AD

Studies have reported various products derived from proteins, lipids, DNA, or RNA that indicate OS in the brain. For example, OS damage to the protein can be determined by measuring 3-nitrotyrosine, protein carbonyls, methionine sulfoxide or highly reactive aldehydes; lipid damage by determining isoprostanes and lipid and cyclic peroxides; DNA damage by estimating 8-hydroxy-deoxyguanosine (8OHdG); and RNA damage has been determined by measuring 8-hydroxyguanine (8OHG; Butterfield and Halliwell, 2019).

Early Detection and Prevention of Alzheimer's Disease: Role of Oxidative Markers and Natural Antioxidants

6. Conclusions

Toxic aldehydes such as 4-HNE, produced via LPO due to the accumulation of ROS, play an important role in the development of aging-related diseases (Figure 3 and Table 1). 4-HNE can covalently bind to the membranes of key neurons that leads to the formation and aggregation of neurofibrillary tangles, and ultimately results in neuronal protein dysfunction, death, cognitive impairment, language disorders, and other neurodegenerative symptoms that collectively aggravate the risk of AD and PD. The electrophilic-

Oxidative Damage to Proteins

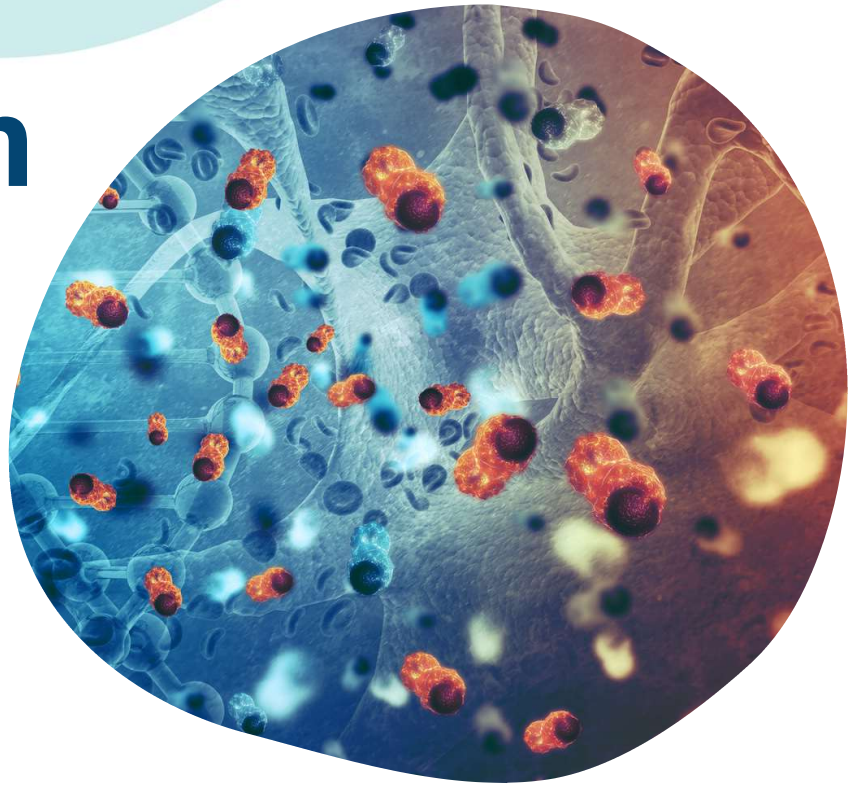
Elevated levels of protein carbonyls and 3-nitrotyrosine in the MCI lymphocyte mitochondria (Sultana et al., 2013) and in the frontal cortex (Ansari and Scheff, 2010) and hippocampus of MCI and AD (Scheff et al., 2016) indicate that OS damage to proteins is an early sign of AD. Oxidative inactivation of

Elevated levels of MDA and 4-HNE have been reported in the brains of subjects with MCI or early AD (Keller et al., 2005; Butterfield et al., 2006b; Greilberger et al., 2008; Reed et al., 2008; Lopez et al., 2013; Scheff et al., 2016). Mitochondria isolated

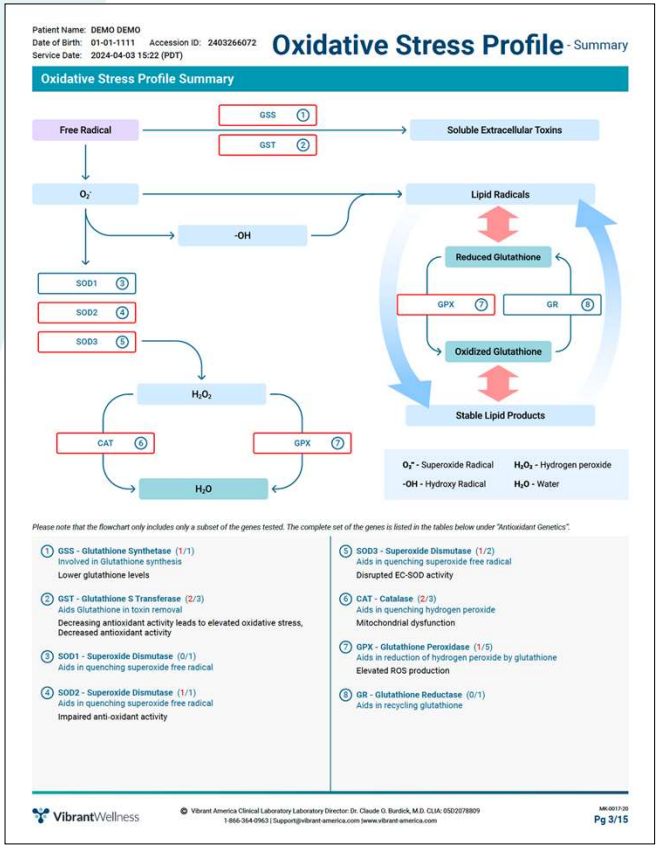
1.Li Y, Zhao T, Li J, et al. Oxidative Stress and 4-hydroxy-2-nonenal (4-HNE): Implications in the Pathogenesis and Treatment of Aging-related Diseases. J Immunol Res. 2022;2022:2233906. doi: 10.1155/2022/2233906.
2.Arslan J, Jamshed H, Qureshi H. Early Detection and Prevention of Alzheimer's Disease: Role of Oxidative Markers and Natural Antioxidants. Front Aging Neurosci. 2020;12:231. doi: 10.3389/fnagi.2020.00231.
3.Hata Y, Ma N, Yoneda M, et al. Nitrative Stress and Tau Accumulation in Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex (ALS/PDC) in the Kii Peninsula, Japan. Front Neurosci. 2018;11:751. doi: 10.3389/fnins.2017.00751.

Clinical Application in Lab Evaluation

Sample Report



Comprehensive Evaluation – Sample Report



Patient Name: DEMO DEMO
Date of Birth: 01-01-1111 Accession ID: 2403266072
Service Date: 2024-04-03 15:22 (PDT)

Oxidative Stress Profile - Summary

Oxidative Stress Profile Summary

Please note that the flowchart only includes only a subset of the genes tested. The complete set of the genes is listed in the tables below under "Antioxidant Genetics".

① GSS - Glutathione Synthetase (1/1)
Involved in Glutathione synthesis
Lower glutathione levels

② GST - Glutathione S Transferase (2/3)
Aids Glutathione in toxin removal
Decreasing antioxidant activity leads to elevated oxidative stress, Decreased antioxidant activity

③ SOD1 - Superoxide Dismutase (0/1)
Aids in quenching superoxide free radical

④ SOD2 - Superoxide Dismutase (1/1)
Aids in quenching superoxide free radical
Impaired anti-oxidant activity

⑤ SOD3 - Superoxide Dismutase (1/2)
Aids in quenching superoxide free radical
Disrupted EC-SOD activity

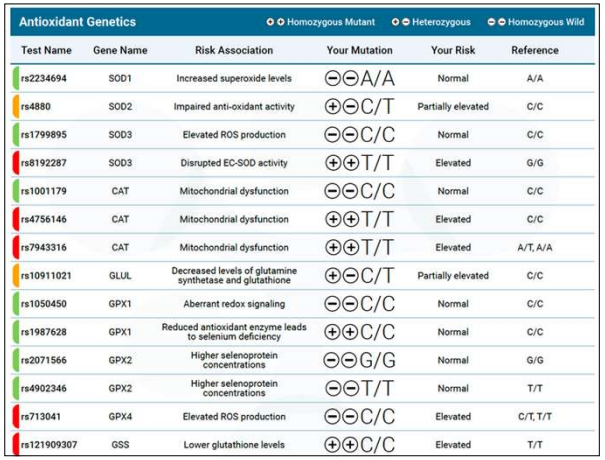
⑥ CAT - Catalase (2/3)
Aids in quenching hydrogen peroxide
Mitochondrial dysfunction

⑦ GPX - Glutathione Peroxidase (1/5)
Aids in reduction of hydrogen peroxide by glutathione
Elevated ROS production

⑧ GR - Glutathione Reductase (0/1)
Aids in recycling glutathione

VibrantWellness

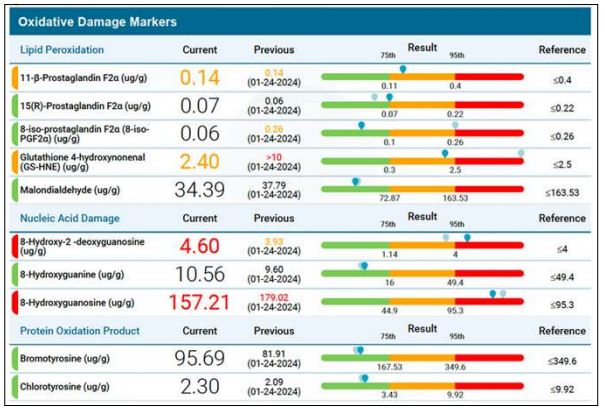
MK-0017-20



Antioxidant Genetics

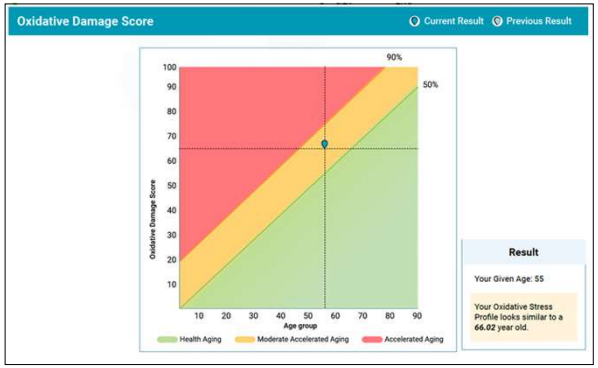
⊖⊖ Homozygous Mutant ⊕⊖ Heterozygous ⊕⊕ Homozygous Wild

Test Name	Gene Name	Risk Association	Your Mutation	Your Risk	Reference
rs2234694	SOD1	Increased superoxide levels	⊖⊖A/A	Normal	A/A
rs4880	SOD2	Impaired anti-oxidant activity	⊕⊖C/T	Partially elevated	C/C
rs1799895	SOD3	Elevated ROS production	⊖⊖C/C	Normal	C/C
rs8192287	SOD3	Disrupted EC-SOD activity	⊕⊕T/T	Elevated	G/G
rs1001179	CAT	Mitochondrial dysfunction	⊖⊖C/C	Normal	C/C
rs4756146	CAT	Mitochondrial dysfunction	⊕⊕T/T	Elevated	C/C
rs7943316	CAT	Mitochondrial dysfunction	⊕⊕T/T	Elevated	A/T, A/A
rs10911021	GLUL	Decreased levels of glutamine synthetase and glutathione	⊕⊖C/T	Partially elevated	C/C
rs1050450	GPX1	Aberrant redox signaling	⊖⊖C/C	Normal	C/C
rs1987628	GPX1	Reduced antioxidant enzyme leads to selenium deficiency	⊕⊕C/C	Normal	C/C
rs2071566	GPX2	Higher selenoprotein concentrations	⊖⊖G/G	Normal	G/G
rs4902346	GPX2	Higher selenoprotein concentrations	⊖⊖T/T	Normal	T/T
rs713041	GPX4	Elevated ROS production	⊖⊖C/C	Elevated	C/T, T/T
rs121909307	GSS	Lower glutathione levels	⊕⊕C/C	Elevated	T/T



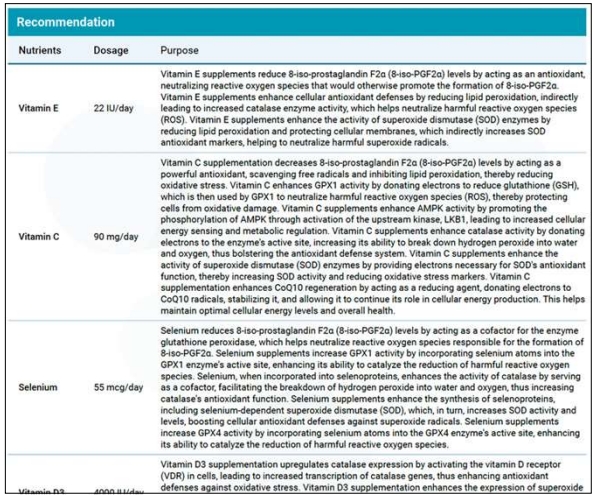
Oxidative Damage Markers

Lipid Peroxidation	Current	Previous	Result (75th – 95th)	Reference
11-β-Prostaglandin F2α (ug/g)	0.14	0.14 (01-24-2024)	0.11 – 0.4	≤0.4
15(R)-Prostaglandin F2α (ug/g)	0.07	0.06 (01-24-2024)	0.07 – 0.22	≤0.22
8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g)	0.06	0.26 (01-24-2024)	0.1 – 0.26	≤0.26
Glutathione 4-hydroxynonenal (GS-HNE) (ug/g)	2.40	>10 (01-24-2024)	0.3 – 2.5	≤2.5
Malondialdehyde (ug/g)	34.39	37.79 (01-24-2024)	72.87 – 163.53	≤163.53
Nucleic Acid Damage	**Current**	**Previous**	**Result (75th – 95th)**	**Reference**
8-Hydroxy-2 -deoxyguanosine (ug/g)	4.60	3.93 (01-24-2024)	1.14 – 4	≤4
8-Hydroxyguanine (ug/g)	10.56	9.60 (01-24-2024)	16 – 49.4	≤49.4
8-Hydroxyguanosine (ug/g)	157.21	179.02 (01-24-2024)	44.9 – 95.3	≤95.3
Protein Oxidation Product	**Current**	**Previous**	**Result (75th – 95th)**	**Reference**
Bromotyrosine (ug/g)	95.69	81.91 (01-24-2024)	167.53 – 349.6	≤349.6
Chlorotyrosine (ug/g)	2.30	2.09 (01-24-2024)	3.43 – 9.92	≤9.92



Oxidative Damage Score

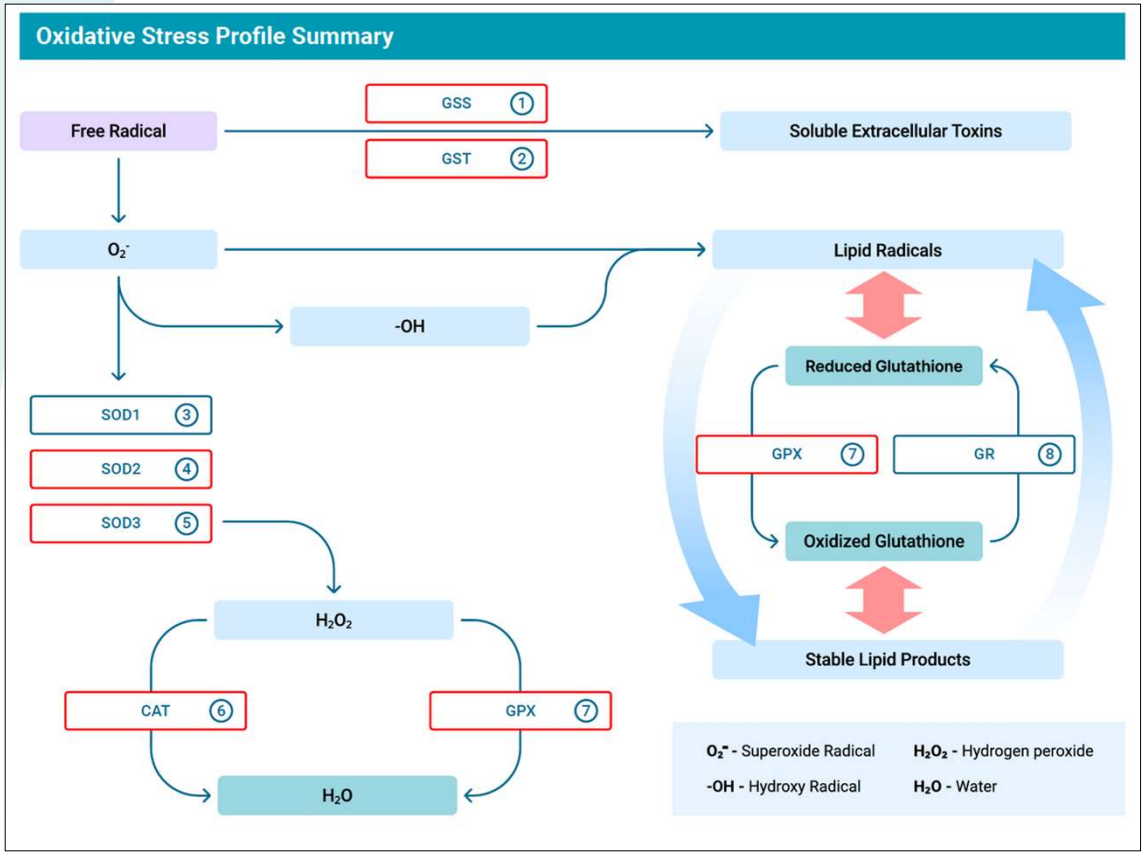
Current Result Previous Result



Recommendation

Nutrients	Dosage	Purpose
Vitamin E	22 IU/day	Vitamin E supplements reduce 8-iso-prostaglandin F2α (8-iso-PGF2α) levels by acting as an antioxidant, neutralizing reactive oxygen species that would otherwise promote the formation of 8-iso-PGF2α. Vitamin E supplements enhance cellular antioxidant defenses by reducing lipid peroxidation, indirectly leading to increased catalase enzyme activity, which helps neutralize harmful reactive oxygen species (ROS). Vitamin E supplements enhance the activity of superoxide dismutase (SOD) enzymes by reducing lipid peroxidation and protecting cellular membranes, which indirectly increases SOD antioxidant markers, helping to neutralize harmful superoxide radicals.
Vitamin C	90 mg/day	Vitamin C supplementation decreases 8-iso-prostaglandin F2α (8-iso-PGF2α) levels by acting as a powerful antioxidant, scavenging free radicals and inhibiting lipid peroxidation, thereby reducing oxidative stress. Vitamin C enhances GPX1 activity by donating electrons to reduce glutathione (GSH), which is then used by GPX1 to neutralize harmful reactive oxygen species (ROS), thereby protecting cells from oxidative damage. Vitamin C supplements enhance AMPK activity by promoting the phosphorylation of AMPK through activation of the upstream kinase, LKB1, leading to increased cellular energy sensing and metabolic regulation. Vitamin C supplements enhance catalase activity by donating electrons to the enzyme's active site, increasing its ability to break down hydrogen peroxide into water and oxygen, thus bolstering the antioxidant defense system. Vitamin C supplements enhance the activity of superoxide dismutase (SOD) enzymes by providing electrons necessary for SOD's antioxidant function, thereby increasing SOD activity and reducing oxidative stress markers. Vitamin C supplementation enhances CoQ10 regeneration by acting as a reducing agent, donating electrons to CoQ10 radicals, stabilizing it, and allowing it to continue its role in cellular energy production. This helps maintain optimal cellular energy levels and overall health.
Selenium	55 mcg/day	Selenium reduces 8-iso-prostaglandin F2α (8-iso-PGF2α) levels by acting as a cofactor for the enzyme glutathione peroxidase, which helps neutralize reactive oxygen species responsible for the formation of 8-iso-PGF2α. Selenium supplements increase GPX1 activity by incorporating selenium atoms into the GPX1 enzyme's active site, enhancing its ability to catalyze the reduction of harmful reactive oxygen species. Selenium, when incorporated into selenoproteins, enhances the activity of catalase by serving as a cofactor, facilitating the breakdown of hydrogen peroxide into water and oxygen, thus increasing catalase's antioxidant function. Selenium supplements enhance the synthesis of selenoproteins, including selenium-dependent superoxide dismutase (SOD), which, in turn, increases SOD activity and levels, boosting cellular antioxidant defenses against superoxide radicals. Selenium supplements increase GPX4 activity by incorporating selenium atoms into the GPX4 enzyme's active site, enhancing its ability to catalyze the reduction of harmful reactive oxygen species.
Vitamin D3	4000 IU/day	Vitamin D3 supplementation upregulates catalase expression by activating the vitamin D receptor (VDR) in cells, leading to increased transcription of catalase genes, thus enhancing antioxidant defenses against oxidative stress. Vitamin D3 supplementation enhances the expression of superoxide

Antioxidant Defense System – patient's unique Flowchart



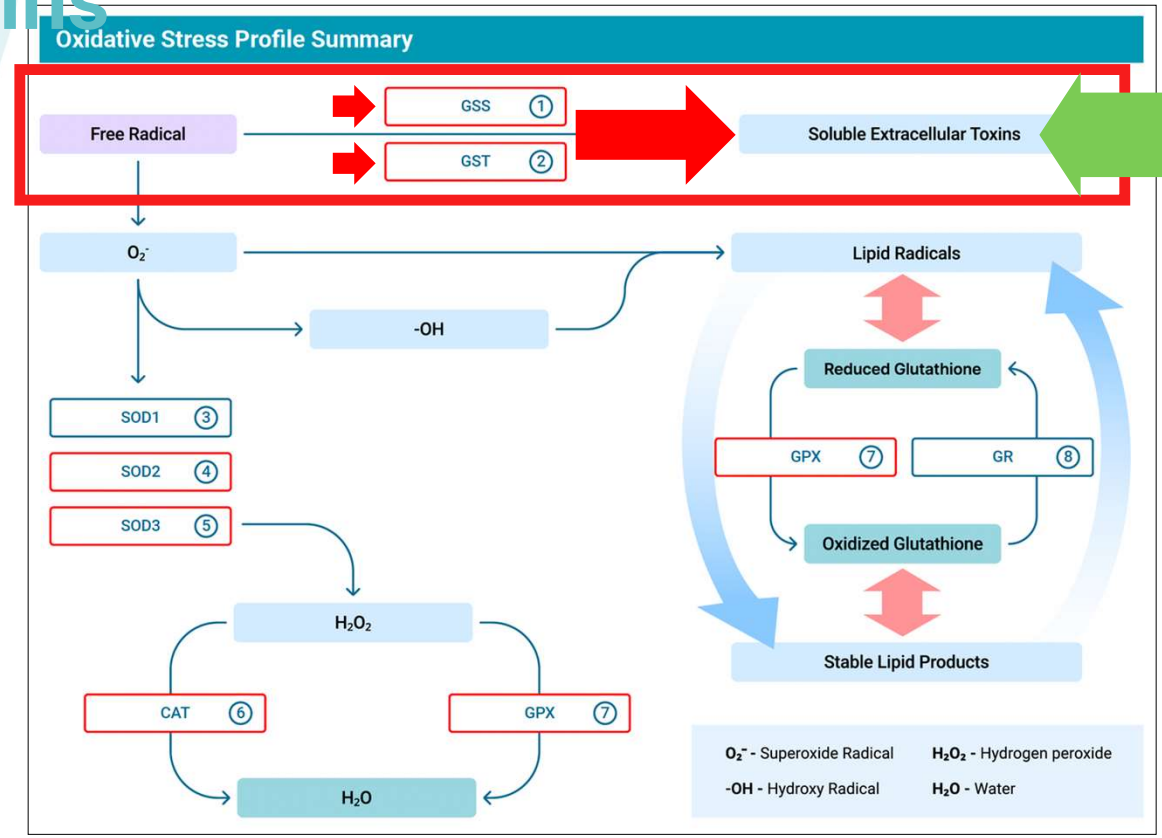
Ideally, free radicals get converted to a more stable forms via these antioxidant pathways. Your antioxidant genetics determine how these pathways function.

If everything works in the pathway, the patient will always end up with water and stable lipid products.

However, if you have an elevated risk SNP (and the enzymes don't work optimally), proper flow does not happen.

And when the flow is blocked, the patient is predisposed to experience increased oxidative stress and damage.

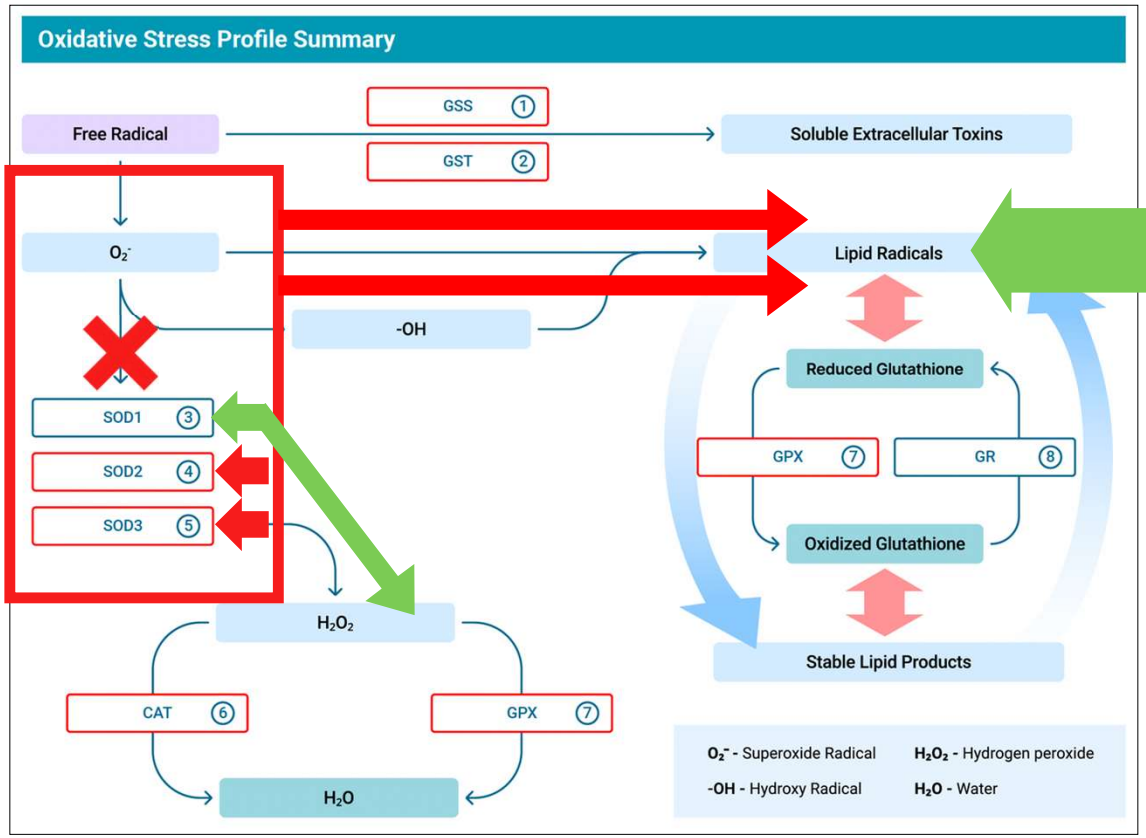
Elevated Risk GSS & GST = *More* Extracellular Toxins



Nutrient Support for GST Enzyme Activity

- Broccoli Extract
- Pomegranate-Black Carrot Juice
- S-Adenosylmethionine
- Grape Pomace Extract
- **Glutathione**

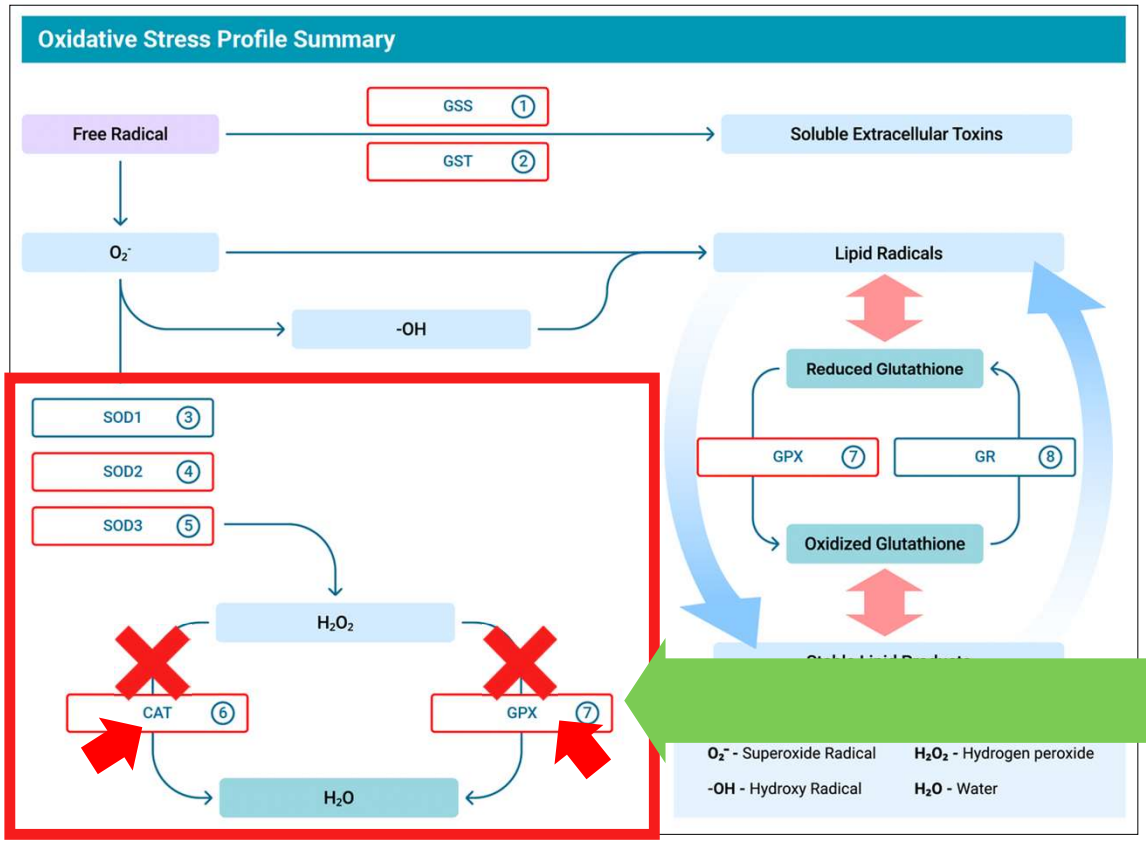
Elevated Risk SOD2 & SOD3 = More Lipid Radicals



Dietary & Supplemental Antioxidant Support

- Alpha-lipoic acid (ALA)
- Coenzyme Q10
- Vitamin A
- Vitamin E

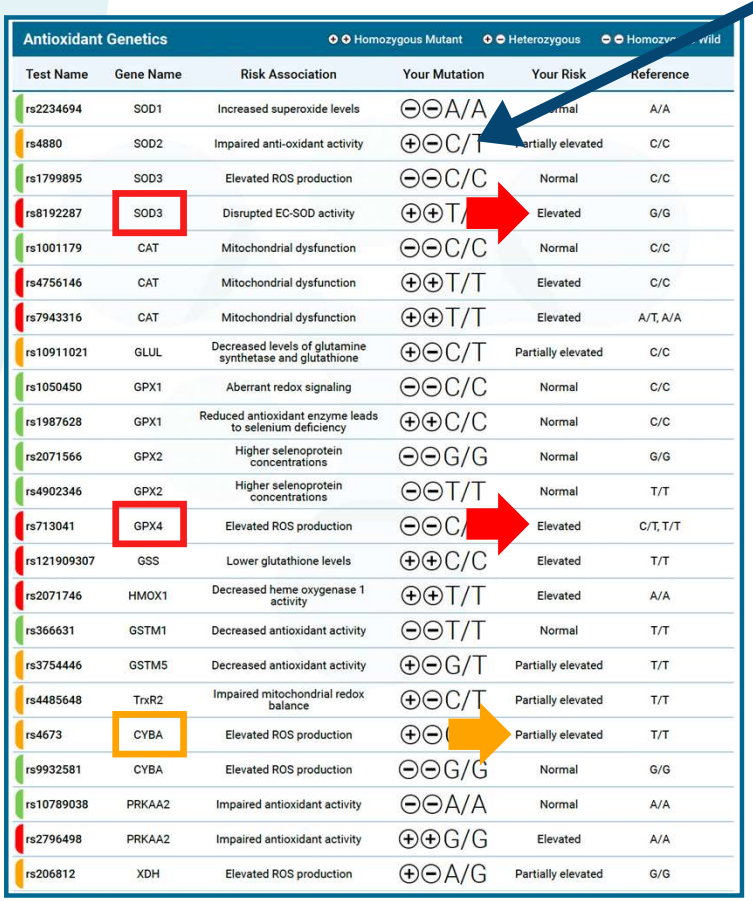
Elevated Risk CAT & GPX = *More* Oxidative Damage



Nutrient Support for GPX4 Enzyme Activity

- Selenium
- Glutathione

Antioxidant Genetics: Full Report & Interpretation



Antioxidant Genetics — ⊕⊕ Homozygous Mutant ⊕⊖ Heterozygous ⊖⊖ Homozygous Wild

Test Name	Gene Name	Risk Association	Your Mutation	Your Risk	Reference
rs2234694	SOD1	Increased superoxide levels	⊖⊖A/A	Normal	A/A
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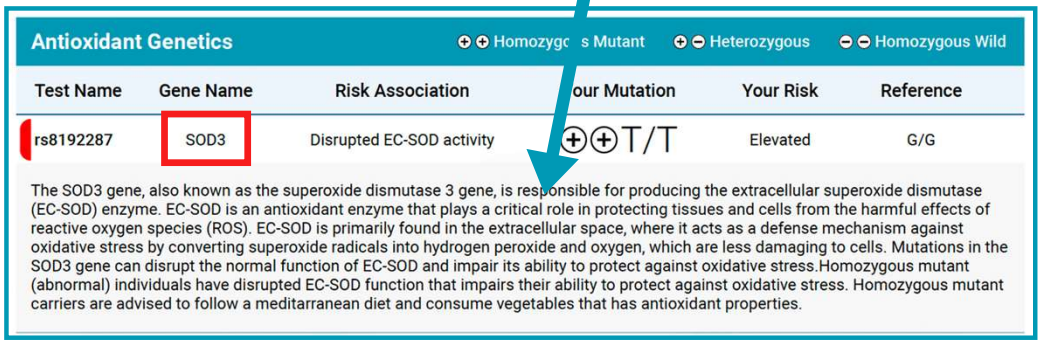
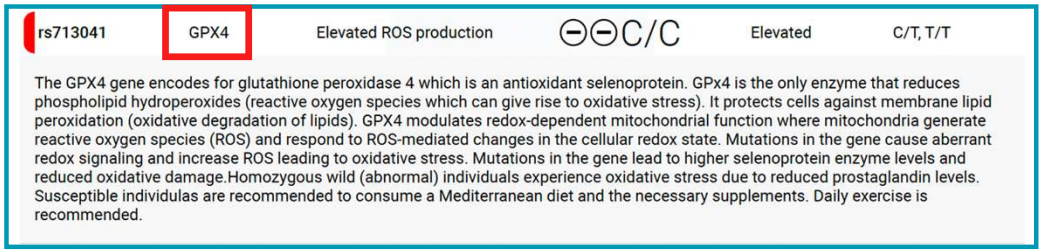
rs1799895	SOD3	Elevated ROS production	⊖⊖C/C	Normal	C/C
rs8192287	SOD3	Disrupted EC-SOD activity	⊕⊕T/T	Elevated	G/G
rs1001179	CAT	Mitochondrial dysfunction	⊖⊖C/C	Normal	C/C
rs4756146	CAT	Mitochondrial dysfunction	⊕⊕T/T	Elevated	C/C
rs7943316	CAT	Mitochondrial dysfunction	⊕⊕T/T	Elevated	A/T, A/A
rs10911021	GLUL	Decreased levels of glutamine synthetase and glutathione	⊕⊖C/T	Partially elevated	C/C
rs1050450	GPX1	Aberrant redox signaling	⊖⊖C/C	Normal	C/C
rs1987628	GPX1	Reduced antioxidant enzyme leads to selenium deficiency	⊕⊕C/C	Normal	C/C
rs2071566	GPX2	Higher selenoprotein concentrations	⊖⊖G/G	Normal	G/G
rs4902346	GPX2	Higher selenoprotein concentrations	⊖⊖T/T	Normal	T/T
rs713041	GPX4	Elevated ROS production	⊖⊖C/C	Elevated	C/T, T/T
rs121909307	GSS	Lower glutathione levels	⊕⊕C/C	Elevated	T/T
rs2071746	HMOX1	Decreased heme oxygenase 1 activity	⊕⊕T/T	Elevated	A/A
rs366631	GSTM1	Decreased antioxidant activity	⊖⊖T/T	Normal	T/T
rs3754446	GSTM5	Decreased antioxidant activity	⊕⊖G/T	Partially elevated	T/T
rs4485648	TrxR2	Impaired mitochondrial redox balance	⊕⊖C/T	Partially elevated	T/T
rs4673	CYBA	Elevated ROS production	⊕⊖C/T	Partially elevated	T/T
rs9932581	CYBA	Elevated ROS production	⊖⊖G/G	Normal	G/G
rs10789038	PRKAA2	Impaired antioxidant activity	⊖⊖A/A	Normal	A/A
rs2796498	PRKAA2	Impaired antioxidant activity	⊕⊕G/G	Elevated	A/A
rs206812	XDH	Elevated ROS production	⊕⊖A/G	Partially elevated	G/G



Antioxidant Genetics — ⊕⊕ Homozygous Mutant ⊕⊖ Heterozygous ⊖⊖ Homozygous Wild

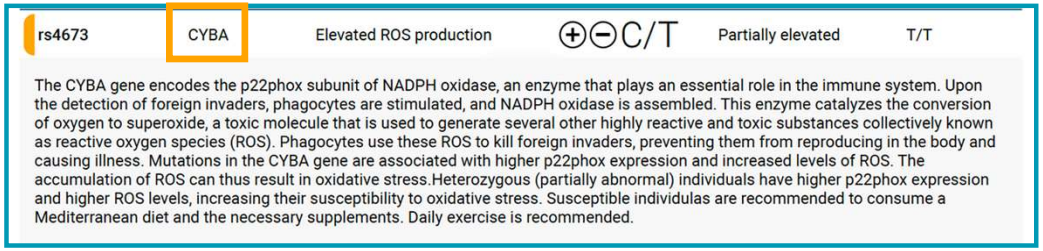
Test Name	Gene Name	Risk Association	Your Mutation	Your Risk	Reference
rs8192287	SOD3	Disrupted EC-SOD activity	⊕⊕T/T	Elevated	G/G

The SOD3 gene, also known as the superoxide dismutase 3 gene, is responsible for producing the extracellular superoxide dismutase (EC-SOD) enzyme. EC-SOD is an antioxidant enzyme that plays a critical role in protecting tissues and cells from the harmful effects of reactive oxygen species (ROS). EC-SOD is primarily found in the extracellular space, where it acts as a defense mechanism against oxidative stress by converting superoxide radicals into hydrogen peroxide and oxygen, which are less damaging to cells. Mutations in the SOD3 gene can disrupt the normal function of EC-SOD and impair its ability to protect against oxidative stress.Homozygous mutant (abnormal) individuals have disrupted EC-SOD function that impairs their ability to protect against oxidative stress. Homozygous mutant carriers are advised to follow a meditarranean diet and consume vegetables that has antioxidant properties.



rs713041	GPX4	Elevated ROS production	⊖⊖C/C	Elevated	C/T, T/T

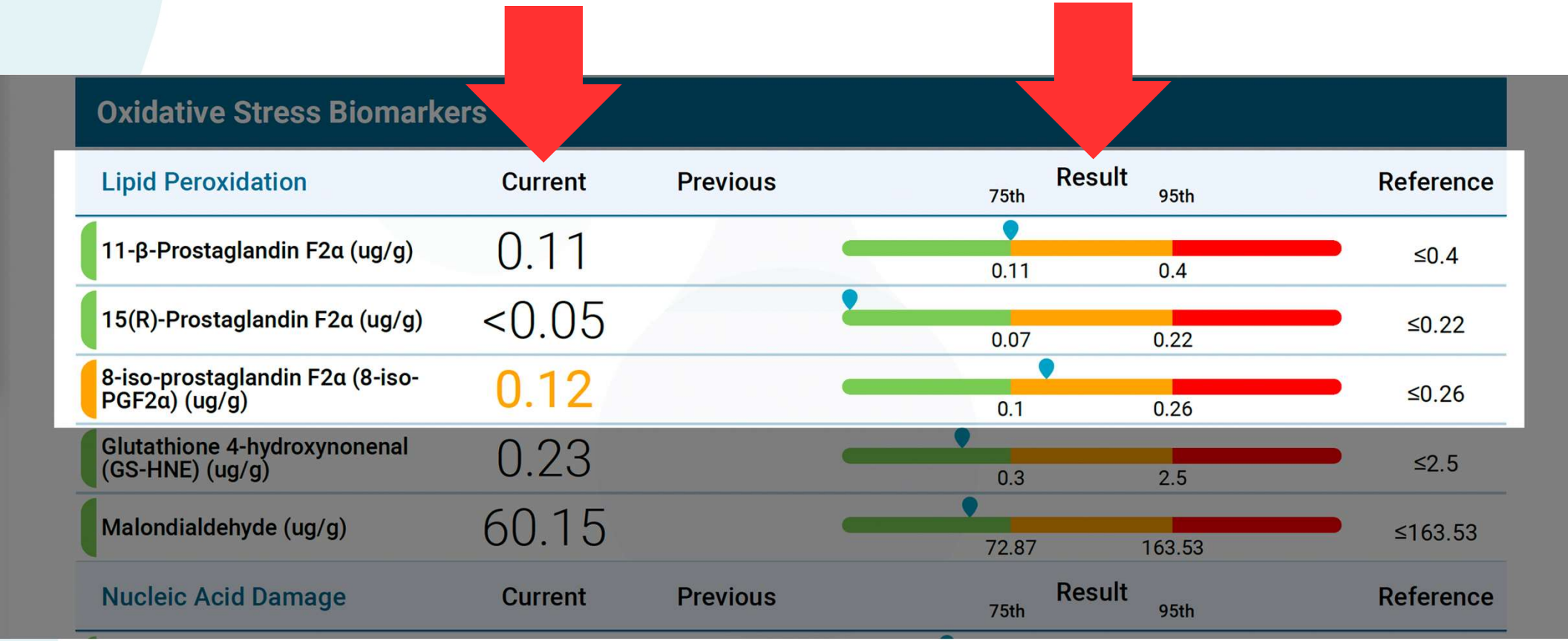
The GPX4 gene encodes for glutathione peroxidase 4 which is an antioxidant selenoprotein. GPx4 is the only enzyme that reduces phospholipid hydroperoxides (reactive oxygen species which can give rise to oxidative stress). It protects cells against membrane lipid peroxidation (oxidative degradation of lipids). GPX4 modulates redox-dependent mitochondrial function where mitochondria generate reactive oxygen species (ROS) and respond to ROS-mediated changes in the cellular redox state. Mutations in the gene cause aberrant redox signaling and increase ROS leading to oxidative stress. Mutations in the gene lead to higher selenoprotein enzyme levels and reduced oxidative damage.Homozygous wild (abnormal) individuals experience oxidative stress due to reduced prostaglandin levels. Susceptible individulas are recommended to consume a Mediterranean diet and the necessary supplements. Daily exercise is recommended.



rs4673	CYBA	Elevated ROS production	⊕⊖C/T	Partially elevated	T/T

The CYBA gene encodes the p22phox subunit of NADPH oxidase, an enzyme that plays an essential role in the immune system. Upon the detection of foreign invaders, phagocytes are stimulated, and NADPH oxidase is assembled. This enzyme catalyzes the conversion of oxygen to superoxide, a toxic molecule that is used to generate several other highly reactive and toxic substances collectively known as reactive oxygen species (ROS). Phagocytes use these ROS to kill foreign invaders, preventing them from reproducing in the body and causing illness. Mutations in the CYBA gene are associated with higher p22phox expression and increased levels of ROS. The accumulation of ROS can thus result in oxidative stress.Heterozygous (partially abnormal) individuals have higher p22phox expression and higher ROS levels, increasing their susceptibility to oxidative stress. Susceptible individulas are recommended to consume a Mediterranean diet and the necessary supplements. Daily exercise is recommended.

Full Report: Oxidative Damage Markers

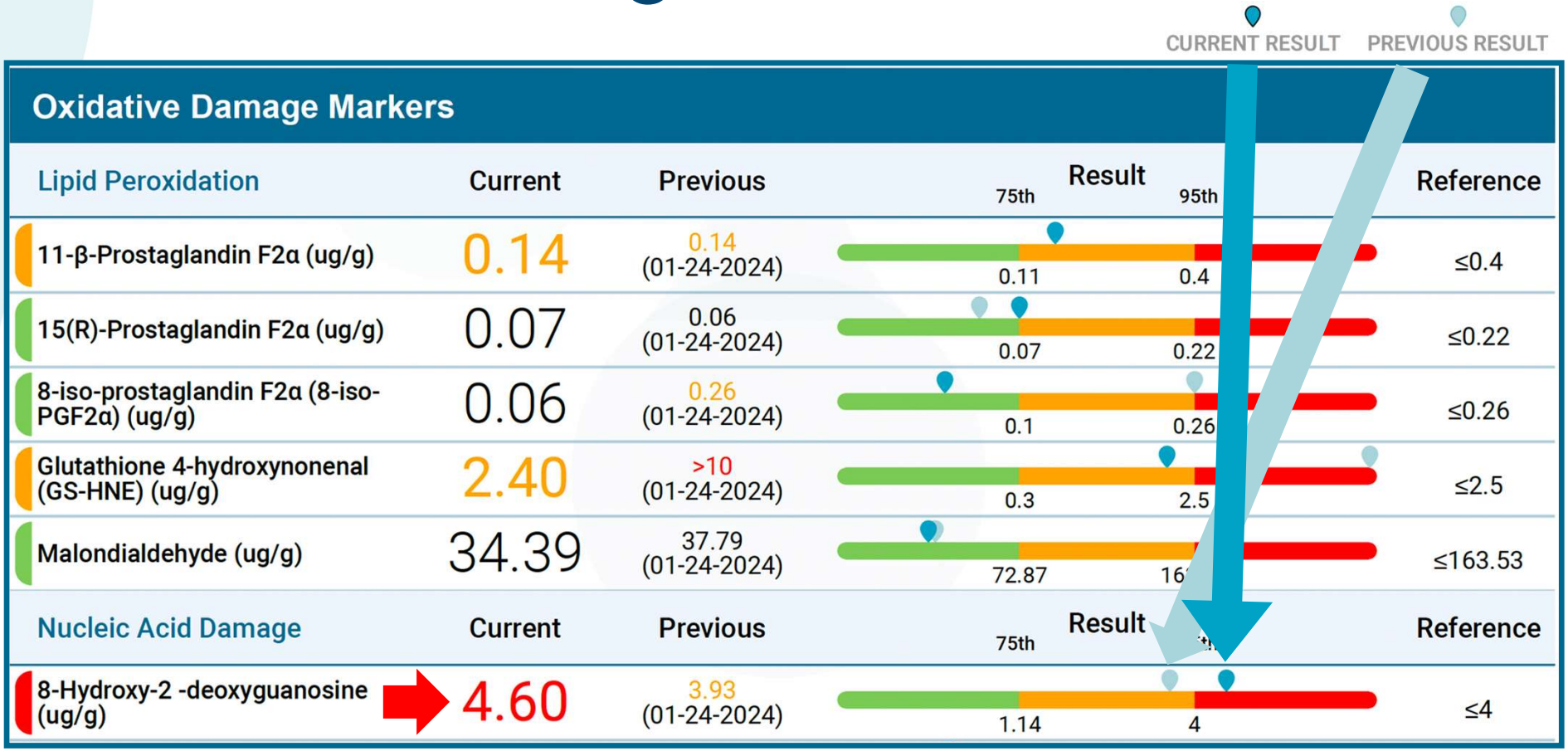


Oxidative Stress Biomarkers

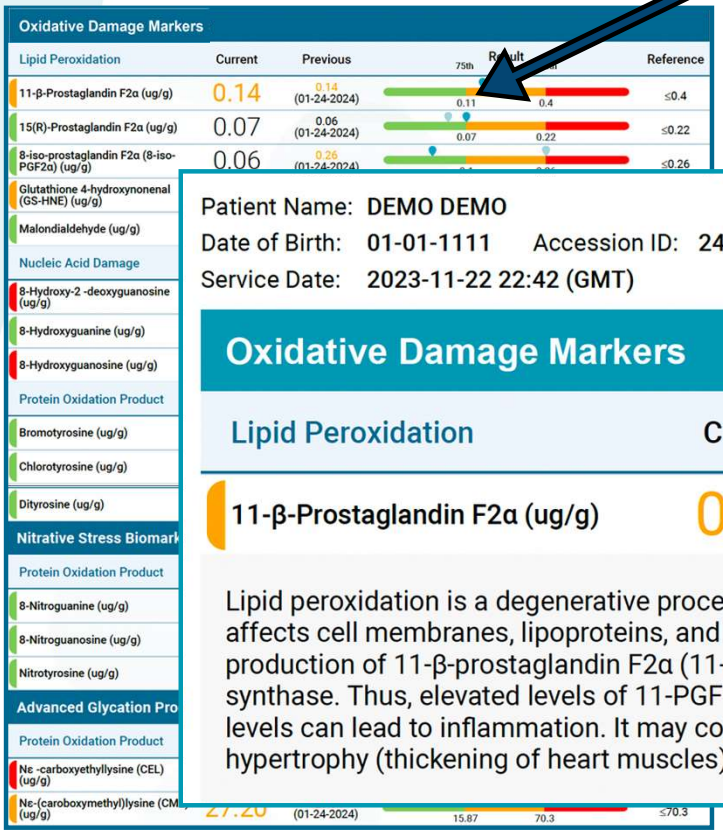
Lipid Peroxidation	Current	Previous	Result (75th / 95th)	Reference
11-β-Prostaglandin F2α (ug/g)	0.11		0.11 / 0.4	≤0.4
15(R)-Prostaglandin F2α (ug/g)	<0.05		0.07 / 0.22	≤0.22
8-iso-prostaglandin F2α (8-iso-PGF2α) (ug/g)	0.12		0.1 / 0.26	≤0.26
Glutathione 4-hydroxynonenal (GS-HNE) (ug/g)	0.23		0.3 / 2.5	≤2.5
Malondialdehyde (ug/g)	60.15		72.87 / 163.53	≤163.53

Nucleic Acid Damage	Current	Previous	Result (75th / 95th)	Reference

Oxidative Damage Markers



Damage Markers: Full Report & Interpretation



Patient Name: DEMO DEMO
Date of Birth: 01-01-1111 Accession ID: 2402266014
Service Date: 2023-11-22 22:42 (GMT)

Oxidative Stress Profile - Summary

Oxidative Damage Markers

Lipid Peroxidation	Current	Previous	Result (75th / 95th)	Reference
11-β-Prostaglandin F2α (ug/g)	0.14	0.14 (01-24-2024)	0.11 / 0.4	≤0.4

Lipid peroxidation is a degenerative process wherein free radicals attack and break down lipids under oxidative stress. The process affects cell membranes, lipoproteins, and other lipid-containing structures. The non-enzymatic oxidation of arachidonic acid leads to the production of 11-β-prostaglandin F2α (11-PGF2α). It is irreversibly produced from prostaglandin D2 via the enzyme prostaglandin-F synthase. Thus, elevated levels of 11-PGF2α are indicative of the increased oxidation of arachidonic acid by free radicals. Its increased levels can lead to inflammation. It may contribute to cardiac diseases owing to their involvement in vasoconstriction and cardiomyocyte hypertrophy (thickening of heart muscles). 11-PGF2α is also regarded as a marker of oxidative stress linked to inflammation.

Oxidative Damage Score

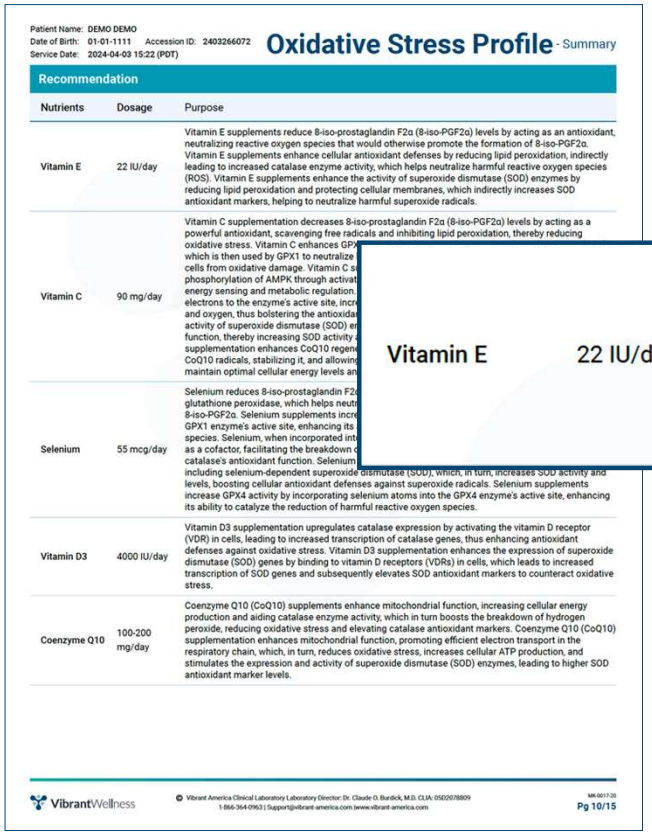
Calculated from the 16 damage markers giving a biologic age based on oxidative damage

Result

Your Given Age: 55

Your Oxidative Stress Profile looks similar to a ***66.02*** year old.

Supplement Recommendations



Patient Name: DEMO DEMO
Date of Birth: 01-01-1111 Accession ID: 2403266072
Service Date: 2024-04-03 15:22 (PDT)

Oxidative Stress Profile - Summary

Recommendation

Nutrients	Dosage	Purpose
Vitamin E	22 IU/day	Vitamin E supplements reduce 8-iso-prostaglandin F2α (8-iso-PGF2α) levels by acting as an antioxidant, neutralizing reactive oxygen species that would otherwise promote the formation of 8-iso-PGF2α. Vitamin E supplements enhance cellular antioxidant defenses by reducing lipid peroxidation, indirectly leading to increased catalase enzyme activity, which helps neutralize harmful reactive oxygen species (ROS). Vitamin E supplements enhance the activity of superoxide dismutase (SOD) enzymes by reducing lipid peroxidation and protecting cellular membranes, which indirectly increases SOD antioxidant markers, helping to neutralize harmful superoxide radicals.
Vitamin C	90 mg/day	Vitamin C supplementation decreases 8-iso-prostaglandin F2α (8-iso-PGF2α) levels by acting as a powerful antioxidant, scavenging free radicals and inhibiting lipid peroxidation, thereby reducing oxidative stress. Vitamin C enhances GPX… which is then used by GPX1 to neutralize… cells from oxidative damage. Vitamin C su… phosphorylation of AMPK through activat… energy sensing and metabolic regulation. … electrons to the enzyme's active site, incre… and oxygen, thus bolstering the antioxida… activity of superoxide dismutase (SOD) en… function, thereby increasing SOD activity … supplementation enhances CoQ10 regene… CoQ10 radicals, stabilizing it, and allowing… maintain optimal cellular energy levels an…
Selenium	55 mcg/day	Selenium reduces 8-iso-prostaglandin F2… glutathione peroxidase, which helps neutr… 8-iso-PGF2α. Selenium supplements incre… GPX1 enzyme's active site, enhancing its … species. Selenium, when incorporated int… as a cofactor, facilitating the breakdown o… catalase's antioxidant function. Selenium… including selenium-dependent superoxide dismutase (SOD), which, in turn, increases SOD activity and levels, boosting cellular antioxidant defenses against superoxide radicals. Selenium supplements increase GPX4 activity by incorporating selenium atoms into the GPX4 enzyme's active site, enhancing its ability to catalyze the reduction of harmful reactive oxygen species.
Vitamin D3	4000 IU/day	Vitamin D3 supplementation upregulates catalase expression by activating the vitamin D receptor (VDR) in cells, leading to increased transcription of catalase genes, thus enhancing antioxidant defenses against oxidative stress. Vitamin D3 supplementation enhances the expression of superoxide dismutase (SOD) genes by binding to vitamin D receptors (VDRs) in cells, which leads to increased transcription of SOD genes and subsequently elevates SOD antioxidant markers to counteract oxidative stress.
Coenzyme Q10	100-200 mg/day	Coenzyme Q10 (CoQ10) supplements enhance mitochondrial function, increasing cellular energy production and aiding catalase enzyme activity, which in turn boosts the breakdown of hydrogen peroxide, reducing oxidative stress and elevating catalase antioxidant markers. Coenzyme Q10 (CoQ10) supplementation enhances mitochondrial function, promoting efficient electron transport in the respiratory chain, which, in turn, reduces oxidative stress, increases cellular ATP production, and stimulates the expression and activity of superoxide dismutase (SOD) enzymes, leading to higher SOD antioxidant marker levels.

VibrantWellness

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MK-0017-20

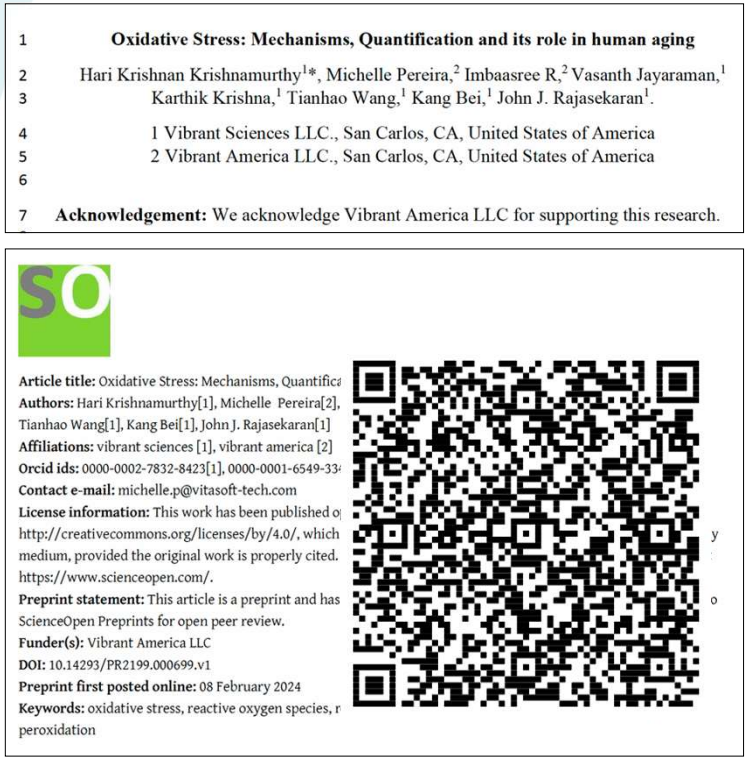
Pg 10/15

Vitamin E 22 IU/day

Vitamin E supplements reduce 8-iso-prostaglandin F2α (8-iso-PGF2α) levels by acting as an antioxidant, neutralizing reactive oxygen species that would otherwise promote the formation of 8-iso-PGF2α. Vitamin E supplements enhance cellular antioxidant defenses by reducing lipid peroxidation, indirectly leading to increased catalase enzyme activity, which helps neutralize harmful reactive oxygen species (ROS). Vitamin E supplements enhance the activity of superoxide dismutase (SOD) enzymes by reducing lipid peroxidation and protecting cellular membranes, which indirectly increases SOD antioxidant markers, helping to neutralize harmful superoxide radicals.

Learn More - NEW Research

Oxidative Stress Mechanisms, Quantifications and its Role in Human Aging



Oxidative Stress: Mechanisms, Quantification and its role in human aging

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Keywords: oxidative stress, reactive oxygen species, r peroxidation

ABSTRACT

Oxidative stress refers to the imbalance between the production of oxidant species and the body's ability to quench them using antioxidants, favoring the rise in oxidant levels. This leads to the damage of cellular macromolecules such as lipids, DNA, RNA, and proteins. The body's ability to manage oxidative stress and maintain it at an optimum level is crucial for overall health. Oxidative damage, if left unmitigated, contributes to the aging process characterized by the progressive deterioration of physiological functions and cellular structures. Understanding the mechanisms of oxidative stress along with its reliable quantification can enable consistency and comparability in clinical practice across diseases. While direct quantification of oxidant species in the body would be ideal for assessing oxidative stress, it is not feasible owing to their high reactivity, short half-life, and quantification challenges using conventional techniques. Quantifying oxidative damage products and antioxidants pose as appropriate markers, indicating the degree of oxidative stress in the body. This review comprehensively discusses the mechanism of generation of key oxidant species, their sources, the beneficial roles played by them at low levels and the detrimental effects exerted by their elevated levels. The review also provides insights into the effective quantification techniques for damage products of lipids nucleic acids, and proteins along with the endogenous and exogenous antioxidant markers. Effective quantification of oxidative stress may improve our understanding on the phenomenon which may aid in maintaining cellular integrity, preventing age-associated diseases, and thereby promoting optimal well-being and longevity.

Keywords: oxidative stress, reactive oxygen species, reactive nitrogen species, free radicals, antioxidants, lipid peroxidation

https://www.scienceopen.com/document_file/0440cca8-e66d-4d53-9605-4db471c9e647/ScienceOpenPreprint/Manuscript%20%28Full%20draft%29%20-%20OS%20Mechanisms,%20Quantification%20and%20its%20role%20in%20human%20aging.pdf

Thank you!

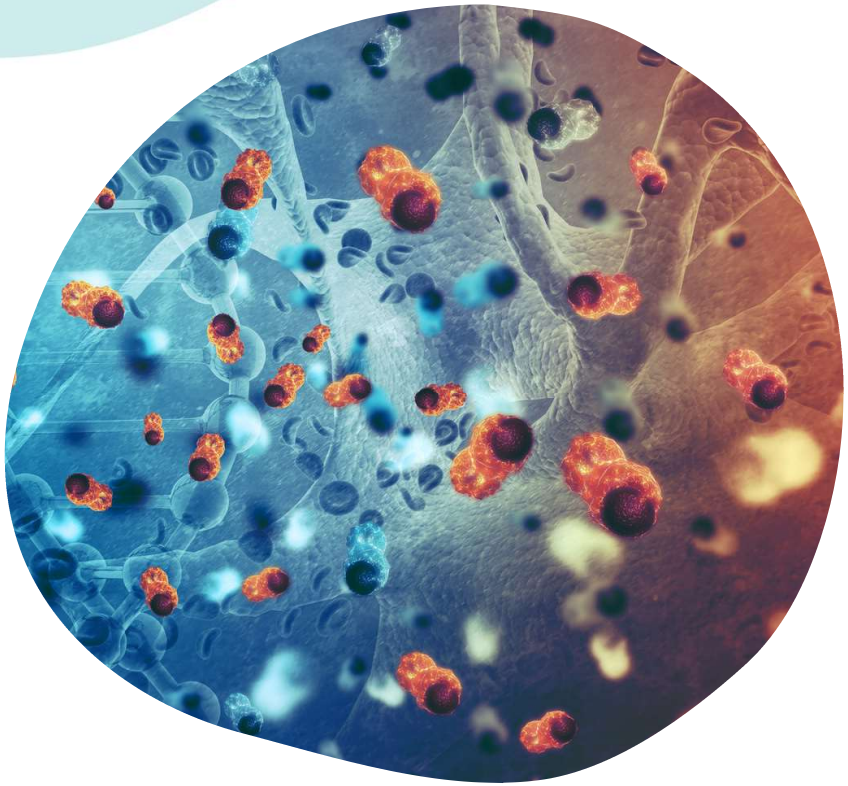
Dr. Kim Bruno, DC, CCN
Visit me for questions at the Vibrant Booth!

Let's Connect!
IG - @DrKimBruno @VibrantLabs

APPENDIX:

Clinical Considerations

Approaches for Management



Which Patients Benefit Most?

- Toxins
  - Heavy Metals
  - Environmental Toxins
  - Ionizing Radiation
- Too Many Calories
- Hyperglycemia
- Chronic Infections
  - Tickborne, mycotoxins etc.
- Rapid Aging
- Cigarette Smoke
- Alcohol
- UV Radiation
- Lack of Improvement
  - Despite inflammation-focused treatment

Patients With Worsening Health

From 0 to 10, how is your level of wellness?

- 0 being “cannot function”
- 10 being “perfect vibrant effortless health”

Approaches To Managing Oxidative Stress

Identify And Treat the Cause!

Possible causes:

- **Toxin exposure:** pesticides, PFAS, heavy metals, mycotoxins, etc.
- **Metabolic conditions:** Hyperglycemia, NAFLD (lipotoxicity)
- **Lifestyle**: Diet, smoking, alcohol, excessive exercise, inadequate sleep
- **Stress**
- **UV and ionizing radiation**
- **Inflammation:** chronic infections, gut health, dietary/food sensitivity
- **Genetic predisposition**

Supplement Considerations for Oxidative Stress

- **Vitamins** A, C, E, and carotenoids
- **Minerals** selenium and zinc
- **Omega-3** fatty acids
  - Reduce sat. fat balance (long-chain SFA are pro-oxidant)
  - Reduce omega-6:omega 3 ratio
- **Alpha-lipoic acid**
- **Olive oil** (due phenols, likely not the MUFAs)
- **Endogenous antioxidants** glutathione, melatonin, CoQ10

Targeting Upregulation of Endogenous Antioxidant Response Element

- Phytonutrients: green tea catechins, coffee polyphenols, curcumin, resveratrol, quercetin, sulforophane, anthocyanins, berberine, cocoa polyphenols
- Medicinal plants: ashwagandha, astragalus, bacopa, saffron, rhodiola, eleutherococcus, ginseng, ginkgo
- Herbs and Spices: clove, cinnamon, cumin, rosemary, oregano, parsley, basil, turmeric, mints, sage, ginger, garlic

Modifiable Personal Lifestyle Factors

- Diet
- Exercise
- Sleep
- Stress
- Psychosocial Support & Relationships

Dietary Risk Factors for **Oxidative Stress**

- **Detrimental chemicals** in diet— pesticides, heavy metals, xenobiotics
- **Alcohol**
- **Lack of phytonutrients**
- **Processed meat**
- **High saturated fat** and cholesterol
- **High fructose**, and high sugar in general
- **Gluten**, possibly even in non-celiac
- **Excess calories**

Dietary Patterns And **Oxidative Stress**

- **Plant-based diet** was associated with lower levels of oxidative stress and inflammation
- **Mediterranean diet** reduced levels of lipid peroxidation and oxidative DNA damage
- **DASH diet** lowered levels of lipid peroxidation and increased nitric oxide levels.
- **Western diets** were associated with higher oxidative stress and inflammation levels

Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: A systematic review of observational and intervention studies. Redox Biol. 2021;42:101869. doi: 10.1016/j.redox.2021.101869.

Movement & Exercise

- Exercise-induced oxidative stress varies depending on the intensity and duration of the exercise, the patient's fitness level, age, and overall health.
- Vigorous intensity exercise generates oxidative stress.
- Generally, oxidative stress markers increase following exercise but are often restored to baseline levels within a short period, typically within hours to a day after exercise.
- Of note, **creatine supplementation** decreases oxidative DNA damage and lipid peroxidation induced by a single bout of resistance exercise.

Sleep Support

The relationship between oxidative stress and impaired sleep quality is a complex interplay of various physiological mechanisms involving:

- Circadian rhythm disruption
- Inflammatory pathways
- Endocrine changes
- Mitochondrial dysfunction

Leading to increased oxidative damage and reduced antioxidant defense capabilities.

Sleep duration is inversely correlated with oxidative stress.

Evidence suggests that individuals with **<6 hours** of sleep/night exhibit significantly higher levels of oxidative stress biomarkers compared to those with **adequate sleep (7-8 hours).**

Stress Management

- Cognitive Behavioral Therapy (CBT)
- Mindfulness-Based Stress Reduction (MBSR)
- Meditation
- Yoga
- Tai Chi
- Breathing exercises
- Biofeedback

Psychosocial Support & Relationships

- Social isolation, loneliness, lack of social support, and adverse social determinants of health can all contribute to an increased physiological stress response, which, in turn, can elevate oxidative stress biomarkers.
- The physiological link between these social factors and oxidative stress is rooted in the body's stress response.
- Chronic psychological stress can lead to an overproduction of stress hormones and free radicals and a decrease in antioxidant defenses.
- **Healthcare providers and patients may wish to target psychosocial and relationship support in their oxidative stress reduction care plans.**