[lecture 9]

Plasma Protein

Biochemistry Team

Teams

The Objectives

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

Red = Import-ant

Blue = explain

Green = addition notes

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Biochemistry Team

Mind Map

Types of Plasma Protein

- Albumin
  - Prealbumin
- β-Globulins
  - β2-microglobulin
  - CRP
  - Transferrin
- α1-Globulins
  - α-fetoprotein
  - α_1-Antitrypsin
- γ-Globulins
  - Hypergammaglobulinemia
  - Polyclonal hypergammaglobulinemia
  - Monoclonal Hypergammaglobulinemia
- α2-Globulins
  - haptoglobin
  - Ceruloplasmin

Plasma Proteins (PPs)

In general

- Plasma contains >300 different proteins
- Many pathological conditions affect level of plasma proteins
- Mostly **synthesized in the liver**, except Immunoglobulins which are mostly synthesized by plasma cells.
- Some are produced in other sites (e.g. immunoglobulins).
- A normal adult contains ~70 g/L of PPs

Functions

- Transport (**Albumin**, **prealbumin**, **globulins**)
- Maintain plasma oncotic pressure (**Albumin**)
- Defense (**Immunoglobulins** & **complement**)
- Clotting & fibrinolysis (Thrombin & plasmin)

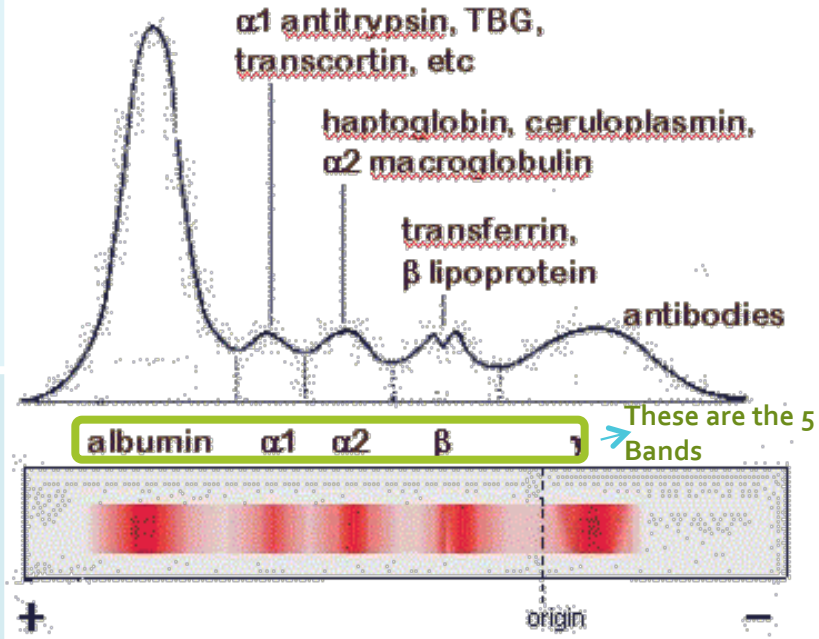
Measurement

A) Quantitative measurement of a specific protein:
Chemical or immunological reactions (Measures the exact quantity of proteins)

B) Semiquantitative measurement by electrophoresis:

(Measures the relative amount (how much of the protein is present in relation to other proteins

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



Normal pattern of Plasma Protein Electrophoresis

Electrophoresis is: Exposure of plasma to an electric current to separate the serum protein components into five major fractions by size & electrical charge.

Types of PPs	Function	Pattern in electrophoresis	Clinical significance
Prealbumin (Transthyretin)	A transport protein for: • Thyroid hormones. • Retinol (vitamin A).	• Migrates faster than albumin in electrophoresis (as it's smaller in size than albumin). • Separated by **immunoelectrophoresis.**	• Lower levels found in: -**Liver disease** -Nephrotic syndrome -Acute phase inflammatory response -**malnutrition** • **Short half-life (2 days)**

Immunoelectrophoresis is a biochemical method for separation & of proteins based on electrophoresis & reaction with antibodies (immunoglobulins).

Types of PPs	Synthesis & Functions	Clinical significance
Albumin	Synthesized in the liver as preproalbumin & secreted as albumin. **Functions:** 1- Maintains oncotic pressure: • The osmotic pressure exerted by plasma proteins that pulls water into the circulatory system. • Maintains fluid distribution in & outside cells & plasma volume. 2- **80% of plasma oncotic pressure is maintained by albumin**, as it's the most abundant plasma protein (~40 g/L) in normal adult. 3- A **non-specific** carrier of: hormones, calcium, free fatty acids, drugs, etc. 4-Tissue cells can take up albumin by pinocytosis where it is hydrolyzed to amino acids. 5-Useful in treatment of **liver diseases**, hemorrhage, shock & burns.	• $T_{1/2}$ in plasma: 20 days • Decreases rapidly in injury, infection & surgery. **Hypoalbuminemia** **causes:** -Decreased albumin synthesis (liver cirrhosis, malnutrition) -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) **Effects:** 1- Edema due to low oncotic pressure • Albumin level drops in liver disease causing low oncotic pressure • Fluid moves into the interstitial spaces causing edema 2-Reduced transport of drugs & other substances in plasma (may cause drug toxicity). 3-Reduced protein-bound calcium • Total plasma calcium level drops • Ionized calcium level may remain normal (because ionized Ca doesn't need albumin to be transported). **Hyperalbuminemia** • No clinical conditions are known that cause the liver to produce large amounts of albumin. • **The only cause of hyperalbuminemia is dehydration.**

Types of PPs		Synthesis & Function	Types	Clinical significance & Lab diagnosis
α1-Globulins	α_1-Antitrypsin	Synthesized by the liver & macrophages. Functions: -Is an acute-phase protein that **inhibits proteases.** -Proteases are produced endogenously & from leukocytes & bacteria: • **Digestive enzymes (trypsin, chymotrypsin).** • **Other proteases (elastase, thrombin).** -Infection leads to protease release from bacteria & leukocytes.	-Over 30 types, the most common is **M type** -Genetic deficiency of α1-Antitrypsin **(commonly affects Z type not M type) :** • Synthesis of the defective 1-Antitrypsin occurs in the liver but it cannot secrete the protein • 1-Antitrypsin accumulates in hepatocytes & is deficient in plasma	**Consequences of α1-Antitrypsin Deficiency:** -**Neonatal jaundice** with evidence of cholestasis -**Childhood liver cirrhosis.** -Pulmonary emphysema in young adults. **Laboratory Diagnosis** Lack of α1-globulin band in protein electrophoresis **Quantitative measurement of α1-Antitrypsin by:** **Radial immunodiffusion, isoelectric focusing or nephelometry**

acute phase proteins are proteins whose level changes within 24 hours of infection or injury, if raised→ positive, if reduced→ negative.

Radial immunodiffusion: used to determine the quantity of an antigen.

Isoelectric focusing: the protein migrates in a gel according to its isoelectric point or charge in a pH gradient.

Nephelometry: is a technique used to determine the levels of several blood plasma proteins. For example the total levels of antibodies, isotypes, or classes: IgM, IgG, & IgA. It is important in quantification of M-proteins for diseases for disease classification & for disease monitoring once a patient has been treated.

Types of PPs		Synthesis & Function	Clinical significance
α1-Globulins	α-fetoprotein	• 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 **Function:** • is unknown but it may protect fetus from immunologic attack by the mother • No known physiological function in adults	• Elevated maternal AFP levels are associated with: - Neural tube defect, anencephaly • Decreased maternal AFP levels are associated with: - Increased risk of Down's syndrome • AFP is a tumor marker for: - Hepatoma and testicular cancer

Types of PPs		Function	Clinical significance
α2-Globulins	Ceruloplasmin	▪ Synthesized by the liver ▪ Contains >90% of serum copper ▪ An oxidoreductase that inactivates ROS causing tissue damage in acute phase response (ROS =reactive oxygen species) ▪ Important for iron absorption from the intestine	▪ **Wilson's disease:** • Due to low plasma levels of ceruloplasmin • Copper is accumulated in the liver and brain
	haptoglobin	• Synthesized by the liver • Binds to free hemoglobin to form complexes that are metabolized in the RES • Plasma level decreases during hemolysis • Limits iron losses by preventing Hb loss from kidneys	

Types of plasma proteins		Function	Clinical significance
β-Globulins	CRP (C-Reactive Protein)	• An acute-phase protein synthesized by the liver • Important for phagocytosis	• High plasma levels are found in many inflammatory conditions such as rheumatoid arthritis • A marker for ischemic heart disease
	transferrin	• A major iron-transport protein in plasma • 30% saturated with iron • A negative acute phase protein	• Plasma level drops in: Malnutrition, liver disease, inflammation, malignancy • Iron deficiency results in increased hepatic synthesis
	β2-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 • May be a tumor marker for: Leukemia, lymphomas, multiple myeloma

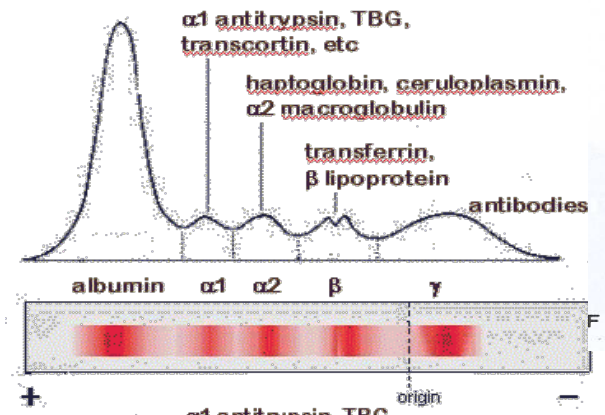
γ-Globulins

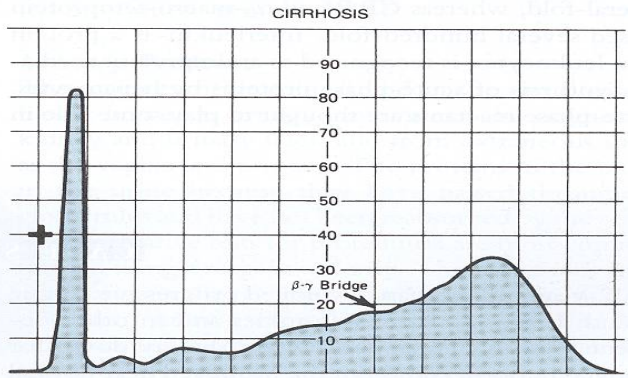
- **Hypergammaglobulinemia :**

May result from stimulation of :

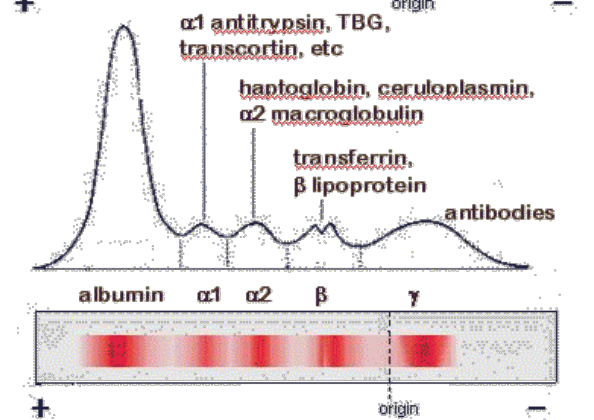
- B cells (**Polyclonal hypergammaglobulinemia**)
- **Monoclonal** proliferation (**Paraproteinemia**)

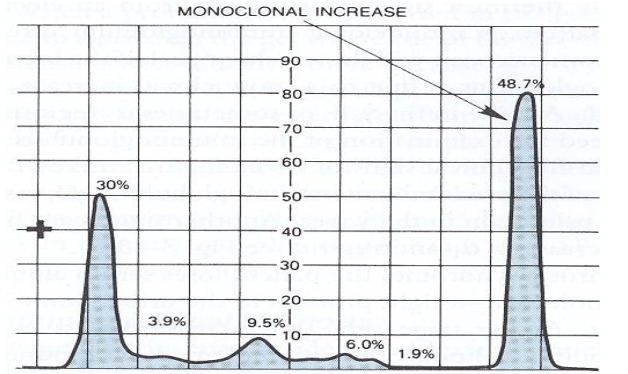
Polyclonal hypergammaglobulinemia	• Stimulation of many clones of B cells produce a wide range of antibodies. • γ-globulin band appears large in electophoresis. • **Clinical conditions:** acute and chronic infections, autoimmune diseases, chronic liver diseases.
Monoclonal Hypergammaglobulinemia	• Proliferation 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





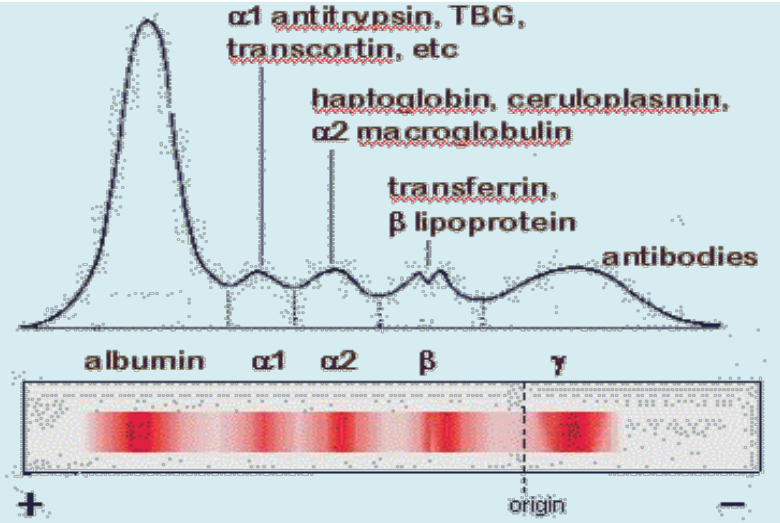
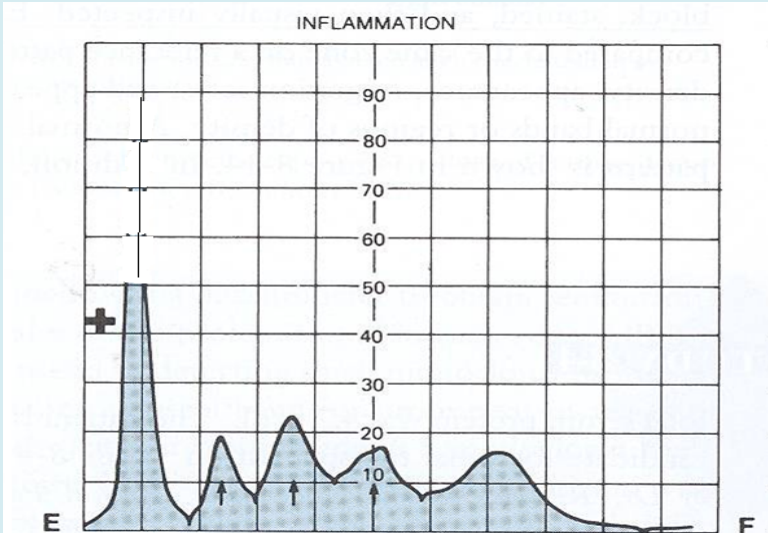
Polyclonal hypergammaglobulinemia





Monoclonal Hypergammaglobulinemia

Acute Phase Proteins

Types of Acute Phase Proteins	Function	Pattern in electrophoresis
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:** α_1-Antitypsin, haptoglobin, ceruloplasmin, fibrinogen, c-reactive protein • Mediators cause these proteins to increase after injury • **Mediators:** Cytokines (IL-1, IL-6), tumor necrosis factors α and β , interferons, platelet activating factor • **Functions:** 1. Bind to polysaccharides in bacterial walls 2. Activate complement system 3. Stimulate phagocytosis	
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

-Most plasma proteins are synthesized in the liver.
-They are measured in quantitative & semi-quantitative measurements.
-**Low level of Prealbumin** is found in: liver disease, nephrotic syndrome, acute phase inflammatory response, & malnutrition.
-Albumin functions: has the major role in **maintaining oncotic pressure**, **transport** hormones, Ca, FFA, & drugs, & it is useful in **treating liver diseases**.
-**Neonatal jaundice** & **childhood liver cirrhosis** are associated with a1-antitrypsin deficiency.
-Infection, inflammation , malignancy, trauma, surgery **increase** plasma protein level **in positive acute phase proteins.**
- CRP , a marker **for ischemic heart disease.**
-Ceruloplasmin Important for **iron absorption from the intestine.**
-α-fetoprotein Synthesized in the developing embryo and fetus **by the parenchymal cells of the liver.**
-AFP is a tumor marker for Hepatoma and testicular cancer.
-β2-microglobulin May be a tumor marker for Leukemia, lymphomas, multiple myeloma
-transferrin a major iron-transport protein in plasma.

Test your knowledge ..!

1- Most abundant type of plasma proteins is:
A-γ- Globulins
B-Albumin
C-Transthyretin

2- Which one of the following acts as a transport protein for thyroid hormone:
A-Albumin
B-Prealbumin
C-Ceruloplasmin

3- Deficiency of which of the following can lead to drug toxicity:
A- a1-Antitrypsin
B-Haptoglobin
C-Albumin

4-which one of the following is major iron-transport protein in plasma :
A-Ceruloplasmin
B-transferrin
C-haptoglobin

5- which one of the following is Wilson's disease cause :
A- low β2-microglobulin level.
B- increase haptoglobin level
C-low Ceruloplasmin level.

6-which one of the following is a marker for ischemic heart disease:
A-haptoglobin
B-transferrin
C-CRP

Answers:
1-B 2- B 3-C 4-B 5-C 6-C

Test your knowledge ..!

7-Which of the following is not a feature of Hypoalbuminemia ?

A. Reduced transport of drugs
B. Edema due to low oncotic pressure
C. The only cause for it is dehydration
D. Decreased albumin synthesis

8-Increased risk of Down's syndrome is associated with which of the following?

A. Elevated maternal AFP
B. Decreased maternal AFP
C. Polyclonal hypergammaglobulinemia
D. Monoclonal Hypergammaglobulinemia:

9- Which one of the following is Positive Acute Phase Proteins?

A. Albumin, α1-Antitypsin and fibrinogen
B. haptoglobin, ceruloplasmin and transferrin
C. Antitypsin , transferrin and haptoglobin
D. haptoglobin, ceruloplasmin and fibrinogen

10-Which one of the following conditions results in decreased level of Albumin?

A. Down's syndrome
B. nephrotic syndrome
C. dehydration
D. none of the above

11-Deficiency in which of following proteins results in emphysema?

A- Albumin
B- α-fetoprotein
C- α1-Antitypsin
D- fibrinogen

Answers:
7-C 8- B 9-D 10-B 11-C

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Thank you