



## An In-Depth Look:

ALBUMIN IN HEALTH  
AND DISEASE

## Albumin in Health and Disease: Protein Metabolism and Function\*

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### ABSTRACT:

Albumin is a highly charged, 69,000 D protein with a similar amino acid sequence among many veterinary species. Albumin is the major contributor to colloid oncotic pressure and also serves as an important carrier protein. Its ability to modulate coagulation by preventing pathologic platelet aggregation and augmenting antithrombin III is important in diseases that result in moderately to severely decreased serum albumin levels. Synthesis is primarily influenced by oncotic pressure, but inflammation, hormone status, and nutrition impact the synthetic rate as well. Albumin degradation is a poorly understood process that does not appear to be selective for older molecules. The clinical consequences of hypoalbuminemia reflect the varied functions of the ubiquitous albumin protein molecule.

**T**he albumin molecule has several characteristics that make it a unique protein. Most veterinarians are aware of the importance of this molecule in maintaining colloid oncotic pressure, but albumin has many other less commonly recognized functions as well. The clinical consequences of hypoalbuminemia are reflections of the many functions albumin fulfills. Understanding the functions, synthesis, and degradation of the albumin molecule can improve understanding of the causes, consequences, and treatment of hypoalbuminemia.

### STRUCTURE

Albumin has a molecular weight of approximately 69,000 D, with minor variations among species. There is 83% to 88% amino acid homology among albumin molecules of many veterinary species.<sup>1</sup> The protein consists of a single peptide chain containing 580 to 585 amino acids, depending on the species.<sup>2</sup> A large number of these amino acid

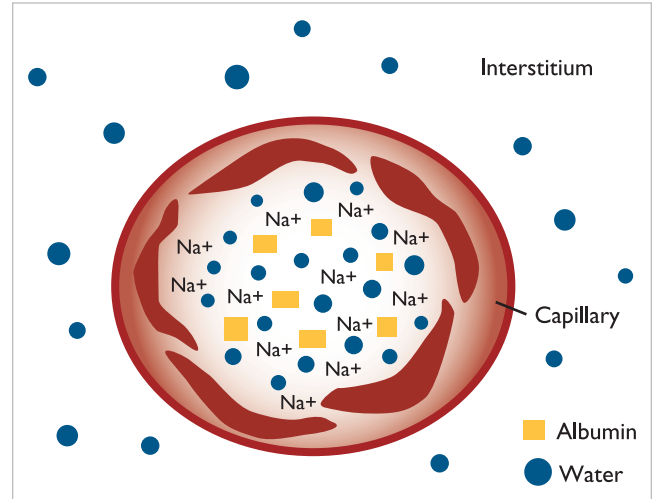
\*A companion article on causes and treatment of hypoalbuminemia appears on page 940.

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**Figure 1. Three-dimensional structure of the albumin molecule.** (Adapted from Cistola DP: Fat sites found! *Nat Struct Biol* 5[9]:751–753, 1998.)

residues are charged, resulting in a high net negative charge at physiologic pH.<sup>3</sup> This negative charge is important for the protein's role in maintaining oncotic pressure, which will be discussed later. The tertiary structure of albumin is quite variable: It flexes, contracts, and expands with changes in its environment<sup>4</sup> (Figure 1). As is typical of extracellular proteins, the folded protein structure of albumin has a large amount of disulfide binding, adding



**Figure 2. Oncotic pressure.** Because albumin molecules have a relatively low molecular weight compared with other plasma proteins and are more numerous in the circulation, albumin is the largest contributor to colloid oncotic pressure. The protein's high net negative charge attracts cations such as sodium ( $\text{Na}^+$ ), causing water to follow and move across the semipermeable capillary membrane into the intravascular space.

### Oncotic Support

Colloid oncotic pressure is the force created by macromolecules present within the vascular space that prevents water from escaping from the intravascular space (Figure 2). Albumin accounts for 50% to 60% of total plasma protein but provides 75% to 80% of colloid oncotic pressure in healthy animals. This disproportionately large contribution to colloid oncotic pressure is

**Serum albumin levels may not reflect total body albumin levels because approximately 60% of albumin is in the extravascular space.**

stability to the molecule. It may be in these disulfide bonds that heterogeneity exists among individuals.

### FUNCTIONS

Albumin has a number of important roles in the body, including maintaining oncotic pressure and binding a variety of molecules. The protein also contributes to the pool of amino acids used for protein synthesis, buffers extravascular fluids, aids in preventing pathologic thrombus formation, and helps maintain normal microvascular permeability.

partly due to the relatively small size (69,000 D) of the albumin molecule compared with that of other serum protein molecules, such as fibrinogen (624,000 D) and globulin (up to 160,000 D).<sup>5</sup> As described by van't Hoff's law, colloid oncotic pressure generated by a particle is indirectly proportional to the molecular weight of the particle. This effect accounts for about 66% of the colloid oncotic pressure created by small albumin molecules. The remainder of albumin's contribution to colloid oncotic pressure relates to its negative charge and is described by the Gibbs-Donnan effect. The negative

## Important Endogenous and Exogenous Substances Carried by Albumin<sup>2,5</sup>

### Endogenous

Bilirubin	Fatty acids
Calcium	Free radicals
Copper	Glucocorticoids
Cysteine	Thyroxine (T <sub>4</sub> )
Fat-soluble vitamins	Tryptophan

### Exogenous

#### Antiinflammatory

Ibuprofen	Salicylic acid
Phenylbutazone	

#### Antimicrobial

Cephalosporins	Sulfonamides
Penicillins	Tetracyclines

#### Cardiovascular

Digitoxin	Propanolol
Furosemide	Quinidine
Hydralazine	

#### Central nervous system active

Amitriptyline	Phenobarbital
Chlorpromazine	Thiopental
Diazepam	

#### Miscellaneous

Glipizide	Warfarin
Radiocontrast media	

charge of the protein attracts cations such as sodium and hence water as well.<sup>4</sup>

### Carrier Function

Albumin binds a host of endogenous and exogenous substances, filling an important role in transporting substances to sites of action, metabolism, or excretion (see box on this page). This carrying capability also imparts albumin with a reservoir function. The reservoir effect is especially pronounced regarding preferentially bound hydrophobic substances.<sup>6</sup> For ligands that are highly bound to albumin, only the substance that is not bound and is free in circulation is available to exert its physiologic action.

Albumin's ability to bind may render otherwise harmful substances innocuous. Albumin binds free radicals and bacterial toxins at sites of inflammation, rendering them harmless. The protein is destroyed in the process, but its constituent amino acids can be used for tissue repair. Many exogenous toxins bind albumin as well. Frequently, a substance that is toxic in the unbound state will be innocuous when bound to albumin. For

example, the carcinogens aflatoxin G<sub>1</sub> and benzene are inactivated when bound to albumin.<sup>4</sup>

### Miscellaneous Functions

Albumin provides other major and minor functions. Albumin can provide a source of nutrition, although its role is minor. When catabolized, its constituent amino acids are added to the body-wide pool available for protein synthesis.<sup>4</sup> Albumin has a role as a buffering protein. Hemoglobin is the more important acid-base buffer intravascularly; in some circumstances, however, albumin can be an important extravascular buffer (e.g., ascitic fluid).<sup>4</sup> Albumin binds arachidonic acid to prevent formation of substances that promote platelet aggregation.<sup>7</sup> In this way, albumin may prevent a state of hyperaggregability.<sup>8</sup> Albumin also exerts a heparin-like effect by augmenting neutralization of factor Xa by antithrombin III.<sup>9</sup> In addition, albumin appears to play an important role in maintaining microvascular integrity. Although the mechanism for this action is unknown, the most plausible theory describes albumin occupying water channels in vessel walls to narrow the channels and repel macromolecules.<sup>7</sup>

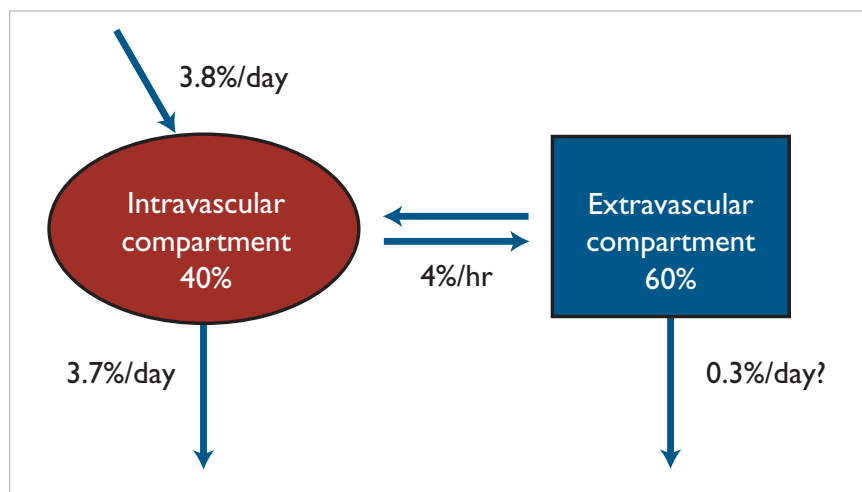
### DISTRIBUTION

Albumin is distributed into two compartments: the intravascular, which accounts for 40% of total body albumin, and the extravascular, which accounts for the remaining 60%. There is a constant slow flux of protein between these two pools, averaging 4% an hour (Figure 3). In states of acute albumin loss from the intravascular space (e.g., hemorrhage), this rate of exchange can increase to maintain the intravascular pool at the expense of the extravascular pool, thereby preserving oncotic pressure.<sup>2,4</sup> Serum albumin measures only the intravascular contribution to total body albumin and therefore may not be an accurate approximation of total albumin in diseased animals.<sup>6</sup>

### METABOLISM

#### Synthesis

The liver is the primary site of albumin synthesis, with albumin synthesis occupying nearly 50% of the liver's metabolic efforts.<sup>6,10</sup> Small amounts of albumin may be synthesized in the mammary glands and skeletal muscle as well.<sup>4</sup> There is no storage pool of albumin. As albumin is produced by hepatocytes, it is released into the hepatic interstitium and subsequently into the sinusoids and hepatic veins.<sup>6</sup> In healthy ani-



**Figure 3. Summary of metabolism and distribution of albumin.** Albumin synthesis in healthy animals replaces about 3.8% of total body albumin per day, which closely approximates the rate of degradation (i.e., 3.7%/day). The normal exchange rate between the intravascular and extravascular compartments is about 4%/hr. Loss from the extravascular compartment in healthy animals is estimated to be about 0.3%/day.

mals, hepatic albumin synthesis occurs at about 30% of capacity, replacing about 3.8% of total body albumin each day. During times of increased albumin loss, the liver can increase the rate of synthesis, at times nearly tripling the rate of baseline albumin production.<sup>3,4,10</sup>

Synthetic rate is influenced by multiple factors, including oncotic pressure, inflammation, hormone status, and nutrition. In healthy animals, oncotic pressure is the primary determinant of the albumin synthetic rate. Osmoreceptors in the hepatic interstitium detect changes in oncotic pressure. When oncotic pressure decreases, albumin synthesis increases; when oncotic pressure increases, albumin synthesis decreases. In fact, synthetic colloids can effectively raise the colloid oncotic pressure enough to depress albumin synthesis.<sup>2,3,11</sup> Inflammation exerts a negative influence on albumin

### ***Albumin accounts for about 75% to 80% of the colloid oncotic pressure in healthy animals.***

synthesis, with albumin mRNA decreasing by as much as 90% during inflammation. This potentially profound decrease in synthetic rate is due to the fact that albumin is a negative acute phase protein. Cytokines produced during inflammation shunt amino acids to increase synthesis of acute phase proteins important to the inflammatory process. These same cytokines shunt amino acids away from albumin synthesis because albumin is not essential to inflammation.<sup>12</sup> Various hormones have a role in albumin synthesis as well. Adrenocortical hormones, growth hormone, insulin, testos-

terone, and thyroid hormone have all demonstrated a positive effect on synthesis, and deficiencies in these hormones may result in decreased albumin synthesis.<sup>3</sup> Nutrition is another determinant of the albumin synthetic rate, with the most profound decreases occurring with protein malnutrition.

### Degradation

Albumin degradation is less clearly understood than is albumin synthesis. The degradation rate is essentially the same as the synthetic rate in healthy animals.<sup>4</sup> Catabolism occurs primarily in muscle and skin, with these sites accounting for 40% to 60% of all albumin degradation. The liver, kidneys, and other viscera also contribute to albumin degradation. As much as 10% of albumin is lost intact from the gastrointestinal (GI) tract and skin, even in the absence of disease at these sites. It is unclear how individual proteins are selected

### Fluid Accumulation and Loss of Intravascular Volume

Because of albumin's importance in maintaining plasma colloid oncotic pressure, severe hypoalbuminemia may result in extravascular fluid accumulation. Assuming vascular integrity, fluid extravasation seldom occurs in veterinary species when serum albumin concentrations are greater than 1.5 g/dl.<sup>13</sup> When vascular permeability is increased because of vasculitis of any cause, milder decreases in intravascular albumin may predispose patients to fluid accumulation. Unfortunately, as albumin declines, microvascular permeability may increase, potentiating further decreases in serum albumin and more fluid accumulation. Fluid accumulation can be seen peripherally in subcutaneous tissues (i.e., edema of distal limbs and ventrum) or within body cavities. Fluid rarely accumulates in the pulmonary interstitium because it is protected against edema. This is partly because of the pres-

## ***Colloid oncotic pressure is the major determinant of the albumin synthetic rate.***

for degradation because there does not appear to be a recognizable change that tags particular proteins for degradation. The process does not seem to select older proteins for degradation.<sup>2-4,11</sup> Therefore, the term *half-life* cannot be correctly used in discussing albumin degradation because the survival of specific molecules of albumin is variable and unrelated to time of synthesis. The average life span of an albumin molecule depends on the species, with an average survival of 8 days in dogs.<sup>5</sup> The life span of exogenously administered albumin is unknown at this time but is likely less than that of endogenous albumin. Heterologous albumin transfusion would be expected to have an even shorter half-life than would homologous albumin transfusion because of the potential antigenicity of another species' albumin.

### CONSEQUENCES OF HYPOALBUMINEMIA

The clinical consequences of hypoalbuminemia reflect the functions of the molecule. Mild hypoalbuminemia has few, if any, associated clinical consequences. However, moderate to severe hypoalbuminemia may result in significant, potentially life-threatening consequences.

ence of sodium channels and sodium-potassium ATPases in the alveolar epithelium that set up an osmotic gradient and allow water to move passively out of the alveoli and interstitium.<sup>14</sup> Intravascular plasma volume is lost simultaneously with extravascular fluid accumulation. This is mostly because of the loss of intravascular colloid oncotic pressure and the resultant inability to retain fluid in the intravascular compartment.

The consequences of fluid accumulation depend on the location and extent of extravascular fluid accumulation. Wound healing may be compromised because of interstitial edema formation.<sup>9</sup> Edema of GI mucosa may lead to decreased nutritional absorption, gastric and small intestinal ileus, and decreased tolerance of enteral feedings.<sup>15</sup> GI edema may exacerbate hypoalbuminemia through both decreased nutrient absorption and further loss of albumin from the altered mucosal surface. Ascites and peripheral edema may cause patient discomfort, and severe pleural or peritoneal effusion may ultimately result in respiratory compromise.

### Thromboembolic Risk

The risk of thromboembolic events is increased in patients in disease states accompanied by moderate to



severe hypoalbuminemia. Antithrombin III, the major protein anticoagulant, is very similar in size to the albumin molecule. Disease states such as protein-losing nephropathy that result in profound loss of albumin often lead to simultaneous loss of antithrombin III. When antithrombin III is lost in excess of procoagulant factors, thromboembolism may result.<sup>16</sup> Protein-losing enteropathy appears to be associated with less frequent thromboembolism than does protein-losing nephropathy. This may be because pro- and anticoagulant factors are both lost through larger lesions in the GI mucosa, allowing greater balance between pro- and anticoagulant factors. The increased risk of thromboembolic events in animals with hypoalbuminemia is not entirely explained by concurrent loss of antithrombin III. Albumin modulates coagulation directly, as previously described. Loss of this modulating capacity may lead to platelet hyperaggregability and therefore increased risk of thromboembolism.

### Decreased Carrier Availability

Decreased albumin levels result in decreased carrier capacity for substances that are primarily transported by albumin (i.e., some medications, bilirubin, free radicals). Hypoalbuminemia results in increased concentrations of these substances in the free, unbound form. For medications highly bound to albumin, hypoalbuminemia may result in increased free drug concentration and hence increased incidence of adverse effects. Alternatively, increased concentration of free drug may result in decreased efficacy. Because there is more free drug and less bound drug in circulation resulting from the decreased albumin concentration, more free drug is available to be rapidly catabolized.<sup>6</sup>

### CONCLUSION

The albumin molecule has several important roles aside from its contribution to colloid oncotic pressure, including maintenance of vascular permeability, modulation of coagulation, and function as a carrier of endogenous and exogenous substances. Albumin exists in both the intra- and extravascular spaces, making accurate measurement of total body albumin impossible. Therefore, disease process and chronicity of disease must be taken into account when evaluating serum albumin levels. Because of the many important functions of albumin, moderate or severe hypoalbuminemia can result in serious consequences, possibly including fluid accumulation, thromboembolism, and increased concentration of some medications in the free, unbound form.

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### ARTICLE #2 CE TEST



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#### I. What characteristic of the albumin molecule is responsible for its relatively large contribution to colloid oncotic pressure?

- a. extensive disulfide bridging
- b. relatively high net positive charge

- c. comparatively low molecular weight
  - d. primary distribution to the intravascular space
- 2. Which substance is not known to be carried by albumin?**
- a. bilirubin
  - b. bacterial toxins
  - c. free radicals
  - d. fibrinogen
- 3. How does albumin affect coagulation?**
- a. It prevents pathologic platelet aggregation.
  - b. It promotes factor X activity.
  - c. It inhibits the action of antithrombin III.
  - d. It promotes arachidonic acid catabolism.
- 4. How is albumin distributed in the body of a healthy animal?**
- a. 100% within the intravascular space
  - b. 60% in the intravascular space; 40% in the extravascular space
  - c. 50% in each compartment
  - d. 60% in the extravascular space; 40% in the intravascular space
- 5. In the absence of vasculitis, peripheral edema generally does not occur until albumin concentrations are below \_\_\_\_\_ g/dl.**
- a. 2.5
  - b. 2.2
  - c. 1.8
  - d. 1.5
- 6. Which statement regarding albumin synthesis is true?**
- a. The synthetic rate is constant unless the organ synthesizing the protein fails.
  - b. The synthetic rate in a healthy animal is typically only about one-third of the maximum rate.
  - c. Not all synthesized albumin is released into the circulation; large amounts are stored.
  - d. Hormones exert only a very small influence on the rate of albumin synthesis in healthy animals.
- 7. Which factor is the most important determinant of the albumin synthetic rate?**
- a. hormone status
  - b. nutritional status
  - c. oncotic pressure
  - d. presence of inflammation
- 8. Which statement regarding albumin degradation is incorrect?**
- a. Catabolism is specific for older molecules.
  - b. Catabolism occurs primarily in muscle and skin.
  - c. Some loss of intact albumin occurs from healthy skin and the GI tract.
  - d. The average life span of an albumin molecule in a dog is 8 days.
- 9. Which of the following may contribute to an increased risk of thromboembolic events in a patient with protein-losing nephropathy?**
- a. pathologic platelet aggregation resulting from hypoalbuminemia
  - b. concurrent loss of antithrombin III in excess of a loss of coagulation factors
  - c. increased platelet aggregation with uremia
  - d. a and b
- 10. Which of the following is not an expected consequence of severe hypoalbuminemia?**
- a. pulmonary edema
  - b. edema of the distal limbs
  - c. ascitic fluid accumulation
  - d. edema of the ventral trunk