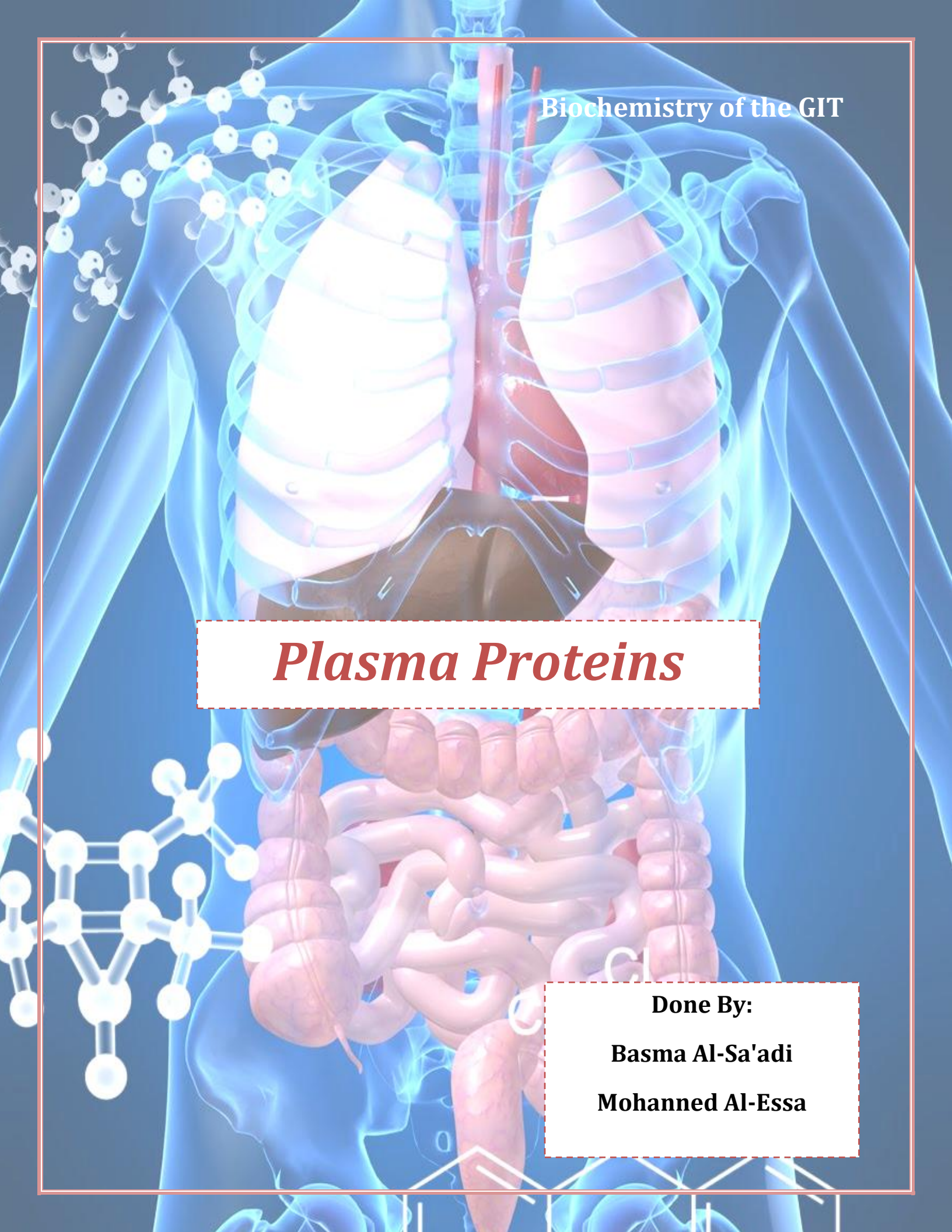

Biochemistry of the GIT

Plasma Proteins

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- Plasma contains more than 300 different proteins.
- Mostly synthesized in the liver, some are produced in other sites
- Many pathological conditions affect level of pps. Hence, these molecules that can be used as markers for detecting a condition or a disease.
- A normal adult contains ~70 g/L of pps

❖ Functions of pps:

- Transport and this is done by: (Albumin, prealbumin, globulins)
- Maintain plasma oncotic pressure by: (Albumin)
- Defense (Immunoglobulins "anti-bodies" and complement)
- Clotting and fibrinolysis (Thrombin and plasmin)

❖ Measurement of Plasma Proteins:

A) Quantitative measurement of a specific protein:

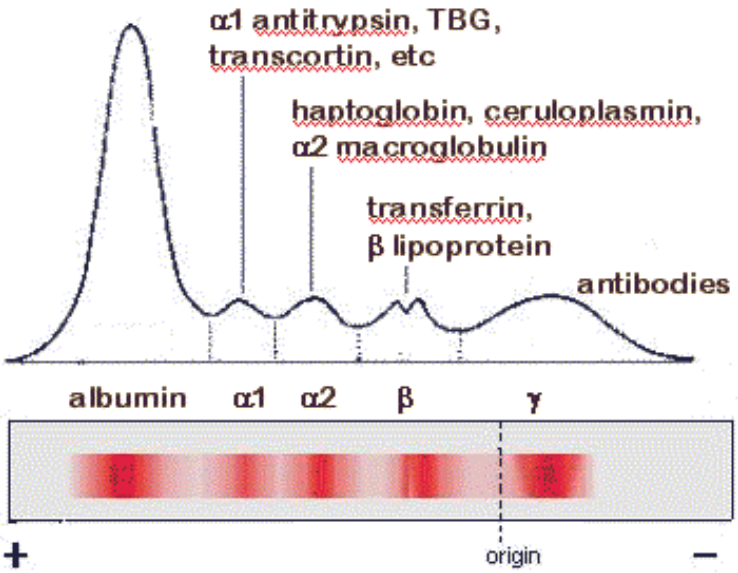
- Chemical or immunological reactions

B) Semiquantitative measurement by electrophoresis:

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

Electrophoresis: *is a technique used to separate different elements (fractions) of a blood sample into individual components.*

❖ Normal Pattern of Plasma Protein Electrophoresis:



❖ Types of Plasma Proteins:

- Prealbumin
- Albumin
- α1-Globulins:
  - a1-Antitrypsin, α-fetoprotein
- α2-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. That's why we call it Prealbumin
- 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 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.
- Tissue cells can take up albumin by pinocytosis where it is hydrolyzed to amino acids
- Useful in treatment of liver diseases, hemorrhage shock and burns

Pinocytosis: *A mechanism by which cells ingest extracellular fluid and its contents; it involves the formation of invaginations by the cell membrane, which close and break off to form fluid-filled vacuoles in the cytoplasm.*

❖ 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**. Thus, prolong the effect of the drugs.
- **Reduced protein-bound calcium**
  - Total plasma calcium level drops, because of the decreased binding with albumin.
  - 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

α_1-Antitrypsin

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

❖ Types of α1-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
  - α1-Antitrypsin accumulates in hepatocytes and is deficient in plasma

❖ Clinical Consequences of α1-Antitrypsin Deficiency:

- Neonatal jaundice with evidence of cholestasis
- Childhood liver cirrhosis
- Pulmonary emphysema in young adults, because of the destruction of elastic by elastase

❖ Laboratory Diagnosis:

- Lack of α1-globulin band in protein electrophoresis
- Quantitative measurement of α1-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, 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
- 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, because it's not bound to Ceruloplasmin

Haptoglobin

- Synthesized by the liver
- Binds to free hemoglobin to form complexes that are metabolized in the RES (reticuloendothelial system)
- 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. "Every molecule of transferrin binds to two molecule of iron "
- Plasma level drops in:
  - Malnutrition, liver disease, inflammation, malignancy
- Iron deficiency results in increased hepatic synthesis, to compensate the loss and can maximally bind to the available iron.
- A negative acute phase protein

β_2–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
  - 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: α1-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