Module 5: Nutrition and Oxidative Stress

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I. Defining Oxidative Stress and the Modern Context (Approx. 15 Minutes)

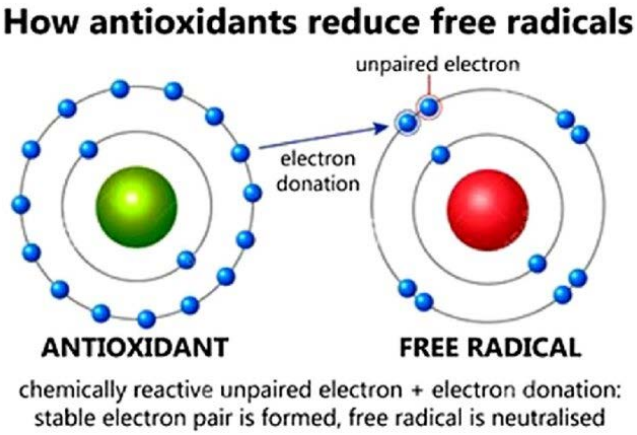
A. Defining Oxidative Stress (OS)

The contemporary definition of oxidative stress is complex, moving beyond simple concepts.

1. **Imbalance**: Oxidative stress is defined as an imbalance in pro-oxidant and antioxidant reactions that results in either:
    - Macromolecular damage (e.g., damage to DNA, lipids, proteins).
    - Disruption of biologic redox signaling and control.
2. **Redox Reactions:** All OS processes involve electron transfer, or "redox" reactions
    - Oxidation: Loss of one or more electrons from a donor chemical.
    - Reduction: Gain of one or more electrons by an acceptor chemical.

B. Pro-oxidants vs. Antioxidants

1. **Pro-oxidants:** Agents that stimulate unusual electron transfer. These include:
    - Free Radicals: Organic molecules or ions with an unpaired electron, often highly reactive (e.g., superoxide, hydroxyl radical, nitric oxide.
    - Nonradical Oxidants: Chemicals that participate in oxidation without involving radical mechanisms (e.g., hydrogen peroxide, ozone, hypochlorous acid, and quinones).



2. **Antioxidants (AOXs):** Agents that function at low concentrations to stop oxidative stress. The term is loosely defined.
    - Radical Scavengers: Accept or donate electrons to terminate radical chain reactions (e.g., Vitamin C).
    - Protective Systems: Chemicals and enzyme systems that eliminate or protect against oxidants (e.g., Glutathione peroxidases [GPX]).

- Preventive Agents: Agents that prevent radical initiation (e.g., inhibitors of Cytochrome P-450) or bind catalysts of oxidation (e.g., metal ion chelators).

Defining Oxidative Stress (OS)

Oxidative stress is defined as an imbalance in pro-oxidant and antioxidant reactions. This imbalance results in two main problems:

1. Macromolecular Damage: Direct harm to cell components (DNA, proteins, lipids).
2. Disruption of Biologic Redox Signaling and Control: Interference with how cells communicate and regulate themselves.

All processes involving OS are "redox" reactions (electron transfer): Oxidation is the loss of electrons, and reduction is the gain of electrons.

II. The Modern Understanding of OS

Historically, OS was viewed simply as a global imbalance. However, research findings, especially large-scale clinical trials since 2000, have introduced complexity:

- Supplement Trials: Double-blind studies using simple free radical scavenging antioxidants (like Vitamin C or E) have generally shown little or no benefit against chronic human disease.
- Refinement: This means OS is not fixed just by removing antioxidants from the system. An imbalance is now considered only in terms of specific reactions or pathways, not the system globally.
- Redox Signaling: Modern research emphasizes that nutrition is central to supporting redox signaling. These are pathways where oxidants (often at low levels) act as signals to regulate cell function.

III. The Players and Sources of Oxidative Stress

Pro-oxidants (The Attackers) and Antioxidants (The Defenders)

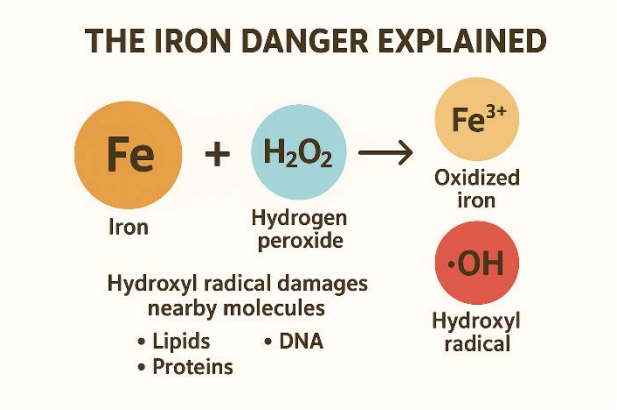
Player Category	Description	Examples
Pro-oxidants	Agents that stimulate harmful electron transfer.	Radicals: Highly reactive molecules with an unpaired electron: superoxide, hydroxyl radical.
		Nonradical Oxidants: Chemicals that oxidize without using radical chemistry: hydrogen peroxide, hypochlorous acid.
Antioxidants	Agents that function at low concentrations to stop OS.	Radical Scavengers: Break radical chain reactions (e.g., Vitamin C, Vitamin E).
		Enzyme Systems: Eliminate oxidants (e.g., Glutathione peroxidases.
		Preventive Agents: Bind metals (metal ion chelators) or stabilize structures (e.g., Zinc)

IV. Sources of Oxidative Stress

1. **Environmental Causes (Limited Nutritional Protection):**
    - Physical Forces: UV light (sunburn, skin cancer) and visible/blue light (damages retina, contributing to age-related macular degeneration [AMD]).
    - Protection Exception: Carotenoids (Lutein and Zeaxanthin) accumulate in the retina to filter light and scavenge singlet oxygen.
2. **Endogenous Sources (Internal Metabolism):**
    - Mitochondria: The cell's power plants constantly produce the radical superoxide as a byproduct of high-rate electron transfer during ATP production.
    - Enzymatic Production: Enzymes like NADPH Oxidases are activated to *purposely produce* for defense (killing bacteria) and for cell signaling.
    - The Iron danger: Transition metals like Iron are dangerous because they catalyze the Fenton reaction. This reaction converts into the extremely aggressive hydroxyl radical, which damages all surrounding molecules.

Iron (Fe) is an essential trace element in the human body—it helps transport oxygen and supports many vital enzymes. However, when free iron (not bound to proteins) is present in excess, it becomes dangerous because it can promote the formation of highly reactive molecules.

In this reaction, ferrous iron (Fe^{2+}) reacts with hydrogen peroxide (H_2O_2)—a common byproduct of normal metabolism—to produce a hydroxyl radical (·OH).

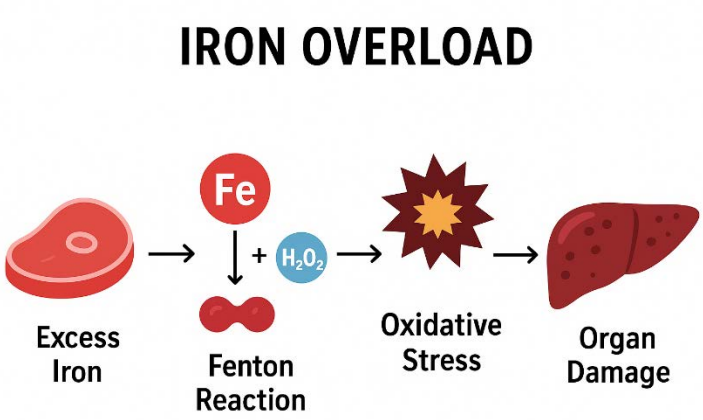


The hydroxyl radical is one of the most aggressive reactive oxygen species (ROS) in biology. It can instantly attack nearby molecules, such as:

- **Lipids** → causing membrane damage
- **Proteins** → leading to enzyme dysfunction

- **DNA** → inducing mutations and strand breaks

Because of this, the Fenton reaction can trigger oxidative stress, cellular injury, and even tissue degeneration if not controlled. The key reaction responsible for this is the Fenton reaction.



Oxidative stress occurs when the production of *reactive oxygen species (ROS)* exceeds the body's ability to neutralize them using antioxidants. This imbalance leads to cellular and molecular damage affecting lipids, proteins, and DNA.

Mechanisms of Damage and Nutritional Defenses

V. How Oxidants Cause Damage

1. **Radical Mechanisms: Lipid Peroxidation**
   - This is a radical chain reaction that causes rancidity in food and damages cell membranes.
   - It involves polyunsaturated fatty acids (PUFA). A radical initiates the process, which then propagates (repeats) by abstracting hydrogen atoms from other PUFAs, creating toxic products like 4-hydroxynonenal (HNE).
   - Vitamin E and Vitamin C act as radical scavengers to terminate these chain reactions.
2. **Nonradical Mechanisms: Redox Disruption**
   - Nonradical oxidants (like H2O2) are quantitatively more significant and cause chronic toxicity by disrupting redox signaling circuits.
   - They target specific, sensitive groups on proteins that are used for signaling, mainly the thiol group in Cysteine (Cys) and Methionine (Met) is also targeted.

VI. Key Nutritional Defense Systems

The body's peroxide-eliminating systems are highly dependent on nutritional status and precursors, and their capacity is ultimately limited by energy metabolism.

Defense System	Main Role (Function)	Key Nutritional / Biological Requirement	Major Food Sources
Glutathione (GSH) System	One of the body's main antioxidants; removes harmful peroxides and protects cells from oxidative damage.	Needs amino acids cysteine, methionine, and glutamine for glutathione production.	Cysteine & Methionine: eggs, fish, poultry, legumes, garlic, onions. Glutamine: meat, milk, nuts, beans.
Glutathione Recycling	Converts "used" (oxidized) glutathione back to its active form to	Requires adequate energy (ATP) from balanced carbohydrate and fat metabolism.	Energy sources: whole grains, fruits, vegetables, healthy fats (olive oil, nuts).

	keep antioxidant defense working.		
Thioredoxin (Trx) System	Works with glutathione to reduce peroxides and repair oxidized proteins.	Depends on selenium, which is part of thioredoxin reductase (contains selenocysteine).	Selenium-rich foods: Brazil nuts, seafood, eggs, whole grains, sunflower seeds.
Catalase	Rapidly breaks down hydrogen peroxide (H_2O_2) into water and oxygen, preventing oxidative damage.	Found in peroxisomes; enzyme activity supported by adequate protein and mineral intake (especially iron).	Iron-rich foods: lean red meat, liver, lentils, spinach, fortified cereals.

VII. Nutritional Policy and Antioxidant Guidelines

- **Main Antioxidant Vitamins:**
  Only Vitamin C and Vitamin E have official recommended daily intakes (DRIs) because their antioxidant roles are well proven.
- **Antioxidant Mineral:**
  Selenium has a DRI since it is needed to make important antioxidant enzymes in the body.
- **Other Helpful Nutrients:**
  Zinc, B vitamins, and Vitamin D help the body maintain healthy antioxidant systems, even though they are not classified as direct antioxidants.
- **Be Careful with High Doses:**
  Health policy warns against taking too much Vitamin E, Selenium, Iron (especially for men and postmenopausal women), or Copper, as too much can be harmful. Premenopausal women lose iron regularly through menstruation, helping to maintain balance. Men and postmenopausal women do not have this natural loss mechanism, so iron can accumulate gradually. Over time, this can contribute to liver damage, cardiovascular disease, diabetes, and other chronic conditions.

VIII. Clinical and Nutritional Implications of Oxidative Stress

Oxidative stress contributes to the pathogenesis of several **nutrition-related chronic diseases**, such as:

- Atherosclerosis
- Type 2 diabetes mellitus
- Obesity and metabolic syndrome
- Neurodegenerative diseases (Alzheimer's, Parkinson's)
- Cancer and premature aging

XI. Compartmentalization and Future Research

Modern research now uses advanced **"-omics" technologies** (like genomics and metabolomics) to study how oxidation happens in detail inside cells. The aim is to go beyond general vitamin supplements and learn exactly how nutrients influence the body's redox balance (the control of oxidation and reduction). Understanding these subtle changes helps scientists explain how oxidative stress contributes to chronic diseases such as diabetes, heart disease, and cancer.

End of Module 5…