Oxidative stress and Diabetes Mellitus

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MSC Biochemistry

Introduction

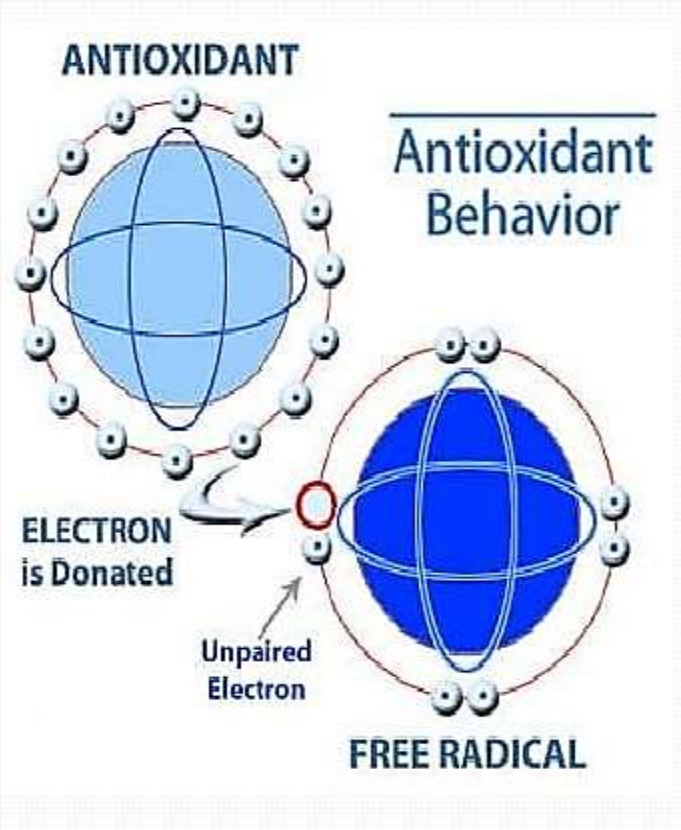
• Antioxidants: Any substance that when present in low concentrations compared to that of an oxidisable substrate significantly delays or inhibits the oxidation of that substrate.

• An antioxidant is a molecule capable of inhibiting the oxidation of other molecules.

• Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent.

• Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions.

• Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions.

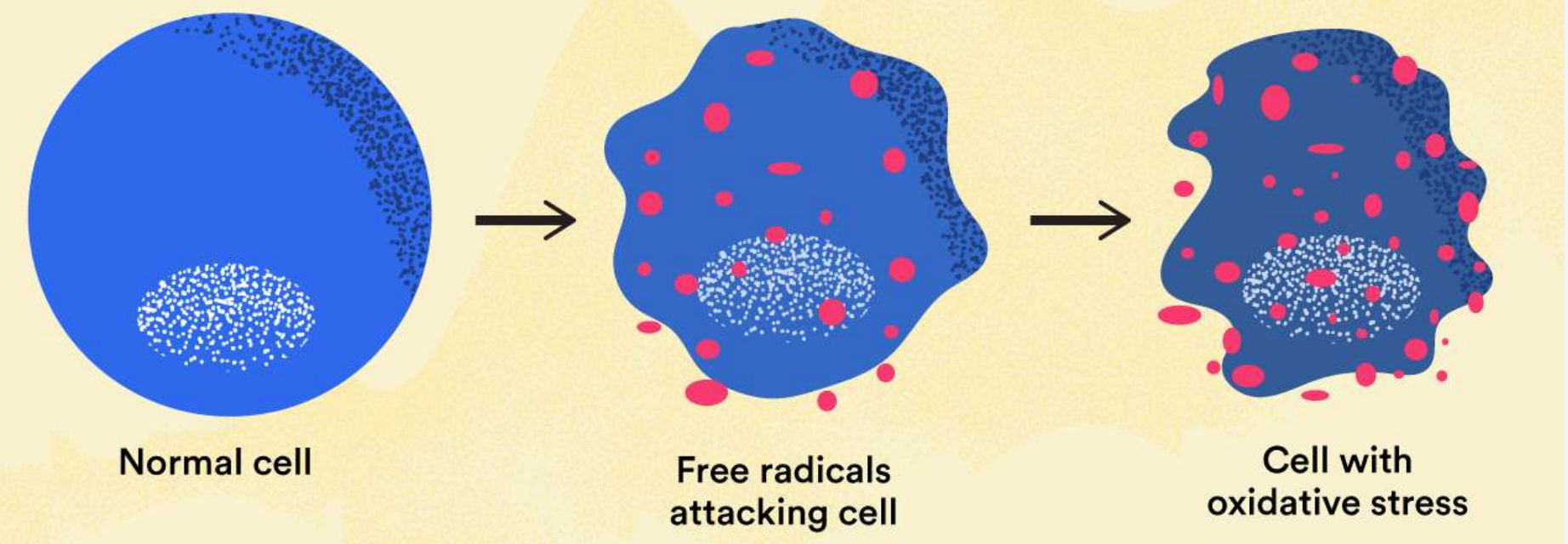


• Free radicals: are ionized particles in the human body.

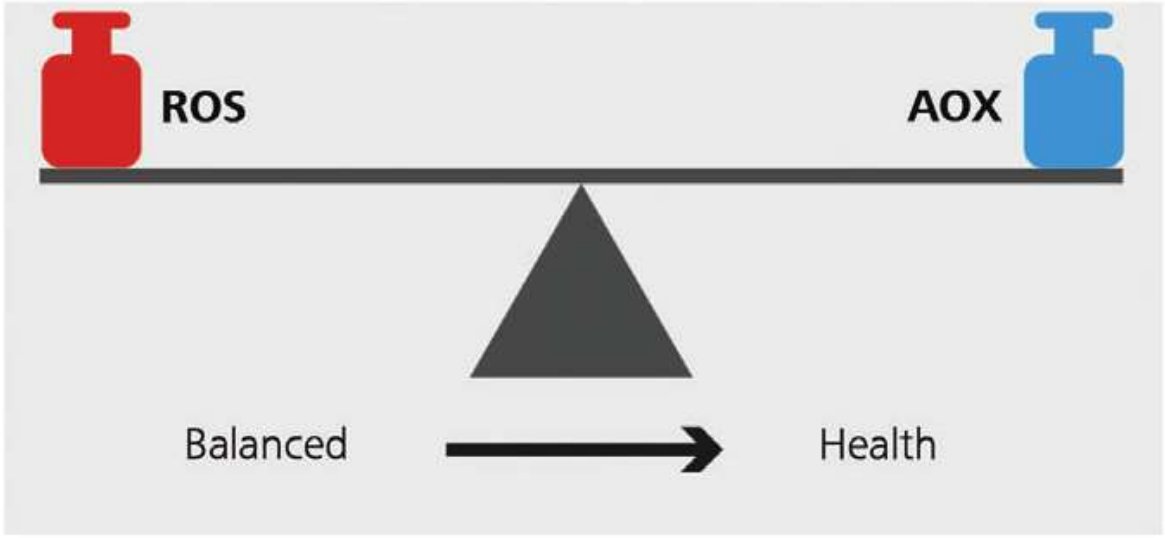
Free radicals can be caused by environmental toxins, stress, food additives and cooking among others.

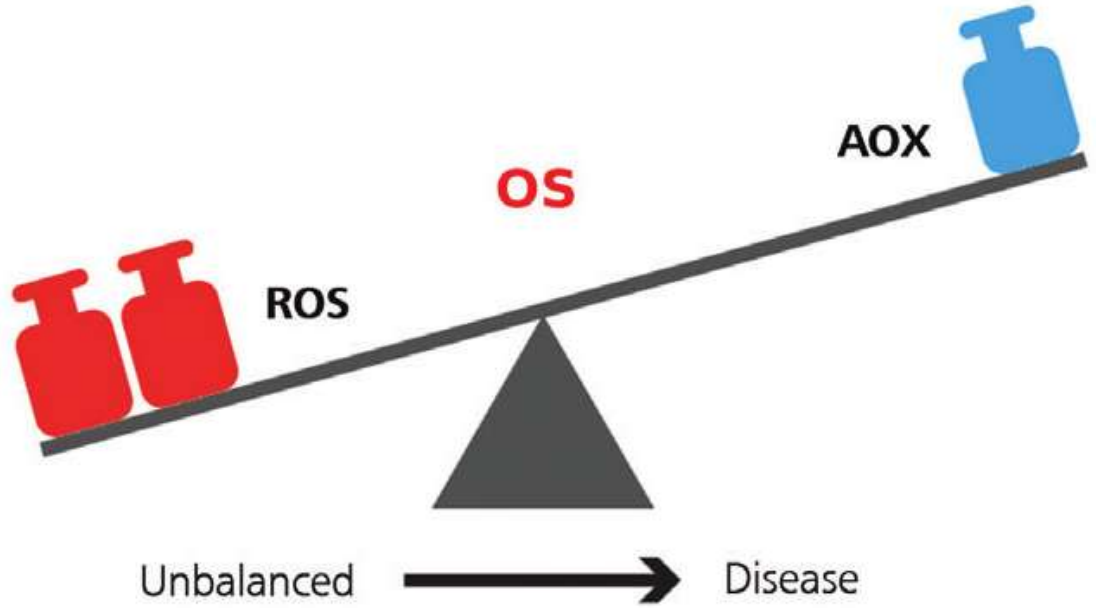
• Free radicals are also formed when oxygen is used by the body during normal metabolism.

• Oxidative stress in disease: Oxidative stress is thought to contribute to the development of a wide range of diseases including Alzheimer's disease, Parkinson's disease, the pathologies caused by diabetes, rheumatoid arthritis, and neurodegeneration in motor neuron diseases.



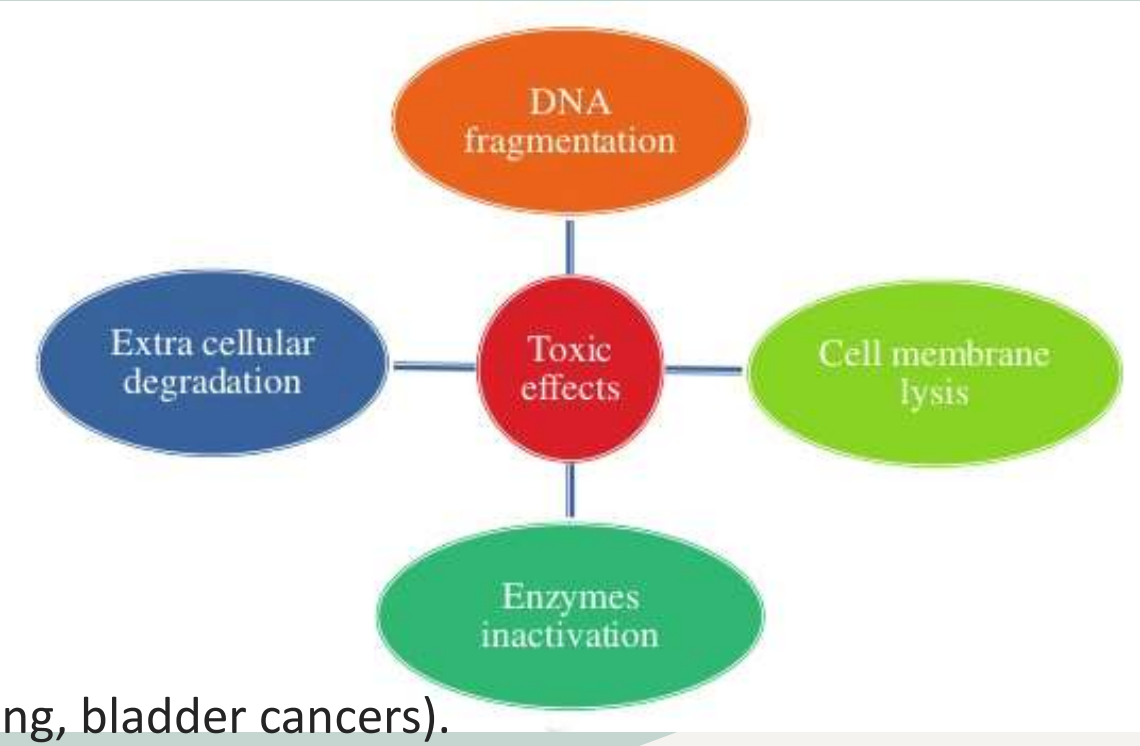
• The free radicals, both the reactive oxygen species (ROS) and reactive nitrogen species (RNS), are derived from both endogenous sources (mitochondria, peroxisomes, endoplasmic reticulum, phagocytic cells etc.) and exogenous sources (pollution, alcohol, tobacco smoke, heavy metals, transition metals, industrial solvents, pesticides, certain drugs like halothane, paracetamol, and radiation).

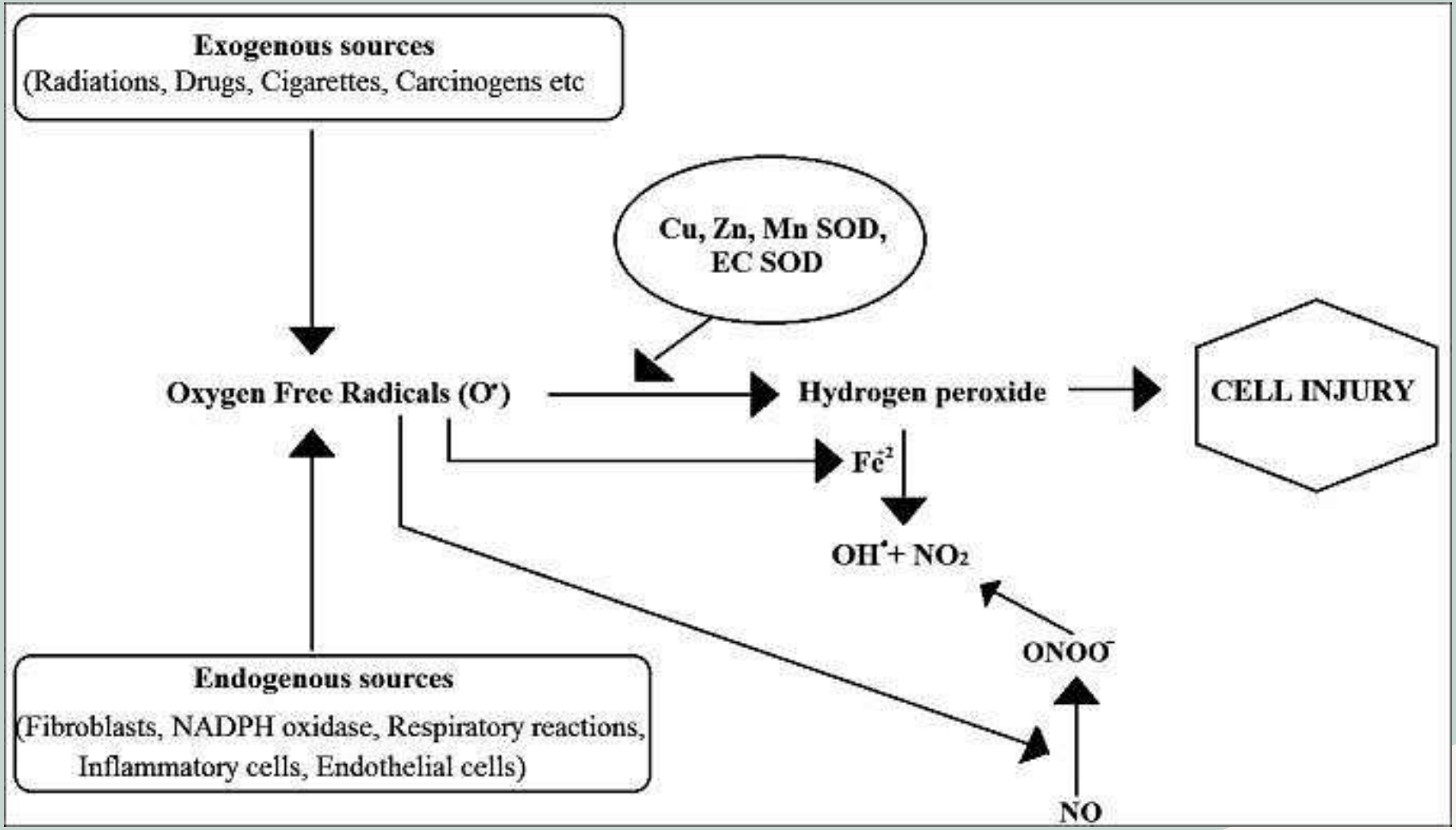




• Free radicals can adversely affect various important biological molecules such as nucleic acids, lipids, and proteins, thereby altering the normal redox status leading to increased oxidative stress.

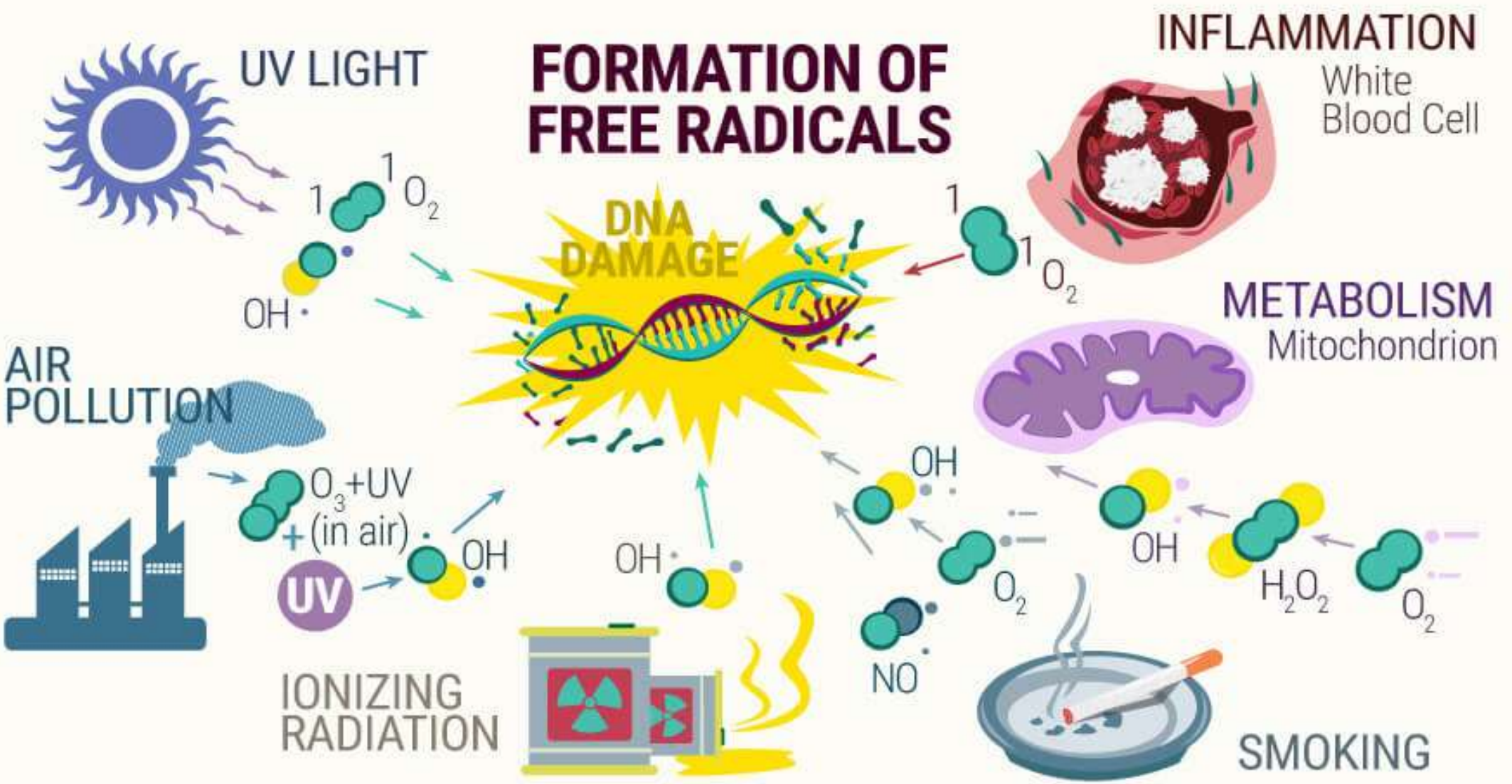
• The free radicals induced oxidative stress is involved in several diseased conditions such as diabetes mellitus, neurodegenerative disorders (Parkinson's disease-PD, Alzheimer's disease-AD) , cardiovascular diseases (atherosclerosis and hypertension), respiratory diseases (asthma), cataract development, rheumatoid arthritis and In various cancers (colorectal, prostate, breast, lung, bladder cancers).



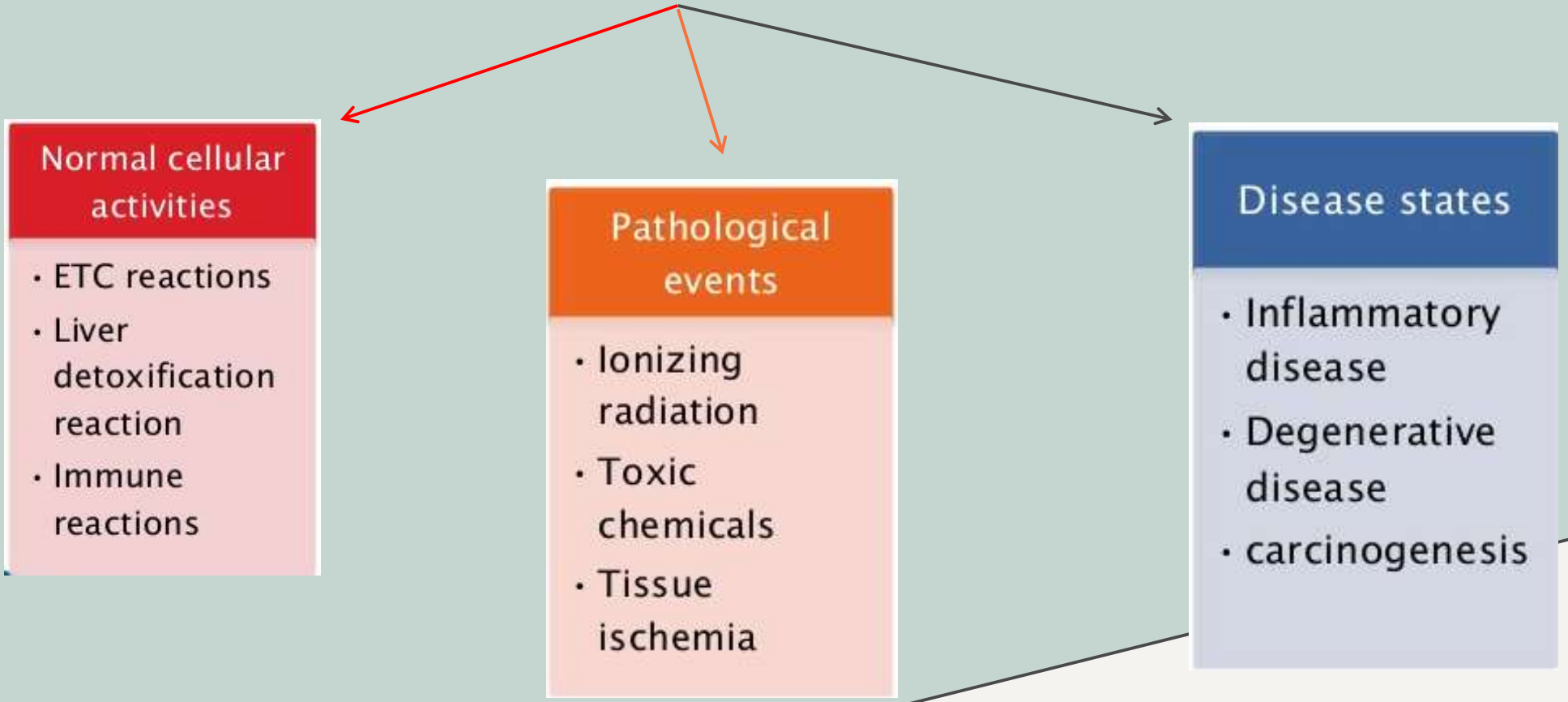

Exogenous sources
(Radiations, Drugs, Cigarettes, Carcinogens etc
Cu, Zn, Mn SOD,
EC SOD
Oxygen Free Radicals (O˙)
Hydrogen peroxide
CELL INJURY
Fe+2
OH˙+ NO2
ONOO-
Endogenous sources
(Fibroblasts, NADPH oxidase, Respiratory reactions,
Inflammatory cells, Endothelial cells)
NO

Types of Free Radicals

- 1. Hydroxyl radical (OH)
- 2. Superoxide anion radical (O• 2-)
- 3. Singlet oxygen
- 4. Hydrogen peroxide
- 5. Lipid peroxyl free radical
- 6. Nitric oxide
- 7. Alkoxyl radical


FORMATION OF FREE RADICALS
UV LIGHT
$^1O_2$
OH
DNA DAMAGE
INFLAMMATION
White Blood Cell
$^1O_2$
METABOLISM
Mitochondrion
AIR POLLUTION
O_3+UV
+(in air)
UV
OH
OH
OH
O_2^-
OH
H_2O_2
O_2^-
NO
IONIZING RADIATION
SMOKING

Free radicals are produced during:



Types of antioxidants: -

Mainly Hydrophilic and Hydrophobic

Antioxidant enzymes:

1. Catalase
2. Glutathione peroxidase
3. Glutathione reductase
4. Super oxide dismutase (both Cu-Zn and Mn)

Metals binding proteins:

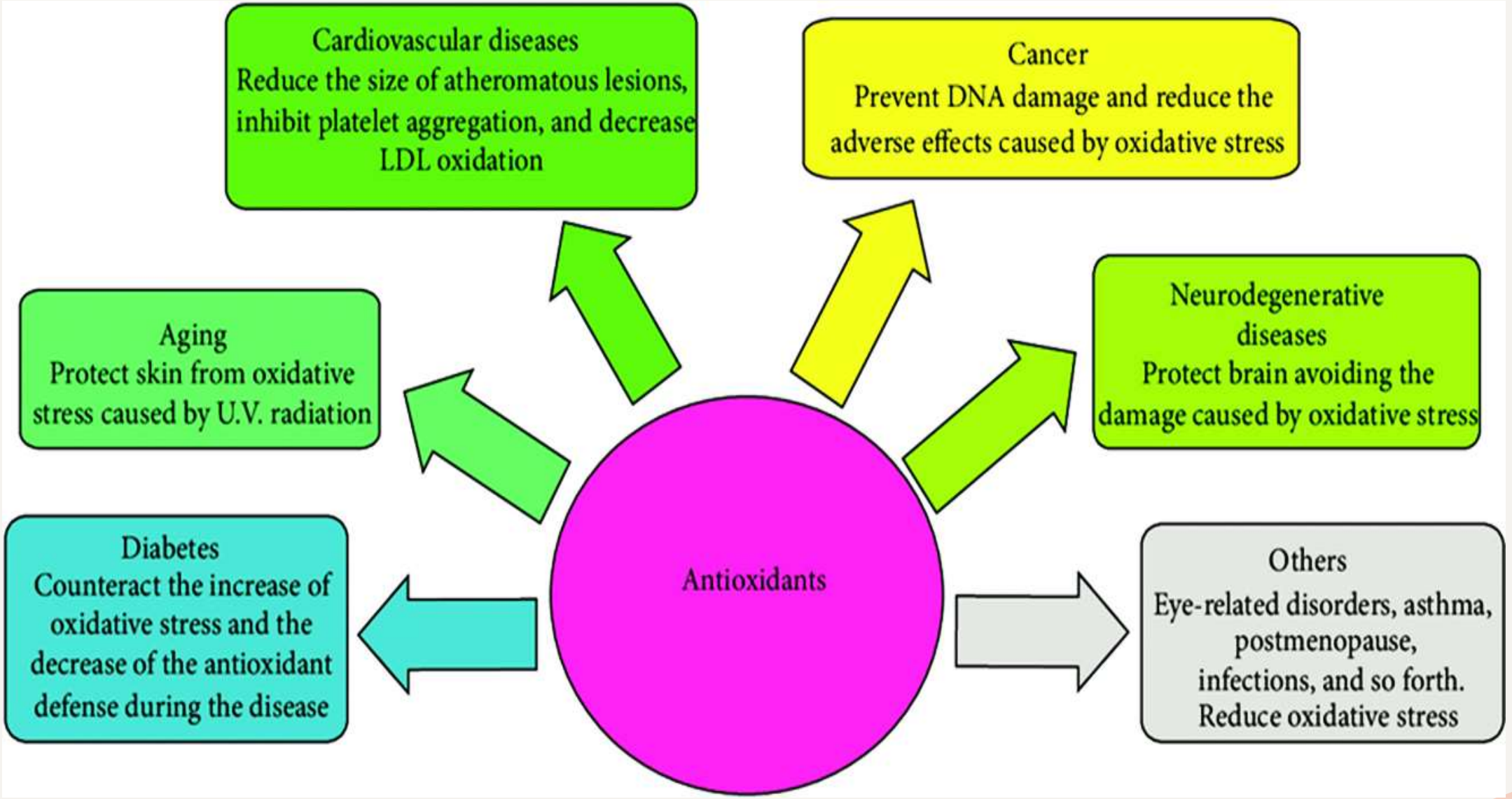
1. Ceruloplasmin
2. Ferritin
3. Lactoferrin
4. Metallotheinein
5. Transferrin
6. Hemoglobin
7. Myoglobin

Health effects of antioxidants:

- Disease treatment
- Disease prevention
- Physical exercise
- Adverse effects

Benefits of antioxidants:

- Destroy the free radicals that damage cells.
- Protect cells against premature, abnormal aging.
- Promote the growth of healthy cells.
- Help fight age-related macular degeneration.
- Provide excellent support for the body's immune system, making it an effective disease preventative.


Cardiovascular diseases
Reduce the size of atheromatous lesions, inhibit platelet aggregation, and decrease LDL oxidation
Cancer
Prevent DNA damage and reduce the adverse effects caused by oxidative stress
Aging
Protect skin from oxidative stress caused by U.V. radiation
Neurodegenerative diseases
Protect brain avoiding the damage caused by oxidative stress
Antioxidants
Diabetes
Counteract the increase of oxidative stress and the decrease of the antioxidant defense during the disease
Others
Eye-related disorders, asthma, postmenopause, infections, and so forth.
Reduce oxidative stress

Diabetes Mellitus and Oxidative Stress

- Diabetes mellitus is heterogeneous group of chronic disorders characterized by elevated blood glucose levels (hyperglycemia) resulting from defective insulin secretion (in type I diabetes), resistance to insulin action (in type II diabetes) or both. insufficiency in production or action of insulin produced by the pancreas inside the body .
- The major symptoms are thirst, hunger, emaciation, and weakness, eventually lead to coma.
- Insulin is a protein (hormone) synthesized in beta cells of pancreas in response to various stimuli such as glucose. Long term elevation in blood glucose levels is associated with macro- and micro-vascular complications leading to heart diseases, stroke, blindness and kidney diseases.

Types of diabetes mellitus

- 1. Type I diabetes (Insulin dependent) is due to immune mediated beta-cells destruction, leading to insulin deficiency.
- 2. Idiopathic diabetes is the type 1 diabetes with no known etiologies and is strongly inherited.
- 3. Type II diabetes (Non-Insulin dependent) is due to insulin secretory defect and insulin resistance.
- 4. Gestational diabetes mellitus is any form of intolerance to glucose with onset or first recognition of pregnancy.

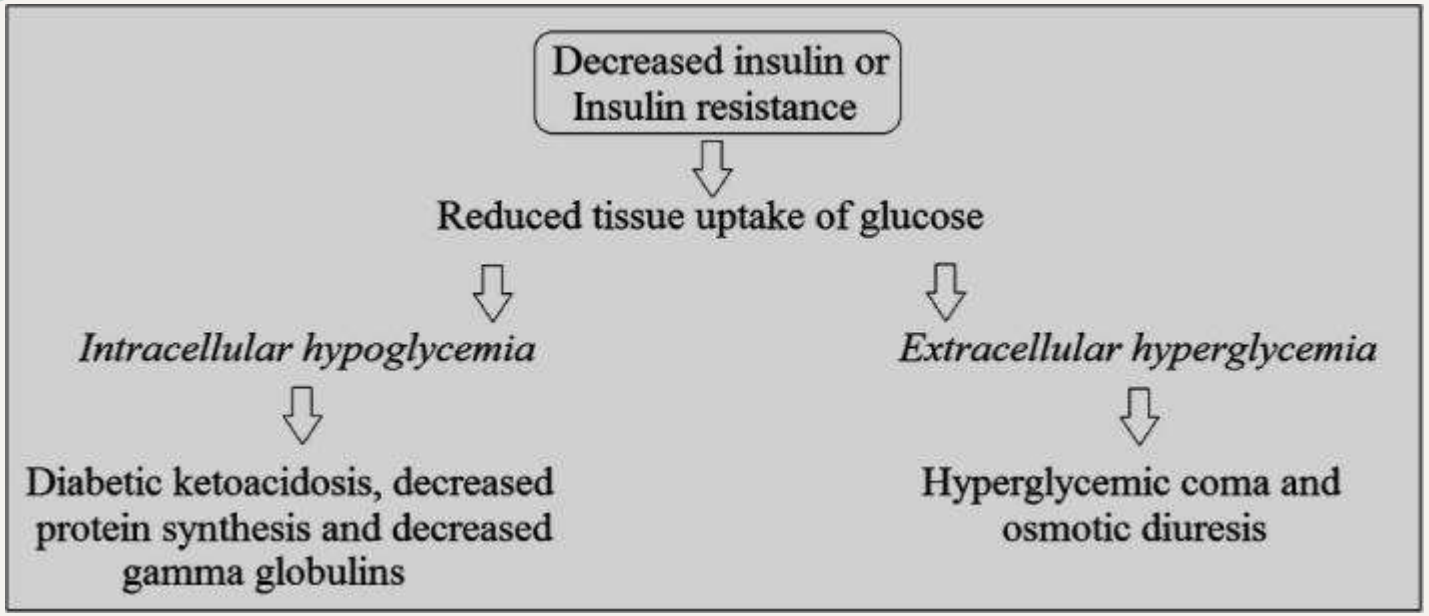
- However diabetes is mostly classified basically into TWO major types: Type I Diabetes (IDDM) and Type II Diabetes (NIDDM).

Pathophysiology of diabetes

- Whenever somebody takes the meal, there is rise in blood glucose levels that stimulates insulin secretion resulting in an increase in transportation, biotransformation and storage in muscles and fat tissues.
- In fasting conditions, the glucose in blood is provided by liver that is used by the brain, without any dependency on insulin.
- Besides the storage of glucose, insulin also inhibits the secretion of glucagon and lowers the concentration of serum fatty acids leading to a decline in liver glucose production.
- Insufficient insulin or resistance to insulin in the body results in reduced tissue uptake of glucose that results in intracellular hypoglycemia and extracellular hyperglycemia.

Pathophysiology of diabetes

- The intracellular hypoglycemia causes glucogenesis and gluconeogenesis that leads to fats breakdown (causing diabetic ketoacidosis) and decreases protein synthesis and gamma globulins (causing cachexia, polyphagia, and impaired wound healing), while the extracellular hyperglycemia leads to hyperglycemic coma and osmotic dieresis



Complications of diabetes

- Diabetes is such a sort of disorder in which the patients are at all the time on risk of complications.
- Complications may be macrovascular (coronary heart disease, peripheral vascular disease and stroke), microvascular (neuropathy, retinopathy and nephropathy) and both micro- and macrovascular (diabetic foot).
- The mortality and morbidity of diabetes are associated more with macrovascular degeneration as compared to the risks of microvascular complications in older people.

Complications of diabetes

- In general, complications of diabetes mellitus can be categorized into two groups :
- a. Metabolic acute complications: These are short term and include hypoglycemia, ketoacidosis and hyperosmolar non-ketonic coma.
- b. Systemic late complications: These are long term chronic sort of complications that include diabetic nephropathy, microangiopathy, diabetic neuro- and retinopathy, atherosclerosis and infections.

Complications of diabetes

Acute complications (Metabolic)	**Chronic complications (Systemic)**
Infection (s)	Blindness, retinopathy
Diabetic ketoacidosis (DKA)	Neuropathy
Hyperglycemic, hyperosmolar, non-ketonic coma	Atherosclerosis
Polydipsia, polyuria, fatigue, blurred vision	Peripheral vascular disease
	Infection, amputation
	Cerebrovascular disease

Macrovascular complications	**Microvascular complications**
Stroke	Retinopathy and cataracts
Heart disease and hypertension	Renal disease
Peripheral vascular disease	Neuropathy
Foot problems	Foot problems

Oxidative stress in diabetes mellitus

- Diabetes mellitus is associated with the increased production of free radicals or decreased activity of the antioxidant systems, which leads to development of oxidative stress .
- It is believed that oxidative stress plays important role in the development of vascular complications in diabetes particularly type 2 diabetes.
- ROS level elevation in diabetes may be due to decrease in destruction or/and increase in the production by catalase (CAT—enzymatic/non-enzymatic), superoxide dismutase (SOD) and glutathione peroxidase (GSH–Px) antioxidants.
- The variation in the levels of these enzymes makes the tissues susceptible to oxidative stress leading to the development of diabetic complications.
- Free radical formation in diabetes by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation leads to damage of enzymes, cellular machinery and also increased insulin resistance due to oxidative stress.

Pathophysiology of oxidative stress in diabetes

- Free radical formation in diabetes by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation leads to damage of enzymes, cellular machinery and also increased insulin resistance due to oxidative stress.
- lipid is not only but also the apolipoprotein component of LDL that forms insoluble aggregates oxidative due to hydroxyl radical-induced cross-linkage between apo-B monomers that is responsible for oxidative damage in diabetic complications .
- In diabetes mellitus, main sources of oxidative stress are mitochondria.
- During oxidative metabolism in mitochondria, a component of the utilized oxygen is reduced to water, and the remaining oxygen is transformed to oxygen free radical (O•) which is an important ROS that is converted to other RS such as ONOO−, OH and H2O2.
- Insulin signaling is modulated by ROS/RNS by two ways. On one side, in response to insulin, the ROS/RNS are produced to exert its full physiological function and on the other side, the ROS and RNS have got negative regulation on insulin signaling, interpreting them to develop insulin resistance which is a risk factor for diabetes type 2.

- Free radical and oxidative stress induced complications from DM include coronary artery disease, Neuropathy, nephropathy, retinopathy and stroke .

- In-vivo the role of hyperglycemia in the generation of oxidative stress leading to endothelial dysfunction in blood vessels of diabetic patient.

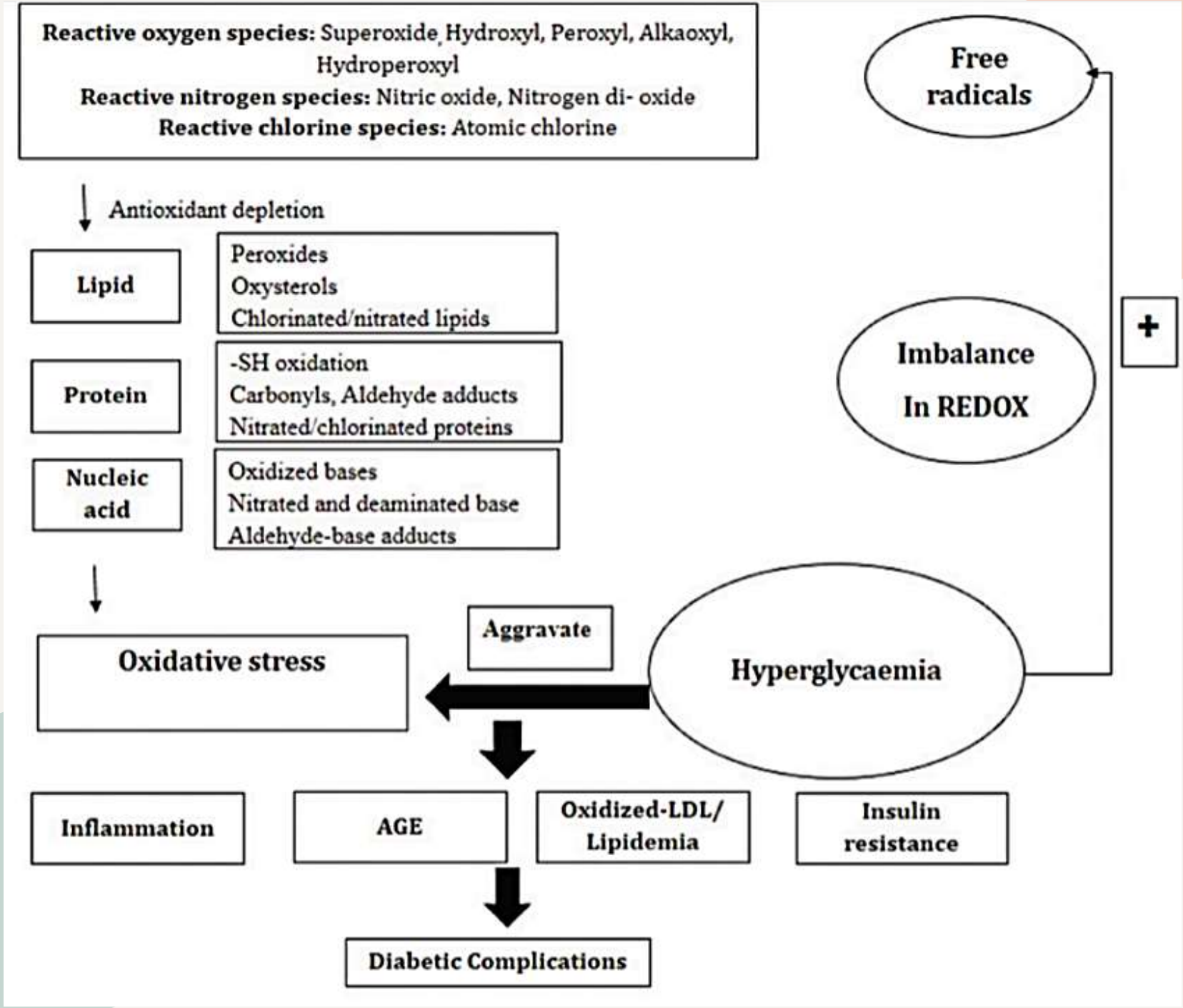
- Increase in the levels of glucose and insulin along with dyslipidemia in patients suffering from diabetes develops macroangiopathies that cause oxidative stress leading to atherosclerosis.

Oxidative stress and diabetic complications

- Many evidences from experiments have given link between diabetes and oxidative stress by measuring various biomarkers that include DNA damage biomarkers and lipid peroxidation products.

- It is believed that in the onset and progression of late diabetic complication, free radicals have got a major role due to their ability to damage lipids, proteins and DNA.

- A variety of pathological conditions are induced by oxidative stress such as Rheumatoid arthritis, Diabetes mellitus and cancer .


Reactive oxygen species: Superoxide, Hydroxyl, Peroxyl, Alkaoxyl, Hydroperoxyl
Reactive nitrogen species: Nitric oxide, Nitrogen di- oxide
Reactive chlorine species: Atomic chlorine
Free radicals
Antioxidant depletion
Lipid
Peroxides
Oxysterols
Chlorinated/nitrated lipids
Protein
-SH oxidation
Carbonyls, Aldehyde adducts
Nitrated/chlorinated proteins
Nucleic acid
Oxidized bases
Nitrated and deaminated base
Aldehyde-base adducts
Imbalance In REDOX
+
Aggravate
Oxidative stress
Hyperglycaemia
Inflammation
AGE
Oxidized-LDL/ Lipidemia
Insulin resistance
Diabetic Complications

Biomarkers of oxidative stress in diabetes mellitus

➢ Proteins

- ROS reacts with some amino acid in vitro, producing anything from modified, denatured and non-functioning proteins that in further may be responsible for oxidative stress .
- Diabetic hyperglycemia, by the process of free radical production, causes protein glycation and oxidative degeneration.
- The degree of such protein glycation is estimated by using some biomarkers such as glycated hemoglobin and fructosamine levels.

Biomarkers of oxidative stress in diabetes mellitus

➢ Proteins

- Alteration in function and structure of antioxidant protein enzymes may also be due to nonenzymatic glycation such that detoxification of free radicals is effected enhancing oxidative stress in diabetes .
- According to in vitro studies myeloperoxidase catalyzes the conversion of l-tyrosine to 3,3-dityrosine which serves as a crosslink between polypeptide chains of the same or different proteins making it a convenient biomarker for protein oxidation .

Biomarkers of oxidative stress in diabetes mellitus

➢ Lipids

- Diabetes mellitus produces disturbances in the lipid profile of body making the cells more susceptible to lipid peroxidation.
- Experimental studies show that polyunsaturated fatty acids in cell membrane are extremely prone to attack by free radicals due to the presence of multiple bonds .
- Lipid hyperperoxides (LHP) through intermediate radical reactions produce such fatty acids that generate highly reactive and toxic lipid radicals that form new LHP .

Biomarkers of oxidative stress in diabetes mellitus

➢ Lipids

- A critical biomarker of oxidative stress is Lipid peroxidation which is the most explored area of research when it comes to ROS .
- Malondialdehyde (MDA) is formed as a result of lipid peroxidation that can be used to measure lipid peroxides after reacting it with thiobarbituric acid.

Biomarkers of oxidative stress in diabetes mellitus

➢ Vitamins

- Vitamins are very important part of biological system as they play important role in different biochemical processes.
- Among such vitamins, Vitamin A, C and E act as antioxidants by detoxifying the free radicals.
- Any alteration in their levels is significant biomarkers of oxidative stress.
- These vitamins also promote toxicity by producing pro-oxidants in certain conditions.
- Body levels of vitamin E have been reported to be either increased or decreased by diabetes.

Biomarkers of oxidative stress in diabetes mellitus

➢ Glutathione

- Diabetes induces alterations in activity of enzymes glutathione peroxidase and glutathione reductase.
- These enzymes are found in cell that metabolizes peroxide to water and converting glutathione disulfide back into glutathione .
- Any alteration in their levels will make the cells prone to oxidative stress and hence cell injury.

Biomarkers of oxidative stress in diabetes mellitus

➢ Superoxide dismutase (SOD)

- Superoxide dismutase provides first line defense against ROS mediated cell injury by catalyzing the proportion of superoxide, the primary ROS in oxygen metabolism, to molecular oxygen and peroxide.
- We can say that superoxide is dismutated to other compounds that are less toxic by SODs.

Biomarkers of oxidative stress in diabetes mellitus

➢ Catalase (CAT)

- Catalase is regulator of hydrogen peroxide metabolism that can, in excess, cause serious damage to lipids, RNA and DNA.
- CAT converts H2O2 catalytically into water and oxygen and thus neutralizes it.
- In case of catalase deficiency, beta cell of pancreas that contain large amount of mitochondria, undergoes oxidative stress by producing excess ROS that leads to β-cells dysfunction and ultimately diabetes.

Conclusion

- Oxidative stress has been demonstrated to participate in the progression of diabetes which plays important role during diabetes, including impairment of insulin action and elevation of the complication incidence.
- Antioxidants have already shown to be prospective in the treatment of diabetes both type 1 and type 2.
- Increase in the levels of oxygen and nitrogen free radicals (ROS/RNS) has been linked with lipid peroxidation, non-enzymatic glycation of proteins and oxidation of glucose which contributes toward diabetes mellitus and its complications.

Thank You For Listening!