Serum Albumin and Globulin

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Definition

Hundreds of proteins are dissolved in the plasma. By measuring the concentration of these proteins, the clinician can obtain information regarding disease states in different organ systems. The measurement of protein is done on serum, which is the fluid that remains after plasma has clotted, thus removing fibrinogen and most of the clotting factors. Total protein content provides some information regarding a patient's general status; more clinically useful data are obtained from fractionating the total protein. The normal serum protein level is 6 to 8 g/dl. Albumin makes up 3.5 to 5.0 g/dl, and the remainder is the total globulins. These values may vary according to the individual laboratory.

Technique

The most widely used method of measuring serum protein is the biuret reaction. The principle of this reaction is that serum proteins react with copper sulfate in sodium hydroxide to form a violet "biuret" complex. The intensity of the violet color is proportional to the concentration of protein.

Albumin is generally measured by a dye-binding technique that utilizes the ability of albumin to form a stable complex with bromocresol green dye. The BCG-albumin complex absorbs light at a different wavelength from the unbound dye. This method may overestimate albumin by binding to other proteins. The total globulin fraction is generally determined by subtracting the albumin from the total protein.

Electrophoresis is the most common means of further fractionating serum proteins. In this process, protein solutions in appropriate buffered solvents are placed on a medium such as paper or starch blocks and exposed to an

electrical current. Differences in their electrical charge cause the protein components to migrate at different rates toward the anode or cathode.

Immunoelectrophoresis is used to evaluate an increase in the gamma fraction. Specific antisera to each immunoglobulin type are used to determine whether the increase is monoclonal (i.e., composed of one immunoglobulin type) or polyclonal (i.e., due to an increase in the number of many different immunoglobulins).

Basic Science

Albumin makes up more than half of the total protein present in serum. Approximately 30 to 40% of the body's total albumin pool is found in the intravascular compartment. The remainder is extravascular and is located in the interstitial spaces, mainly of the muscles and skin. Albumin is also found in small amounts in a variety of body tissue fluids such as sweat, tears, gastric juice, and bile.

Albumin does not diffuse freely through intact vascular endothelium. Hence, it is the major protein providing the critical colloid osmotic or oncotic pressure that regulates passage of water and diffusable solutes through the capillaries. Albumin accounts for 70% of the colloid osmotic pressure. It exerts a greater osmotic force than can be accounted for solely on the basis of the number of molecules dissolved in the plasma, and for this reason it cannot be completely replaced by inert substances such as dextran. The reason is that albumin has a negative charge at normal blood pH and attracts and retains cations, especially Na^+ in the vascular compartment. This is called the *Gibbs–Donnan effect*. Albumin also binds a small number of Cl^- ions that increase its negative charge and ability to retain Na^+ions inside the capillaries. This enhanced osmotic force causes the colloid osmotic pressure to be 50% greater than it would be by protein concentration alone.

Albumin serves in the transport of bilirubin, hormones, metals, vitamins, and drugs. It has an important role in fat metabolism by binding fatty acids and keeping them in a soluble form in the plasma. This is one reason why hyperlipemia occurs in clinical situations of hypoalbuminemia. The binding of hormones by albumin regulates the amount of free hormone available at any

time. Because of its negative charge, albumin is also able to furnish some of the anions needed to balance the cations of the plasma.

Albumin is synthesized in the liver. The rate of synthesis is constant in normal individuals at 150 to 250 mg/kg/day, resulting in the production of 10 to 18 g of albumin daily in a 70-kg man. The liver produces albumin at less than half of its capacity. The primary factors affecting albumin synthesis include protein and amino acid nutrition, colloidal osmotic pressure, the action of certain hormones, and disease states. Fasting or a protein-deficient diet cause a decrease in albumin synthesis as long as the deficiency state is maintained. In the normal individual, the liver increases albumin synthesis in response to the increased availability of amino acids provided by the portal blood following each protein-containing meal. A decrease in extravascular colloidal pressure serves as a stimulus for albumin synthesis and is thought to act within the liver. Thyroid hormone, corticosteroids, growth hormone, and insulin all can increase albumin synthesis.

The main site of albumin degradation is not known. Albumin appears to be catabolized in locations that are capable of rapid equilibration with the bloodstream. It is degraded into amino acids that are utilized for energy requirements of the cell or secreted into the pool of extracellular amino acids.

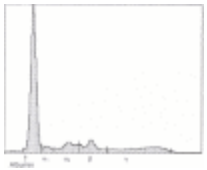

Figure 101.1

Normal serum protein electrophoresis.

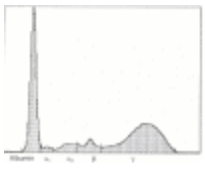

Figure 101.2

Serum protein electrophoresis with polyclonal gammopathy.

The globulin fraction includes hundreds of serum proteins including carrier proteins, enzymes, complement, and immunoglobulins. Most of these are synthesized in the liver, although the immunoglobulins are synthesized by plasma cells. Globulins are divided into four groups by electrophoresis. The four fractions are α_1, α_2, β and γ, depending on their migratory pattern between the anode and the cathode. Increases in the globulin fraction usually result from an increase in immunoglobulins, but there can be an increase in other proteins in pathologic states that have characteristic electrophoretic patterns (see Figures 101.1,101.2). Malnutrition and congenital immune deficiency can cause a decrease in total globulins due to decreased synthesis, and nephrotic syndrome can cause a decrease due to protein loss through the kidney.

Immunoglobulins (i.e., antibodies) migrate mainly in the γ region, but some migrate in the β and α_2 regions as well. Each immunoglobulin molecule is composed of two heavy chains that are of the same class and two light chains that are also alike. Each heavy chain has a variable region (in which amino acid substitutes make each chain different from the next) and a constant region (in which there are very few amino acid differences from the constant region of any other immunoglobulin of that heavy chain type). Light chains are of either λ or κ type and have constant and variable regions. The different kinds of immunoglobulins are named by capital letters that correspond to their heavy chain type: IgG, IgA, IgM, IgE, and IgD. Three-fourths of the immunoglobulin level in normal serum is of the IgG type. Many antibodies to bacteria and viruses are IgG.

The normal collection of IgG molecules is made up of minute amounts of different IgG antibodies produced from diverse clones of plasma cells; thus it is polyclonal. If a single clone escapes its normal controls, it can reproduce excessively and synthesize an excess of a monoclonal protein with a single heavy chain class and light chain type.

Clinical Significance

The only clinical situation that causes an elevation in serum albumin is acute dehydration. A variety of clinical entities result in a decreased albumin level, either from depressed synthesis or increased losses. A decrease in albumin

synthesis is caused by end-stage liver disease, intestinal malabsorption syndromes, and protein-calorie malnutrition. Examples of albumin loss are nephrotic syndrome and severe burns because the skin is the most important extra storage pool for albumin. The consequence of a decrease in serum albumin is a shift of fluid from the intravascular to the interstitial space, resulting in intravascular volume depletion and edema formation.

Any increase or decrease in the globulin fraction should be evaluated by serum electrophoresis. The pattern should be visually inspected for abnormalities in particular regions.

The α_1 fraction consists mainly of α_1 antitrypsin. Significant decreases of this fraction are seen in patients with congenital α_1 antitrypsin deficiency; an increase is seen in acute inflammatory disorders because α_1 antitrypsin is an acute phase reactant.

The major proteins migrating in the $\alpha_2$region include α_2 macroglobulin and haptoglobin. There is an increase in α_2 macroglobulin in the nephrotic syndrome when lower molecular weight proteins are lost in the urine. Haptoglobin rises in response to stress, infection, acute inflammation, or tissue necrosis, probably by stimulation of synthesis. Haptoglobin levels decrease after a hemolytic reaction because the haptoglobin complexes with free hemoglobin and is cleared from the circulation.

The major β globulin is transferrin. Elevations occur in severe iron deficiency. Complement components C3, C4, and C5 also migrate in the β region.

The most frequent abnormalities in the γ region are a broad-based polyclonal increase or a narrow monoclonal spike. Polyclonal increases are seen in chronic infections, connective tissue diseases, and liver disease. Monoclonal spikes suggest multiple myeloma, Waldenstrom's macro-globulinemia, primary amyloidosis, lymphoma, or monoclonal gammopathy. Any abnormality in the γ region suggesting a monoclonal spike should be further evaluated by immunoelectrophoresis.

Hypogammaglobulinemia is characterized by a decrease in the γ component. It is seen in congenital immune deficiency syndromes or in association with

diseases such as nephrotic syndrome, chronic lymphocytic leukemia, and corticosteroid treatment.

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