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REVIEW ARTICLE

The role of albumin in critical illness

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The last 25 yr have seen major advances in our understanding of albumin. We now know the amino acid sequences of bovine and human albumin, the complete gene sequence of human albumin, and the location of mutations in the gene sequence. During the 1990s, the heart-shaped crystalline structure of albumin has been described and a new protein, termed α-albumin (afamin), has been added to the albumin superfamily, which otherwise consists of serum albumin, vitamin D-binding protein and α-fetoprotein.[74]

The function of circulating albumin in critical illness is not fully understood. It may differ significantly from that in healthy subjects. A low serum albumin concentration in critical illness is associated with a poor outcome.[2 11 66] Despite theoretical advantages for using human albumin solution as a plasma substitute, studies have shown that correcting hypoalbuminaemia has no impact on outcome in the critically ill.[28 96 97]

This review will examine the role of serum albumin in health and critical illness. It will also review aspects of the physiology of this protein that may be expected to lead to significant dysfunction in critical illness. Finally, the case for and against the use of exogenous albumin in the management of critically ill patients will be discussed.

Structure of albumin

In humans, albumin is the most abundant plasma protein, accounting for 55–60% of the measured serum protein.[34] It consists of a single polypeptide chain of 585 amino acids with a molecular weight of 66 500 Da. The chain is characterized by having no carbohydrate moiety, a scarcity of tryptophan and methionine residues, and an abundance of charged residues, such as lysine, arginine, glutamic acid and aspartic acid.[77] The mature, circulating molecule is arranged in a series of α-helices, folded and held by 17 disulphide bridges. The folding creates subdomains of three contiguous α-helices in parallel (Fig. 1). A pair of subdomains face each other to form domains. These can be seen as cylindrical structures with polar outer walls and a hydrophobic central core.[23]

The tertiary structure of human albumin crystal has been isolated by x-ray crystallography. It is seen as a heart-shaped molecule 80 × 30 Å.[36] In solution, the shape is quite different. The three domains appear to be arranged in an ellipsoid pattern, giving the molecule low viscosity (Fig. 2).

The molecule is very flexible and changes shape readily with variations in environmental conditions and with binding of ligands.[77] Despite this, albumin has a resilient structure and will regain shape easily, owing to the disulphide bridges, which provide strength, especially in physiological conditions.[14] After their rupture, the molecule can re-establish these bridges and regain its structure. Denaturation occurs only with dramatic and non-physiological changes in temperature, pH and the ionic or chemical environment.

Albumin metabolism

The serum albumin concentration is a function of its rates of synthesis and degradation and its distribution between the intravascular and extravascular compartments. The total body albumin pool measures about 3.5–5.0 g kg^{-1} body weight (250–300 g for a healthy 70 kg adult). The plasma compartment holds about 42% of this pool, the rest being in extravascular compartments. Some of this is tissue-bound and is therefore unavailable to the circulation. Each day, 120–145 g of albumin is lost into the extravascular space. Most of this is recovered back into the circulation by lymphatic drainage. Albumin is also lost into the intestinal tract (about 1 g each day), where digestion releases amino acids and peptides, which are reabsorbed. There is minimal urinary loss of albumin in healthy subjects. Of the 70 kg of albumin that passes through the kidneys each day, only a few grams pass through the glomerular membrane. Nearly all of this is reabsorbed, and urinary loss is usually no more than 10–20 mg day^{-1}.

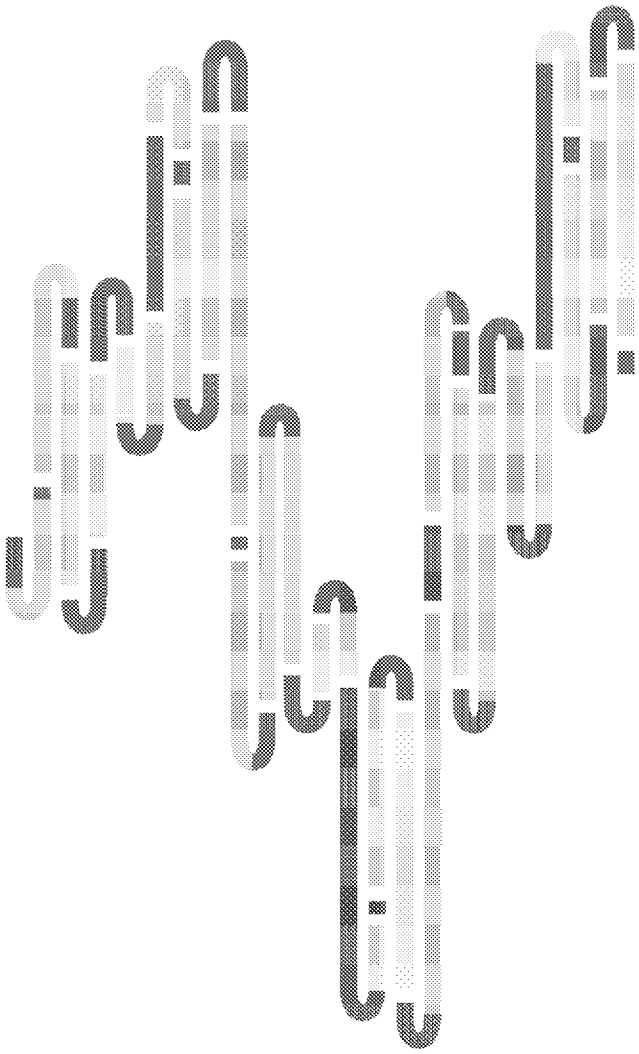

Fig 1 Two-dimensional representation of the albumin molecule reflecting the heart-shaped structure (see Fig. 2). The regions of the molecule that are normally in the α-helix configuration are shown in dark grey. The seventeen disulphide bridges are depicted in light grey. The three domains, separated into A and B subdomains, are shown along the bottom axis. Reproduced with permission from Carter and Ho, 1994.[14]

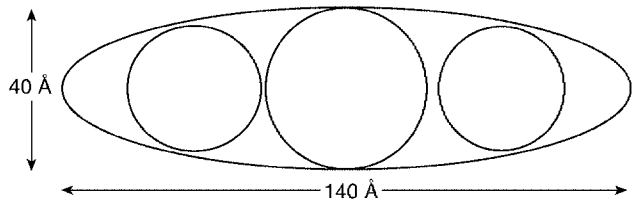

Fig 2 The ellipsoid structure of albumin in solution.[14]

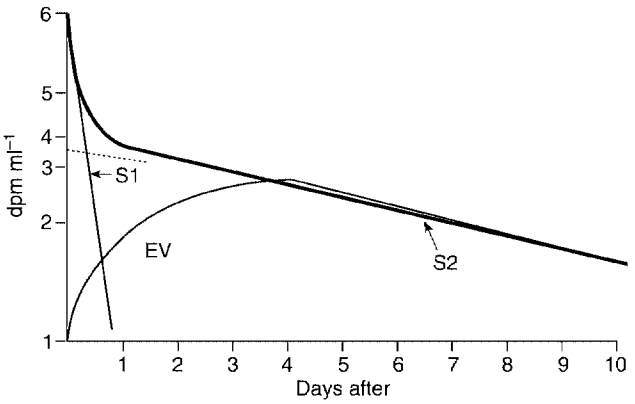

Fig 3 Decay pattern of labelled albumin versus time after i.v. injection of a tracer dose of ^{125}I-labelled human serum albumin (thick line). Slope 1 (S1) is the transcapillary escape rate, which equals about 4.5% h^{-1}. Slope 2 (S2) is the fractional degradation rate, which is about 3.7% per hour. EV is the calculated increase in extravascular labelled albumin concentration. Note that the activity of extravascular albumin is greater than that of intravascular albumin from about day 3 onwards. This suggests that degradation occurs directly from the vascular compartment. Reproduced with permission from Peters, 1996.[76]

The distribution of albumin between body compartments can be examined by injecting radiolabelled albumin into the venous circulation. A typical biexponential plot of log plasma concentration versus time shows a first-order process (Fig. 3). A two-compartment model can be constructed. There is a rapid phase of disappearance from the plasma over the first 2 days. This represents the transcapillary exchange rate of 4.5% h^{-1}, giving a distribution half-time of about 15 h. Then there is a slower exponential decay, representing the fractional degradation rate (FDR), of about 3.7% day^{-1} with an elimination half time of about 19 days. The FDR closely parallels the rate of synthesis in steady state (3.8% day^{-1}).

The extravascular pool is divided into exchangeable and remote components (Fig. 4). Significant locations of this large extravascular pool are listed in Table 1.

The mechanism of the escape of albumin into the extravascular compartment has come under review recently. Albumin must cross capillaries. Most organs in the body have continuous capillaries, but in some there are wide-open sinusoids (liver, bone marrow) or fenestrated capillaries (small intestine, pancreas, adrenal glands). Starling's theory holds that the rate of escape depends on the permeability of the wall and hydrostatic and oncotic pressures on either side of the wall.[29] Half of the escaping albumin does so through the continuous capillaries, and there appears to be an active transport mechanism to facilitate this.[76] Albumin binds to a surface receptor called albondin, which is widely distributed in many capillary beds, except in the brain.[90 91] Bound albumin enters vesicles within the endothelial cell and is discharged on the interstitial side within 15 s. The rate of transfer is increased with the addition of long-chain fatty acids (LCFAs) to albumin, and with the cationization and glycosylation of the molecule.[76]

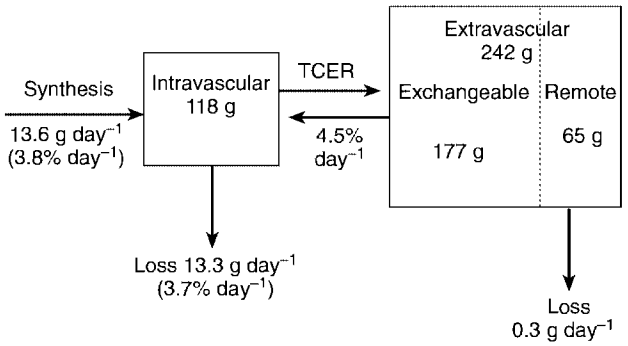

Fig 4 Typical albumin distribution in a healthy 70 kg adult. Reproduced with permission from Peters, 1996.[76]

Synthesis

In humans, albumin synthesis takes place only in the liver.[56 60] Albumin is not stored by the liver but is secreted into the portal circulation as soon as it is manufactured. In healthy young adults, the rate of synthesis is 194 (SD 37) mg kg^{-1} day^{-1}, or about 12–25 g of albumin per day.[76] The rate of synthesis rate varies with nutritional and disease states. The liver can increase albumin synthesis to only 2–2.7 times normal because most of the liver's synthetic machinery is already devoted to albumin at rest.[76] The synthetic pathway is common to eukaryotes and is also used for synthesis of other proteins.[62]

Albumin will be synthesized only in a suitable nutritional, hormonal and osmotic environment. The colloid osmotic pressure (COP) of the interstitial fluid bathing the hepatocyte is the most important regulator of albumin synthesis.[70 85 107] Synthesis requires:

- mRNA for translation;
- an adequate supply of amino acids, activated by binding to tRNA;
- ribosomal machinery for assembly;
- energy in the form of ATP and/or GTP.

The mRNA concentration available for action on ribosomes is an important factor controlling the rate of albumin synthesis. Trauma and disease processes will affect the mRNA content.[55 64] A reduction in albumin mRNA concentration, caused by a decrease in gene transcription, is seen in the acute-phase reaction mediated by cytokines, mainly interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α).[12 15 72] A decrease in gene transcription is also seen in hepatoma cells and in hepatocytes damaged with carbon tetrachloride.[76]

The hormonal environment can affect the mRNA concentration. Insulin is required for adequate albumin synthesis. Diabetic subjects have a decreased synthetic rate, which improves with insulin infusion.[20] Perfused livers of diabetic rats have a 50% decrease in gene transcription.[55] Corticosteroids have complex effects on albumin synthesis. There is increased albumin synthesis with combinations of steroids and insulin, and of steroids with amino acids.[40 76]

Table 1 Distribution of extravascular albumin in the body[76]

Organ	Fraction of body weight (%)	Fraction of total extravascular albumin (%)
Skin	18.0	41
Muscle	45.5	40
Gut	2.8	7
Liver	4.1	3
Subcutaneous, etc.	8	9

Table 2 Factors that modify albumin metabolism (see text for details)

Reduced albumin synthesis	
Decreased gene transcription	Trauma, sepsis (cytokines)
	Hepatic disease
	Diabetes
	Decreased growth hormone
	Decreased corticosteroids (*in vitro*)
Ribosome disaggregation	Fasting, especially protein depletion

Hydrocortisone and dexamethasone both increase gene transcription *in vitro*,[65 67] but the overall *in vivo* effects are complex. Steroids also increase albumin catabolism. Growth hormone has been shown to stimulate gene transcription in cultured hepatocytes.[41]

The rate of synthesis depends on nutritional intake, more so than for other hepatic proteins[76] Fasting reduces albumin production, but specifically omitting protein from the diet causes a greater reduction in synthesis. Early in protein deprivation, there is rapid disaggregation of free and bound polysomes, which can be reversed rapidly by refeeding the subject with amino acids.[21] Two amino acids are particularly effective, tryptophan and ornithine.[83] Ornithine, unlike tryptophan, is not incorporated into albumin. It is a product of the urea cycle and acts as a precursor of the polyamine spermine. The increases in polysome aggregation and albumin synthesis with ornithine refeeding suggest that the urea cycle plays more of a role in protein metabolism than mere waste disposal.[69] Protein deprivation for a longer time leads to a 50–60% decrease in the activity and concentration of the mRNA, presumably through increased breakdown, as gene transcription is not slowed in rats on a 0–4% protein diet.[86]

Calories are important, however. There is a reduction in synthesis in starved rats, and polysomes will reaggregate with glucose feeding alone.[80] Energy rather than the amino acid supply may be more important in determining polysome aggregation under normal circumstances.[23] Table 2 summarizes factors known to alter albumin synthesis.

Degradation

Total daily albumin degradation in a 70 kg adult is around 14 g day^{-1} or 5% of daily whole-body protein turnover. Albumin is broken down in most organs of the body. Muscle

and skin break down 40–60% of a dose of labelled albumin.[108] The liver, despite its high rate of protein metabolism, degrades 15% or less of the total. The kidneys are responsible for about 10%, while another 10% leaks through the stomach wall into the gastrointestinal tract.

The mechanism of breakdown involves uptake into endocytotic vesicles, which fuse with lysosomes in endothelial cells. This may involve binding to endothelial surface membrane scavenger receptors, called gp18 and gp30, which are widespread in the body tissues.[89] They bind altered or denatured albumin, and it is likely that chemical modification of the circulating albumin is a signal for receptor-linked lysosomal degradation. It is also possible that modification prevents degradation. Binding of LCFAs to albumin seems to protect the molecule from breakdown. In analbuminaemia, the LCFA/albumin ratio is increased and degradation is suppressed.[76] The final breakdown products are free amino acids that add to the pools of amino acids within cells and in the plasma.

Albumin and critical illness

Critical illness alters the distribution of albumin between the intravascular and extravascular compartments. There are also changes in the rates of synthesis and degradation of the protein. The serum albumin concentration will decrease, often dramatically, from early in the course of a critical illness. It will not increase again until the recovery phase of the illness. The kinetics of albumin given i.v. will differ greatly between critically ill patients and healthy subjects. The implication of this, given the important functions albumin has in health, is that using exogenous albumin to increase the intravascular albumin concentration during critical illness is beneficial. But studies have failed to show any benefit of albumin over other colloidal therapies in adults.

The altered distribution in critical illness is related to an increase in capillary leakage.[26] This occurs in sepsis[26] and after major surgical stress.[39 99] It involves dysfunction of the endothelial barrier, resulting in capillary leakage and loss of protein, inflammatory cells and large volumes of fluid into the interstitial space. The precise mediators of this capillary leakage are still being discovered and currently include:

- endotoxin from Gram-negative bacteria;[3 71]
- cytokines—TNF-α and IL-6;[12 15]
- arachidonic acid metabolites—leukotrienes and prostaglandins;[10 31]
- complement components C3a and C5a;[31]
- other vasoactive peptides—bradykinin, histamine;[71]
- chemokines—macrophage inflammatory protein 1α.[95]

The normal transcapillary escape rate for albumin increases by up to 300% in patients with septic shock, and by 100% after cardiac surgery.[26] In septic patients, the transcapillary exchange rate may well improve with appropriate treatment. With increased flow of albumin across capillary membranes, there should be an increase in lymphatic return to the intravascular compartment. Studies of albumin kinetics during major surgery have shown a reduction in the flow rate of lymph and the albumin concentration in lymph.[38] It is not known if this extends into the postoperative period. Measurement of total circulating and total exchangeable albumin pools shows a 30% reduction with major surgery,[38] consistent with sequestration of albumin into non-exchangeable sites, such as wounds, the intestine and extra-abdominal sites.[65]

The rate of albumin synthesis may be significantly altered in the critically ill.[27] In the acute-phase response to trauma, inflammation or sepsis, there is an increase in the gene transcription rate for the positive acute-phase proteins such as C-reactive protein, and decreases in the rate of transcription of albumin mRNA and the synthesis of albumin.[64] IL-6 and TNF-α both act to reduce gene transcription.[12 15] Induced inflammation in rats decreased the concentration of albumin mRNA and the rate of albumin synthesis, which reached a minimum by about 36 h and then began to rise again.[54 92] A sustained inflammatory response in critical illness may lead to prolonged inhibition of albumin synthesis.

Catabolism of albumin may also be altered. The FDR is mass-dependent. That is, as the serum albumin concentration decreases, so does the FDR. Studies have shown a significantly shorter plasma half-life in hypoalbuminaemic patients on total parenteral nutrition (9 days), but with a catabolic rate similar to normal.[94] However, in situations of increased transcapillary albumin flux, an increase in the FDR has been observed.[85] It is possible that the vascular endothelium has an important role in the degradation of albumin. In animal experiments, the tissues most actively involved in albumin catabolism are those with fenestrated or discontinuous capillaries.[108] It may be that a high rate of tissue exposure in situations of increased capillary permeability may increase catabolism. However, studies of albumin extravasation in myxoedema found that, while there was an increase in the extravascular pool of albumin, there was a decrease in the catabolic rate, implying tissue exposure and trapping of albumin, protecting it from degradation.[84]

Functions of albumin

Albumin has extensively studied and well-established physiological functions in health. There are, however, few studies on the function of albumin in the critically ill.

Oncotic pressure

In healthy subjects, the role of albumin in the maintenance of normal COP is well recognized, but there appears to be little correlation between albumin and COP in the critically ill.[35] In health, albumin contributes up to 80% of the normal COP of about 25 mmHg.[34 101 106] This is because of its high

molecular weight and concentration in plasma. Albumin is present at a higher concentration than other plasma proteins, and though its molecular weight of 66.5 kDa is less than the average for serum globulins (about 147 kDa), it still has the greatest osmotic significance. This direct osmotic effect provides 60% of the oncotic pressure of albumin. The remaining 40% is a result of its negative charge, providing an attractive force for the intravascular retention of positively charged solute particles (the Gibbs–Donnan effect). Due to the large extravascular pool of albumin, its water-solubility and its negative charge, albumin also plays a significant role in the regulation of tissue fluid distribution.

Critically ill patients have a lowered serum COP. A sequential series of 200 critically ill patients had an mean COP of 19.1 mmHg.[106] A lowered COP is associated with increased morbidity and mortality in critically ill patients.[63 100 106] A serum COP of 15 mmHg was associated with a survival rate of 50%.[100] Proponents of albumin supplementation argue that giving albumin will increase the COP and avoid potentially fatal complications such as pulmonary oedema, though the association with fatal progression of respiratory failure[63] has not been substantiated by other studies. The pulmonary lymphatic system is capable of a sevenfold increase in flow rate in response to isobaric reduction in COP, to a level sufficient to induce massive peripheral oedema and ascites in baboons.[109] There is evidence to suggest that the pulmonary dysfunction in critically ill, septic patients is independent of COP.[52]

Binding of substances to albumin

The structure of the albumin molecule is such that it can incorporate many different substances. It is a flexible molecule, and bound compounds can be buried within the structure. Some general trends have emerged from binding studies. Most strongly bound are medium-sized hydrophobic organic anions, including long-chain fatty acids, bilirubin and haematin. Less hydrophobic and smaller substances can be bound specifically but with lower affinity, such as ascorbate and tryptophan. The chirality of the compound may be important: L-tryptophan is bound more strongly than D-tryptophan.[75] Monovalent cations do not bind, but divalent cations do, namely calcium and magnesium. Albumin has a strong negative charge, but there is little correlation between the charge of the compound and the degree of binding to albumin.[51] Acidic drugs tend to bind to other plasma proteins such as α1-acid glycoprotein whereas basic drugs tend to bind to albumin. There are exceptions, and drugs may bind to both.

Other endogenous compounds that bind to albumin include bile acids, eicosanoids, copper, zinc, folate and aquacobalamin. Albumin is also a secondary or tertiary carrier for some substances that have specific binding proteins, for example, steroids, including derivatives such as vitamin D and thyroxine. This can be clinically significant. Steroids have a low binding affinity for albumin but there is a large capacity owing to the high concentration of albumin.[75] Thus a significant amount may be carried by albumin, and the lower binding affinity means that there is easy off-loading at target sites.

Drug-binding studies have traditionally been performed *in vitro*, measuring affinity and competition between ligands, at non-physiological temperature and with non-human albumin species. It is difficult to draw conclusions about *in vivo* binding from these studies. In recent years techniques such as DNA sequencing, fluorescence emission of 'reporter' compounds, which respond to the presence of ligands, x-ray diffraction and the isolation of functional fragments of albumin have given insight into the functional sites of binding.[75]

Drug binding strongly affects the delivery of bound drug to tissue sites and the metabolism and elimination of the drug. The free serum concentration is the relevant factor in these processes. Highly bound drugs have only a small percentage of the total serum concentration in the free form. Other factors that are important in drug–albumin interactions and may be responsible for the wide interindividual variation seen include age (binding may decrease at the extremes); temperature, pH and ionic strength, which can affect the number of binding sites *in vitro*; and competition between drugs for binding sites.[51]

Displacement of drugs from their binding sites by other drugs or by endogenous substances occurs and may alter the distribution, pharmacological action, metabolism and excretion of the displaced drug. There are a variety of binding sites on the albumin molecule. Sudlow *et al.*[98] have classified drugs into two groups according to two broad binding sites, site I and site II. Site I appears to lie along the long loop of subdomain IIa, extending into the shorter loop.[75] Many different drugs seem to bind here, including salicylates, warfarin, phenylbutazone, indometacin, digitoxin, furosemide, phenytoin, chlorpropamide and some penicillins.[75] Dyes such as sulfobromophthalein, iophenoxate (a radio-opaque dye), methyl red, Evans blue and bromocresol green also bind here, as do endogenous compounds such as bilirubin.

Site II is a hydrophobic pocket of residues located in subdomain IIIa.[14] It is responsible for binding compounds such as L-tryptophan, thyroxine (which may also bind at site I), medium-chain fatty acids and chloride. Drugs that bind here include diazepam and other 2,3-benzodiazepines, non-steroidal anti-inflammatory agents that have ionized carboxyl groups (such as ibuprofen and naproxen) and clofibrate. Many other substances bind to various different sites on the albumin molecule.

There are many factors influencing drug–albumin interactions that become relevant in critically ill patients. Renal failure provides a good example of the mechanisms involved. The serum albumin concentration may be directly altered, due to increased loss of albumin through damaged glomeruli. Renal failure may influence drug binding to albumin.[1] Possible mechanisms involved include changes in

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