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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ




THALASSEMIAS

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LECTURE OUTLINE

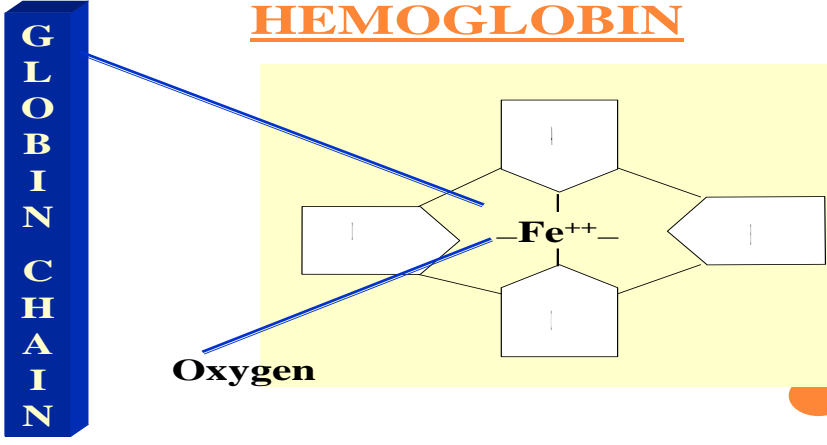
By the end of the lecture, the student should know:

- The different types of hemoglobin present at different ages.
- **Thalassemia**
- **Types of Thalassemias**




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HEMOGLOBIN



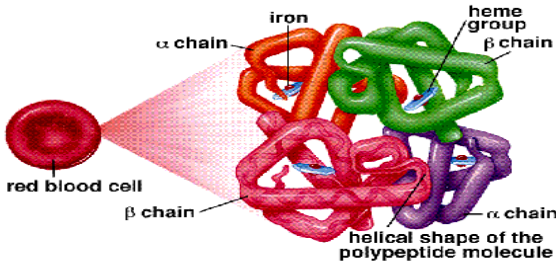
Oxygen



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Hemoglobin Structure

- Four subunits
 - two α
 - two β
- Iron
- Heme
- Binds 4 O₂



The diagram illustrates the structure of a hemoglobin molecule. On the left, a red blood cell is shown with a magnifying glass effect focusing on a single hemoglobin molecule. The molecule is composed of four polypeptide chains: two α chains (colored orange and green) and two β chains (colored pink and purple). Each chain is in a helical shape. An iron atom is located at the center of each heme group, which is coordinated to the α and β chains. The heme group is shown as a green and purple structure. Labels include: red blood cell, α chain, β chain, iron, heme group, and helical shape of the polypeptide molecule.

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NORMAL HAEMOGLOBIN

- HbA - $\alpha_2\beta_2$
- HbA₂ - $\alpha_2\delta_2$
- HbF - $\alpha_2\gamma_2$
- Gowers Hb (2 Epsilon and 2 Zeta chains)

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A SET OF DISEASES CALLED THALASSEMIAS INVOLVES UNDERPRODUCTION HEMOGLOBIN, THROUGH PROBLEMS AND MUTATIONS IN GLOBIN GENE REGULATION.

The term thalassemia is derived from the Greek thalassa meaning "sea" and was applied to these disorders because of the high frequency of their occurrence in individuals living around the Mediterranean Sea.

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**THE
PARTIAL OR TOTAL ABSENCE OF ONE
OR MORE
A- OR B-CHAINS OF HEMOGLOBIN**

- **Underproduction of hemoglobin.**
- **Often produce anemia.**




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EACH GLOBIN CHAIN HAS A SEPARATE GENETIC CONTROL

A –THALASSAEMIA AFFECT A-CHAIN SYNTHESIS


B –THALASSAEMIA AFFECT B -CHAIN SYNTHESIS



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**DECREASED OR ABSENT PRODUCTION OF
A-GLOBIN CHAINS RESULTS IN A-
THALASSEMIAS**

- **A complete or partial lack of α -globin.**
- **β -globin chain is normal.**
- **Each individual genome contains four copies of the α -globin gene.**
- **Defect may be present in one more or all the four genes.**



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THERE ARE SEVERAL LEVELS OF A-GLOBIN CHAIN DEFICIENCIES

- **Silent carrier;** Only one α -globin gene is deletion with no clinical manifestation.
- **α -thalassemia trait;** Two α - globin genes are deleted.
- **Hemoglobin H (HbH) disease;** Three α -globin genes are deleted with mild to moderate hemolytic anemia.
- **Hydrops fetalis;** All α - globin genes are deleted, results in fetal death.



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SILENT CARRIER STATE

- ▶ **Deletion of one alpha gene, leaving three functional alpha genes.**
- ▶ **No hematologic abnormalities present.**



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ALPHA THALASSEMIA TRAIT (ALPHA THALASSEMIA MINOR)

- ▶ **Also called Alpha Thalassemia Minor.**
- ▶ **Caused by two missing alpha genes.**
- ▶ **Exhibits mild microcytic, hypochromic anemia.**



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HEMOGLOBIN H DISEASE

- ▶ **Second most severe form alpha thalassemia.**
- ▶ **Usually caused by presence of only one gene producing alpha chains.**
- ▶ **Results in accumulation of excess beta chains.**
- ▶ **Hemoglobin H (β_4).**

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BART'S HYDROPS FETALIS SYNDROME

- ▶ **Most severe form. Incompatible with life. Have no functioning alpha chain genes (--/--).**
- ▶ **Predominant hemoglobin is Hemoglobin Bart(four gamma chains).**
- ▶ **Hemoglobin Bart's has high oxygen affinity so cannot carry oxygen to tissues.**
- ▶ **Pregnancies dangerous to mother. Increased risk of toxemia and severe postpartum hemorrhage.**

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DECREASED OR ABSENT PRODUCTION OF B-GLOBIN CHAINS RESULTS IN B-THALASSEMIAS

- **A complete or partial lack of β -globin.**
- **α -globin cannot form stable tetramers and, therefore precipitate causing premature death of the RBCs (hemolysis leads to hemolytic anemia)**
- **β -thalassemia:**
 - **β^0 -thalassemia; A complete lack of β -chain.**
 - **β^+ -thalassemia; production of a small amount of functional β -chain.**

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B-THALASSEMIAS CAN BE CATEGORIZED ON THE BASIS OF CLINICAL SEVERITY

- **β-thalassemia Major.**
- **β-thalassemia Minor.**

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B-THALASSEMIA MINOR

- **Afflicted individuals harbor one normal β-globin gene and one that harbors a mutation leading to production of reduced or no β-globin.**
- **Microcytic hypochromic rbc's.**
- **Target cells.**
- **Have high Hb A2 levels (3.5-8.0%) and normal to slightly elevated Hb F levels.**

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B-THALASSEMIA MAJOR

- **Characterized by severe microcytic, hypochromic anemia.**
- **Detected early in childhood:**
- **Severe anemia causes marked bone changes due to expansion of marrow space for increased erythropoiesis (Bone marrow hyperplasia).**
- **Marked hepatosplenomegaly.**
- **Without intervention death within the decade of life.**

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SEVERE ANAEMIA AND BONE MARROW HYPERPLASIA IN B-THALASSEMIA MAJOR

- Severe anaemia beginning in the first year of life leading to the need for blood transfusions.
- As a consequence of the anaemia the bone marrow dramatically increases its' effort at blood production.

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ENLARGEMENT OF LIVER AND SPLEEN IN B-THALASSEMIA MAJOR

Marked hepatosplenomegaly as the liver and spleen act as additional sites of blood production.

SMEAR FINDINGS

- Microcytic hypochromic rbc's.
- Target cells
- Nucleated red blood cells

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EARLY DEATH IN B-THALASSEMIA MAJOR

- β -thalassemia major patient require repeated blood transfusions and ultimate bone marrow transplant.
- However, the long term transfusions lead to the accumulation of iron in the organs, particularly the heart, liver and pancreas.
- Organ failure ensues with death in the teens to early twenties.