# Plasma proteins

- Plasma contains >300 different proteins, their levels are affected by many pathological conditions.
- Mostly synthesized in the liver
- Some are produced in other sites
- A normal adult has 6-8g/dl of plasma proteins
- The proteins of the plasma are a complex mixture that includes not only simple proteins but also conjugated proteins such as glycoproteins and various types of lipoproteins.

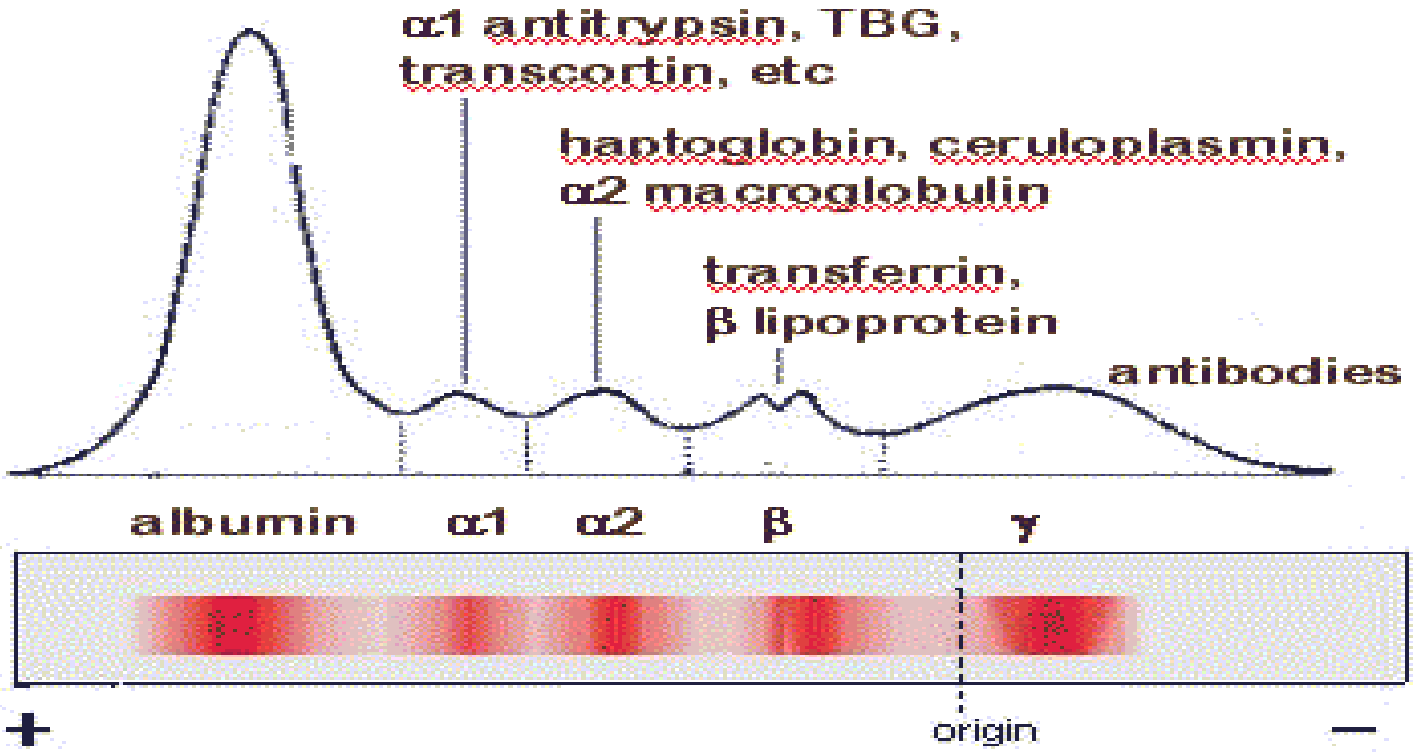
<u>Functions</u>

- Transport (Albumin, prealbumin, globulins)
- Maintain plasma oncotic pressure (Albumin)
- Defense (Immunoglobulins and complement)
- Clotting and fibrinolysis (Thrombin and plasmin)
- Buffering pH
- Catalytic functions (enzymes as LPL)

# Measurement of Plasma Proteins

A- Quantitative measurement of a specific protein by chemical or immunological reactions

B- Semiquantitative measurement by electrophoresis: proteins are separated by their electrical charge in electrophoresis (five separate bands of proteins are observed, these bands change in disease).



## Types of Plasma Proteins

- Prealbumin
- Albumin
- α1-Globulins: as α 1-Antitrypsin, α–fetoprotein
- α2-Globulins: as Ceruloplasmin, haptoglobin
- β Globulins:  as CRP, transferrin, β2-microglobulin
- γ Globulins

## Prealbumin (Transthyretin)

- A transport protein for: thyroid hormones and retinol
- Migrates faster than albumin in electrophoresis
- Separated by immunoelectrophoresis
- Lower levels found in: liver disease, nephrotic syndrome, acute phase inflammatory response, malnutrition
- Short half-life (2 days)

# Albumin

- Most abundant plasma protein (3.5-5 g/l) in normal adult
- Synthesized in the liver as preproalbumin and secreted as albumin
- Half-life in plasma: 20 days
- Decreases rapidly in injury, infection and surgery

**Functions**

- Maintains oncotic pressure:
    - The osmotic pressure exerted by plasma proteins that pulls water into the circulatory system
    - Maintains fluid distribution in and outside cells and plasma volume (80% of plasma oncotic pressure is maintained by albumin)
- A non-specific carrier of hormones, calcium, free fatty acids, drugs, etc.
- It is by pinocytosis in the cells where it is hydrolyzed to amino acids
- Nutritive function
- Buffering function
- Useful in treatment of liver diseases, hemorrhage, shock and burns

## Synthesis of albumin

-The liver produces albumin, it represents about 25% of total hepatic protein synthesis.

- Albumin is initially synthesized as a preproprotein
- Its signal peptide is removed as it passes into rough endoplasmic reticulum, and a hexapeptide at the resulting amino terminal is subsequently cleaved off farther along the secretory pathway.
- Mature human albumin consists of one polypeptide chain of 585 amino acids and contains 17 disulfide bonds
- It has an ellipsoidal shape, which means that it does not increase the viscosity of the plasma as much as an elongated molecule such as fibrinogen does.
- Has a relatively low molecular mass about 66 kDa

## Clinical significance of albumin

### Blood brain barrier

- Albumin- free fatty acid complex can not cross the blood brain barrier, hence fatty acids can not be utilized by the brain.
- Loosely bound bilirubin to albumin can be easily replaced by drugs like aspirin
- In new born if such drugs are given, the released bilirubin gets deposited in brain causing Kernicterus.

### Protein bound calcium

- Calcium level is lowered in conditions of hypoalbuminemia
- Serum total calcium may be decreased
- Ionic calcium remains the same
- Tetany does not occur
- Calcium is lowered by 0.8 mg/dl for a fall of 1g/dl of albumin

## Drug interactions

-Two drugs having same affinity for albumin when administered together, can compete for available binding sites with consequent displacement of other drug, resulting in clinically significant drug interactions. As phenytoin, dicoumarol interactions

## Oedema

## Hypoalbuminemia

**Causes**

- Decreased albumin synthesis (liver cirrhosis, malnutrition)
- Increased losses of albumin
    - Increased catabolism in infections
    - Excessive excretion by the kidneys (nephrotic syndrome).
    - Severe burns (plasma loss in the absence of skin barrier)
    - Excessive loss in bowel

**Effects**

- 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
  - Ionized calcium level may remain normal

**Hyperalbuminemia**

- No clinical conditions are known that cause the liver to produce large amounts of albumin
- The only cause of hyperalbuminemia is dehydration

## α1-antitrypsin

- Called α1- antiprotease
- Synthesized by the liver and macrophages
- An acute-phase protein that inhibits proteases (trypsin, elastase, and other proteases) by forming complexes with them.
- Infection leads to protease release from bacteria and leukocytes.
- Normally α1-antitrypsin protects the lung tissues from the released active elastase from macrophages.
- In its deficiency, the active elastase destroys the lung tissue by proteolysis.

## Types of $\alpha_1$-Antitrypsin

- Over 30 types are known (the most common is M type).
- Genetic deficiency of α1-antitrypsin (synthesis of the defective α1-antitrypsin occurs in the liver but it cannot secrete the protein) → its accumulation in hepatocytes and its deficiency in plasma

**Clinical consequences of α1-antitrypsin deficiency**

- Neonatal jaundice
- 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 and isoelectric focusing.

# 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 (normal level is 1 μg/100 ml).
- 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

**Ceruloplasmin**

- Synthesized by the liver (glycoprotein with enzymatic activity).
- Carries about 90% of serum copper, albumin carries 10%.
- An oxidoreductase that inactivates ROS causing tissue damage in acute phase response
- 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
- The amount of ceruloplasmin in plasma is also decreased in liver diseases, malnutrition and nephrotic syndrome.

## Haptoglobin

- Synthesized by the liver (glycoprotein).
- Binds to free hemoglobin to form complexes that are metabolized in the RES, when bound to hemoglobin, it is cleared from the plasma about 80 times faster than normally.
- Limits iron losses by preventing Hb loss from kidneys
- Plasma level decreases during hemolysis and increases in inflammation.

## Transferrin

- A major iron-transport protein in plasma
    - 30% saturated with iron
- Plasma level drops in:
    - Malnutrition, liver disease, inflammation, malignancy
- Iron deficiency results in increased hepatic synthesis
- A negative acute phase protein

## 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
    - Impaired kidney function
- May be a tumor marker for:
    - Leukemia, lymphomas, multiple myeloma

## C-reactive protein (CRP)

- An acute-phase protein synthesized by the liver (so named because it reacts with the polysaccharide of the capsule of pneumococci, important for phagocytosis
- High plasma levels are found in many inflammatory conditions such as rheumatoid arthritis
- A marker for ischemic heart disease

## α2– Macroglobulin

- Major component of α2 proteins
- Comprises 8–10% of the total plasma protein in humans.
- Tetrameric protein with molecular weight of 725 kDa.
- Synthesized by hepatocytes and macrophages
- Inactivates all proteases and thus is an important in vivo anticoagulant.
- Carrier of many growth factors
- Normal serum level-130-300 mg/dl
- Concentration is markedly increased in nephrotic syndrome, since other proteins are lost through urine in this condition.

# 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 electrophoresis
- 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

**Positive acute phase proteins (acute phase reactants)**

- Plasma protein levels increase in:
  Infection, inflammation , malignancy, trauma, surgery
- Synthesized due to body's response to injury as $\alpha_1$-antitypsin, haptoglobin, ceruloplasmin, fibrinogen and C-reactive protein
- Mediators cause these proteins to increase after injury as cytokines (IL-1, IL-6), tumor necrosis factors $\alpha$ and $\beta$ , 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 and transferrin
- Mediated by inflammatory response via cytokines and hormones
- Synthesis of these proteins decrease to save amino acids for positive acute phase proteins

## Abnormal proteins

### 1- Bence Jone's proteins

- Abnormal proteins (monoclonal light chains).
- Present in the urine of a patient suffering from multiple myeloma (50% of patients)
- Molecular weight 45 kDa
- Identified by heat coagulation test
- Best detected by zone electrophoresis and immunoelectrophoresis

### 2- Cryoglobulins

- These proteins coagulate when serum is cooled to very low temperature
- Commonly monoclonal IgG or IgM or both
- Increased in rheumatoid arthritis, multiple myeloma, lymphocytic leukemia, lymphosarcoma and systemic lupus erythematosus