University of Jordan
Faculty of Medicine

Medical Committee
The University of Jordan

Biochemistry

● Sheet ○ Slides

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Title: Functions of Plasma

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Functions of Plasma protein

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1. General functions

These functions are applied to all plasma proteins and they are:

- **nutritive role:**

  1. Plasma proteins participate in nutrition through transporting nutrients through the blood.
  2.because they are proteins, they can be broken down into amino acids which give acetyl-coA that goes into the Krebs cycle that will eventually give ATP.

- **Maintenance of blood pH (amphoteric property):**

  charged amino acids help in maintaining the ph of the blood through reacting with H+ (the negative charged A.A take H+, and the positive charged A.A give H+).
  If variation happens in the ph of the solution, the protein will work as a source for the buffering system with the help of the main buffering system in the blood which is the bicarbonate system.

- **Contributes to blood viscosity:**

  Any material that is soluble in water, makes bond with the atoms in the water molecule and these reactions and bonds will reduce the movement of water therefore the solution will become more viscous (more bonds → less movement).
  Proteins that are polar and have negatively and positively charged amino acids can make bonds with water in the plasma so the blood will be more viscous.

- **Maintenance of blood osmotic pressure:**
  - ❖ Osmotic pressure is the pressure that is excreted by the particles that are found in the solution which will absorb water from the outside to the inside (water inflow) in order to reach equilibrium and reduce the concentration.

  In the same way proteins that are in the vascular system (plasma) increase the inflow of water into the vascular system.

2. Specific functions

They are protein specific (according to the protein).

- **Enzymes (e.g. rennin, coagulation factors, lipases):**
  - ❖ Rennin is an enzyme that is excreted by the kidney and goes to the lungs and changes agnotensin1 to produce a2 which is responsible for the contraction of the vessels in order to increase the blood pressure.
  - ❖ Coagulation factors work as enzymes to break other coagulation factors

- ❖ Lipases are enzymes that break down lipids

- **Humoral immunity (immunoglobulins)**

  We get humoral immunity from protein Antibodies (immunoglobulins).

- **Hormonal (Erythropoietin)**

  Some of the plasma proteins work as hormones such as Erythropoietin that give the message to bone marrow to increase the synthesis of blood cells .

- **Transport proteins (Transferrin, Thyroxine binding globulin, Apolipoprotein)**
  - Thyroxine binding globulins: globulins that transfer thyroxine
  - Apolipoproteins: proteins that are responsible for transferring lipids through the plasma.
- **Blood coagulation factors**

  Are protein factors that assist in the clotting of the blood.

Starling forces

-The forces which contribute to the delivery of nutrients and water to the tissues and taking back wastes and water from the tissues into the blood(allowing the flow of fluid and nutrients across the capillary wall).

-Blood pressure is the force that is exerted by the fluids on the walls of the vessels forcing water to move to the outside of the vascular system.

-At the artierial end the 40mmgh pressure is pushing the water outwards and the 25 mmhg is pushing the water inward which will eventually end in 15 mmhg pushing the water and nutrients outwards to the tissues.However on the venous side the pressure is 10mmhg to the oustside and the pressure exerted by the protiens is also 25 mmhg to the insde so the net will be 15 mmhg to the inside taking up water and wastes

if there is a problem in proteins (deficiency) the pressure that is applied by the proteins will be less (lets say 15 mmhg) so the net pressure on the arterial side is 25mmhg to the outside which means more water out however the pressure on the venous side will be 5mmhg to the inside then u will start collecting water in your tissues (edema)

Arterial end (40mmhg) Pushing water to the outside	Oncotic pressure (25mmhg) Pushing water to the inside	The net flow is 15mmhg to outside (giving water and nutrients to the tissues)
Venous end (10 mmHg) Pushing water to the outside	Oncotic pressure (25mmHg) Pushing water to the inside	The net is also 15 but to the inside (taking back water with wastes)

Acute -phase proteins

Acute phase proteins such as C-reactive protein (CRP), α1 -antitrypsin, haptoglobin, & fibrinogen are class of proteins whose plasma concentration either increase or decrease in response to acute, chronic inflammations and cancer.

In these cases some of the plasma proteins' concentration increase from (0.5 – 1000 folds).

-negative acute-phase proteins: are proteins that do not increase in concentration upon acute, chronic inflammations and cancer cases such as prealbumin, albumin, transferrin) sometimes their concentration decrease.

QUESTION: which of the following proteins goes through a decrease in its concentration upon a chronic inflammation? The right answer can be any of these 3 → prealbumin, albumin, and transferrin.

QUESTION: what is the role of CRP (C-reactive protein) or (classic complement pathway) during inflammation? Increase in CRP is an indicator for tissue injury or atherosclerosis

QUESTION: what is alpha 1 antitrypsin? It's a protein that inhibits the function of certain proteases such as elastase,and trypsin).

-Cytokines are intermediates that are produced by the cell in cases of pathology and have many types such as Interleukin-1 (IL-1).

- Nuclear factor kappa-B (NFKB) is a transcription factor that binds DNA and starts to synthesis more of the mRNA and then translation in order to increase the synthesis of proteins.

PROCESS: Interleukin-1 (IL-1) activates nuclear factor kappa-B (NFKB) which is a transcription protein that goes to the genes that synthesis C-reactive protein (CRP), α1 -antitrypsin, haptoglobin, & fibrinogen.

Albumin

- Is produced by the liver in a quantity of 12g per day and 25% of what liver makes per day of protein is albumin.

- From the concentration of the albumin in the blood you can tell if the liver is functioning well or not because if we have little concentration of albumin this indicates that there is a problem in the liver and so it can act as a liver function test.

- Signal peptide will split from the whole protein by a Proteases once it excites from the hepatic cells after that 6 amino acids will split also from the protein and then another protolytic process will occur (enzyme will degraded it) which results in the final shape of albumin that has 3 main domains (domain 1,2 and 3) .

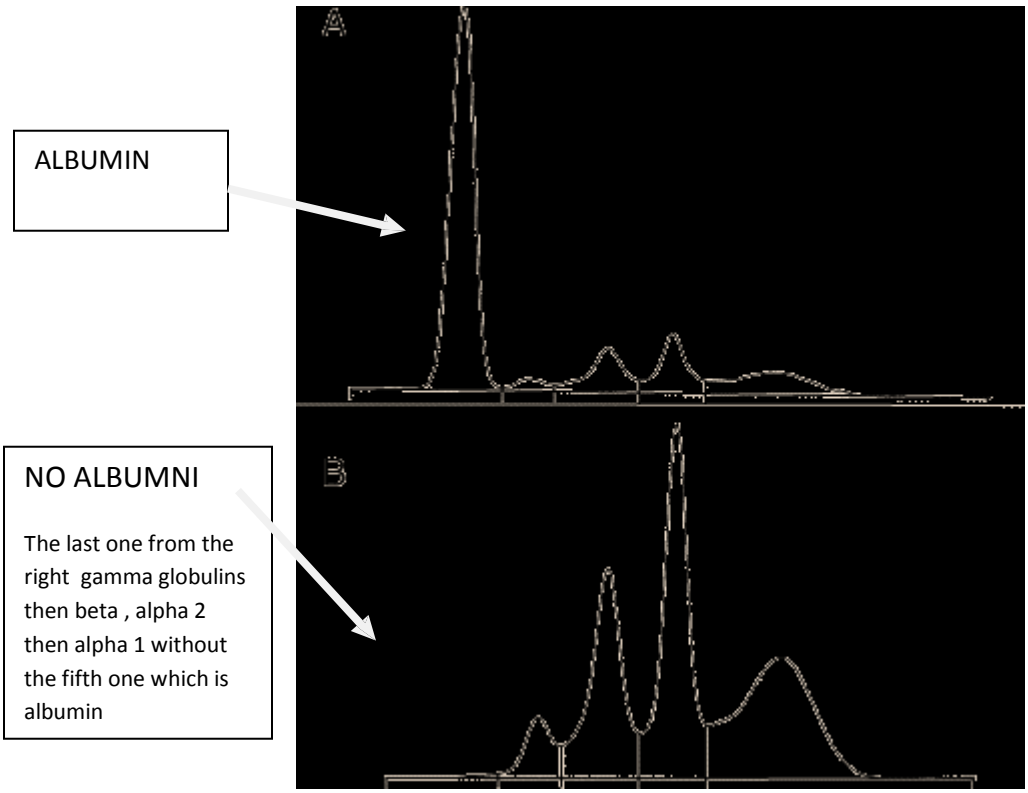
- A domain is a special secondary structure that indicates for the same function in any protein you find it in and is the site where drugs bind to the albumin through.
    - Albumin is a no polypeptide chain so it doesn't have a quaternary structure.
    - It has also around 17 disulfide bonds that indicates that its structure is fixed and unable to change due to its various functions and in order to keep the protein in its form we need disulfide bonds) .
    - Proteases subdivide albumin into 3 domains.
    - Ellipsoidal shape (viscosity) vs. fibrinogen.
    - Anionic at pH 7.4 with 20 negative charges.
- Albumin has a very high binding capacity that can bind to a variety of ligands such as
    - Free fatty acids (FFA)
    - Certain steroid hormones
    - Bilirubin
    - Plasma tryptophan
    - Metals: Calcium, copper and heavy metals like mercury
    - Drugs: sulfonamides, penicillin G, dicumarol (مميع دم) , aspirin (drug-drug interaction)

Diseases related to albumin

1. analbuminia (no albumin)

The graph (A) is a normal interpretation of gel electrophoresis on the densitometer.

The graph (B) is an analbuminemia case which has no albumin in it.



If a patient is diagnosed with analbuminemia he won't suffer from edema because when a person is going through a lack in albumin the proteins will be much less and might cause edema however there will be no edema because the body of the patient reacts by increasing other plasma proteins (beta alpha and gamma) to cover for the deficiency in the osmotic pressure caused by the albumin.

2. Hypoalbiminemia: decrease in albumin from (3.5-5 g/dl) to 2 g/dl in the blood which will cause edema.

3. Hyperalminiemia: increase in concentration of albumin in the plasma (a rare case) it happens due to dehydrations that cause an increase in the protein. So, we hydrate the patient to assure a normal concentration of albumin in his plasma.

4. Drug-drug interaction:

Different drugs bind to albumin, so if given two drugs that can bind to the same site in albumin these drugs will compete to the site and the one with higher affinity to albumin will bind leaving the other free in the plasma causing increasing the affect of the free drug.

- Bilirubin toxicity (aspirin is a competitive ligand):

  -Blood brain barrier is not complete in children (not closed yet)
  - Billirubin is known in children to be high concentrated
  - Bilirubin is one of the heme metabolites when the heme is degraded one of the metabolites is bilirubin.

  Why aspirin if not allowed for kids?
  Aspirin and bilrubin have the same binding site for the albumin so if the child is given aspirin, aspirin will disassociate bilrubin from the albumin which will cause an increase in the concentration of free bilirubin inside the blood and will start crossing the blood brain barrier and start to be collected inside the brain causing kernicterus which is the presence of bilirubin inside the brain and since the brain is not mature, mental retardation might occur.

- Phenytoin-dicoumerol interaction is an anticonvulsive drug (مضاد للتشنجات) that have the same site of binding as the dicoumarol which is an anticoagulant (مميع دم) which might cause drug – drug interactions.

Prealbumin

-Is a protein that can appear on the gel and migrate before albumin but because it is smaller than albumin and has a weak band. However albumin is the fastest in migration towards the positive electrode (the smallest and most negative protein) BUT we consider that it appears first on the gel (the doctor said that the prealbumin appears first but it won't be on the test and we must consider that the albumin is the first to appear so the prealbumin won't be on the test as the first to migrate).

Prealbumin:
- has a molecular weight of 62 kda and has a very low concentration in blood (0.25g/l).
-having a half life of 2 days makes it good as a sensitive indicator of disease or poor protein nutrition.
-it is synthesized in the liver. So, if there is a problem in the liver albumin allows us to diagnose this problem but only after 20 days due to its long half life. However we can test for liver function in less time USING PREALBUMIN because it has a shorter half life so it is a sensitive indicator for liver function much more than albumin.

-And it is a glycoprotein while albumin is not glycosylated
-Prealbumin is also called transthyrotin because its main function is binding T3 "thyroxine" and T4 (thyroid hormones)

Globulins

- Alpha 1-antitrypsin is the main constituent of α1-globulins bands.
- It is called so because it inhibits trypsin.
- It inhibits the work of trypsin & trypsin-like enzymes such as (elastase) which is a protease that degrade elastin .So it won't function right (elastase is excreted from immune cells especially macrophages to fight the proteins in the microbes)
  Elastin is most abundant in the lungs in the elastic tissue. In case of inflammation in the lungs the macrophages will secrete elastase to fight the infection in the lungs
  Antitrypsin will then neutralize the action of elastin to prevent the degradation of elastin in the lungs...when it is deficient (antitrypsin) or does not function well then the lung tissue will be ruined and since the lungs consist of alveoli which increase the surface area for gas exchange, once u break down these walls between alveoli then you are decreasing the surface area but increasing the volume of the lung (emphysema (انتفاخ الرئة): breaking down the walls between the alveoli resulting in increasing the chest size and decreasing the ability to exchange gases and breath)
- 90% of the alpha band consist of alpha1 anti trypsin it is a polymorphic protein.

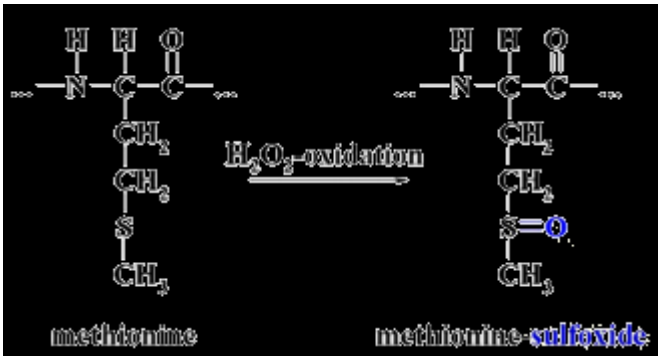
Alpha 1 anti trypsin has many forms; the regular one and most common one form two alleles is MM form and the worst one is the ZZ form (each allele is giving antitrypsin in the z form)

Causes of emphysema:
Either genetics (a person born with deficient enzyme) or acquired such as smokers, Emphysema that is due to acquired reasons that can only be developed in people with ZZ or SZ forms but all other types won't be affected)

ZZ has only (10%) capacity to fight trypsin or proteases is much less than the capacity of MM form (100%), so lucky people are MM. "can smoke for ever with no problems"

People are different from each other in forms of alpha 1 antitrypsin, lucky people MM, unlucky people ZZ who will develop emphysema for sure.
People with ZZ form are more susceptible to emphysema because there is nothing to fight the elastases.

Smoking is irritant to the tissues so in continuous smoking u r making chronic inflammation in the lung and irritating it which will cause high concentration of immune cells into the lungs always producing elastase that will exceed the amount of antitrypsin in the lungs therefore emphysema will start.
Antitrypsin binds to the proteases in specific methionin residue that is an amino acid inside the antitrypsin... smoking will oxidize this methionin so when it oxidized it will not be able to connect to the proteases .smoking oxidize methionin into methionin sulfoxide which will inhibit alpha one antitrypsin .so smoking in person with zz form or sz form or emphysema is devastating because you are then omitting the function of alpha one antitrypsin.



Alpha one is produced in the liver... it has a loop in its shape from amino acids and it also has a beta sheet... the loop can bind this beta sheet in zz form... if u have zz polymorphism the loop can be attached to this beta sheet in another molecule so it will produce a complex and start aggregating inside the liver so it will affect the cells and kill them so it will result in fibrosis which will result In cirrhosis (تشمع الكبد) so 10%of people with ZZ form will eventually have cirrhosis

(DEAR COLLEGUES THE LECTURE WAS LONG BUT I HAVE NOTHING TO DO WITH IT I ONLY WROTE THE NOTES THAT THE DOCOTR SAID THAT WERE NOT MENTIONED IN THE SLIDES SO PLEASE REFER TO THE SLIDE ☺)