REVIEW OF RESEARCH
ISSN: 2249-894X
IMPACT FACTOR : 5.7631(UIF)
VOLUME - 11 | ISSUE - 8 | MAY - 2022

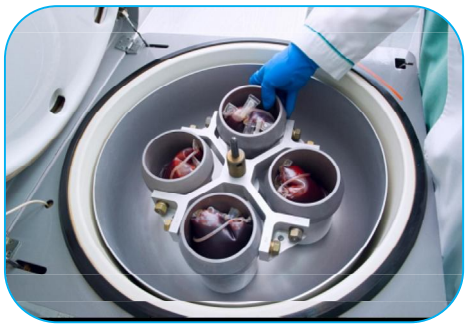
PLASMA PROTEINS, PLASMA PHERESIS: FUNCTIONS AND CLINICAL SIGNIFICANCE

Prasanth Babu[1], Sravani Pragna K.[1], Kalyan Chakravarthi C.[1], Muralinath E.[1], Guru D. V. Pandyan[4], Daniel Krupa D.[5], Varaprasad Reddy L. S. S.[2], Guru Prasad.[3], Hemanth Gowda[7], Katyani[8], Tulasi Rukmini. K[1], Srihari Reddy. K[1], Jayasurya, S[1], Navitha Reddy[1], Nikhil. J[6] and Gnana Prassunamba. T[1]

[1]College of Veterinary Science, Proddatur, Andhra Pradesh.
[2]College of Veterinary, Tirupathi, Andhra Pradesh.
[3]Sterline Bioremedies Pvt. Ltd, Andhra Pradesh.
[4]VCRI, Thanjavur, Tamil Nadu.
[5]Anatomy Faculty, SPSS Medical College & LTH, Maharashtra.
[6]College of Veterinary Science, Gannavaram, Andhra Pradesh.
[7]Hasan Veterinary College, Hasan, Karnataka.
[8]College of Veterinary Sciences, Kerala.

INTRODUCTION

Plasma Proteins: Different types of plasma proteins are serum Albumin, serum globulin and Fibrinogen (Fig.1). Only albumin and globulin observed in the serum whereas the fibrinogen is absent in serum due to conversion of fibrinogen to fibrin during blood clotting. Due to this reason, the albumin and globulin are termed as serum albumin and serum globulin.



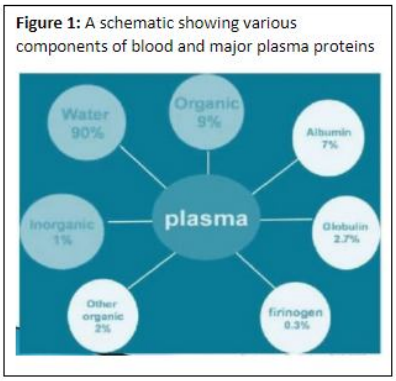


Figure 1: A schematic showing various components of blood and major plasma proteins

Normal values: The normal values of plasma proteins are:
Total Proteins: 7.3 g/dl
Albumin: 4.7g/dl
Globulin: 2.3g/dl
Fibrinogen: 0.3g/dl

Albumin/ Globulin (A/G) ratio: Plasma A/G ratio, bearing a normal of value of 2:1, is an excellent indicator of diseases of kidney or liver.

Isolation of plasma proteins: - Several methods, as outlined below, are utilized for separation of plasma proteins.

1. Salting Out method: salting out method, serum blobulin is resoved into two fractions known as Euglobulin and pseudo globulin, by utilizing different solutions. Euglobulin is seperated either by full saturation with sodium chloride solution or half saturation with magnesium sulfate solution or one-third saturation with ammonium sulfate solution. Pseudoglobulin is separated by full saturation with magnesium sulfate and half saturation with ammonium sulfate. Pseudoglobulin is soluble in water but cannot be salted out with the help of sodium chloride solution.

2. Precipitation method: It is performed by precipitating globulin with 22% sodium sulfate solution, while albumin retains in solution.

3. Cochin's frictional precipitation method: The separation of plasma proteins occurs into albumin and different factions of globulins based on their solubility. In this way, plasma proteins are separated due to their difference in electrical charge noted in a Tiselus apparatus that utilize paper, cellulose or starch block. With the help of this method, separation of proteins occur into albumin (55%), & alpha globulin (13%), beta globulin (14%) and fibrinogen (7%).

4. Gel filtration chromatography: It is a column chromatographic method by which the separation of proteins occurs based on their size. By passing through a bed of porous beads, proteins are resolved. The diffusion of different proteins into the beads is dependent on their size only.

5. Ultracentrifugation method: By this method, the separation of albumin, globulin and fibrinogen takes place based on their density. Therefore ultracentrifugation helps to estimate the molecular weight of these proteins.

6. Immunoeletrophoretic method: The separation of proteins is based on electrophoretic patterns formed by precipitation at the site of antigen antibody reaction. Thus revealing quantitative estimates of different proteins.

Characteristics of plasma proteins:

1. Osmotic pressure: The plasma proteins are liable for the oncotic or osmotic pressure in (right) the blood. The osmotic pressure exerted by proteins in the plasma is termed as colloidal osmotic (oncotic) pressure. Generally, it is around 25 mmHg. Albumin participates in causing oncotic pressure of plasma to the maximum extent.

2. Specific gravity: Specific gravity of plasma proteins is 1.026.

3. Role in clotting of the blood: Fibrinogen is responsible in clotting of blood.

4. Buffer action: Ability to regulate pH by accepting reducing equivalents is called buffer action. The Plasma proteins have 1/6 of total buffering action of the blood.

5. Molecular weight of plasma proteins (Daltons):

Albumin : 69,000
Globulin : 1,56,000
Fibrinogen: 4,00,000

Table 1. Functions of plasma proteins

Function	Example
Transport	**Thyroxine-binding globulin** (thyroid hormones) **Apolipoproteins** (cholesterol, triglyceride)
Humoral immunity	Immunoglobulins
Maintenance of oncotic pressure	All proteins, particularly albumin
Enzymes	Renin, coagulation factors, complement proteins
Protease inhibitors	α1-antitrypsin (acts on protease)
Buffering	All proteins

Origin of plasma proteins:

Embryonic: In embryonic stage, the plasma proteins are synthesized by the mesenchyme cells. The albumin is synthesized first and other proteins are synthesized later.

Adulthood: Synthesis of plasma proteins occurs primarily from reticulo-endothelial cells of the liver. The synthesis of plasma proteins also takes place from bone marrow, disintegrating graft blood cells, generate tissue cells and spleen. The synthesis of gamma globulins occur from B lymphocytes.

Functions of plasma proteins: Plasma proteins have diverse functions

1. **Role in coagulation of blood:** Fibrinogen is a requisite factor for coagulation of blood.
2. **Role in defence mechanism of body:** Particularly the gamma globulins exhibit an important role in the defence mechanism of the body by behaving as antibodies (immune compounds). The antibodies react with antigens of different microorganism, which cause diseases such as diphtheria, hepatitis, measles, rubella, polio myelitis etc.
3. **Role in transport mechanism:** Plasma proteins are required for the transport of different compounds in the blood. Besides albumin, alpha globulin and beta globulin are indispensable for transportation of hormones, enzymes etc. The alpha and beta globulins participate in the synthesis of proteins by mesenchyme cells. The alpha and beta globulins plays an important role in the transport of metals in the blood.
4. **Role in maintenance of osmotic pressure in blood:** At the capillary level, exchange of the compounds takes place between the blood and the tissues. However, plasma proteins pas through capillary membrane. easily because of their larger size and hence are retained in the blood. In blood, these proteins exert the colloid of osmotic (oncotic) pressure. The osmotic pressure caused by the plasma proteins is about 25mm Hg. Plasma levels of albumin constitute more than half of the total plasma proteins, which is significantly greater than globulins and fibrinogen. So albumin contribution to plasma oncotic pressure is maximum. Plasma proteins provide viscosity to the blood, which is also important to maintain blood pressure. Furthermore, albumin, compared to other plasma proteins, provides maximum viscosity to plasma.

Figure 2: Cell separator used for blood cell isolation for re-transfusion.

Plasmapheresis: Plasmapheresis is an experimental procedure used to assess the importance of plasma Proteins in maintaining homeostasis in animals. Previously, this procedure was called Whipple's experiment because it was established by George Hoyt Whipple.

Procedure: This procedure is also broadly referred to as 'Tissue plasma exchange'. Blood will be removed from the body of experimental dog. Erythrocytes are then separated form plasma and are re-

suspended in a physiological solution called Locke's solution. Then this suspension is re-infused into the body of the same dog. Because this procedure involves removal of plasma proteins and a sudden deficiency of plasma proteins. plasma proteins leads to state of shock in animal. If the animal is provided diet with sufficiently high quantity of proteins, the restoration of plasma proteins to normal values occur within seven days and the animal survives. The synthesis of new plasma proteins takes place by the liver of the dog. If the experiment is conducted in animals after extirpation of liver, and even if the diet contains adequate quantity of proteins, the production of plasma proteins doesn't happen significantly.

The shock retains in the animal and the animal dies. Plasmapheresis' experiments provide useful insights into two major physiological aspects that are pivotal to the success of this procedure:

1. Importance of plasma proteins for survival
2. Synthesis of plasma proteins by the liver

Clinical importance of plasma proteins – Therapeutic plasma exchange: Plasmapheresis is known as a blood purification procedure for an effective temporary treatment for various autoimmune diseases. It is also synonymously known as therapeutic plasma exchange. In an autoimmune disease, antibodies are produced by the host animal body that attacks its' own tissues. The antibodies are proteins in nature and circulate in the bloodstream before attacking the target tissues. Plasmapheresis is used to purge these antibodies out of the blood.

Procedure: From the patient, venous blood is removed and blood cells are separated using an equipment called 'Cell separator' (Fig. 2). After removing the blood from body an anticoagulant is applied to prevent clotting of blood. After isolation of blood cells by centrifugation procedure, plasma is discarded. Blood cells are then suspended in physiological saline, and is re-transfused into the bloodstream of the patient along with human albumin protein.

Clinical utility of Plasmapheresis: Even though Plasmapheresis is capable of removing antibodies from the blood, it cannot prevent the production of new antibodies by the immune system of the body. So, it can arrange only a temporary relief of giving the protection to the tissues from the antibodies. The patients must undergo for repeated sessions of this treatment. Plasmapheresis is an effective temporary treatment particularly for the following diseases:

1. Myasthenia gravis – an autoimmune disease of neural tissue manifested as severe muscle weakness.
2. Thrombocytopenic purpura – bleeding disorder.
3. Paraproteinemic peripheral neuropathy – An antibody called paraprotein-A attacks peripheral nerves and causes the dysfunction of peripheral nervous system.
4. Chronic demyelinating polyneuropathy – Disorder of neural tissue characterized by damage of myelin sheath in peripheral nerves resulting in impaired sensory function in limbs.
5. Guillain-Barre syndrome – is autoimmune disease causing weakness and Tingling-like sensations in the limbs, which may lead to paralysis.
6. Lambert-Eaton syndrome –autoimmune disorder of the neuromuscular junction.

Variations in Plasma proteins level: Level of plasma proteins (Fig. 2) vary independently of one another, besides each of their functions (Fig. 3). Regardless, the quantity of albumin and globulin change in opposite direction in several disease conditions. Enhancement of all fractions of plasma proteins is called hyperproteinemia and reduction in all fractions of plasma proteins is called hypoproteinaemia.

Conditions that result in increased plasma protein levels: Acute infections like acute hepatitis and acute nephritis, alcoholism, dehydration, excuses of glucocorticoids, hemolysis, leukemia, respiratory distress syndrome (RDS), rheumatoid arthritis.

Conditions that result in decreased plasma protein levels: **C**hronic hepatitis or nephritic haemorrhage, malnutrition, burns, liver cirrhosis, pregnancy, and prolonged starvation, all can lead to reduced plasma protein levels.

Conditions that result in increased albumin protein levels in plasma: Congestive Heart failure (CHF), dehydration and glucocorticoid excess.

Conditions that result in reduced albumin protein levels in plasma: Burns, cirrhosis of liver, excess intake of water, hypothyroidism, malnutrition and nephrosis.

Conditions leading to increased plasma globulins: Chronic infections, cirrhosis of liver, nephrosis, rheumatoid arthritis.

Conditions leading to decreased plasma globulins: Acute hemolytic anemia, emphysema, glomerulonephritis and hypo gamma globulinemia.

Conditions that enhance plasma fibrinogen: Acute infections, Glomerulo nephritis, Myocardial infarction, rheumatoid arthritis, stroke, trauma.

Conditions that reduce plasma fibrinogen: Liver dysfunction, use of anabolic steroids and use of phenobarbital.

Enhanced albumin/globulin ratio is seen in the following conditions: Excess of glucocorticoids, hypo gamma globulinemia, hypothyroidism and intake of carbohydrate or protein diet.

Reduced Albumin/ Globulin ratio is observed during the following conditions: Liver dysfunction and nephrosis.

Symptoms associated with low plasma protein levels: Brittle of ridged nails, bruising easily, fatigue, headaches, hair loss, nausea, rashes and slow clotting of blood after an injury.

Symptoms associated with plasma high protein levels: Excessing thirst, frequent infections, loss of appetite, numbness of tingling in your hands, feet or legs, weight loss.

Utility of plasma protein tests: Plasma protein tests are useful in measuring the amounts of specific proteins in the blood. Total protein levels may be higher or lower than average in the case of certain abnormalities. Such as bone marrow disorders, edema (fluid build-up in in the tissues), hepatitis (liver infection, HIV, inflammatory bowel disease (IBD), kidney disease, leukemia and liver disease. Birth control pills and estrogen medication may reduce blood protein levels. Plasma proteins and pregnancy: Low levels of pregnancy – associated plasma proteins A (Papp-a) in early pregnancy are linked with certain complications. Examples for these complications are Down's syndrome, gestational diabetic mellitus, hypoxia or a lack of oxygen for the baby at birth, intra uterine growth restriction (IUGR), low birth weight, pre-eclampsia and still birth.

Follow-up for plasma protein tests: If patients total protein estimations are abnormal, a series of follow-up tests must be performed namely C- reactive protein test, immunoglobulin -A (Ig-A) test, liver enzyme tests and protein electrophoresis. C-reactive protein test is used for evaluating inflammation. Immunoglobulin A (Ig-A) test is helpful for measuring antibodies and diagnosing auto immune diseases. Liver enzyme test are essential for detecting related diseases and inflammation. Proteins electrophoresis is meant for knowing bone marrow, disorders of patient's abnormal protein levels are caused by AIDS, heart disease, kidney disease, liver disease and HIV.

REFERENCES

1. Burnouf T. Modern plasma fractionation. Transfus Med Rev. 2007 Apr;21(2):101-17.
2. Benjamin RJ, McLaughlin LS. Plasma components: properties, differences, and uses. Transfusion. 2012 May;52 Suppl 1:9S-19S.
3. Peters T. Intracellular precursor forms of plasma proteins: their functions and possible occurrence in plasma. Clin Chem. 1987 Aug;33(8):1317-25.
4. Heim MU, Meyer B, Hellstern P. Recommendations for the use of therapeutic plasma. Curr Vasc Pharmacol. 2009 Apr;7(2):110-9.
5. Traclet J, Delaval P, Terrioux P, Mornex JF. Augmentation therapy of alpha-1 antitrypsin deficiency associated emphysema. Rev Mal Respir. 2015 Apr;32(4):435-46.