

Free Radicals

Free Radicals in Diabetes Mellitus

- In diabetes (both Type 1 and Type 2), there is often an imbalance between free radical production and the body's antioxidant defenses.
- This leads to oxidative stress, which contributes to the development and progression of diabetes-related complications.

Increased Production of Free Radicals

- High blood glucose levels promote overproduction of free radicals through various pathways.
- Glucose can auto-oxidize or react with proteins, lipids, and nucleic acids to form advanced glycation end products (AGEs), which further increase oxidative stress.

Impaired Antioxidant Defense

- Diabetes impairs the efficiency of the body's natural antioxidant systems.
- Key antioxidant enzymes such as:
 - Superoxide dismutase (SOD)
 - Catalase
 - Glutathione peroxidase are often less active in diabetic individuals, leading to insufficient neutralization of free radicals.

Oxidative Stress and Diabetic Complications

- Free radicals can damage important cellular components (DNA, proteins, and lipids), contributing to:
 - **Neuropathy** – nerve damage, leading to pain and sensory loss.
 - **Retinopathy** – retinal damage causing vision problems.
 - **Nephropathy** – kidney damage, affecting kidney function.
 - **Cardiovascular diseases** – such as atherosclerosis, heart attacks, and strokes.

Insulin Resistance

- Oxidative stress interferes with insulin signaling pathways.
- This leads to reduced insulin sensitivity, worsening hyperglycemia and contributing to the progression of diabetes.

Inflammatory Response

- Free radicals activate inflammatory pathways, promoting chronic low-grade inflammation, a key contributor to diabetic complications.

Management

- **Lifestyle changes** like a healthy diet, regular physical activity, and weight management.
- **Antioxidant supplementation** (under medical supervision) may help reduce oxidative stress and improve diabetes outcomes.

Free Radicals in Inflammation

- Free radicals, particularly reactive oxygen species (ROS) and reactive nitrogen species (RNS), play dual roles in both promoting and resolving inflammation.

Activation of Inflammatory Cells

- Immune cells such as macrophages and neutrophils produce ROS/RNS in response to infection or injury.
- This "oxidative burst" helps destroy pathogens but can also damage host tissue if uncontrolled.

Signal Transduction and Gene Expression

- Free radicals modulate signaling pathways and gene expression.
- For example, ROS activate nuclear factor kappa B (NF- κ B), a transcription factor that triggers the production of inflammatory cytokines, chemokines, and adhesion molecules.

Tissue Damage and Inflammatory Response

- Excessive ROS/RNS damage cellular components, leading to:
 - Lipid peroxidation
 - Protein oxidation
 - DNA damage
- Damaged cells release damage-associated molecular patterns (DAMPs), further promoting inflammation and immune cell recruitment.

Resolution of Inflammation

- Despite their damaging potential, ROS also help resolve inflammation by:
 - Modulating signaling pathways involved in tissue repair.
 - Promoting the clearance of apoptotic cells and restoring tissue homeostasis.

Chronic Inflammation and Disease

- Persistent oxidative stress due to inadequate antioxidant defense leads to chronic inflammation.
- This contributes to the development of diseases like:
 - Atherosclerosis
 - Rheumatoid arthritis

- Chronic obstructive pulmonary disease (COPD)

Antioxidant Defense Mechanisms

The body utilizes both enzymatic and non-enzymatic antioxidants to neutralize free radicals:

Enzymatic Antioxidants:

- Superoxide dismutase (SOD)
- Catalase
- Glutathione peroxidase

Non-Enzymatic Antioxidants:

- Vitamin C
- Vitamin E
- Glutathione

Free Radicals in Ischemic Reperfusion Injury (IRI)

- Ischemic reperfusion injury (IRI) is a paradox where the restoration of blood flow (reperfusion) to previously oxygen-deprived tissue (ischemia) causes additional tissue damage instead of recovery.
- This is seen in myocardial infarction, stroke, organ transplantation, and surgical procedures.
- Free radicals, particularly reactive oxygen species (ROS), play a central role in the pathophysiology of IRI.

Mechanisms of Free Radical Production in IRI

1. Oxygen Supply Restoration

- During ischemia, lack of oxygen shifts metabolism to anaerobic pathways, causing buildup of metabolites (e.g., lactic acid).
- Upon reperfusion, the sudden influx of oxygen leads to overproduction of ROS via mitochondrial electron transport chains and other cellular processes.

2. Activation of Enzymes

- Enzymes activated during reperfusion include:
 - Xanthine oxidase – converts hypoxanthine to uric acid, generating superoxide radicals.
 - NADPH oxidase
 - Lipoxygenases
- These contribute to an oxidative burst of ROS.



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