"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Plasma Proteins

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

GNT block

Overview:

- Functions and characteristics of plasma proteins
- Measurement of plasma proteins and diagnosis of diseases
- Electrophoretic patterns of plasma proteins
- Acute phase proteins

Plasma Proteins (pps)

- Plasma contains ≥300 different proteins.
- Many pathological conditions affect level of plasma proteins.[1]
- Mostly synthesized in the liver.
- Some are produced in other sites.[2]
- A normal adult contains ~70 g/L of Plasma Proteins (pps).[3]

Functions:

Transport (Albumin, prealbumin, globulins)	Maintain plasma oncotic pressure (Albumin)[4]
Defense (Immunoglobulins and complement)	Clotting and fibrinolysis (Thrombin and plasmin)

[1] The changes in the level of the plasma protein can be predictable for many diseases, this indicate the importance of studying plasma proteins.
[2] For example: Immunoglobulins are synthesized in B-lymphocytes.
[3] The majority of the plasma proteins are Albumins, it accounts for 40 g/L (60%), so when we say plasma proteins we are mainly talking about albumin.
[4] All the proteins in the plasma are responsible for maintaining plasma oncotic pressure, but just because the Albumin is the most abundant pps it has the major contribution toward the oncotic pressure.
Oncotic pressure (colloid osmotic pressure): is a form of osmotic pressure exerted by proteins, notably albumin, in a blood vessel that usually tends to pull water into the circulatory system.

Measurement Of Plasma Proteins

Quantitative Measurement

Quantitative measurement of specific protein[1].

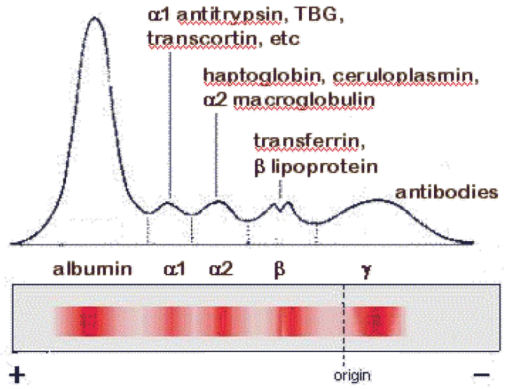
- Chemical or immunological reactions.

Semi Quantitative measurement

By Electrophoresis[2].

- Proteins are separated by their electrical charge in electrophoresis.
- Five separate bands of proteins are observed.
- These bands change in disease.

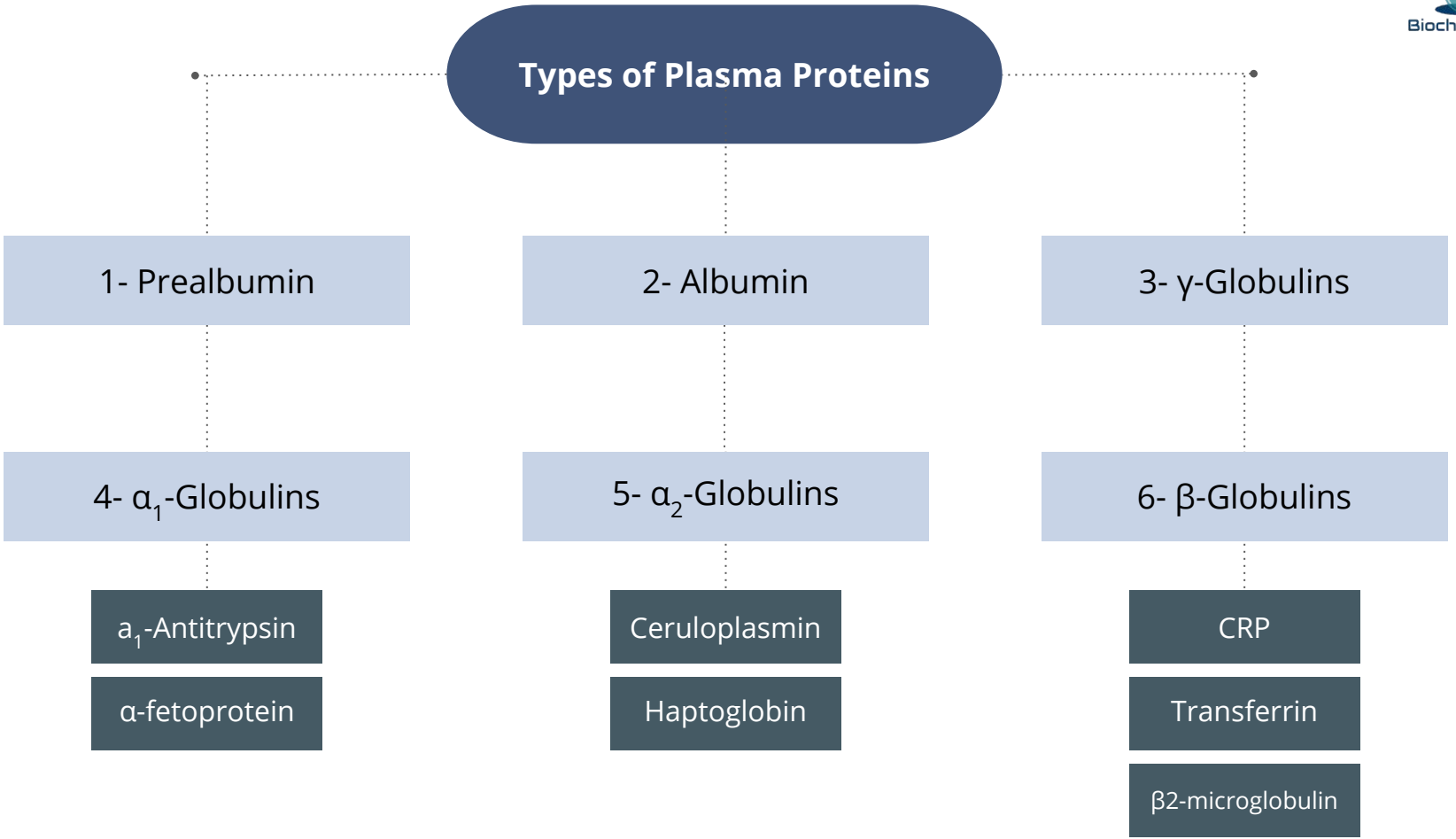
You don't need to memorize the graph, just understand it.



Normal Pattern of Plasma Protein Electrophoresis[3]

The test separates proteins in the blood based on their electrical charge & Molecular weight.

[1] Measures the exact levels of plasma proteins.
[2] It give a relative idea and a complete overview of the levels but does not give the exact levels of Plasma proteins, we use it before using the Quantitative measurement.
[3] In the graph: we can see 5 band, Albumin comes first because it will be the fastest moving molecule because of its small size, gamma proteins stays behind because they are large molecules "depends on the intensity"
Electrophoresis: electrophoresis is a technique commonly used in laboratories to separate charged molecules like DNA, RNA and proteins according to their size.


Types of Plasma Proteins
1- Prealbumin
2- Albumin
3- γ-Globulins
4- α1-Globulins
5- α2-Globulins
6- β-Globulins
a1-Antitrypsin
α-fetoprotein
Ceruloplasmin
Haptoglobin
CRP
Transferrin
β2-microglobulin

Prealbumin (Transthyretin)[1]

- A transport protein for:
  - Thyroid hormones.
  - Retinol (vitamin A).[2]

- Lower levels found in:
  - Liver disease[3]
  - Nephrotic syndrome
  - Acute phase inflammatory response
  - Malnutrition[4]

- Migrates faster than albumin in electrophoresis.
- In Electrophoresis test, The smallest molecules are the fastest.
- Separated by immunoelectrophoresis[6]
- Short half-life (2 days)[5]

[1] Not a precursor of Albumin, its a different protein, and you need to know both names.
[2] We studied in CNS block the retinol is transported by Retinol Transport Protein, but Retinol Transport Protein cannot work alone it need transthyretin (prealbumin) to transport retinol.
[3] Because it's synthesized in the liver.
[4] Prealbumin is a very good marker for malnutrition.
[5] It's an advantage, because when we treat a patient we can see the improvement right away.
6 it's separated by this so we can do further investigation and specific results

Albumin

- Most abundant plasma protein (~40 g/L) in normal adult
- Synthesized in the liver as preproalbuminand secreted as albumin
- Half-life in plasma: 20 days
- Decreases rapidly in injury, infection and surgery, cancer, liver disease (anything that will increase the catabolism)
- Albumin has logestic support to many enzyme

Functions	1.Maintains oncotic pressure: (80% of plasma oncotic pressure is maintained by albumin). The osmotic pressure exerted by plasma proteins that pulls water into the circulatory system 2.Maintains fluid distribution in and outside cells and plasma volume 3. A non-specific carrier of: hormones, calcium, free fatty acids, drugs, etc. Therefore, it can cause drug toxicity if we increased the dose without enough Albumin to carry it. 4.Tissue cells can take up albumin by pinocytosis (fluid endocytosis) where it is hydrolyzed to amino acids, So albumin is given by infusion in some diseases. 5.Useful in treatment of liver diseases, hemorrhage, shock and burns

Hyperalbuminemia

1. No clinical conditions are known that cause the liver to produce large amounts of albumin
2. The only cause of hyperalbuminemia is dehydration
   - Can be seen clinically with wrongly done blood test

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Hypoalbuminemia

Causes	Effects
1. Decreased albumin synthesis (liver cirrhosis, malnutrition) 2. Increased losses of albumin: • Increased catabolism in infections • Excessive excretion by the kidneys (nephrotic syndrome) • Excessive loss in bowel (bleeding) • Severe burns (plasma loss in the absence of skin barrier)	• Edema due to low oncotic pressure → Albumin level drops in liver disease causing low oncotic pressure → Fluid moves into the interstitial spaces causing edema • Reduced transport of drugs and other substances in plasma • Reduced protein-bound calcium: → Total plasma calcium level drops (bound form) → Ionized calcium level may remain normal (active form)

α_1-Antitrypsin[1]

- Synthesized by the liver and macrophages
- An acute-phase protein [2] that inhibits proteases
- Proteases [3] are produced endogenously and from leukocytes and bacteria
- Infection leads to protease release from bacteria and from leukocytes
  (then α_1-Antitrypsin goes and inhibit these proteases)
- Proteases could be:
  - **Digestive enzymes** (trypsin, chymotrypsin)
  - **Other proteases** (elastase, thrombin)

Types of α_1-Antitrypsin:

- Over 30 types are known [4]
- The most common is M type

1.although the name suggests it is inhibitor of trypsin, but in general it is inhibitor of a lot of proteases
2.acute-phase proteins are the proteins whose levels change in the first 24 hours after inflammation,trauma or infection. These proteins could be positive acute phase proteins or negative. The positive acute phase proteins: their level increase (a lot of them involved in the defence process) .the negative acute phase proteins: their levels decrease (doing other functions not involved in defence, like albumin)
3. Recall that proteases are enzymes required for protein digestion. But we also need them in the defence process. but if their action goes unchecked, they will start chopping off structural proteins and other important proteins. That is why we have antiproteases (for example α_1-Antitrypsin) to limit their action
4. The doctor said although it is written here 30 types, if you go and look in the literature the number has rised to 75

α_1 Antitrypsin Deficiency

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Genetic deficiency of α_1-Antitrypsin:

- Synthesis of the defective α_1-Antitrypsin occurs in the liver but it cannot secrete the protein [1]
- α_1-Antitrypsin accumulates in hepatocytes and is deficient in plasma

Clinical Consequences of this deficiency:

Neonatal jaundice with evidence of cholestasis

Childhood liver cirrhosis

Pulmonary emphysema in young adults

Laboratory Diagnosis

Lack of α_1-globulin band in protein electrophoresis

Quantitative measurement of α_1-Antitrypsin by:

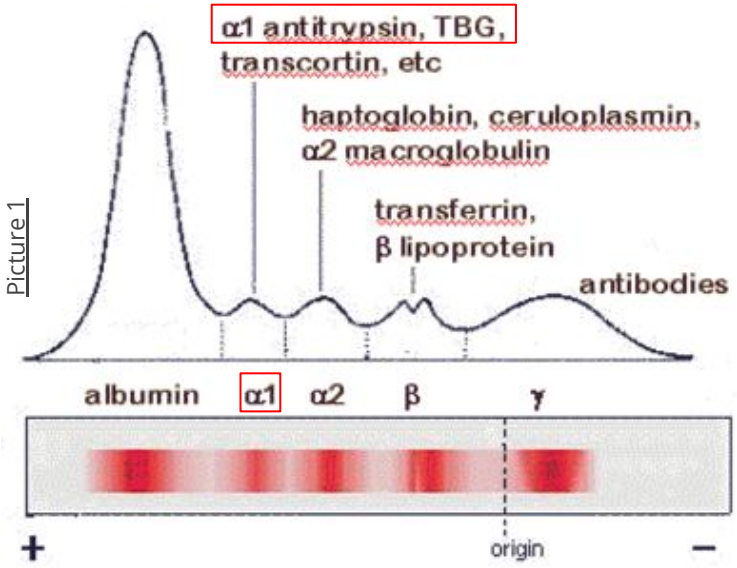
Radial immunodiffusion, isoelectric focusing or nephelometry "like spectrophotometer"

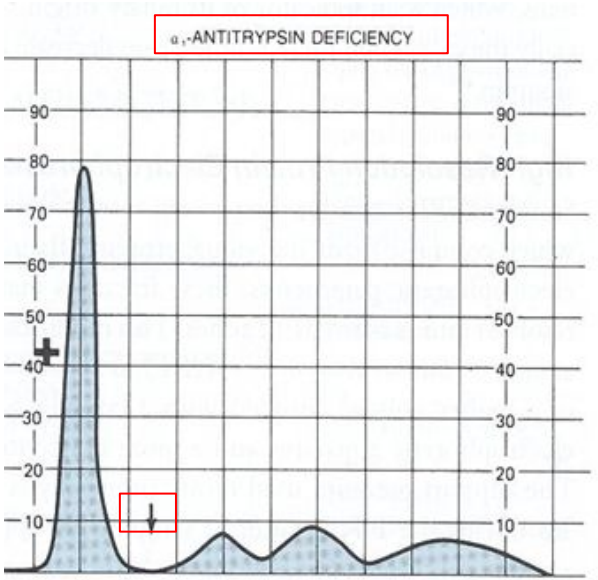
1.Although there is genetic deficiency does not affect synthesis but it is not secreted out, It stays in the liver, because the synthesised α_1-Antitrypsin is not the functional correct one
2. It causes pulmonary emphysema because in the lung there is neutrophils that produce elastase so to inhibit the activity of elastase you need $\alpha_1$antitrypsin, when there is a deficiency in $\alpha_1$antitrypsin this elastase will start damaging the alveoli, smoking worsen the disease because smoking causing more inflammation and also because it inactivate $\alpha_1$antitrypsin

2 risk increases with smoking

α_1 Antitrypsin Deficiency

Picture 1





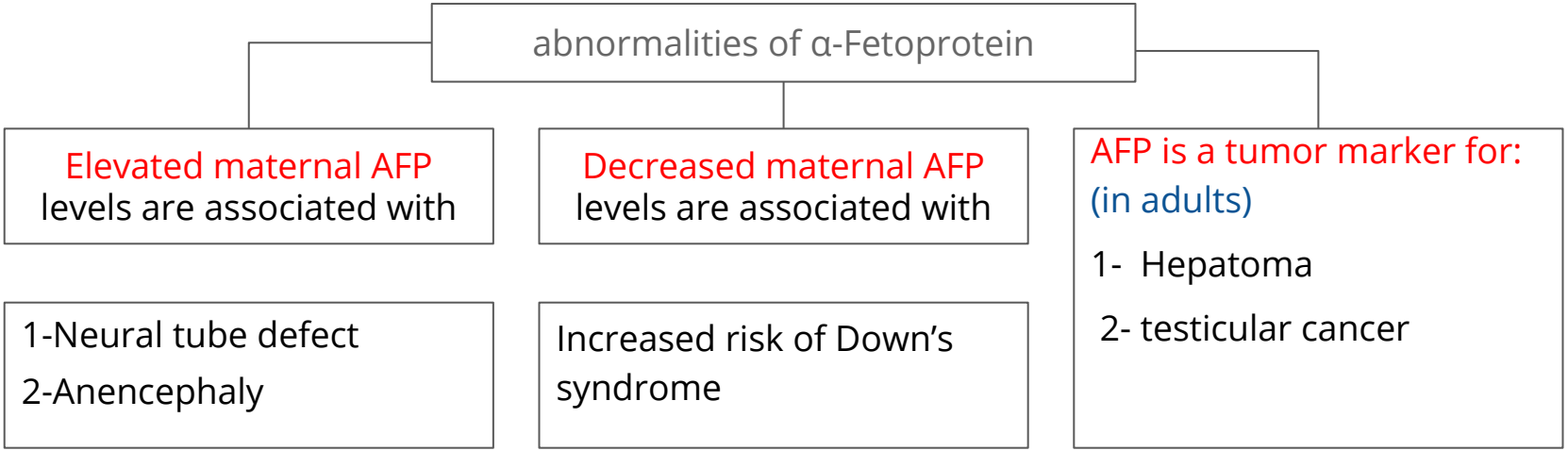
Picture 2

Doctors notes:

1. In picture (1) normal serum electrophoresis pattern
2. In picture (2) $\alpha_1$antitrypsin\ α_1-globulin band is gone, which means this patient has no $\alpha_1$antitrypsin. The organ which is more affected is the lung

α-Fetoprotein (AFP)

- Synthesized in the developing embryo and fetus by the parenchymal cells of the liver
- AFP levels decrease gradually during intra-uterine life and reach adult levels at birth "very low in adults"
- Function is unknown but it may protect fetus from immunologic attack by the mother
- No known physiological function in adults



α_2- Globulins

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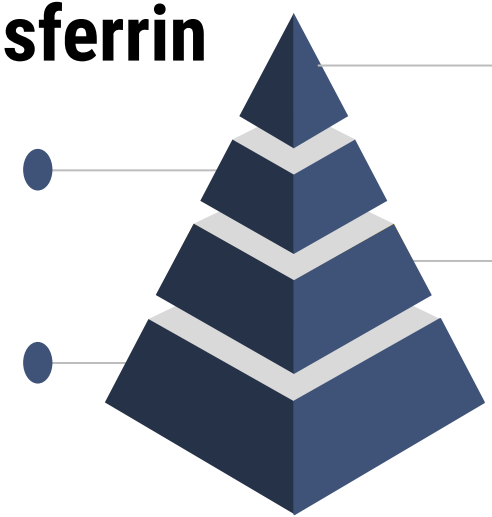
Ceruloplasmin	Haptoglobin
Synthesized by the liver	Synthesized by the liver
Contains "carries" >90% of serum copper	Binds to free hemoglobin to form complexes that are metabolized in the RES
An oxidoreductase that inactivates ROS causing tissue damage in acute phase response	Plasma level decreases during hemolysis & it level increases in patients who have iron deficiency
Important for iron absorption from the intestine	Limits iron losses by preventing Hb loss from kidneys & protects it
Wilson's Disease - Due to low plasma levels of ceruloplasmin - Copper is accumulated in the liver & brain	

- Function of ceruloplasmin is carrying copper: (copper travels in the blood till it reaches the liver, where it will bind to ceruloplasmin and then it will carry it through the bloodstream and take it to the tissue where it is needed)
- Level of it will elevate during the acute phase b/c it is involved in the defense process

- During hemolytic diseases, the RBCs break down in the blood releasing free HB
- This free HB is carried by haptoglobin to the reticuloendothelial system "RES" for proper degradation.
- This protects the kidney and limits iron loss

Transferrin



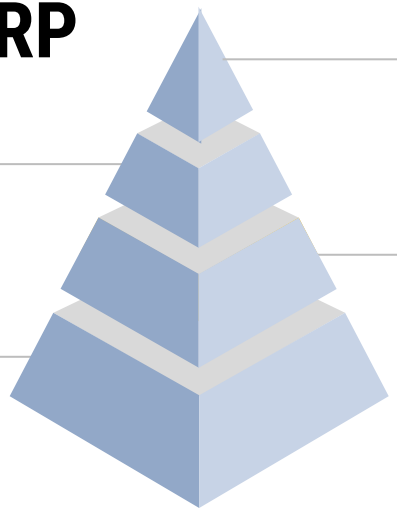
A major iron transport protein in plasma
- 30% saturated with iron

Iron deficiency results in increased hepatic synthesis

Plasma level drops in:
- Malnutrition, liver disease, inflammation, & malignancy.

A negative acute phase protein
(during acute phase it level will decrease)

CRP



An acute-phase protein synthesized by the liver

Important for phagocytosis

A marker for ischemic heart disease*

High plasma levels are found in many inflammatory conditions e.g. (rheumatoid arthritis)

- CRP helps in the process of opsonization of pathogens.
- CRP binds to the antigens present on the pathogen, which will attract the binding complement proteins and then it will coat the pathogen, this process is called **(opsonization)**
* There is a fraction of CRP called ultra sensitive CRP which is responsible for it.

B2 –Microglobulin

- ★ A component of human leukocyte antigen (HLA)
- ★ Present on the surface of lymphocytes and most nucleated cells
- ★ Filtered by the renal glomeruli due to its small size but most (>99%) is reabsorbed
- ★ Elevated serum levels are found in
  - ○ Overproduction in disease e.g (in infections, SLE, and rheumatoid arthritis)
- ★ May be a tumor marker for:
  - ○ Leukemia, lymphomas, or multiple myeloma

Hypergammaglobulinemia

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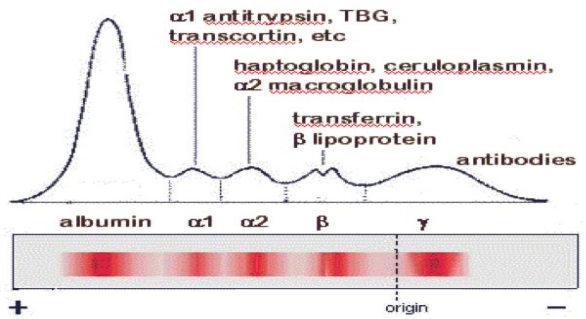
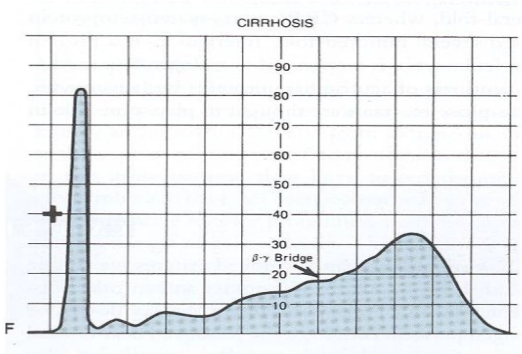
★ May result from stimulation of:
- B cells (Polyclonal* hypergammaglobulinemia) → *mixture of antibodies from different plasma cells
- Monoclonal** proliferation (Paraproteinemia) → **specific type of antibody from one type of plasma protein

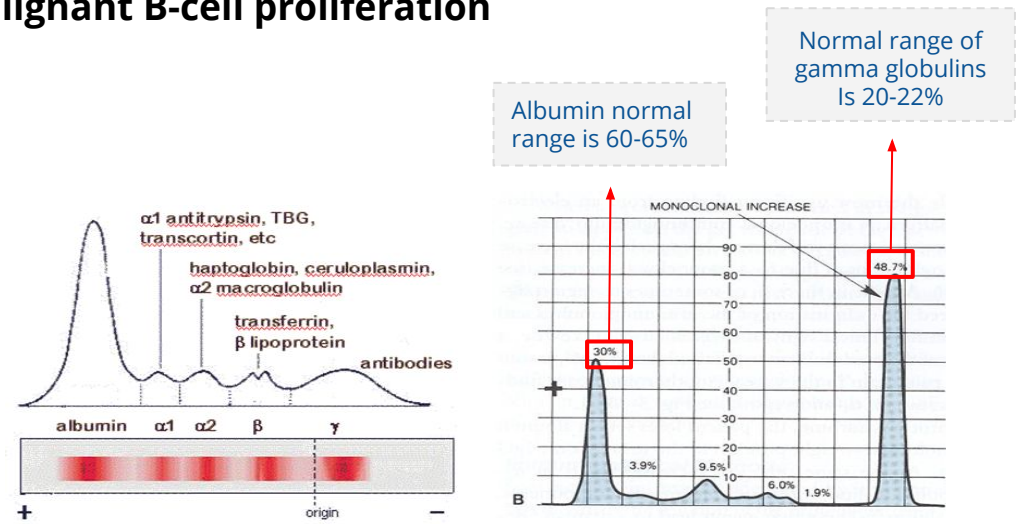
★ Polyclonal hypergammaglobulinemia:
- Stimulation of many clones of B cells produce a wide range of antibodies.
- γ-globulin band appears large in electrophoresis
- Decrease in albumin will always increase globulin synthesis to compensate for the loss to maintain the pressure
- Clinical conditions: acute and chronic infections, autoimmune diseases, chronic liver disease





Monoclonal Hypergammaglobulinemia

- Proliferation of a single B-cell clone produces a single type of Ig
- Appears as a separate dense band (paraprotein or M band) in electrophoresis
- **Paraproteins are characteristic of malignant B-cell proliferation**
- Clinical condition: **multiple myeloma**

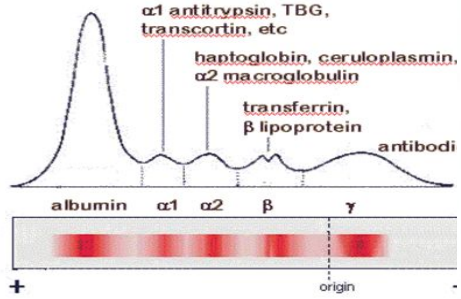


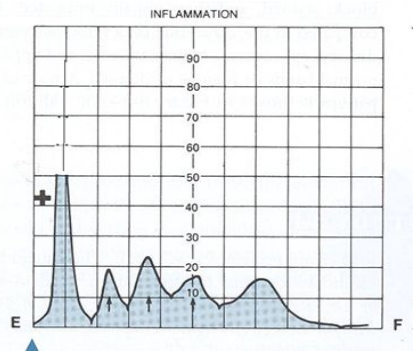
Positive Acute Phase Proteins

- Plasma protein levels increase in:
  - Infection, inflammation , malignancy, trauma, surgery
- These proteins are called acute phase reactants
- Synthesized due to body's response to injury
- Examples: a_1-Antitypsin, haptoglobin, ceruloplasmin, fibrinogen, c-reactive protein
- Mediators cause these proteins to increase after injury

The're involved in the body defense mechanism

- **Mediators:**
  - Cytokines (IL-1, IL-6)
  - tumor necrosis factors a and b
  - Interferons
  - platelet activating factor
- **Functions:**
  1. Bind to polysaccharides in bacterial walls
  2. Activate complement system
  3. Stimulate phagocytosis





Also they lower the synthesis of the negative acute phase proteins

Negative Acute Phase Proteins

- These proteins decrease in inflammation
- Albumin, prealbumin, transferrin
- Mediated by inflammatory response via cytokines and hormones
- Synthesis of these proteins decrease to save amino acids for positive acute phase proteins

Summary

emzyme	Function	Condition
Prealbumin	Transport :- 1) Thyroid hormones. 2) Retinol.	Lower level in :- 1) liver disease. 2) Nephrotic syndrome. 3) Malnutrition. 4) Acute phase inflammatory response.
Albumin	1) Maintain oncotic pressure. 2) Non specific carrier. 3) Useful in treatment of liver disease & shock & hemorrhage.	Hypoalbuminemia:- 1) Decrease albumin synthesis. 2) Loss of albumin:- • Excessive loss in bowel • Nephrotic syndrome.
a1 -antitrypsin	Anti proteases	Genetic deficiencyofa1–antitrypsin:- _Neonatal jaundice. _Childhood livercirrhosis. _Pulmonaryemphysema.
a-fetoprotein	Unknown function	_Elevated maternal in neural tube defect. _Decreased maternal in down syndrome. _Tumor marker in hepatoma &testicular cancer.
Ceruloplasmin	Important in iron absorption from intestine	Wilson's disease.
Haptoglbin	Bind to free hemoglobin to form complexes to limit iron loss and to prevent Hb loss in kidney .	Decrease during hemolysis.
B2 -Microglobulin		Elevated level found in _ over production in disease. _Tumormarker in leukemia&lymphomas& multiple myeloma.
C-Reactive protein	Important In phagocytosis	Elevated-in:- 1) Inflammation (rheumatoid arthritis) 2) Marker for ischemic heart disease

MCQs:

1.A normal adult contains?
A) 70 g/L of plasma proteins
B) 60 g/L of plasma proteins
C) 80 g/L of plasma proteins

2. Which one of the following does not consider a function of pps?
A) Defense
B) hydrolysis
C) fibrinolysis

3.which one of the following plasma proteins is synthesis by the macrophages?
A) a -Fetoprotein
B) β2- microglobulin
C) a1-Antitrypsin

4.The most common types of a1-Antitrypsin?
A) Type A
B) Type C
C) Type M

5.Transferrin Plasma level drops in?
A) nephrotic syndrome
B) acute phase inflammatory
C) malignancy

6.Which one of the following is an effect of hypoalbuminemia?
A) Ionized calcium level drops
B) long drug's half life
C) anaemia

7.Which one of the following is the cell that synthesize alpha-Fetoprotein?
A) parenchymal cells of liver
B) macrophages
C) lumen cells of liver

1-A
2-B
3-C
4-C
5-C
6-B
7-A

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- اروى الجهني
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