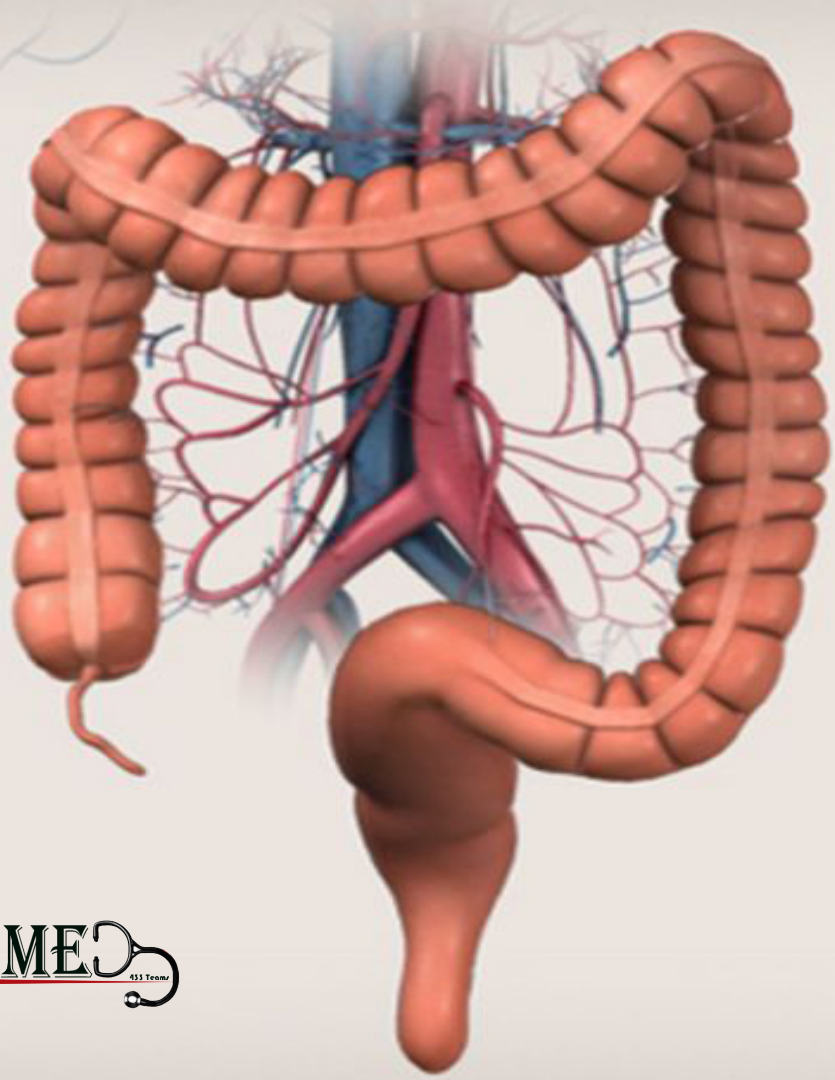

Structure And Function Of Hemoglobin

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HEMOGLOBIN (Hb)

Definition: A hemeprotein found only in RBCs

Consist of: Heme (prosthetic group) + Globin protein chains

Function:
- O_2 transport from the lungs to the tissues
- and then transport CO_2 back from the tissues to the lungs.

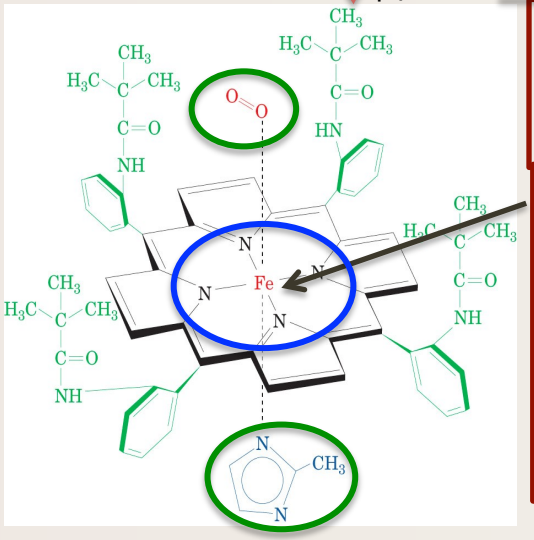
Normal level:

Normal level (g/dL):
Males: 14-16
Females: 13-15

Types:

- Abnormal
  - Carboxy Hb
  - Met Hb
  - Sulf Hb
- Normal
  - Hb A (97%)
  - HbA_2 (2%)
  - HbF (1%)
  - HbA_{1c}

HEME group:



protoporphyrin IX + Ferrous iron (Fe^{2+}) = Heme group

- Fe2+ is present in the center of the Heme
- Fe^{2+} binds to four nitrogen atoms of the porphyrin ring
- Forms two additional bonds with histidine residue of globin chain and Oxygen

Forms of Hemoglobin

R-form (Relaxed)	T-form (Taut or tense)
The oxygenated form of Hb	The deoxy (without O_2) form of Hb
High-oxygen-affinity	Low-oxygen-affinity
The dimers have more freedom of movement	The movement of dimers is constrained

Types of Hemoglobin

Hemoglobin A (HbA)

Major Hb in adults

Composed of four polypeptide chains:

Two α and two β chains

Contains two dimers of $\alpha\beta$ subunits which are held together by non-covalent interactions

Each chain is a subunit with a heme group in the center that carries oxygen

A Hb molecule contains 4 heme groups and carries 4 moelcules of O_2

Fetal Hemoglobin (HbF)

Major hemoglobin found in the fetus and newborn

Tetramer with two α and two γ chains

Higher affinity for O_2 than HbA

Transfers O_2 from maternal to fetal circulation across placenta

HbA_2

Appears ~12 weeks after birth

Constitutes ~2% of total Hb

Composed of two α and two δ globin chains

HbA_{1c}

HbA undergoes non-enzymatic glycosylation

Glycosylation depends on plasma glucose levels

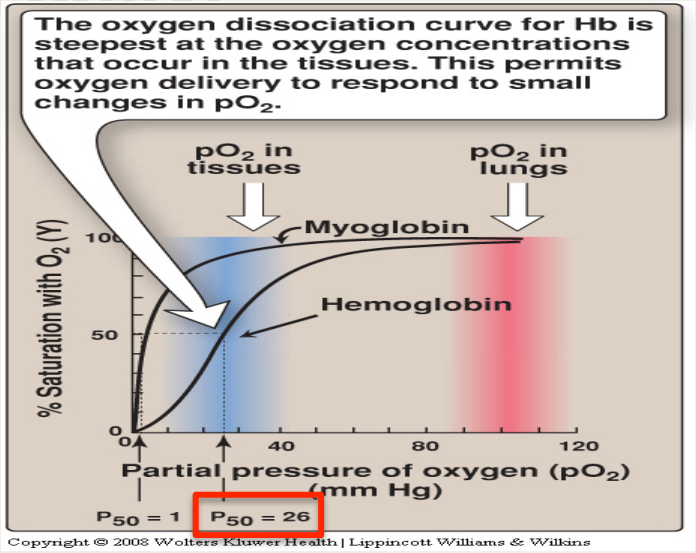
HbA1c levels are high in patients with diabetes mellitus

Factors affecting oxygen binding*
(allosteric effectors)

pO_2 (partial pressure of O_2)	pH of the environment	pCO_2 (partial pressure of carbon dioxide)	Availability of 2,3 bisphosphoglycerate

OXYGEN DISSOCIATION CURVE

- The curve is sigmoidal[1] (s-shaped)
- Indicates cooperation of subunits in O_2 binding
- Binding of O_2 to one heme group increases O_2 affinity of others
- Heme-Heme interaction[2]



*: About 97% of oxygen transported in the blood is bound to hemoglobin.

1- The sigmoidal curve reflect structural changes that are initiated at one heme group and transmitted to other heme groups in the Hb tetramer

2- The affinity of Hb for the last O_2 bound is about 300 times greater than its affinity for the first O_2 bound

P_{50} (mm Hg)

- ✓ It is the pressure at which Hb is 50% saturated with O_2
- ✓ Indicates affinity of Hb to O_2
- ❑ High affinity → slow unloading of O_2.
- ❑ Low affinity → fast unloading of O_2.
  (inverse proportion) .
- ❑ Lung pO_2 is 100 mm → Hb saturation 100%
- ❑ Tissue pO_2 is 40 mm → Hb saturation reduces.

=> Hence O_2 is delivered to tissues.

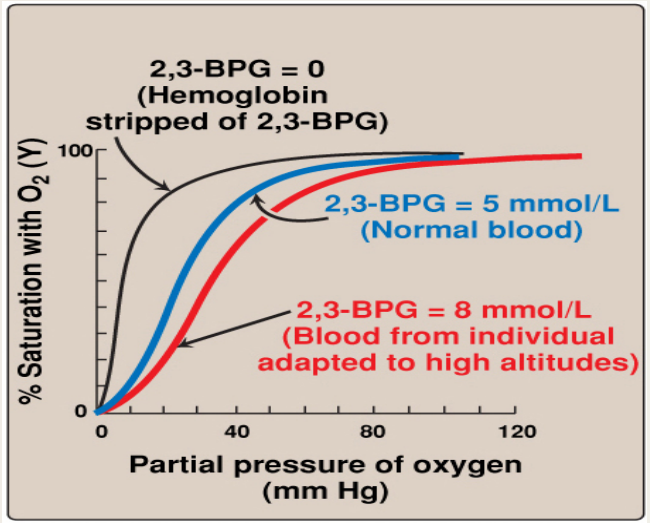
- ❑ P_{50} of hemoglobin = 26-28 mm Hg)

Availability of 2,3 bisphosphoglycerate

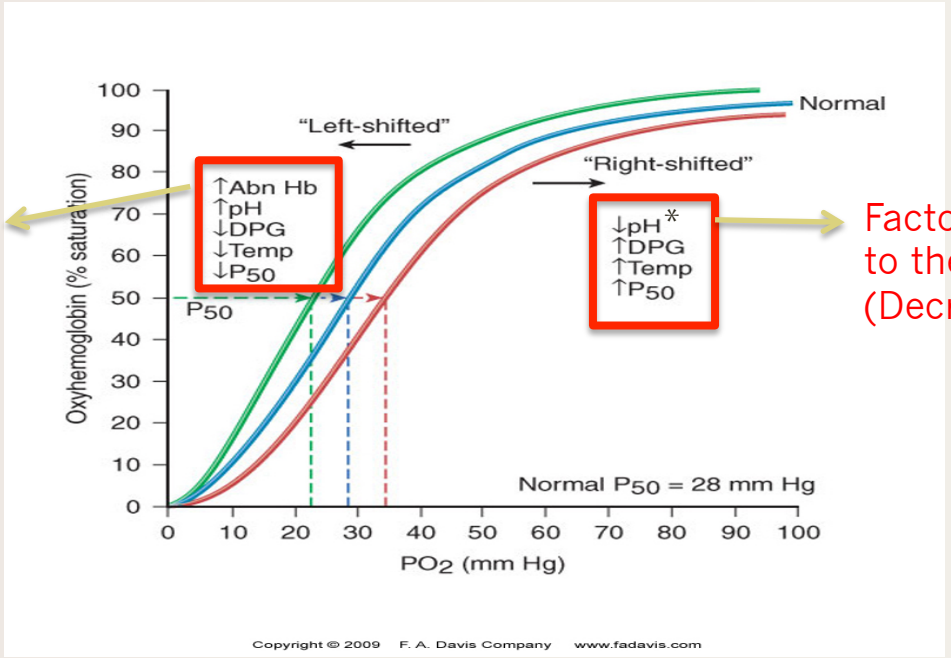
Binds to deoxy-hb and stabilizes the T-form

When oxygen binds to Hb, BPG is released

$$\underset{\text{oxyhemoglobin}}{HbO_2} + \text{2,3-BPG} \rightleftarrows \underset{\text{deoxyhemoglobin}}{\text{Hb–2,3-BPG}} + O_2$$



Factors that shift the curve to the LEFT
(Increase Hb affinity to O_2)



Factors that shift the curve to the RIGHT
(Decrease Hb affinity to O_2)

High altitude & O_2 affinity

In hypoxia and high altitude:

- 2,3 BPG levels rise
- This decreases O_2 affinity of Hb
- Thus increases O_2 delivery to tissues

Causes of high O_2 affinity

- Alkalosis
- High levels of Hb F
- Multiple transfusion of 2,3 DPG-depleted blood

*: Decreased PH means increased release of H^+

The Bohr effect

Effect:

- removes insoluble CO2 from blood stream
- Produces soluble bicarbonate

Definition:

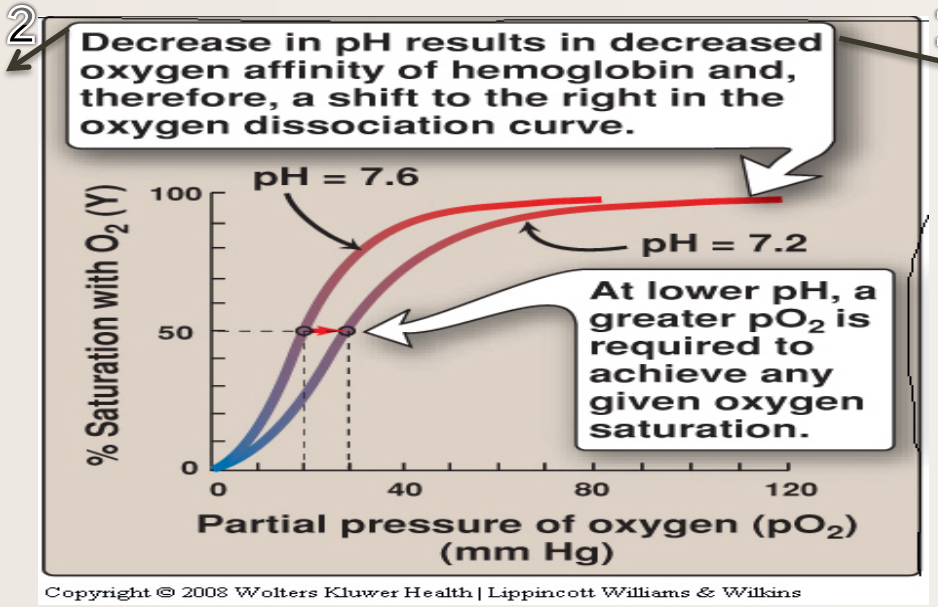
Effect of pH and pCO2 on:

- Oxygenation of Hb in the lungs
- Deoxygenation of Hb in tissues

Tissues have lower pH (acidic) than lungs due to proton generation:

$CO_2 + H_20 \rightarrow HCO_3^- + H^+$

Protons reduce O_2 affinity of Hb
=> Shift to the right



The free Hb binds to two protons.

Protons are released and react with HCO^{3-} to form CO_2 gas

($HCO_3^- + H^+ \rightarrow CO_2 + H_20$)

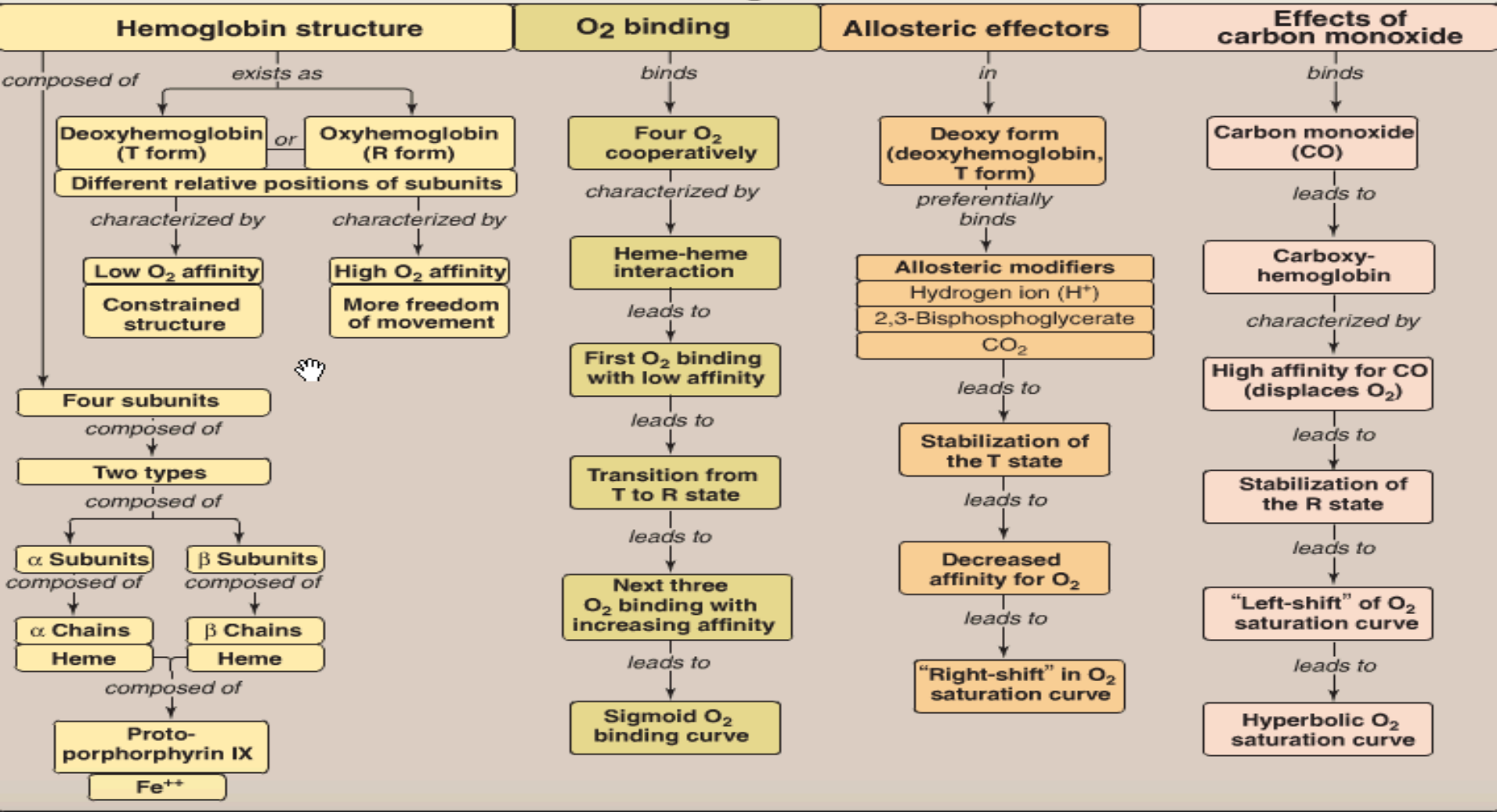
The proton-poor Hb now has greater affinity for O_2 (in lungs)

Abnormal hemoglobin:

Unable to transport O_2 due to abnormal structure

Carboxy-Hb:	Met-Hb:	Sulf-HB:
CO replaces O_2 and binds 200X tighter than O_2 (in smokers)	Contains oxidized Fe^{3+} (~2%) that cannot carry O_2	Forms due to high sulfur levels in blood (irreversible reaction)

Hemoglobin


Hemoglobin structure
composed of
exists as
Deoxyhemoglobin (T form)
or
Oxyhemoglobin (R form)
Different relative positions of subunits
characterized by
Low O_2 affinity
Constrained structure
characterized by
High O_2 affinity
More freedom of movement
Four subunits
composed of
Two types
composed of
α Subunits
β Subunits
composed of
composed of
α Chains
Heme
β Chains
Heme
composed of
Proto-porphorphyrin IX
Fe^{++}
O_2 binding
binds
Four O_2 cooperatively
characterized by
Heme-heme interaction
leads to
First O_2 binding with low affinity
leads to
Transition from T to R state
leads to
Next three O_2 binding with increasing affinity
leads to
Sigmoid O_2 binding curve
Allosteric effectors
in
Deoxy form (deoxyhemoglobin, T form)
preferentially binds
Allosteric modifiers
Hydrogen ion (H^+)
2,3-Bisphosphoglycerate
CO_2
leads to
Stabilization of the T state
leads to
Decreased affinity for O_2
leads to
"Right-shift" in O_2 saturation curve
Effects of carbon monoxide
binds
Carbon monoxide (CO)
leads to
Carboxy-hemoglobin
characterized by
High affinity for CO (displaces O_2)
leads to
Stabilization of the R state
leads to
"Left-shift" of O_2 saturation curve
leads to
Hyperbolic O_2 saturation curve

1) The form of Iron that is bound to hemoglobin is:
A- Ferric iron
B- Ferrous iron
C- Ferritin
D- All of them

2) Which ONE of the following statements is true about the T-form of hemoglobin :
A- Relaxed-form
B- Oxygenated-form of Hb
C- Have freedom of movement.
D- Low oxygen affinity

3) HbA2 is composed of :
A- two α and two γ chains
B- two α and two δ globin chains
C- four α globin chains
D-Two α and two β chains

4) Which ONE of the following cause shift of O_2 dissociation curve to the left
A- Increased $H^{|+}$
B- High PH
C- Increased 2,3 BPG
D- Increased P_{50}

5) 2,3 bisphosphoglycerate binds to Hb in the form of:
A- Oxyhemoglobin
B- Deoxy-hemoglobin
C-Fetal Hb
D- None of them

6) What do we expect to see in the CBC of a patient from ABHA :
A- High levels of hemoglobin
B-Low O_2 affinity
C- Decreased RBCs
D- Low levels of 2,3 bisphosphoglycerate

7) Which ONE of the following replaces 02 and binds 200X tighter than 02
A-Met hemoglobin
B- Carboxy-hemoglobin
C- Sulf-hemoglobin
D- Fetal hemoglobin

8) Which of the following result from Bohr effect:
A- Removes insoluble CO2 from blood stream
B- Produces soluble bicarbonate
C- Produce CO2 to the blood stream
D- A&B

Answers: 1) B 2) D 3) B 4) B 5) B 6) A 7) B 8) D

Thank You!

Done by:

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