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	Non-free radical
- Superoxide. - hydroxyl radicals	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-**A**ntibiotics e.g., sulfa preparation
- 2a-**A**ntimalarial: e.g., Primaquine
- 3a-**A**ntipyretics

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			
Calss 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	Residual activity		**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