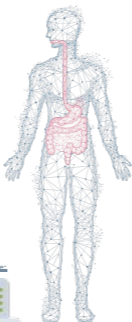




L11:

# G6PD

GNT Block



## Color Index:

- Main text
- Female slides
- Male slides
- Important
- Doctor's notes
- Extra notes

Editing file:





# Objectives:

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Explain the biochemical basis of G6PD deficiency anemia



Recognize the precipitating factors for G6PD deficiency anemia



Classify various classes of G6PD deficiency anemia (variant enzymes)



Describe the diagnostic methods for G6PD deficiency anemia

Lecture presented by :

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**Dr. Sumbul Fatma**

**Dr. Zeyad Kurdee**



# Background

Hexose Monophosphate Pathway (HMP) or Pentose Phosphate Pathway (PPP):

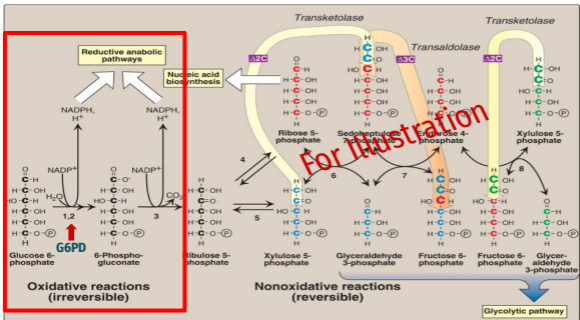
An **alternative** oxidative pathway for **glucose**.

**No ATP** production.

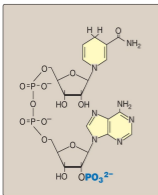
Major pathway for **NADPH** production.

Produces **ribose-5-phosphate for nucleotide** synthesis.

# Pentose phosphate pathway (PPP)



## Uses of NADPH



Structure of NADPH

Antioxidant (part of glutathione system)

Oxygen-dependent phagocytosis by WBCs

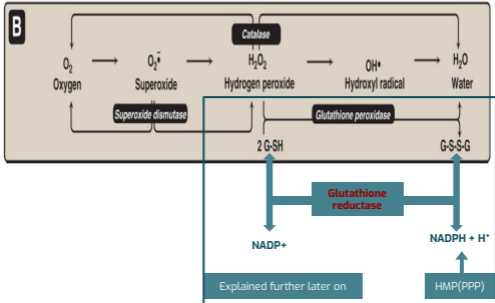
Synthesis of nitric oxide (NO)

Reductive biosynthesis e.g., fatty acid biosynthesis

# Antioxidant Mechanisms

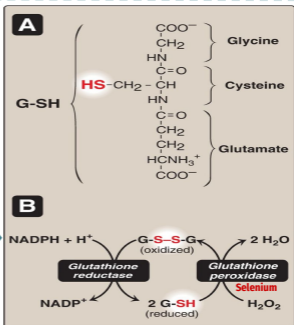
Let's start with Anti-oxidant mechanisms to understand the relationship between G6PD and Anemia !

أولاً، الغاية ننتهي بنتيجة Harmless  
 $H_2O_2$  transform to  $H_2O$  by Glutathione system

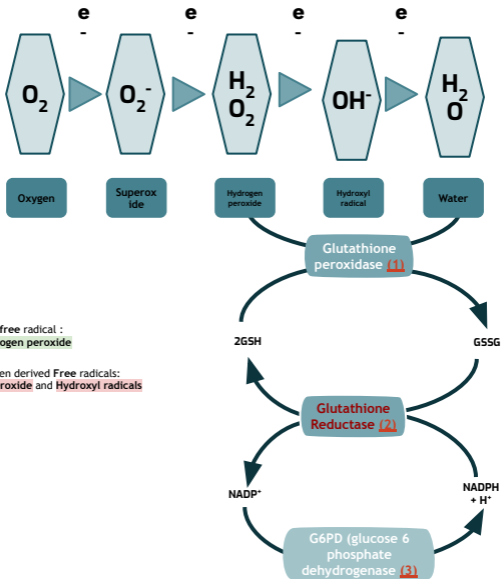


This picture will be explained in details in the next slide

## Glutathione system



# Reactive oxygen species (ROS)



Non-free radical :  
Hydrogen peroxide

Oxygen derived Free radicals:  
Superoxide and Hydroxyl radicals

G6PD is a key and rate limiting enzyme in the **pentose phosphate pathway (PPP)**  
Aka: Hexose monophosphate pathway (HMP)

# Glutathione System

These information were written/drawn in the pictures of the dr's slides.

	<b>GLUTATHIONE PEROXIDASE (1)</b>	<b>GLUTATHIONE REDUCTASE (2)</b> (مايقدر يشتغل لحاله لازم مساعد)	<b>G6PD (3)</b> (GLUCOSE 6 PHOSPHATE DEHYDROGENASE)
SUBSTRATE	2GSH (Reduced form)	GSSG (Oxidized form)	NADP+ (Oxidized form)
END PRODUCT	GSSG (Oxidized form)	2GSH (Reduced form) Reduced glutathione is essential for maintaining the normal structure of red blood cells and for keeping hemoglobin in the ferrous state.	NADPH + H (Reduced form)
ACTION	Oxidase > loss of e <sup>-</sup> from reduced form 2GSH > become oxidized > GSSG	Reductase > gain of e <sup>-</sup> from NADPH give e <sup>-</sup> to the oxidized form (GSSG) > become reduced (2GSH)	-

- معنى ذلك ان ( NADPH ) هو أصل كل العملية

- How NADPH + H can be formed ? By G6PD -

In which pathway ? pentose phosphate pathway PPP -

- So deficiency in this enzyme will decrease the anti-oxidant sequence > oxidation stress in many cells but much severe in RBCs > lead to hemolysis > hemolytic anemia

- Why the oxidation stress is server in RBCs? Because the Other cells have other sources for NADPH production.

# Oxidative stress

## Imbalance between oxidant production and antioxidant mechanisms

Whenever oxidation is increased, RBC will need G6PD > if G6PD is insufficient > the oxidative stress will occur

### Oxidative damage to

DNA

Proteins

Lipids (unsaturated fatty acids)

### Oxidative stress and diseases

Inflammatory conditions  
e.g., Rheumatoid arthritis, Atherosclerosis and Coronary heart disease

Obesity

Cancers

G6PD deficiency hemolytic anemia



# G6PD Deficiency Hemolytic Anemia

- Inherited **X-linked** recessive disease.
- **Most common enzyme-related hemolytic anemia.**
- Highest prevalence: Middle East, Tropical Africa Asia & 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 (1)

G6PD deficient patients will develop hemolytic attack upon the below

## Precipitating Factors for G6PD Deficiency Hemolytic Anemia

### 1- Intake of oxidant drugs (AAA)

Antibiotics e.g. sulfa preparation / Antimalarial e.g: primaquine / Antipyretics

### 2- Ingestion of fava beans

( favism, Mediterranean variant )

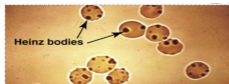
### 3- Exposure to infections (2)

### 4- Chronic nonspherocytic anemia

Hemolytic attack in absence of precipitating factors. Severe form due to class I mutation

## Biochemical basis of G6PD deficiency hemolytic anemia

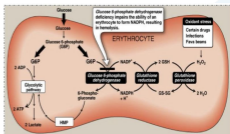
Oxidation of sulfhydryl (SH) groups [because there is little or no reductive agents (NADPH)] of proteins inside RBCs causes protein denaturation and formation of insoluble masses (**Heinz bodies**) that attach to RBCs membranes



جذوب لثمن كالموت، وإذا تصفت كآل على جدار الخلية ليصير  
RBCs will pass through spleen  
مبدأ يفتقد عليها  
Spleen by its macrophages in sinusoids  
يخرج بذلك المكان التي فيه الترسبات عادي، فالتشكل الخلية ليصير مشوهة كآله كآل مبروز أو ممتدح  
known as bite cell

Although G6PD deficiency affects all cells, it is most severe in RBCs ..... Why?

Other cells have other sources for NADPH production: e.g., Malic enzyme that converts malate into pyruvate



# Different Classes of G6PD deficiency hemolytic anemia

There are 4 different classes: (3)

I (very severe)

II (severe, e.g. Mediterranean)

III (Moderate: G6PD A-)

IV (Normal)

This classification is based on the residual enzyme activity (Least in class I, and Highest in class IV)

## Variant Enzymes of G6PD Deficiency Hemolytic Anemia

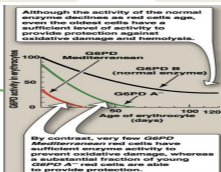
**Important**

### G6PD A- (class III):

Moderate, young RBCs contain enzymatic activity. Unstable enzyme, but kinetically normal

### G6PD Mediterranean (II):

Enzyme with decreased stability and activity (severe). Affect all RBCs (both young and old)



The most IMP in this lecture you have to know everything about it

Diagnosis of G6PD Deficiency Hemolytic Anemia	Diagnosis Of hemolytic anemia	Complete Blood Count (CBC) & reticulocytic count (4)
	Screening (5)	Qualitative assessment of G6PD enzymatic activity (UV-based test)
	Confirmatory Test:	Quantitative measurement of G6PD enzymatic activity
	Molecular test:	Detection of G6PD gene mutation



# Doctor's notes

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Special thanks to 442

1- This happens because:

- (a) Malaria cannot live well in RBCs if they are hemolyzed
- (b) G6PD deficiency will cause an increase in free radicals which will also damage the parasite

2- Infections increase ROS

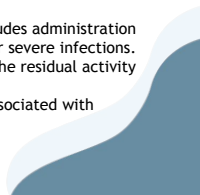
3- Enzymes are measured through 2 criterias: 1- Stability 2- Activity (used in this classification)

4- Results: -RBCs → decreased Reticulocyte count → Increased (due to compensation)

5- Screening is used in some african countries. Since malaria is prevalent in that area, these tests are done before giving anti malaria drugs to prevent extra oxidative stress.

## Take home messages

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- G6PD deficiency impairs the ability of cells to form NADPH.
  - RBCs are particularly affected because they do not have other sources of NADPH.
  - NADPH is essential for the antioxidant activity of Glutathione peroxidase/reductase system
  - G6PD deficiency is an X-linked disease characterized by hemolytic anemia.
  - The precipitating factors of hemolysis includes administration of oxidant drugs, ingestion of fava beans or severe infections.
  - G6PD deficiency is classified according to the residual activity of the G6PD
  - Class I variant (the most severe) class is associated with chronic nonspherocytic hemolytic anemia.
- 

# Quiz

## MCQs

**Q1:** HMP Is major pathway for production of?

- A- ATP
- B- NADPH
- C- NADH
- D- FADH

**Q2:** G6PD deficient patients have increased resistance to:

- A- Cholera
- B- Salmonella
- C- Giardia lamblia
- D- Malaria

**Q3:** HMP Produces ..... for nucleotide synthesis:

- A- ribose-3-phosphate
- B- glucose -5-phosphate
- C- fructose-5-phosphate
- D- ribose-5-phosphate

**Q4:** Oxidation of sulfhydryl (SH) groups of proteins inside RBCs will lead to:

- A- Formation of insoluble masses (Heinz bodies)
- B- Production ATP
- C- Reductive biosynthesis
- D- None of them

**Q5:** Which one of the following enzymes converts H<sub>2</sub>O<sub>2</sub> to H<sub>2</sub>O?

- A- Glutathione Synthetase
- B- Glutathione Peroxidase
- C- Glutathione Reductase
- D- Superoxide dismutase

**Q6:** Which one of these can produce NADPH?

- A- Superoxide dismutase
- B- Malic enzyme
- C- Glutathione Reductase
- D- all of them

Answers: 1-B | 2-D | 3-D | 4-A | 5-B | 6-B

## SAQ

**Q1:** Although G6PD deficiency affects all cells, why it is most severe in RBCs ?

Other cells have other sources for NADPH production: e.g., Malic enzyme that converts malate into pyruvate

**Q2:** What is the Uses of NADPH ?

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

**Q3:** Mention 2 factors which will lead to Hemolytic attacks in G6PD Deficient patients ?

1. Exposure to infection
2. Intake of oxidant drugs

# Members board

## Team Leaders



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Aishah boureggah



Dana A Alkheliwi



Osama Almashjari



Mansour Alotaibi



Aldanah Abdullah



Nazmi M Alqutub



Salma Alsaadoun



Layan Al-Ruwaili



Fahad Mobeirek



Sarah Alajaji



Abdulrahman  
Alosleb



Areej Alquraini



Waad alqahtani

Special Thanks to Aleen Alkulyah for the Design!

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