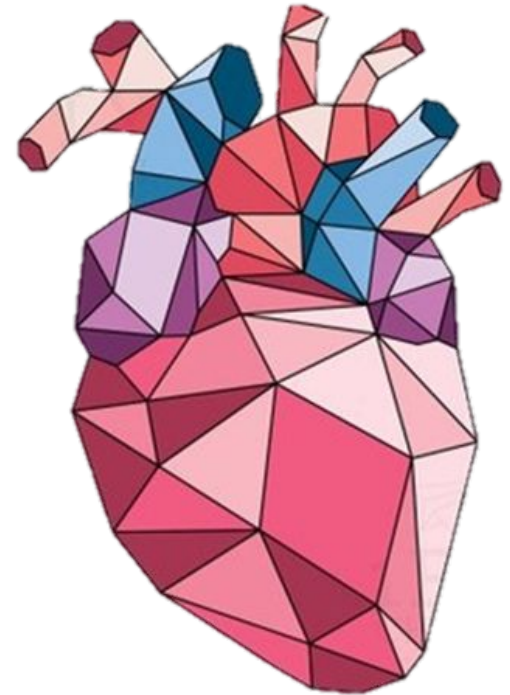










Oxidative Stress










Color Index:

- **Original content**
- **Important**
- Extra info, Dr's notes

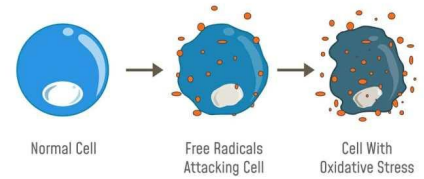
Objectives:

- Slide No. 3  Define oxidative stress
- Slide No. 3  Understand the harmful effects of oxidative stress to the cell and its diseases
- Slides (4,5)  List the types, sources and effects of Reactive Oxygen Species (ROS)
- Slide No. 6  List various antioxidants in the body
- Slide No. 7  Understand the role of glutathione system in detoxifying oxidants in the body
- Slide No. 7  Discuss how G6PD deficiency leads to oxidative stress
- Slide No. 8  Understand the role of Reactive Nitrogen Species (RNS) in contributing to oxidative stress
- Slide No. 9  Correlate the role of oxidative stress to pathogenesis of atherosclerosis

Overview:

-  Oxidative stress
-  Reactive Oxygen Species (ROS): types, sources, effects
-  Antioxidants
-  Glutathione system
-  G6PD deficiency
-  Nitric oxide (NO): Reactive Nitrogen Species (RNS)
-  Oxidative stress and atherosclerosis

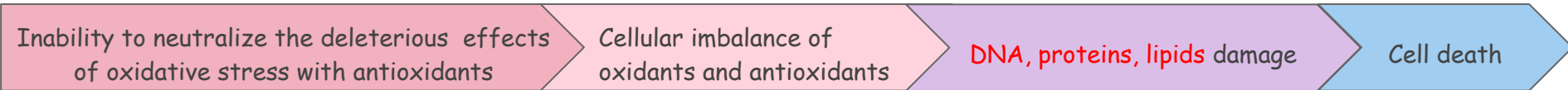
Oxidative Stress



A condition in which cells are exposed to excessive levels of:

Reactive Nitrogen Species (RNS)

Reactive Oxygen Species (ROS)



Diseases due to oxidative stress:

Inflammatory diseases
(rheumatoid arthritis)

atherosclerosis

CAD

obesity

cancer

G6PD deficiency hemolytic anemia

★ Implicated in atherosclerosis, CAD, ageing

★ CAD: coronary artery disease

★ Oxidative stress isn't always "the bad guy" as it has beneficial physiological functions in the body e.g. it can be generated in the killing of microbes by white blood cells.

Reactive Oxygen Species (ROS)

Sources

1 As byproducts of aerobic metabolism
"Or partial reduction of molecular oxygen in ETC."

2 Ingestion of drugs, toxins and chemicals
E.g. chemotherapy

3 When cellular antioxidant level is low

4 Creating oxidative stress in cell

Types

1 Free Radicals

Superoxide (O_2^-)

Hydroxyl radical
(OH)

2 Non-free Radicals

Hydrogen
peroxide (H_2O_2)

A

O_2
Oxygen



O_2^-
Superoxide



H_2O_2
Hydrogen peroxide



OH•
Hydroxyl radical



H_2O
Water

Reactive Oxygen Species (ROS)

Effects

1 Lipid peroxidation
(polyunsaturated fatty acids)

2 DNA damage

3 Protein denaturation

the unfolding and disorganization of a protein's secondary and tertiary structures without the hydrolysis of peptide bonds.

4 Cytoskeletal damage

5 Chemotaxis

recruitment of inflammatory cells.

6 Cell signaling effects

☆ Release of Ca_2^+ from intracellular stores

7 Altered vascular tone

8 Increased endothelial
cell permeability

★ lipid peroxidation

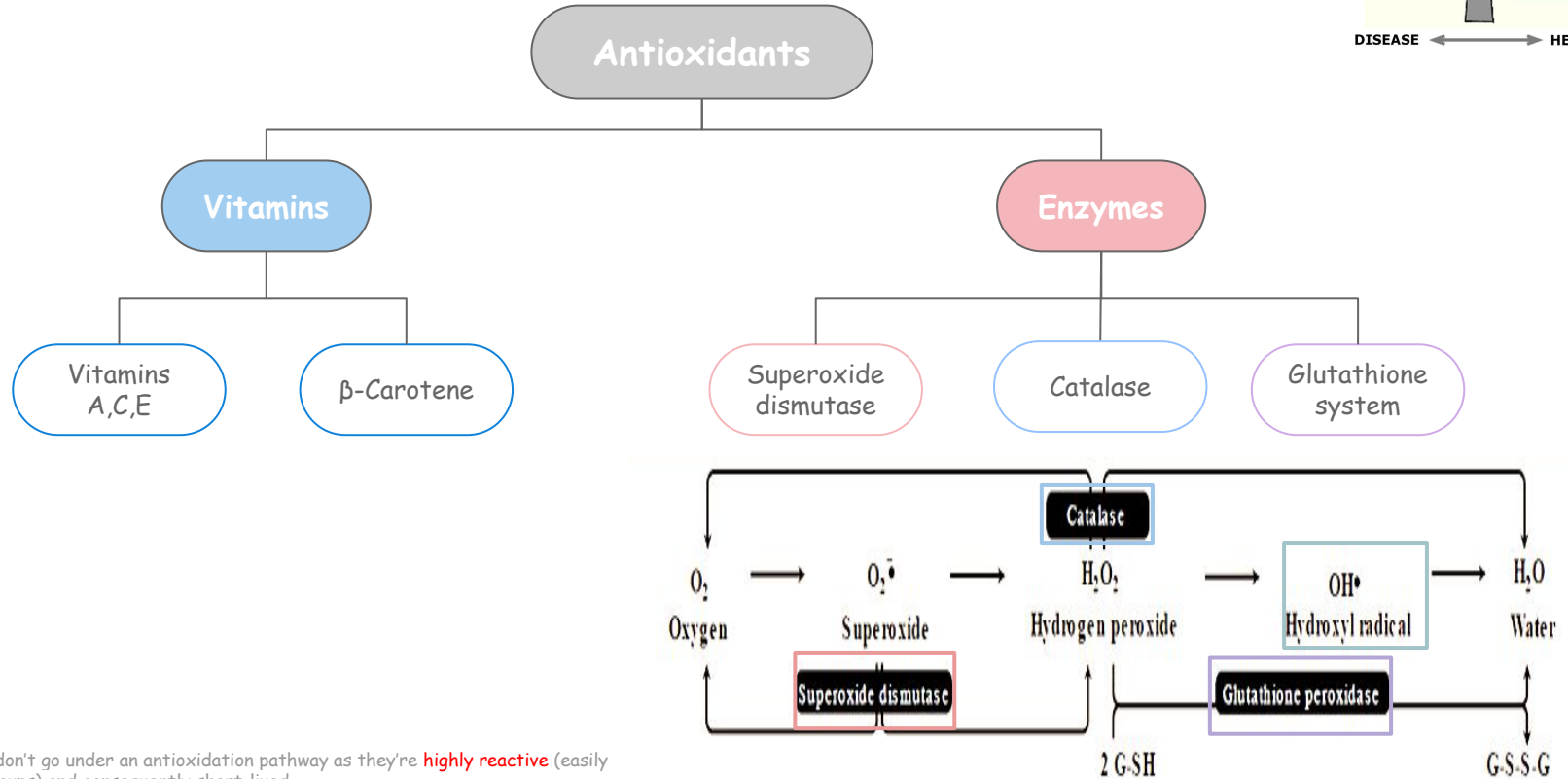
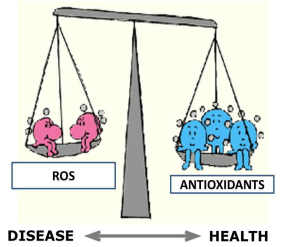
when a hydroxyl radical abstracts an electron from an unsaturated fatty acid. This creates an unstable lipid radical, which can react with oxygen, forming a fatty acid peroxy radical. Repeated cycles of lipid peroxidation can cause serious damage to cell membranes.

→ Why polyunsaturated fatty acids?

Electrons in double bonds are not distributed equally (unstable) so these electrons attract free radicals.

Antioxidants

★ Protective mechanisms in cells that neutralize ROS



★ **Hydroxyl radicals** don't go under an antioxidation pathway as they're **highly reactive** (easily becoming hydroxyl groups) and consequently short-lived.

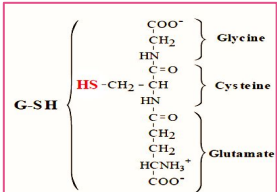
Glutathione System

Reduced Glutathione
Present in most cells

Glutathione peroxidase (selenoprotein)

Glutathione reductase

NADPH production

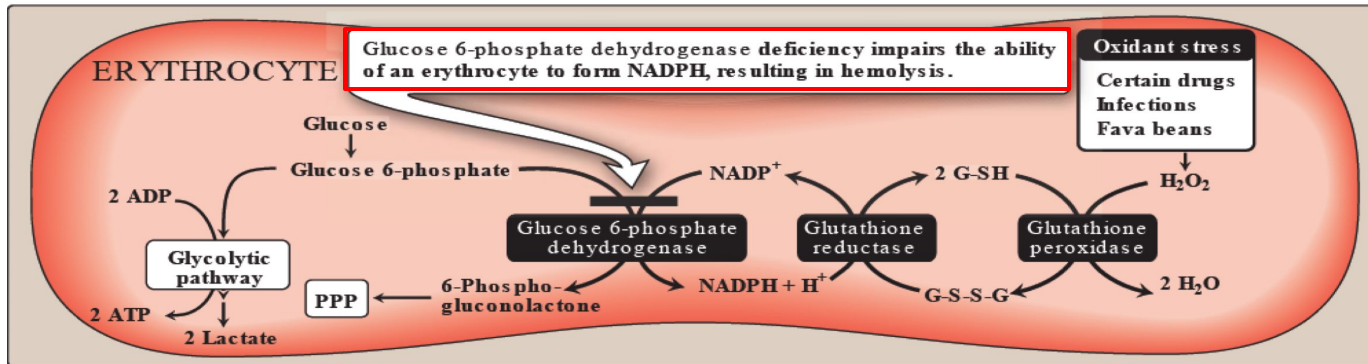


★ Chemically detoxifies H₂O₂ forms oxidized glutathione (G-S-S-G), which no longer has protective properties.

★ Catalyzes the reaction that regenerates G-SH (reduced glutathione) using NADPH as a source of reducing equivalents.

★ Glucose - 6- phosphate dehydrogenase (G6PD) converts NADP⁺ into NADPH

★ By the mechanism mentioned previously NADPH indirectly provides electrons for the reduction of H₂O₂



G6PD deficiency

NADPH deficiency

Cells are unable to reduce free radicals

↑ Oxidation Of cellular proteins

impaired cell functions

☆ Protein denaturation

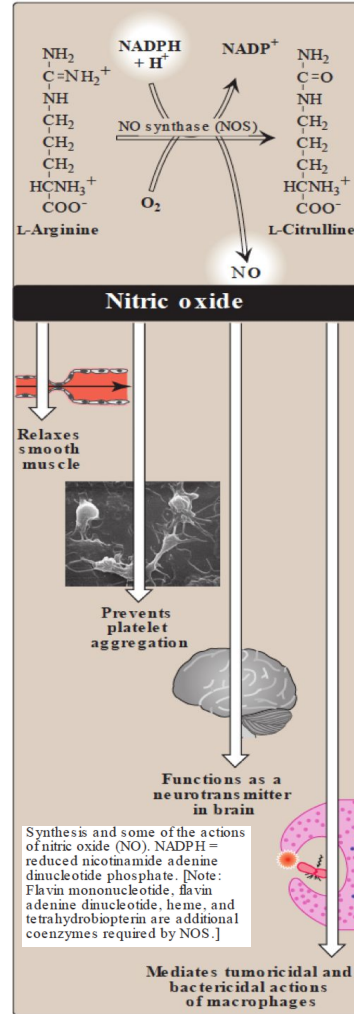
Nitric Oxide (NO)

Endothelial-derived relaxing factor

A gas with short half-life (3-10 sec)

Peroxynitrite is a Reactive Nitrogen Species (RNS)

★ Causes vasodilation by relaxing vascular smooth muscle Through cGMP pathway



☆ The NO will have different functions & different type of nitric oxide synthase enzymes depending on where it's produced.

Nitric oxide synthase

	eNOS	nNOS	iNOS	bNOS
Location	E ndothelium	N eural tissue	<ul style="list-style-type: none"> • Macrophages • Neutrophils 	B acteria
Function	vaso-relaxation	neurotransmission	I nfection	Don't worry about it too much, it's Not produced by humans, produced by bacteria so if you target bacteria you target these molecules.

Constitutive: produced at constant rates but low amounts all the time because they're required for physiological functions.

Inducible: produced when needed

iNOS Activity

★ Normally low

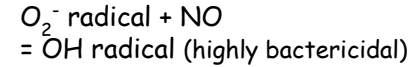
infection
& pro-inflammatory cytokines

↑ iNOS activity

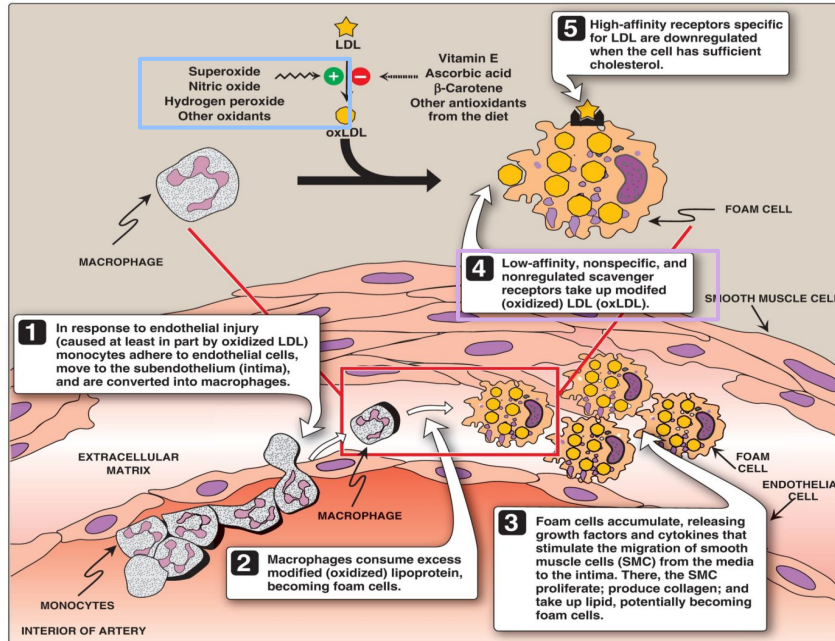
Activated macrophages

Production of free
radicals

oxidative stress



Oxidative Stress And Atherosclerosis



★ From 437

1. Superoxide, nitric oxide, hydrogen peroxide, or any other oxidant oxidize LDL to oxLDL
2. oxLDL binds to scavenger receptors "on the surface of macrophages"
★ Unlike the LDL receptor, the scavenger receptor is not downregulated in response to increased intracellular cholesterol.
3. Cholesteryl esters accumulate in macrophages and cause their transformation into "foam" cells
4. "foam" cells participate in the formation of atherosclerotic plaque

★ Antioxidants responsible for neutralizing oxLDL:
Vitamin E, ascorbic acid, B-carotene, and others.

★ Glutathione system doesn't work here, because it is only present in the mitochondria

Take home message



Oxidative stress is due to excessive production of ROS and NOS in the cells.



Cells neutralize these oxidants by a number of antioxidant processes.



Imbalance between oxidants and antioxidants in the cells can result in the development of many diseases including atherosclerosis.

Quiz



MCQs

Q1: an atom that has unpaired electron in an outer orbit is:

- a) Free radical b) Isotope c) Reactive atom d) Inactive atom

Q2: what's the Amino Acid required for NO synthesis?


- a) L citrulline b) L arginine c) D arginine d) D citrulline

Q3: If NO come in contact with superoxide it will give another RNS called:

- a) eNOS b) OH c) L citrulline d) Peroxynitrite

Q4: what's the most reactive free radical?


- a) OH b) H_2O_2 c) O_2^- d) Glutathione

Q5: Septic shock, a state of acute circulatory failure characterized by persistent arterial hypotension (low blood pressure) and inadequate organ perfusion refractory to fluid resuscitation, results from a severe inflammatory response to bacterial infection. It has a high mortality rate and is associated with changes in the level of nitric oxide. Which statement concerning septic shock is most likely correct? 

- a) Activation of endothelial nitric oxide synthase causes an increase in nitric oxide.
b) High mortality is the result of the long half-life of nitric oxide.
c) Lysine, the nitrogen source for nitric oxide synthesis, is deaminated by bacteria.
d) Overproduction of nitric oxide by a calcium-independent enzyme is the cause of the hypotension.

Q6: Which of the following Supplements would be best to combat free radicals, knowing the vitamins and minerals they contain?

- a) Iron, Vitamin K, and Potassium, vitamin E b) B- carotene, Vitamin A, Vitamin, folic acid
c) Folic acid, Vitamin A, Vitamin E, B carotene d) B- carotene, Vitamin A, Vitamin, E, Vitamin C

Q7: In preparation for a trip to an area of India where chloroquine-resistant malaria is endemic, a young man is given primaquine (oxidant drug) prophylactically. Soon thereafter, he develops a hemolytic condition due to a deficiency in glucose 6-phosphate dehydrogenase. A less-than-normal level of which of the following is a consequence of the enzyme deficiency and the underlying cause of the hemolysis? 

- a) Glucose 6-phosphate b) Oxidized form of nicotinamide adenine dinucleotide
c) Reduced form of glutathione d) Ribose 5-phosphate

SAQs

Q1: Give two diseases related to oxidative stress

Q2: How does G6PD deficiency cause oxidative stress?

Q3: what is the product if oxygen accepts 1, 2, 3, 4 electrons?

Q4: Mention the components of Glutathione system

★ **MCQs Answer key:**

1)A 2)B 3)D 4)A 5)D 6)D 7)C

★ **SAQs Answer key:**

1) Slide 3

2) NADPH deficiency → Cells are unable to reduce free radicals → Oxidation of cellular proteins is increased causing → impaired cellular Functions.

3) 1 e^- → superoxide (o^-)
2 e^- → hydrogen peroxide (H_2O_2)
3 e^- → Hydroxyl radical (OH^-)
4 e^- → water (H_2O)

4) 1- Glutathione 2- Glutathione peroxidase (selenoprotein)
3- Glutathione reductase 4- NADPH

Team members

Girls team :

- Ajeed Al-rashoud
- Alwateen Albalawi
- ★ Elaf Almusahel
- Haifa Alessa
- Lama Alassiri
- Lina Alosaimi
- Nouf Alhumaidhi
- ★ Noura Alturki
- Nouran Arnous
- Reem Algarni
- Shahd Alsalamh
- Taif Alotaibi

Boys team :

- Abdullah Altuwaijri
- Alkaseem binobaid
- Fares Aldokhayel
- Naif Alsolais
- Sultan Alhammad

Team leaders

Deema Almaziad

Mohannad Alqarni

★ "When you really want something, then the whole universe conspires in helping you to achieve it."

By Paulo Coelho
- Alchemist Book



★ This lecture was done by