PLASMA PROTEINS

BIOCHEMISTRY

- PLASMA is the clear, yellowish fluid portion of blood, lymph, or intramuscular fluid in which cells are suspended. It differs from serum in that it contains fibrin and other soluble clotting elements and
- (SERUM) is the clear yellowish fluid obtained upon separating whole blood into its solid and liquid components after it has been allowed to clot. Also called *blood serum*.

- Serum and plasma differs in one protein fibrin which is present in plasma and not in serum.All other protein content is same.

- Blood serum is mostly water that is dissolved with proteins, hormones, minerals and carbon dioxide. It is a very important source of electrolytes.

Difference Between Plasma And Serum | Difference Between | Plasma And Serum
http://www.differencebetween.net/science/health/difference-between-plasma-and-serum/#ixzz1w5PoDms5

THE BLOOD HAS MANY FUNCTIONS

- The functions of blood—except for specific cellular ones such as oxygen transport and cell-mediated immunologic defense—are carried out by plasma and its constituents.

Plasma consists of:

- **water, electrolytes, metabolites, nutrients, proteins, and hormones.**
- The water and electrolyte composition of plasma is practically the same as that of all extracellular fluids.
- Laboratory determinations of levels of Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^-, $PaCO_2$, and of blood pH are important in the management of many patients.

Major functions of blood.

- **Respiration—transport of oxygen from the lungs to the** tissues and of CO_2 from the tissues to the lungs.
- **Nutrition—transport of absorbed food materials.**
- **Excretion—transport of metabolic waste to the kidneys,** lungs, skin, and intestines for removal.
- Maintenance of the normal **acid-base balance in the** body.

- Regulation of **water balance through the effects of** blood on the exchange of water between the circulating fluid and the tissue fluid.
- Regulation of **body temperature by the distribution of** body heat.
- **Defense against infection by the white blood cells and** circulating antibodies.

- Transport of **hormones and regulation of metabolism.**
- Transport of **metabolites.**
- **Coagulation.**

- The concentration of total protein in human plasma is approximately **7.0–7. 5g/dL** and comprises the major part of the solids of the plasma.
- The proteins of the plasma are actually a complex mixture that includes not only simple proteins but also conjugated proteins such as **glycoproteins and various types of lipoproteins.**

- Thousands of **antibodies are present in human plasma,** though the amount of any one antibody is usually quite low under normal circumstances.

Dimensions and molecular masses of important plasma proteins

- Albumin- 69,000.
- Hemoglobin- 64,500
- β1-Globulin-90,000
- γ-Globulin-156,000
- α1-Lipoprotein-200,000
- β1-Lipoprotein-1,300,000
- Fibrinogen- 340,000

Half lives of plasma proteins

- The half-lives obtained for albumin and haptoglobin in normal healthy adults are approximately 20 and 5 days, respectively.
- In certain diseases, the half-life of a protein may be markedly altered. For instance, in some gastrointestinal diseases such as regional ileitis (Crohn disease), considerable amounts of plasma proteins, including albumin, may be lost into the bowel through the inflamed intestinal mucosa.

- Patients with this condition have a **protein-losing gastroenteropathy,** and the half-life of injected iodinated albumin in these subjects may be reduced to as little as 1 day.

Acute Phase Proteins

- **THE LEVELS OF CERTAIN PROTEINS IN PLASMA INCREASE DURING ACUTE INFLAMMATORY STATES OR SECONDARY TO CERTAIN TYPES OF TISSUE DAMAGE.**
- These proteins are called **“acute phase proteins” (or reactants).**

- include C-reactive protein (CRP, so-named because it reacts with the C polysaccharide of pneumococci).
- α1-antitrypsin
- haptoglobin
- α1-acid glycoprotein
- and fibrinogen.

- Their levels are also usually elevated during chronic inflammatory states and in patients with cancer. These proteins are believed to play a role in the body's response to inflammation.

Functions of Plasma Proteins.

Antiproteases

- Antichymotrypsin
- α1-Antitrypsin (α1-antiproteinase)
- α2-Macroglobulin
- Antithrombin

Blood clotting

- Various coagulation factors
- fibrinogen

Enzymes

- Function in blood, eg, coagulation factors,
- cholinesterase
- Leakage from cells or tissues, eg, aminotransferases

Hormones

- Erythropoietin

Immune defense

- Immunoglobulins,
- Complement proteins,
- β2-microglobulin

Involvement in Acute phase response

- proteins (eg,inflammatory C-reactive protein,
- α1-acid glycoresponses
- protein [orosomucoid])

Oncofetal

- α1-Fetoprotein (AFP)

Transport or binding proteins

- Albumin (various ligands including bilirubin, free fatty acids, ions [Ca2+], metals [eg, Cu2+, Zn2+], metheme, steroids, other hormones, and a variety of drugs.

- Ceruloplasmin (contains Cu2+;)
- Corticosteroid-binding globulin (transcortin) (binds cortisol)
- Haptoglobin (binds extracorpuscular hemoglobin)
- Lipoproteins (chylomicrons, VLDL, LDL,HDL)
- Hemopexin (binds heme)

- Retinol-binding protein (binds retinol)
- Sex hormone-binding globulin (binds testosterone, estradiol)
- Thyroid-binding globulin (binds T4, T3)
- Transferrin (transport iron)
- Transthyretin (formerly prealbumin; binds T4 and forms a complex with retinol-binding protein)

Albumin

- **Albumin Is the Major Protein in Human Plasma.**

- Albumin (69 kDa) is the major protein of human plasma (**3.4–4.7 g/dL)** and makes up approximately 60% of the total plasma protein.
- About 40% of albumin is present in the plasma, and the other 60% is present in the extracellular space.

- The liver produces about **12 g** of albumin per day, representing about 25% of total hepatic protein synthesis and half its secreted protein.
- Albumin is initially synthesized as a **preproprotein.** Its **signal peptide is removed as it passes into the** cisternae of the rough endoplasmic reticulum.

- Its **signal peptide is removed as it passes into the** cisternae of the rough endoplasmic reticulum, and a **hexapeptide at the resulting amino terminal is subsequently** cleaved off farther along the secretory pathway.
- The synthesis of albumin is depressed in a variety of diseases, particularly those of the liver.

- The plasma of patients with liver disease often shows a decrease in the ratio of albumin to globulins (decreased albumin globulin ratio)(normal A:G ratio 2:1).

- The synthesis of albumin decreases relatively early in conditions of protein malnutrition, such as kwashiorkor.

- Mature human albumin consists of one polypeptide chain of 585 amino acids and contains 17 disulfide bonds.

- Albumin 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.

FUNCTIONS:

1. Because of its relatively low molecular mass (about 69 kDa) and high concentration, albumin is responsible for 75– 80% of the **osmotic pressure** of human plasma.

- the plasma of certain humans lacks albumin. These subjects are said to exhibit **analbuminemia.**
- **One cause** of this condition is a mutation that affects splicing.

2. important function of albumin is its ability to **bind various ligands. These include:**

- free fatty acids (FFA), calcium, certain steroid hormones, bilirubin,and some of the plasma tryptophan.

3. Albumin play an important role in transport of copper in the human body.

4. A variety of drugs, including sulfonamides, penicillin G, dicumarol,and aspirin, are bound to albumin.

5. Preparations of human albumin have been widely used in the treatment of hemorrhagic shock and of burns.

Increase Levels:

- Hemoconcentration

Decreased Levels:

- Inflammation, infection, trauma, surgery, malignancy.
- Liver disease
- Nephrotic syndrome
- Malnutrition
- Pregnancy
- Premature infants
- Genetic analbuminemia

Haptoglobin

- **Haptoglobin Binds Extracorpuscular Hemoglobin, Preventing Free Hemoglobin From Entering the Kidney.**

- Haptoglobin (Hp) is a plasma glycoprotein that binds extracorpuscular hemoglobin (Hb) in a tight noncovalent complex (Hb-Hp).

- Approximately 10% of the hemoglobin that is degraded each day is released into the circulation and is thus extracorpuscular.

- The other 90% is present in old, damaged red blood cells, which are degraded by cells of the histiocytic system.

- The molecular mass of hemoglobin is approximately 65 kDa, whereas the molecular mass of haptoglobin Hp found in humans is approximately 90 kDa.

- Thus, the Hb-Hp complex has a molecular mass of approximately 155 kDa.

- Free hemoglobin passes through the glomerulus of the kidney, enters the tubules, and tends to precipitate therein (as can happen after a massive incompatible blood transfusion, when the capacity of haptoglobin to bind hemoglobin is grossly exceeded)

- However, the Hb-Hp complex is too large to pass through the glomerulus.

- The function of Hp thus appears to be to prevent loss of free hemoglobin into the kidney. This conserves the valuable iron present in hemoglobin, which would otherwise be lost to the body.

- The levels of haptoglobin in human plasma vary and are of some diagnostic use. Low levels of haptoglobin are found in patients with **hemolytic anemias.**

- Hemopexin is a β1-globulin that binds free heme.

Fibrinogen

- Fibrinogen is converted to fibrin by thrombin.
- Fibrin monomers polymerizes to form fibrin clot.

Increased levels:

- Infection, inflammation, surgery, malignancy
- Nephrotic syndrome
- Pregnancy
- Estrogen therapy

Decreased levels:

- Liver diseases
- Incompatible blood transfusions
- Obstetrical complications
- DIC (disseminated intravascular complication)

Transferrin

- **Absorption of Iron From the Small Intestine Is Tightly Regulated.**

- Transferrin (Tf) is a plasma protein that plays a central role in transporting iron around the body to sites where it is needed.

- Enterocytes in the proximal duodenum are responsible for absorption of iron. Incoming iron in the Fe3+ state is reduced to Fe2+ by a **ferri reductase present on** the surface of enterocytes.

- Vitamin C in food also favors reduction of ferric iron to ferrous iron.

- The transfer of iron from the apical surfaces of enterocytes into their interiors is performed by a proton-coupled divalent metal transporter (DMT1).
- This protein is not specific for iron, as it can transport a wide variety of divalent cations.
- Once inside an enterocyte, iron can either be stored as ferritin or transferred across the basolateral membrane into the plasma, where it is carried by transferrin.

- Passage across the basolateral membrane appears to be carried out by another protein, possibly iron regulatory protein 1 (IREG1).

- This protein may interact with the copper-containing protein hephaestin,a protein similar to ceruloplasmin .

- Hephaestin is thought to have a ferroxidase activity, which is important in the release of iron from cells.

- Thus, Fe^{2+} is converted back to Fe^{3+}, the form in which it is transported in the plasma by transferrin

Overall regulation of iron absorption

1. Dietary regulation

- The level of the enterocyte, where further absorption of iron is blocked if a sufficient amount has been taken up (so-called dietary regulation exerted by “mucosal block”).

Erythropoeitic Regulation

- It also appears to be responsive to the overall requirement of erythropoiesis for iron (erythropoietic regulation).

- Absorption is excessive in hereditary hemochromatosis

Transferrin Shuttles Iron to Sites Where It Is Needed.

- There are receptors (TfRs) on the surfaces of many cells for transferrin. It binds to these receptors and is internalized by receptor-mediated endocytosis.

- The acid pH inside the lysosome causes the iron to dissociate from the protein. The dissociated iron leaves the endosome via DMT1 to enter the cytoplasm.

Ferritin

Ferritin Stores Iron in Cells

- Ferritin contains approximately 23% iron
- Ferritin is composed of 24 subunits of 18.5 kDa, which surround in a micellar form some 3000–4500 ferric atoms.

- Normally, there is a little ferritin in human plasma.
- In patients with excess iron, the amount of ferritin in plasma is markedly elevated.
- The amount of ferritin in plasma serves as an index of body iron stores.

- When iron levels are high, cells use stored ferritin mRNA to synthesize ferritin, and the TfR mRNA is degraded.
- In contrast, when iron levels are low, the TfR mRNA is stabilized and increased synthesis of receptors occurs, while ferritin mRNA is apparently stored in an inactive form.
- This is an important example of control of expression of proteins at the **translational level.**

Decreased Levels:

- Iron deficiency
- Pregnancy
- Chronic blood loss

Increased Levels:

- Liver disease- Cirrhosis
- Infection, inflammation, surgery
- Chronic renal infection
- Chronic viral infection

Iron Deficiency Anemia

- iron metabolism is **particularly important in women due to:**

1. **Menstural loss**
2. **Increase fetal demand in pregnancy.**

- Older people with poor dietary habits may develop iron deficiency.

Iron deficiency anemia is due to:

- inadequate intake,
- Inadequate utilization
- excessive loss of iron

Total iron-binding capacity

- The concentration of transferrin in plasma is approximately 300 mg/dL.

- This amount of transferrin can bind 300 µg of iron per deciliter, this represents the **total iron-binding capacity of plasma.**

- The protein is normally only one-third saturated with iron.

- In **iron deficiency anemia, the protein is even less** saturated with iron, whereas in conditions of storage of excess iron in the body (e.g, hemochromatosis) the saturation with iron is much greater than one-third.

Hereditary Hemochromatosis

- Hereditary (primary) hemochromatosis is a very prevalent autosomal recessive disorder in certain parts of the world (e.g, Scotland, Ireland, and North America).

- It is characterized by excessive storage of iron in tissues, leading to tissue damage.

- Total body iron ranges between **2.5 g and 3.5 g** in normal adults; in primary hemochromatosis it usually exceeds **15 g**.

- Mutations in *HFE, located on chromosome 6* leading to abnormalities in the structure of its protein product.
- Accumulation of iron in various tissues, but particularly liver, pancreatic islets, skin, and heart muscle.
- Iron directly or indirectly causes damage to the above tissues, resulting in hepatic cirrhosis, diabetes mellitus, skin pigmentation, and cardiac problems

- The frequent coexistence of diabetes mellitus (due to islet damage) and the skin pigmentation led to use of the term **bronze diabetes** for this condition.

Secondary hemochromatosis

- **Secondary hemochromatosis can occur after repeated** transfusions (eg, for treatment of sickle cell anemia)

- excessive oral intake of iron (eg, by African Bantu peoples who consume alcoholic beverages fermented in containers made of iron), or a number of other conditions.

Laboratory tests for assessing patients with disorders of iron metabolism

- Red blood cell count and estimation of hemoglobin
- Determinations of plasma iron, total iron-binding capacity (TIBC), and % transferrin saturation
- Determination of ferritin in plasma by radioimmunoassay
- Prussian blue stain of tissue sections
- Determination of amount of iron (μg/g) in a tissue biopsy

Ceruloplasmin

- **Ceruloplasmin Binds Copper, & Low Levels of This Plasma Protein Are Associated With Wilson Disease.**

Copper Is a Cofactor for Certain Enzymes

- Copper is an essential trace element. It is required in the diet because it is the metal cofactor for a variety of enzymes.

- Copper accepts and donates electrons and is involved in reactions involving dismutation, hydroxylation, and oxygenation.

- Excess copper can cause problems because it can oxidize proteins and lipids, bind to nucleic acids, and enhance the production of free radicals.

- The body of the normal adult contains about 100 mg of copper, located mostly in bone, liver, kidney, and muscle.

- The daily intake of copper is about 2–4 mg, with about 50% being absorbed in the stomach and upper small intestine and the remainder excreted in the feces.

Enzymes with Cu as cofactor:

1. Superoxide dismutase
2. Cytochrome oxidase
3. Tyrosinase
4. Amine oxidase

- Copper is carried to the liver bound to albumin, taken up by liver cells, and part of it is excreted in the bile.

- Copper also leaves the liver attached to **ceruloplasmin,** which is synthesized in that organ.

- Ceruloplasmin is an α2-globulin. It has a blue color because of its high copper content and carries 90% of the copper present in plasma.
- Each molecule of ceruloplasmin binds six atoms of copper.
- Albumin carries the other 10% of the plasma copper.

Decreased Levels:

1. liver disease.

2. Wilson disease (hepatolenticular degeneration), **a disease due to abnormal metabolism of copper.**

Wilson disease

- Wilson disease is a genetic disease in which copper **fails to be excreted in the bile** and accumulates in liver, brain, kidney, and red blood cells.

- The increase of copper in liver cells appears to **inhibit the coupling of copper to apoceruloplasmin** and leads to low levels of ceruloplasmin in plasma.

- Defect is in **copper binding P-TYPE ATPASE**

- The amount of copper accumulates, patients may develop a hemolytic anemia, chronic liver disease (cirrhosis, hepatitis), and a neurologic syndrome owing to accumulation of copper in the basal ganglia and other centers.

- A frequent clinical finding is the **Kayser-Fleischer ring. This is a green or golden pigment** ring around the cornea due to deposition of copper in Descemet's membrane.

- Treatment for Wilson disease consists of a diet low in copper along with lifelong administration of **penicillamine,** which chelates copper, is excreted in the urine, and thus depletes the body of the excess of this mineral.

Menkes Disease

3. Menkes Disease Is Due to Mutations in the Gene Encoding a Copper- Binding P-Type ATPase

- Menkes disease ("kinky" or "steely" hair disease) is a disorder of copper metabolism.
- It is X-linked, affects only male infants, involves the nervous system, connective tissue, and vasculature, and is usually fatal in infancy.

1. There is defective exit of copper from the intestinal and other cells, so the utilization of copper is defective.
2. Secondly the incorporation of copper into apoceruloplasmin.

4. Severe liver disease
5. Malnutrition
6. Gastroenteropathies
7. Nephrotic syndrome

Increased levels:

- Physical exercise
- Trauma, surgery
- Rheumatoid arthritis
- Late pregnancy

Learning resource

- **Harpers Biochemistry**