PLASMA PROTEIN

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 pps • Mostly synthesized in the liver • Some are produced in other sites • A normal adult contains ~70 g/L of pps

Functions of pps

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

Measurement of Plasma Proteins

A) Quantitative measurement of a specific protein:
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
- α_1-Globulins:
  - a_1-Antitrypsin, α-fetoprotein
- α_2-Globulins:
  - Ceruloplasmin, haptoglobin
- β-Globulins:
  - CRP, transferrin, β2-microglobulin
- γ- Globulins

Prealbumin (Transthyretin)

- A transport protein for:
  - Thyroid hormones
  - Retinol (vitamin A)
- 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 (~40 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 plasma volume and fluid distribution in and outside cells
- **80% of plasma oncotic pressure is maintained by albumin**
- **A non-specific carrier of**
  - **hormones, calcium, free fatty acids, drugs, etc.**
- **Tissue cells can take up albumin by pinocytosis where it is hydrolyzed to amino acids**
- **Useful in the treatment of liver diseases, hemorrhage, shock and burns**

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
  - Severe burns (plasma loss in the absence of skin barrier)

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

- Synthesized by the liver and macrophages
- An acute-phase protein that inhibits proteases
- Proteases are produced endogenously and from leukocytes and bacteria
  - Digestive enzymes (trypsin, chymotrypsin)
  - Other proteases (elastase, thrombin)
- Infection leads to protease release from bacteria and leukocytes

Types of α1-Antitrypsin	• Over 30 types are known
	• The most common is M type
	• Genetic deficiency of α_1-Antitrypsin
	  ○ Synthesis of the defective α_1-Antitrypsin occurs in the liver but it cannot secrete the protein
	  ○ α_1-Antitrypsin accumulates in hepatocytes and is deficient in plasma

Clinical Consequences of α_1-Antitrypsin 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

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
- 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 (spina bifida), anencephaly
- Decreased maternal AFP levels are associated with:
  - Increased risk of Down syndrome
- AFP is a tumor marker for:

Hepatoma and testicular cancer

Ceruloplasmin

- Synthesized by the liver
- Contains >90% of serum copper
- 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

Haptoglobin

- Synthesized by the liver
- Binds to free hemoglobin to form complexes that are metabolized in the RES
- Limits iron losses by preventing Hb loss from kidneys
- Plasma level decreases during hemolysis

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:
  - Overproduction in disease
- May be a tumor marker for:
  - Leukemia, lymphomas, multiple myeloma

C-Reactive Protein (CRP)

- 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

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

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