SHEET NO.

2

METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2017

SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

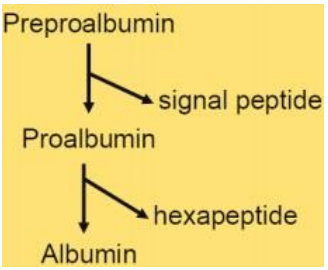
DOCTOR : Dr.Nafeth

We are back again, Get your coffee and Let's start..

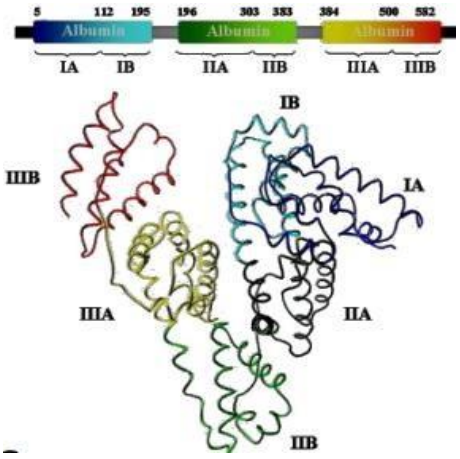
Now we will talk about specific functions of proteins.

A) Albumin

- The major protein in blood plasma
- The main contributor to the osmotic pressure (75-80%)
- Synthesized as a preproprotein
- Synthesized from liver 12g/day (25% of total liver protein products is albumin)



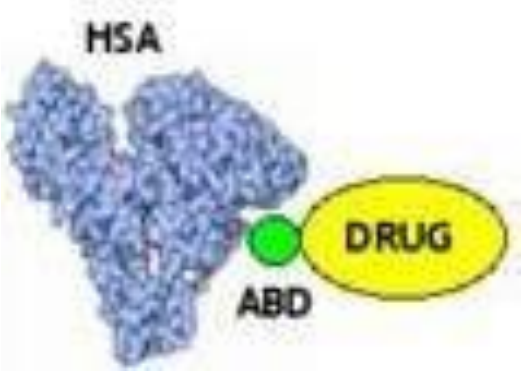
- Albumin is used in liver function test (increase or decrease in albumin means that there is a problem in liver)
- MW= 69 kDa, half-life = 20 days.
- One polypeptide chain, 585 amino acids, 17 disulfide bonds.
- Proteases subdivide albumin into 3 domains (1A 1B, 2A 2B, 3A 3B)



- Anionic at pH 7.4 with 20 negative charges
- Ellipsoidal shape vs. fibrinogen (elongated)

- The fibrinogen shape exposes more negative charges to water thus more viscosity (that's why albumin is not elongated)
- Fibrinogen elongated shape increases blood viscosity in injuries to stop bleeding.
- **Always remember** that albumin is the major transporter for almost everything in blood by binding to ABD (albumin binding domain), **it transports:**

  Free fattyacids (FFA) Certain steroid hormones
  Bilirubin (from broken heme)
  Plasma tryptophan
  Metals: Calcium, copper and heavy metals
  Drugs: sulfonamides, penicillin G, dicoumarol, aspirin.



Since almost all drugs bind on the same protein (albumin), there is a chance of two drugs trying to bind on the same point on albumin and they will compete by their affinities and concentrations (drug-drug interaction)

One drug will bind and the other will be free in plasma (the free drug is the active one) it will go to the tissues and react there, so you can't know its concentration, and this might be fatal.

CLINICAL DISORDERS

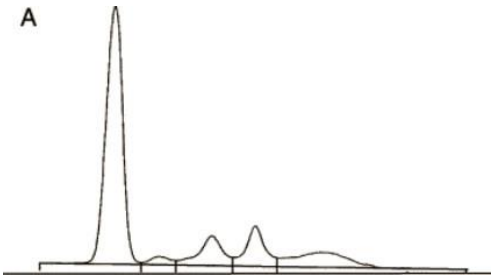
1) **Analbuminemia** (no albumin) a very **rare** condition.

- There are human cases of analbuminemia (rare)

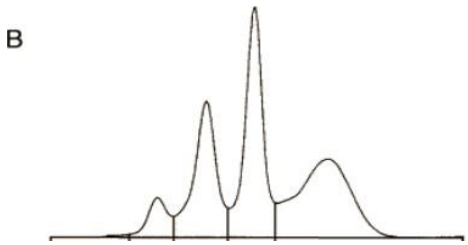
- Autosomal recessive inheritance

- One of the causes: a mutation that affects splicing

- Patients show moderate edema!!!



NORMAL



ANALBUMINEMIA

- This disorder absolutely causes edema, but it is not as severe as expected, because concentrations of other proteins have increased which compensates the decrease of albumin.
- Other proteins contribute to osmotic pressure too, so the loss in its value is not numerous.
- BUT it is life threating because these proteins can't do the **specific function** of albumin **(transporting food and waste)**.

2) Hypoalbuminemi: edema seen in conditions where albumin level in blood is less than 2 g/dl

- **Malnutrition (generalised edema)**
- **Nephrotic syndrome**
- **Cirrhosis (mainly ascites)**
- **Gastrointestinal loss**

- The normal albumin concentration is 3.5-5.5 g/dl
- When it is under 2g/dl, we have Hypoalbuminemia (aka hypoproteinemia) (because albumin is the main protein in plasma)
  This results in **EDEMA**

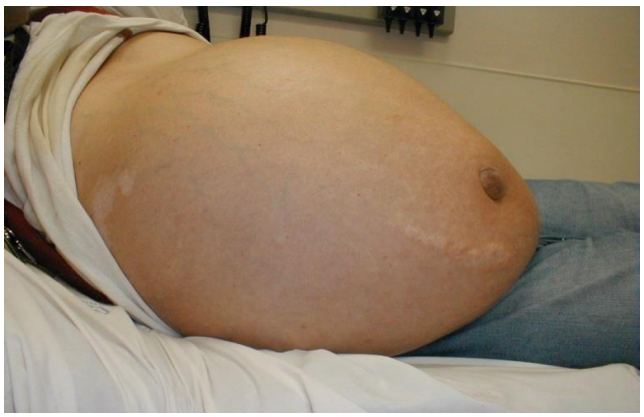
Edema could be generalized (in the whole body) or localized (mostly in the abdomen (**ASCITES**) depending on its cause

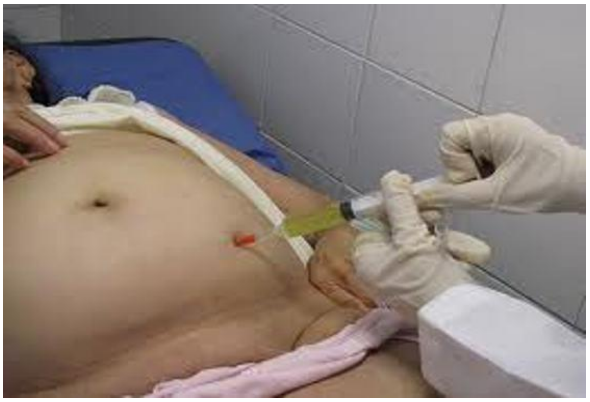
- Ascites (accumulation of fluids in the abdomen region) can be caused by liver cirrhosis (caused by drinking alcohol).
- When the cause is general (protein deficiency, starvation or famine) it will cause general EDEMA

This is treated by having a rough diet or by paracentesis (removing fluid from the abdominal cavity)

3) Hyperalbuminemia typically caused by dehydration, and some liver cancer cases. (this will affect a lot of proteins, not albumin only)

- What really happens is that water decreases (dehydration), so albumin has increased relative to water (pseudo increment), we call this a relative increase
- the simple solution is to drink water (hydration).





4) Bilirubin toxicity

- **Normally,** New born babies have high concentration of bilirubin (enzymes are not mature enough=broken heme), bilirubin binds to albumin till the body deals with it.
- So, in the first 7-10 days babies will have physiological jaundice in skin, eyes, tissues
- Parents are advised to expose their babies to sunlight to mature the enzymes and break the bilirubin.
- The blood brain barrier (border that separates circulating blood from the brain) is not mature yet and brain can't deal with bilirubin, so there shouldn't be bilirubin in the brain.
- Aspirin binds on the same spot where bilirubin binds (competitive ligand), so giving aspirin to a new-born will lead to high concentration of bilirubin thus entering the brain and amassing there. This is called **kernicterus** and it causes mental retardation.

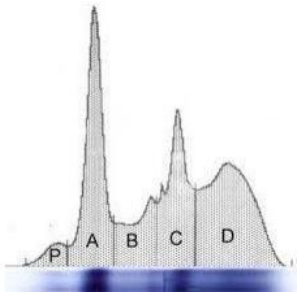
5) Phenytoin-dicoumarol interaction

Phenytoin is an anti-epileptic drug
Dicoumarol is an anti-coagulant

- When two drugs having high affinity to albumin are administered together, there may be competition for the available sites, with consequent displacement of one drug. such an effect may lead to clinically significant drug interactions
- So, they both bind on the same spot, you shouldn't take both of them at the same time

B) Prealbumin or Transthyretin (transport, thyroid gland t3, t4)

- a small glycoprotein (rich in tryptophan, 0.5% carbohydrates) **unlike** albumin. It is different from albumin and called prealbumin because it migrates a head of albumin (faster than albumin) in gel electrophoresis.
- MW=62 kDa, short half-life (only 2 days)
- Blood level is a lot lower than albumin (0.25 g/L).



- Its main function is carrying T3 and T4
- It is more sensitive indicator for liver function (albumin takes a lot of time (20 day) unlike prealbumin (2 days)).
  However, its concentration is much lower than albumin.

C) Globulins

1) α1- fetoprotein (alpha 1 band)

- Synthesized primarily by the fetal yolk sac and then by liver parenchymal cells.
- normally it is not produced in adults, abundant in very low levels.
- Level of α1-fetoprotein increases in: - -
  - Fetus and pregnant women Normally
  - Hepatoma & acute hepatitis (cancer in liver)

Functions of α1-fetoprotein:

- Protecting fetus from immunotypic attacks
- Modulating the growth of fetus
- Transporting compounds e.g. steroids
- Low level in pregnancy: increased risk of Down's syndrome.

2) Haptoglobin (HP)

- It is an acute phase reactant protein
- α2 glycoprotein (MW=90kDa), a tetramer (2α, 2β)
- 3 phenotypes (polymorphs):
  Hp 1-1→ α1, α1 + 2β
  Hp 2-1→ α1, α2 + 2β *notice that the 2 beta subunits are fixed*
  Hp 2-2 → α2, α2 + 2β

Some hemoglobin molecules leave RBCs to plasma, the function of **HP** is to bind to free hemoglobin (65 kDa) to **prevent** them from getting **filtrated in the kidneys** and leaving with urine, because even though our body can produce heme and globin, it can't produce **iron** (trace metal).

Half-life of free **HP** is 5 days, when it is bound to hemoglobin the half-life of the complex becomes 90 mins (MW=150 kDa), so the complex is transported and broken in the liver quickly, and iron is extracted from the complex.

In cases of hemolytic anemia (damaged RBC→ more hemoglobin in plasma) the level of **HP** decreases as it binds to the hemoglobin and gets broken in the liver.

3) Ceruloplasmin

- A copper containing glycoprotein (MW=160 kDa)
- Copper is very important; many enzymes use it, such as:
  oxidative phosphorylation enzymes (complex IV) for ATP production ferroxidase which oxidizes ferrous to ferric (transferrin) amine oxidase, copper dependent superoxidase dismutase, cytochrome oxidase, tyrosinase.
- It contains 6 atoms of copper
- Regulates copper level in **blood** (A protein called metallothionein regulates the **tissue** level of Cu) as it contains 90% of serum Cu (it **stores** Cu)
- The other 10% is bound to Albumin for **transport** (albumin has a lower affinity for Cu)
- Decreased levels in liver disease (it is produced in the liver) (Ex. Wilson's, autosomal recessive genetic disease)
- Ceruloplasmin concentration is decreased, less affinity for binding to the copper, this results in increment of Cu in plasma thus it enters tissues, the person's skin and eyes will become bronzy.

4) α 1 – antitrypsin (52 kDa)

As the name indicates it's part of the alpha-1 globulins, and its function is to neutralize (work against) trypsin & trypsin like enzymes (elastase).

Also known as antiproteinase was first discovered as an antagonist (neutralizer) for trypsin. Trypsin is a serine protease (hydrolase) that breaks down proteins. It was then found that antitrypsin neutralizes many proteases such as elastase, thus they named it: alpha 1 antiprotease.

It makes 90% of the alpha1- globulin band.

1- Elastase

a-Elastase breaks down elastin which Gives elasticity for tissues, elastic tissue can be found in the skin, blood vessels and lungs. In the lungs, elastin is found in the alveolar wall, so it facilitates inhalation and exhalation.

b-Elastase is produced by macrophages (WBC) during inflammation to break down the elastin of microorganism, but it will also affect the elastin in the alveoli walls. And this is when antitrypsin works. Antitrypsin breaks down elastase then the lung tissue is regenerated. So, Antitrypsin **prevents** excessive damage of tissues.

Note: A person will face a problem when there is either:

1) A deficiency of Alpha-1 antitrypsin.

2) Mutated alpha-1 antitrypsin (a copy of the protein that is different than the most common copy of this protein and is pathogenic, it has a slightly different structure, thus affecting its function)

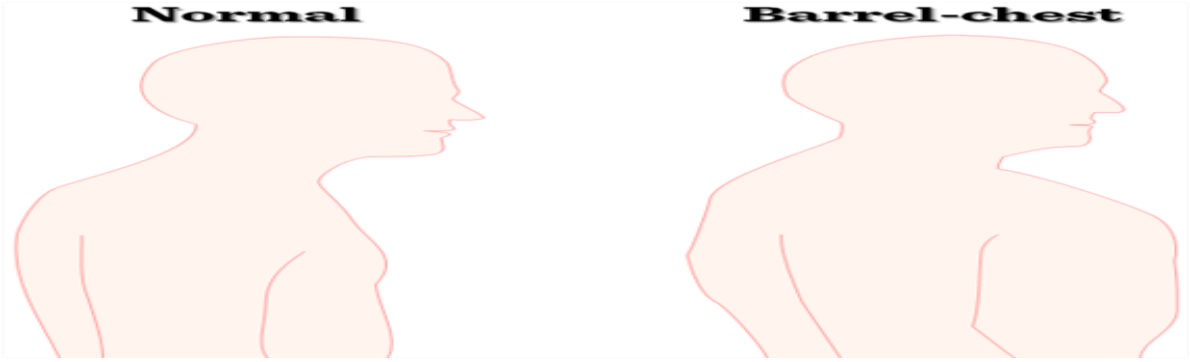
So, if a person has any of the above-mentioned cases, during inflammation, elastase will be released by macrophages and it will work on digesting elastin of the microorganism and elastin of the lungs, but since alpha-1 antitrypsin is not working well or not present in adequate amounts, elastase will continue to digest elastin in the lung causing problems.

Active elastase + α_1-AT → Inactive elastase: α_1-AT complex → No proteolysis of lung → No tissue damage

Active elastase + ↓ or no α_1-AT → Active elastase → Proteolysis of lung → Tissue damage

Note: Elastin is present in the alveoli walls which are present in large amounts in the lungs to increase surface area available for gas exchange and decrease the amount of air present in the lungs, so breaking these walls will decrease the surface area available for gas exchange and increase the amount of air in the lungs, so it would be harder to breathe; less gas exchange because of the decreased surface area, this case is called: **Emphysema.**

- **Emphysema** is characterized by having a barrel chest and difficulty in breathing.



2- Genetics and alpha1- antitrypsin

A- This plasma protein has at least 75 polymorphic forms.

B- Its alleles are: Pi^M Pi^S Pi^Z ,Pi^F .

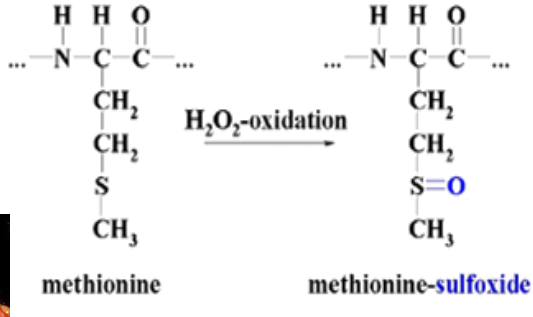
C- The phenotype **MM** is the most efficient and common one. ZZ and ZS are the weakest forms. ZZ is only **10% as effective** as MM. If one M allele is present, antitrypsin will be effective. So, having 2 copies other than M will cause a problem.

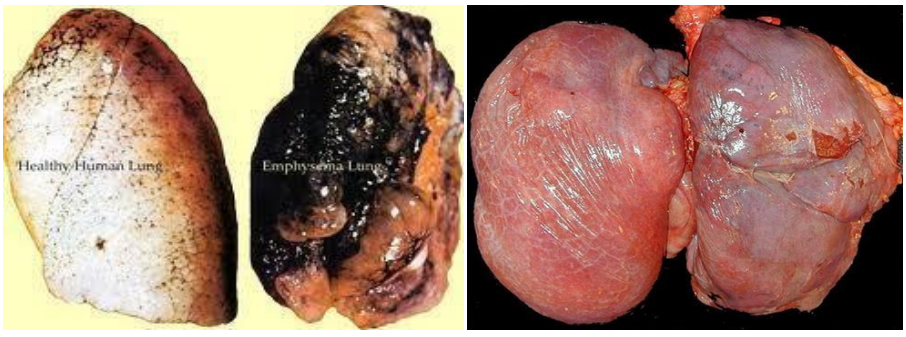
D- The presence of the **ZZ** phenotype can lead to **emphysema**.

E- **Smoking** is a major cause of emphysema. It causes chronic inflammation, so elastase is always produced by immune cells in the lungs,so, Lung tissue will be broken down. If a person smokes and has a ZZ phenotype, their case will be devastating.

F- **Smoking** can oxidize the **358th** amino acid **methionine** to **methionine sulfoxide** in antitrypsin. This residue is on the surface and supposed to bind to the elastase, so smoking will decrease the ability to bind drastically

- Methionine is usually not reactive because its sulfur is internal, but because smoking is harsh it can be oxidized.



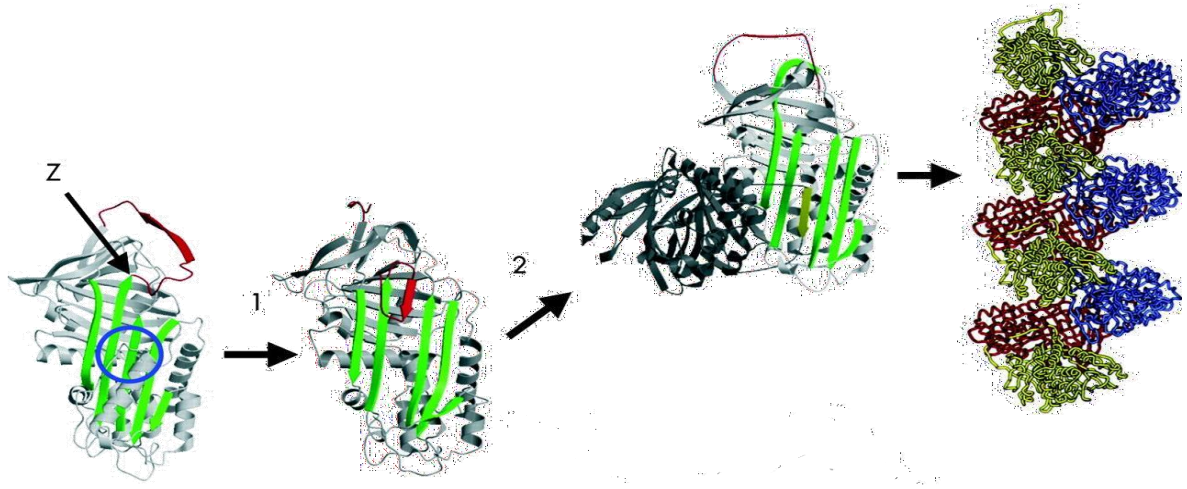


G- Liver

A) Alpha-1 antitrypsin is synthesized in the liver.

B) The ZZ phenotype antitrypsin has an extra loop and beta sheet. The beta sheet of an antitrypsin protein has high affinity towards the loop of another, so they will polymerize and form alpha-1 antitrypsin aggregates in the liver which can't leave and results in the killing of liver cells, and then leads to fibrosis then to cirrhosis of the liver.

C) 10% of people with ZZ antitrypsin have cirrhosis.



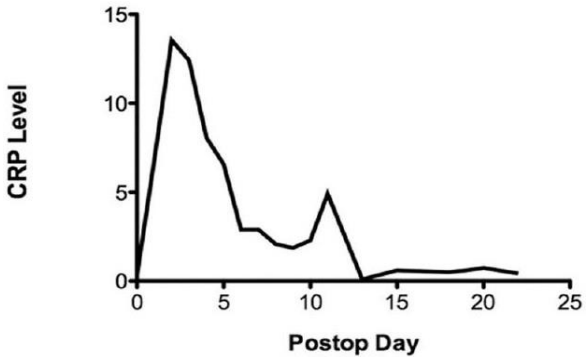
5) C Reactive Protein (CRP)

-When it was first discovered, it was found that it binds with the **C fraction** of the polysaccharide that is present in the cell wall of a type of bacteria called **pneumococci.**

-It is an **acute phase** protein. It is **undetectable** in healthy individuals. But its levels increase in cases of inflammatory diseases (like acute rheumatic fever, bacterial infection, gout), trauma, cancer and tissue damage.

-It helps in the defense against bacteria and foreign object in the body.

-Its level reaches a peak after 48 hours of the incident. Which is used as a monitoring marker. If it is found in high levels there must be a problem that needs to be investigated.



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