

Background

Hexose monophosphate pathway (HMP) or Pentose Phosphate Pathway (PPP)

- They are An alternative pathway for glucose
- Produces ribose-5-phosphate for nucleotide synthesis
 - does not produce ATP
- **Major pathway for NADPH production**

Uses of NADPH

- Reductive biosynthesis e.g., fatty acid biosynthesis
- **Antioxidant (part of glutathione system)**
 - Oxygen-dependent phagocytosis by WBCs
 - Synthesis of nitric oxide (NO)

Reactive Oxygen Species (ROS)

Oxygen-derived Free radicals

- Superoxide.
- hydroxyl radicals

Non-free radical

Hydrogen peroxide (highly reactive).

Oxidative stress

Imbalance between oxidant production and antioxidant mechanisms

It Causes oxidative damage to:
1- DNA.
2- Proteins
3- Lipids (unsaturated fatty acids)

pathological process related to Oxidative stress

- 1- Inflammatory conditions e.g., Rheumatoid arthritis
- 2- Atherosclerosis and coronary heart diseases
- 3- Obesity 4- Cancers 5- **G6PD deficiency hemolytic anemia**

G6PD Deficiency Hemolytic Anemia

overview

- 1- **Inherited X**-linked recessive disease
- 2- **Most common** enzyme-related hemolytic anemia
- 3- **Highest prevalence**: Middle East, Tropical Africa
Asia and Mediterranean
- 4- ~400 different mutations affect G6PD gene, but **only some** can cause clinical hemolytic anemia
- 5- G6PD deficient patients have **increased resistance** to infestation by **falciparum malaria**

Precipitating Factors for G6PD Deficiency Hemolytic Anemia

G6PD deficient patients will develop hemolytic attack upon:

- 1- **Intake of oxidant drugs (AAA)**:
 - 1a-**Antibiotics** e.g., sulfa preparation
 - 2a-**Antimalarial**: e.g., Primaquine
 - 3a-**Antipyretics**
- 2- Exposure to infection
- 3- Ingestion of fava beans (favism, Mediterranean variant)

Chronic nonspherocytic anemia: Hemolytic attack in absence of precipitating factors. Severe form due to class I mutation

Biochemical Basis of G6PD Deficiency Hemolytic Anemia

Oxidation of sulfhydryl (SH) groups of proteins inside RBCs Causes :

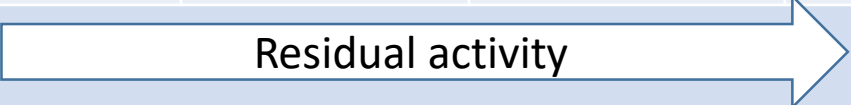
- 1- protein denaturation
- 2- formation of insoluble masses (Heinz bodies) that attach to RBCs membranes

Although G6PD deficiency affects all cells,
it is **most severe** in RBCs

Other cells have **other sources** for NADPH production:
e.g., Malic enzyme (Called malate dehydrogenase) that converts malate into pyruvate ,but **RBC does not**

Different Classes of G6PD Deficiency Hemolytic Anemia

4 classes Based on the residual enzyme activity

Class 1	Mediterranean (Class II)	G6PD A- (Class III)	Class IV
Very severe	Severe	Moderate	Normal
	Affect all RBCs (both young and old).	young Affect RBCs.	
enzyme activity is less than 10%	Enzyme with decreased stability Resulting in decreased activity (severe). enzyme activity is less than 10%	contain enzymatic activity. Unstable enzyme, but kinetically normal. Enzyme activity is 10-16 %	Normal means that symptoms are not present but there is a decrease in enzyme activity especially when the RBC reaches 120 days
LOWEST			HIGHEST

Diagnosis of G6PD Deficiency Hemolytic Anemia

Diagnosis of hemolytic anemia	Complete Blood Count (CBC) & reticulocytic count Decreased RBC count but increased number of reticulocyte On blood smear : Heinz bodies
Screening	Qualitative assessment of G6PD enzymatic activity (UV-based test) Tells you that enzyme activity is low if it becomes positive, do confirmatory test
Confirmatory test	Quantitative measurement of G6PD enzymatic activity Tells you exactly the amount of active enzyme
Molecular test	Detection of G6PD gene mutation Tells you what kind of mutation it is