-G6PD Deficiency Anemia-

Biochemistry Teamwork

Osamah Al-Jarallah	Al-Anood Asiri
Abdulaziz Al-Shamlan	Lama Mokhlis
Abdullah Al-Mazyad	Noha Khalil
Turki Al-Otaibi	Reem Al-Mansour
Khalid Al-Khamis	Hadeel Helmi
Saud Al-awad	Nuha Al-Furayh
Khaled Almohaimede	Jumana Al-Shammari
Meshal Al-Otaibi	Deema Jomar

By : Al-Anood Asiri & Osamah Al-Jarallah

Team notes are either in □ or green. Important info is in red. Anything after "FYI" is for your information.

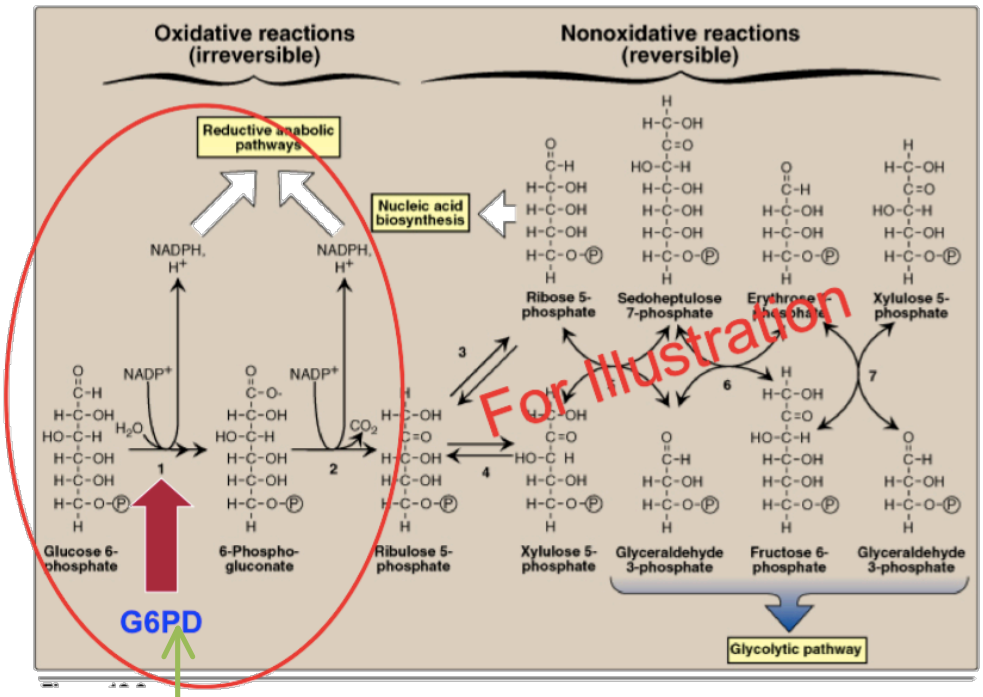
Objectives:

- **The biochemical basis of G6PD deficiency anemia**
- **The precipitating factors for G6PD deficiency anemia**
- **Classes of G6PD deficiency anemia (variant enzyme)**
- **Diagnosis of G6PD deficiency anemia**

Background:

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

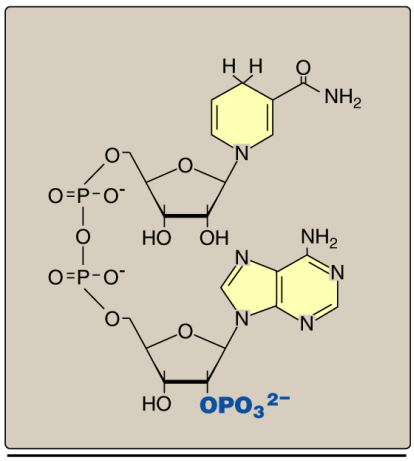
- **An alternative oxidative pathway for glucose**
- **No ATP production**
- **Major pathway for NADPH production**
- **Produces ribose-5-phosphate for nucleotide synthesis**



G6PD is the rate-limiting step in the HMP/PPP

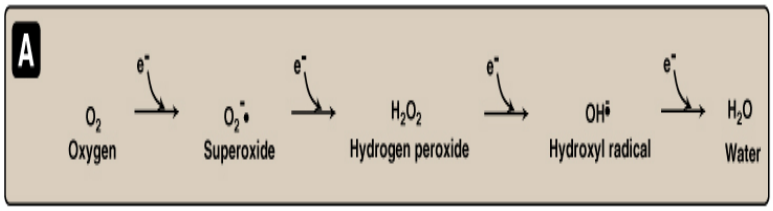
Uses of NADPH:

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



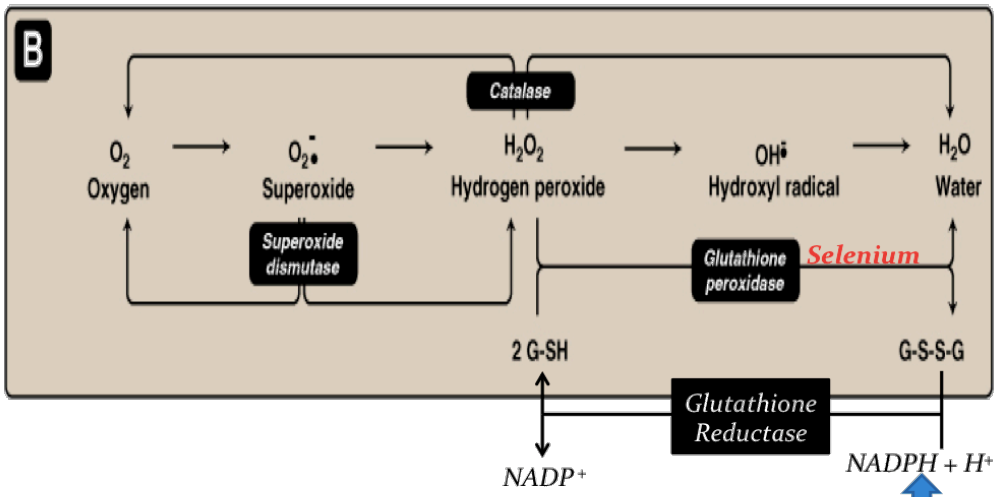
-NADPH-

Reactive Oxygen Species (ROS):



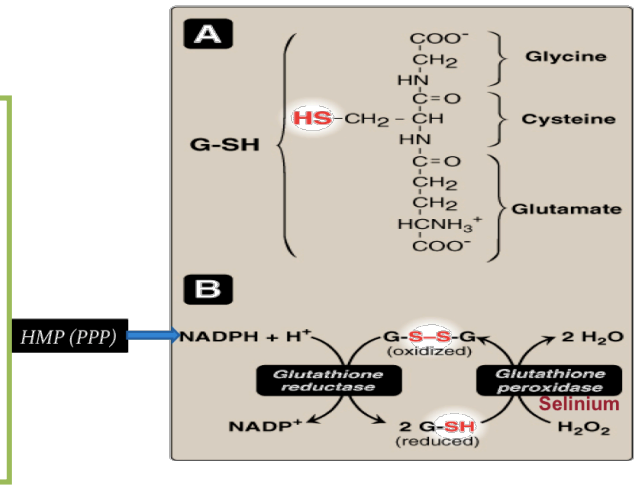
Oxygen-derived Free radicals :e.g., Superoxide and hydroxyl radicals
Non-free radical: Hydrogen peroxide.

Antioxident Mechanism:



Glutathione System:

- Glutathione peroxidase is a selenium dependent enzyme that gets rid of hydrogen peroxide.
- Glutathione reductase reduces G-S-S-G and oxidizes NADPH (that comes from HMP/PPP).
- FYI: Glutathione is composed of Glycine, Cysteine and Glutamate attached to a sulfhydryl (SH) groups



OXIDATIVE STRESS: Imbalance between oxidant production and antioxidant mechanisms:

Oxidative stress and diseases:

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

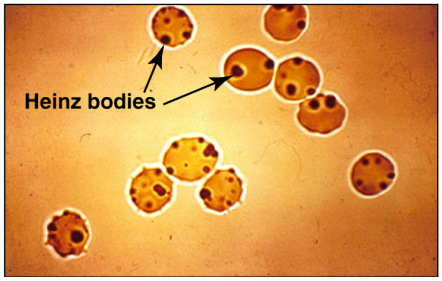
Oxidative damage to:

- **DNA**
- **Proteins (structure-function relationship → lose function)**
- **Lipids (unsaturated fatty acids)**

G6PD (Glucose-6-Phosphate Dehydrogenase) Deficiency hemolytic anemia:

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

FYI: Click http://db.tt/MBAVnSQU to understand the genetic property

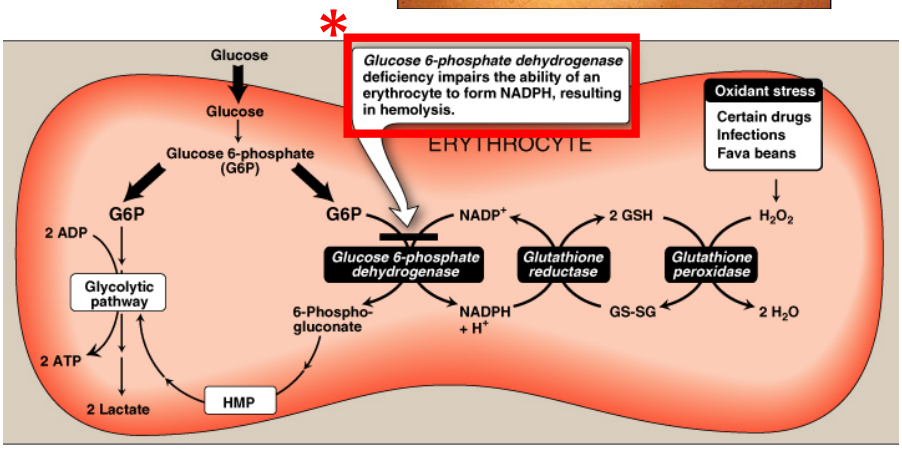


* Heterozygote advantage: the RBCs are too defective for the falciparum to live in.

Biochemical Basis of G6PD Deficiency Hemolytic Anemia:

Oxidation of sulfhydryl (SH) groups of proteins inside RBCs

causes protein denaturation and formation of insoluble masses (Heinz bodies) that attach to RBCs membranes (making them defective and ready for hemolysis)



Although G6PD deficiency affects all cells, It is most severe in RBCs. Why?
Other cells have other sources for NADPH production: (While RBCs do not have other sources)
e.g., Malic enzyme that converts malate into pyruvate (not present in RBCs)

Precipitating Factors for G6PD Deficiency Hemolytic Anemia:

G6PD deficient patients will develop hemolytic attack upon:

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

FYI: some mutations of G6PD cause it to be super-active (activity up to 150%)

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

Different Classes of G6PD Deficiency Hemolytic Anemia:

Class I does not need precipitating factors to go into an oxidative crisis
FYI: name of the test is "Kinetic Enzyme Activity Test"

II -Mediterranean
III- G6PD A- (Africa)
IV- Normal

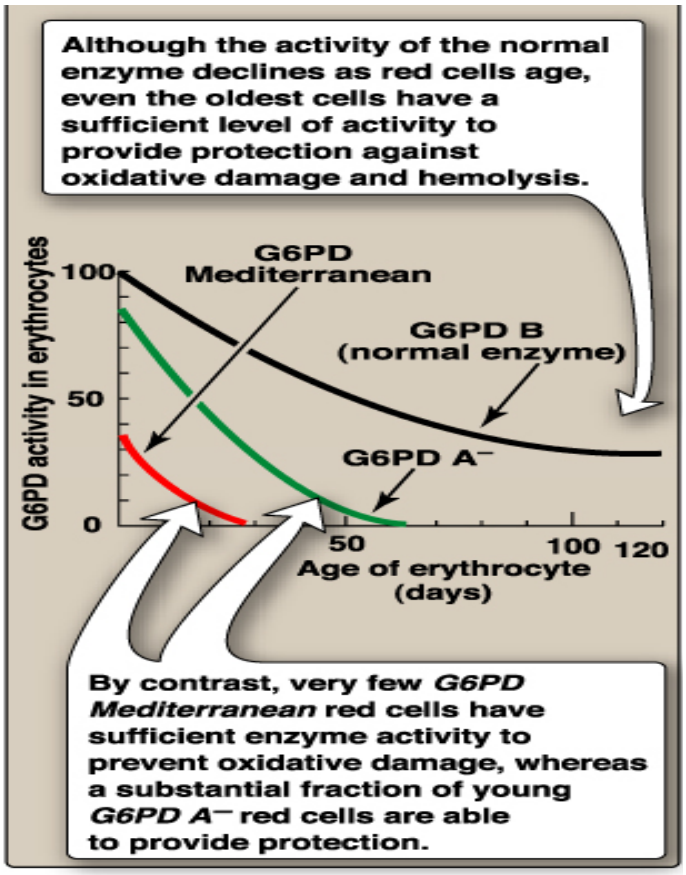
Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	60–150%

Variant Enzymes of G6PD Deficiency Hemolytic Anemia

The green line represents **G6PD A- (class III):**
Moderate, young RBCs Contain enzymatic activity
Unstable enzyme, but Kinetically normal

The red line represents **G6PD Mediterranean (II)**
Enzyme with normal stability
But low activity (severe)
Affect all RBCs (both young and old)

The Black line represents Normal G6PD Enzyme: It shows that even though the RBCs are getting older, their enzyme activity is enough to reach their requirements in protecting the RBCs from oxidative damage.



Diagnosis of G6PD Deficiency Hemolytic Anemia:

Diagnosis of hemolytic anemia

Complete Blood Count (CBC) & reticulocytic count

Screening:

Qualitative assessment of G6PD enzymatic activity (UV-based test) (can only be done after the attack)

Confirmatory test:

Quantitative measurement of G6PD enzymatic activity

Molecular test:

Detection of G6PD gene mutation

MCQs:

1. **In male patients who are homozygous for glucose 6-phosphate dehydrogenase (G6PD) deficiency, pathophysiologic consequences are more apparent in erythrocytes (RBC) than in other cells, such as in the liver. Which one of the following provides the most reasonable explanation for this different response by these individual tissue types?**

A. Excess glucose 6-phosphate in the liver, but not in RBCs, can be channeled to glycogen, thus averting cellular damage.
B. Liver cells, in contrast to RBCs, have alternative mechanisms for supplying the NADPH required for keeping metabolic and cellular integrity.
C. Glucose 6-phosphatase activity in RBCs removes the excess glucose 6-phosphate, thus resulting in cell damage. This does not happen in the hepatocyte.
D. Because RBCs do not have mitochondria, production of ATP required to keep cell integrity depends exclusively on the routing of glucose 6-phosphate to the pentose phosphate pathway.
E. The catalytic properties of the liver enzyme are significantly different than those of the RBC enzyme.

2. **Which of the following is correct about G6PD deficiency hemolytic anemia?**

A. Fava beans is a precipitating factor
B. Qualitative assessment of G6PD enzymatic activity is a Confirmatory test
C. In chronic nonspherocytic anemia: Hemolytic attack occurs in presence of precipitating factors.
D. Glutathione peroxidase is a selenium dependent enzyme that gets rid of hydroxyl radicals
E. A and B

3. **Which of the following is correct about G6PD deficiency hemolytic anemia?**

A. Autosomal recessive disease
B. Affects Females more than males
C. Class I of the disease is mild
D. Inherited X-linked recessive disease

Answers: 1-B 2-A 3-D