Lecture :2.....

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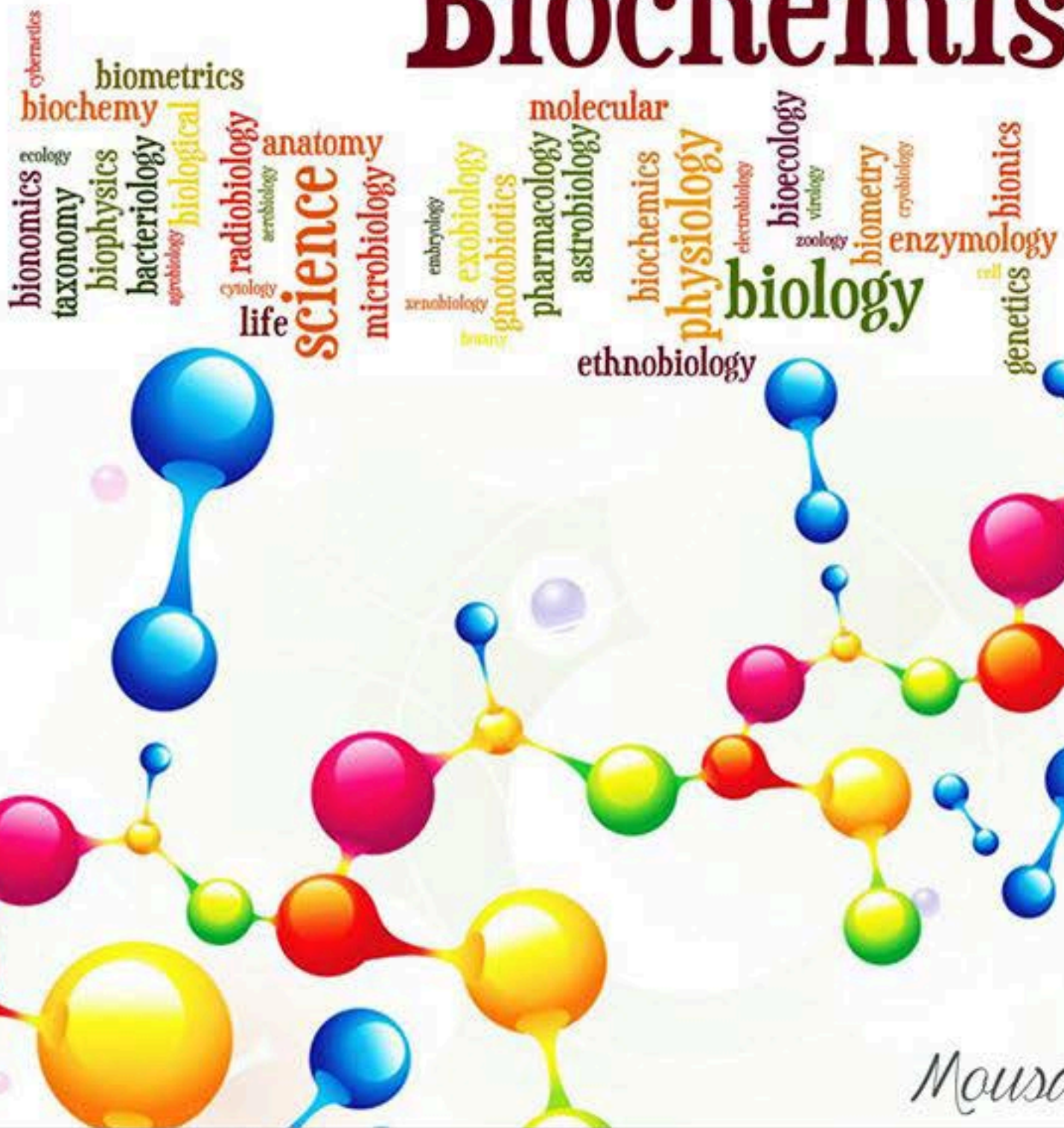
Medical Committee
The University of Jordan

# Biochemistry



# Plasma Proteins & Polymorphism

AssalmuAleikom, first of all congratulations for making it to the second year. This is an easy and short lecture and I did my best in making it coherent and even easier to study. Leggo.

From the previous lecture:

In other words: you should be familiar with the following:

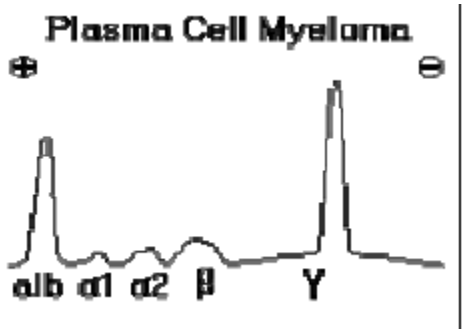
We talked yesterday what plasma is and how to get it from a blood sample by hematocrit, and what the components of plasma are (water and solid organic and inorganic contents), how many proteins we have and the normal concentration of plasma proteins as albumin, and also about the techniques used to extract them, and the synthesis and modifications (mainly glycosylation) of main plasma proteins we'll talk about, and also about different densitometer representations for normal electrophoresis; the highest is the albumin.

There are also three abnormal cases we should be familiar with related to three different problems; the kidney, the liver or the plasma cells.

If the problem is affecting the **liver** then most plasma proteins are affected except immunoglobulin (gamma proteins) ; because they are not produced by the liver.

If the problem is in the **kidney** and we have renal failure, then the kidney is not being able to retain proteins within the blood and they will be excreted in urine. Consequently, their concentration will be less in the blood.

The third thing is having a problem affecting **plasma cells**, mainly cancer called plasma cell myeloma. It would increase the production of immunoglobulin, much higher than the production of any other plasma proteins including albumin. So as a result, the peak of immunoglobulin would be much higher and sharper.




## ❖ Plasma Proteins & Polymorphism: #NewLecture

To start with, what is polymorphism?

It's a genetic mutation affecting the properties of protein producing different forms of proteins & none of the new forms is rare (more than 1%). Sometimes it's not a disease and do nothing harmful like the color of the eyes and ABO blood groups; in others it creates a disease.

The mutation is inherited as a mendelian trait.

Most plasma proteins are polymorphic proteins, what does this mean? They have different forms and each one is found more than 1% in the population.

Examples for polymorphic plasma proteins: α1-antitrypsin, haptoglobin, transferrin, ceruloplasmin, and immunoglobulin.

-Albumin is controversial.

There are two ways to separate polymorphic proteins, either by electrophoresis (used to detect sickle blood disease) which depends on the molecular weight of the protein, or by isoelectric focusing, by putting proteins in a gel-like structure with different pH degrees, each protein would move until it reaches its isoelectric point (remember: isoelectric point is the point at which protein's total charge is zero) so basically this technique depends on the net charge of the protein.

Note :

Polymorphic proteins have the same name , but different properities.

## ❖ Functions of plasma proteins:

There are both general and specific functions for plasma proteins.

**Specific functions:**

- Rennin (which is a hormone ) for example is secreted by kidneys and transported to lungs. It converts angiotensin 2 to angiotensin 1 causing the constriction of blood vessels increasing blood pressure.

- Lipases is responsible of breaking lipids.
- Antibodies (immunoglobulin) responsible for humoral immunity (coming through molecules).
- Blood coagulation factors.
- Hormonal (Erythropoietin)
- Transport proteins (Transferrin which transports iron, Thyroxin binding globulin, Apoliprotein that transport lipids.)

Note :
Cellular immunity : through cells themselves .
Humoral immunity: through macromolecules , like antibodies .

**General functions:**

- A nutritive role; they can be degraded giving us energy.
- Maintenance of blood pH (by the free charges of NH3+ & COO-) working as buffers. This is considered as an amphoteric property.
- Contributes to blood viscosity; most proteins are negatively charged so they would make bonds with water making it viscous.
- Maintenance of blood osmotic pressure; blood osmotic pressure A.K.A. oncotic pressure, in blood we have :
  1- Blood pressure: the hydrostatic pressure, results from the force of the fluid within the vascular system pushing the walls of the veins or arteries, and results in getting water from inside of the vascular system to the outside (tissues).
  2- Osmotic pressure: Proteins are water soluble so they solve in plasma's water and help in retaining water (get water inside

the vascular system). And thus, opposing the hydrostatic pressure , and it is not against the walls .

## Starling Forces:

In capillaries, we have arterial end and venous end. The hydrostatic pressure in the arterial end is about 40 mmHg *(it varies from a tissue to another)* but the oncotic pressure is constant because it's a property for proteins and it's 25 mmHg and it helps to get the water in vessels (from tissues to the inside of the vessels ) at the **arterial** side: the hydrostatic pressure tries to get water to the tissue so the net result is 15 mmHg (40-25=15) to the outside.

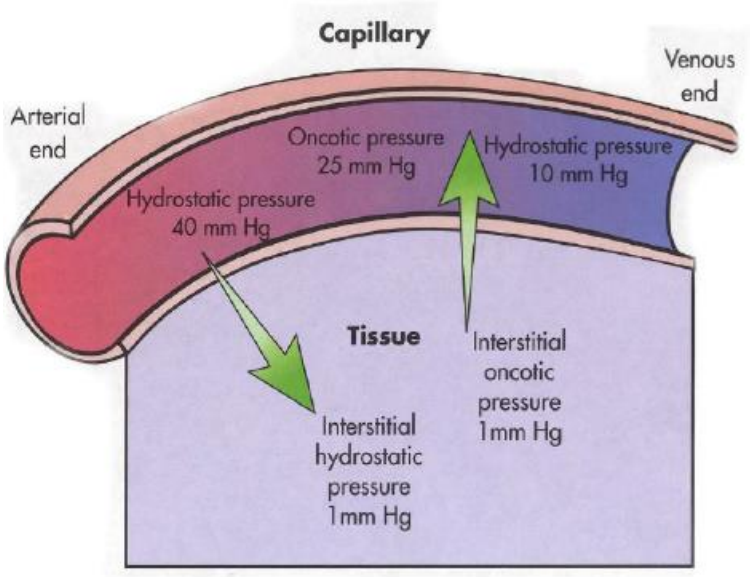
At the **venous** side, everything is opposite, that's why we have exchanging of the materials there. The hydrostatic pressure is lower (10 mmHg), as a result the net pressure is 15 mmHg to the inside (10-25=-15).

So, at the arterial side … nutrients move from the blood to the tissue ( force is to the outside of the vascular system ) . but at the venous side …. Wastes move from tissues to veins ( force is to the inside )

**What happens if the content of plasma proteins decreased?**

The pressure of plasma proteins (oncotic pressure) would become lower than 25 , assume it becomes 10. At the artrial side, the net pressure will become 30 (40-10) and thus more fluid will

get out. On the venous side, the net pressure would be zero. So overall, more fluids will get into the tissues causing edema.




## Acute phase proteins

Proteins increase in their concentration either a little bit or dramatically due to acute or chronic inflammation or cancer.

Examples for acute phase proteins: c-reactive protein (found in the Beta band of the electrophoresis), alpha 1- antitrypsin, haptoglobin (alpha 2 band ) & fibrinogen (blood clotting factor).

Proteins that do not increase but may even decrease in cases of acute or chronic inflammation and cancer are prealbumin, albumin & transferrin. (expect a question : one of the following is not an acute phase protein )

The question is: why/how do they increase in concentration?

Cytokines are molecules secreted by cells to change the activity of the gene, increasing the gene transcription and translation.

Interleukin 1 is stimulated by nuclear factor kappa-B (NFkB).

NFkP translocates from the cytosol where it is inactive to the nucleus in order to become active.

So

NFkB stimulates interleukin 1 -> increase in gene transcription -> increase in translation -> increase in concentration dramatically.

- **Albumin**

Albumin is the major plasma protein with the molecular weight of 69 kDa and half-life of 20 days. It's concentration is 3.6-5 g/dl and composes 60% of plasma proteins. Its shape is ellipsoidal not elongated. It increases the viscosity in the blood but not very high so that it won't prevent the flow of the blood .

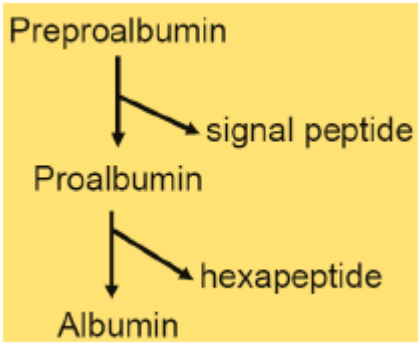
It's the main contributor to the osmotic pressure due to its high concentration.

12 grams of albumin synthesized by the **liver** per day. 25% of the liver's protein synthesis is albumin. If albumin's concentration decreases, it can be used to detect problems in liver. (liver function test).

It is first produced as preproalbumin,

Then the signal peptide detaches producing

Proalbumin, then 6 aminoacids (hexapeptide) is



cleaved by proteolysis. Then albumin is formed.

(it goes through posttranslation modifications)

Albumin consists of 3 domains.

Most of the drugs binds to albumin.

It is a one polypeptide chain. Thus, it has 3° structure, not 4°. It is composed of 585 amino acids and 17 disulfide bonds. (numbers are not important).

## Albumin binding capacity

- Free fatty acids (FFA)
- Certain steroid hormones
- Bilirubin
- Plasma free tryptophan
- Metals (Ca, Copper and heavy metals)
- Drugs: sulfonamides, penicillin G, dicumoral, aspirin
  Drug-drug interactions: there are many drugs that binds to the same site in the albumin, and they could have the same or different affinity. So, increasing the concentration of one of them will decrease the affinity and the binding capacity for the other one to the albumin and vice versa, so you must be careful.

  ➔ **Bilirubin and aspirin** bind to the same site in the albumin. If we gave an infant Aspirin while his neural cells are developing (high bilirubin concentration is required). The infant's blood-brain barrier is not fully formed, so if we gave him aspirin, it

would result in increasing the concentration of **free bilirubin**, and it would exit to the brain and accumulate there (kernicterus) causing mental retardation.

➔ **Phenytoin-dicoumoral** interaction:

Phenytoin is used to treat muscle spasm (anti _epileptic drug ), while dicoumoral is a natural anti-coagulant. So if phenytoin is highly taken, it would increase the concentration of free dicoumoral. Thus, causing bleeding easily when injured and bleeding will take more time to stop.

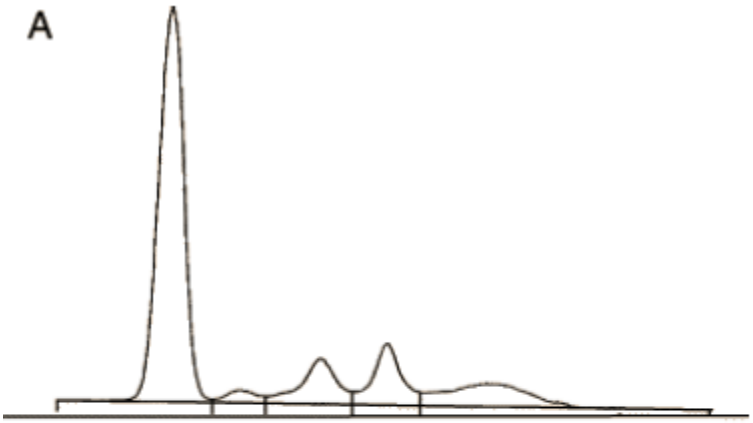
## Analbuminemia

Analbuminemia is the deficiency of albumin causing edema (expected) due to defects in the starling forces. It may be caused from mutations in gene transcription decreasing albumin production.

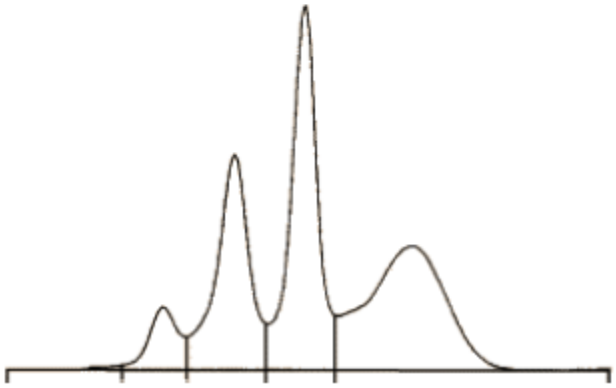
If there is no more albumin in the blood, we expect high edema, but surprisingly, only moderate edema occurs, ***why?***

The absence of albumin causes the increasing of other proteins retaining osmotic pressure. So, specific functions of albumin would be lost but the osmotic pressure would be retained to some extent, because it is a general function of plasma proteins .

Normal




Analbuminenia




## Hypoalbiminemia:

Hypoalbinemia occurs when albumin is produced less than 2g/dl, resulting in generalized edema and abdominal edema (ascites).

It may happens when we have a problem in the liver

## Hyperalbuminemia:

Such thing exists, but it's not real; albumin cannot be over produced. So when does it occur? When the volume of the solvent decreases (dehydration), automatically causing the albumin's concentration to increase.

Treatment? Hydration.

## Prealbumin (Transthyretin)

Smaller than albumin and presents in lower concentrations. In electrophoresis, it moves faster but it doesn't appear in the graph due to its low concentration.

It is called pre because it moves ahead albumin in electrophoresis

Its peak is small as conc. is small.

It's a glycoprotein (unlike the albumnin) with 0.5% carbohydrates.

Its molecular weight is 62 (close to that of albumin's 69)

Its half life is short 2 days. (albumin's is 20 days) this short half-life helps in detecting liver's functions faster.

Main function: carrying T3 and T4 (thyroxin)

| Difference | Prealbumin | Albumin |
|---|---|---|
| glycoprotein | yes | no |
| Molecular weight | 62 KDa | 69 kDa |
| Concentration | low | high |
| Half-life | 2 days | 20 days |

## Globulins

| α1-globulins | α2- globulins | β- globulins | γ-globulins |
|---|---|---|---|
| ▪α1-antitrypsin<br>▪α1-fetoprotein<br>▪α1- acid glycoprotein<br>▪Retinol binding protein | ▪Ceruloplasmin<br>▪Haptoglobin<br>▪α2-macroglobulin | ▪CRP<br>▪Transferrin<br>▪Hemopexin<br>▪β2-microglobulin | ▪IGG<br>▪IGA<br>▪IGM<br>▪IGD<br>▪IGE |

## α 1 antitrypsin

AKA α1-Antiproteinase, it inhibit trypsin (which is a protease),and also it inhibits other protease such as elastase; when elastase levels are high, it would break down elastin found mainly in lungs, so the antitrypsin would prevent such thing to occur.

Elastase is produced by macrophages (found highly at inflammation sites, as they are immune cells )

α 1 antitrypsin composes 90% of the alpha 1 bands.

It has many polymorphic forms, the most common form is MM. it can occur in S ,Z and F forms or mixed forms (contains both M and Z for example) . Copies are named haphazardly .

**MM** is the most common and the best, it has similar functions to that of the original α1-antitrypsin.

At least one copy of the M type must be found in order for the protein to work sufficiently.

**ZZ** is the worst form and doesn't work efficiently.

It's an acute phase protein, so in cases of cancer and inflammation, its concentrations would be high.

MM > M_ > ZZ

(normal) (abnormal)

*"It is our choices that show what we truly are far more than our abilities."* -The Great Albus Dumbledore