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REVIEW ARTICLE

Albumin in chronic liver disease: structure, functions and therapeutic implications

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Abstract Human serum albumin is a critical plasma protein produced by the liver with a number of accepted clinical indications in chronic liver disease including management of circulatory and renal dysfunction in patients with ascites. Advanced cirrhosis is characterised by reduced albumin concentration as well as impaired albumin function as a result of specific structural changes and oxidative damage. Traditionally, the biologic and therapeutic role of albumin in liver disease was attributed to its oncotic effects but it is now understood that albumin has a wide range of other important physiologic functions such as immunomodulation, endothelial stabilisation, antioxidant effects and binding multiple drugs, toxins and other molecules. This review discusses the multifunctional properties of albumin and, in particular, the biologic and clinical implications of structural and functional changes of albumin that are associated with cirrhosis. Based on these insights, we explore the current and potential future therapeutic uses of albumin in liver disease.

Keywords Human serum albumin · Cirrhosis · Chronic liver disease · Non oncotic functions · Albumin function · Oxidation

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Introduction

Human serum albumin (HSA) is an important plasma protein used frequently in the management of patients with cirrhosis and acute-on-chronic liver failure. Although initially used in liver and other diseases as a plasma expander based on its oncotic function, it is now irrefutably clear that albumin has multiple other biologic properties including antioxidant, immunomodulatory and endothelial regulatory functions. Cirrhosis is associated not only with reduced albumin synthesis but also specific alterations to its structure and function such as posttranscriptional changes and oxidative damage, which have been associated with impaired function and clinical outcomes [1–3]. This has led to the concept of "effective albumin concentration" which provides insights into the contribution of HSA to clinical complications of cirrhosis [4]. Improved understanding of the pathobiology of HSA also helps to inform its role in a range of established and proposed therapeutic indications in liver disease. In this review, we discuss structural and functional changes of HSA in cirrhosis with a view to explaining the important clinical implications of albumin in liver disease.

Albumin structure

Human serum albumin (HSA) is the most abundant plasma protein, representing 50 % of circulating proteins in healthy individuals (3.5–5 g/L) [5]. HSA is encoded by a gene on chromosome 4 and comprised of 585 amino acids (66.5 kDa) with a larger proportion of acidic amino acids resulting in a negative charge at pH 7 [6, 7]. HSA has a heart-shaped tertiary structure formed by eight α-helices and containing three structurally similar domains (I, II, and

III), each of these divided into two subdomains (A and B) (Fig. 1) [8, 9]. This structure is remarkable for its stability while also remaining flexible which allows the binding and transport of a wide range of molecules, both endogenous and exogenous [10]. HSA contains a free cysteine at position-34, which represents the main molecular site for thiolation, nitrosylation, and oxidation; all other cysteine residues are involved in internal disulfide bonds to stabilize the spatial conformation of the molecule [11–13]. The chemical structure of HSA is susceptible to modification through enzymatic and non-enzymatic reactions including glycosylation, reversible and irreversible oxidation at the Cys-34 and other sites with emerging evidence that these structural changes are associated with altered biological functions (Fig. 1) [2, 14].

Human serum albumin is synthesized exclusively by hepatocytes and released directly into the intravascular space without storage, from which about two-thirds is distributed in the interstitial space, as well as in the muscles and skin, returning to the circulation via capillaries and the lymphatic system [7].

In the healthy state, the production of albumin equals 9–12 g/day in adults and engages only 20–30 % of hepatocytes [8]. Therefore, the liver has a large functional reserve that may increase 3–4 times in times of need [8, 9]. Catabolism takes place at the level of the vascular endothelium with a daily rate that equals the hepatic synthesis and is influenced by plasma concentrations of atrial natriuretic peptide. The daily turnover of albumin in normal conditions does not exceed 5 % of its total mass. The circulatory half-life is equal to 16–18 h with 4–5 % per hour of intravascular albumin exchanged with the extravascular compartment. The overall half-life is prolonged at 12–19 days but this may be altered in disease states [7–9, 13].

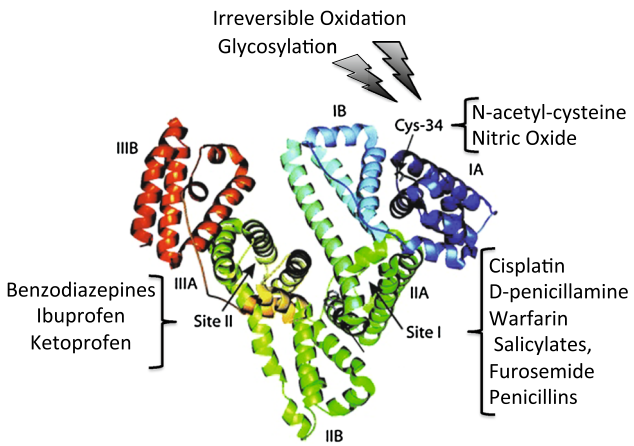

Fig. 1 Albumin structure. Human serum albumin (HSA) is composed of three domains (I, II and III), each divided into two subdomains (A and B). This structure is notable for both stability and flexibility which allows binding and transport of many molecules and drugs at different sites. HSA can undergo structural modifications, such as oxidation at the free Cys-34 site, which are associated with biologically relevant functional impairment. (Modified from Park, Park, Hamilton. Novel 7-(dimethylamino)fluorine-based fluorescent probes and their binding to human serum albumin. Org Biomol Chem, 2009;7:4225–4232; permission requested)

Functions of albumin

Oncotic pressure

Albumin is responsible for about 70 % of plasma oncotic pressure, with two-thirds due to a direct osmotic effect and the remaining one-third due to the *Gibbs–Donnan* effect where the net negative charge attracts sodium molecules and secondarily water into the intravascular compartment [6]. Oncotic function is the most recognised property of HSA and led to its initial introduction in medical practice as a plasma volume expander, used in patients with or without liver diseases for circulatory support [7].

Binding and transport

Albumin is able to reversibly bind a diverse range of endogenous and exogenous molecules, allowing solubilisation and transport to distant sites or organs. Binding occurs at various sites but mainly at sites I and II, which have different affinity and are located in different subdomains of the molecule [12]. For example, the N-terminal portion of the molecule provides a high affinity binding site for several metal cations including copper, nickel and cobalt [15].

In addition, HSA has the capacity to bind many molecules electrostatically through its negative charge [16]. Molecules can compete with each other for a single binding site of albumin or can alter the affinity of remote sites through changes in configuration of its tertiary structure, a property which along with the flexibility of the protein, supports the concept of structural changes having functional consequences [7].

Endogenous molecules bound and transported by HSA include long-chain fatty acids, bilirubin, bile acids, hematin, steroids, vitamin D and L-thyroxine. Exogenous compounds bound by HSA include a wide variety of drugs such as cisplatin, *D*-penicillamine and *N*-acetyl-cysteine (at the free Cys-34 site); warfarin, salicylates, furosemide and some penicillins (at site I); and benzodiazepines, ibuprofen and ketoprofen (site II) [12, 17]. In addition to solubilisation, binding to HSA can decrease toxicity and increase half-life while different drugs may compete for specific binding sites. These properties make albumin a modulator of the pharmacokinetics and pharmacodynamics of many

drugs [12, 13, 17]. Furthermore, HSA binds a range of metallic ions and inflammatory mediators as well as interacting with nitric oxide (NO) which has implications for its effects on inflammation, antioxidant and endothelial function [18].

Antioxidant function

The predominant form of HSA is that of a reduced state characterized by the presence of a free thiol group in the Cys-34 residue [16]. This is the most significant source of extracellular antioxidant function as the thiol group acts as a potent free radical scavenger for reactive oxygen (ROS) and reactive nitrogen (RNS) species such as hydrogen peroxide and peroxynitrite [2, 19]. Indeed, in critical conditions such as sepsis, characterized by high oxidative stress with release of ROS and RNS by innate immune cells, HSA administration may confer a protective effect by replenishing plasma thiols and antioxidant function [19]. HSA also provides antioxidant function through its ability to bind and neutralise free metals at the N-terminal site such as copper and iron which are involved in catalysing the production of toxic free radical species [15]. A further but less direct antioxidant effect of HSA occurs via inhibition of lipid peroxidation, demonstrated in ex vivo studies as part of a complex bound to bilirubin [20]. Moreover, in addition to providing the main extracellular source of antioxidant function, albumin may also modulate cellular responses to oxidative stress by increasing glutathione levels [21].

Therefore, HSA could potentially reduce the effects of oxidative stress during systemic inflammatory response and consequent cellular or organ dysfunction through a number of antioxidant actions. For example, this was demonstrated in an experimental rodent model of cirrhosis with ascites whereby albumin reduced oxidative stress and inflammatory signalling which was associated with improved cardiac contractility, an effect not seen with volume replacement by hydroxyethyl starch [22].

Antithrombotic function

Human serum albumin is capable of antithrombotic function due to its capacity to bind nitric oxide (NO) at the Cys-34 position with the resultant formation of nitrosoalbumin. This complex appears to prolong the biologic activity of NO with potential effects including vasodilation and inhibition of platelet aggregation [23, 24].

Immunomodulation

Human serum albumin may play an important role in modulating innate immune responses to systemic inflammation and sepsis [25]. It is capable of binding inflammatory factors and mediators such as lipopolysaccharide (endotoxin) and other bacterial antigens known to activate innate immune responses. Albumin selectively inhibits TNFα-induced up-regulation of vascular cell adhesion molecule-1 (VCAM-1) expression and monocyte adhesion via inhibition of NF-κB activation in cultured human aortic endothelial cells, suggesting that albumin has an anti-inflammatory role towards endothelial cells [26]. Albumin therapy in patients with cirrhosis and spontaneous bacterial peritonitis (SBP) has been associated with reduction of levels of proinflammatory cytokines and endotoxin [27]. Albumin has been demonstrated to prevent neutrophil dysfunction, which is associated with higher risk of infection, organ failure and mortality in cirrhotic patients with alcoholic hepatitis [28]. This may occur via amelioration of inflammatory response, endotoxemia and immune signalling such as toll-like receptor pathways [29]. Recently, cirrhosis has been associated with PGE2-mediated immune dysfunction related to reduced albumin concentrations but which can be improved with albumin replacement [30].

Endothelial stabilization

In cirrhotic patients with SBP, albumin has been shown to improve systemic hemodynamics and endothelial function via mechanisms not accounted for by volume expansion and oncotic function alone. HSA appears to help maintain endothelial permeability via interactions with the interstitial matrix [31]. The ability of HSA to modulate inflammation and oxidative stress as well as inhibit neutrophil adhesion could provide some protection from endothelial dysfunction mediated by these factors [32]. Recent studies provide further insights into the impact of HSA on endothelial stabilization. Analbuminemic rats with cirrhosis displayed significantly worse systemic hemodynamics associated with markers of endothelial dysfunction and inflammation. In an in vitro setting, albumin confers protection via multiple immunomodulatory effects reducing endothelial activation, inflammation and oxidative stress [33].

Albumin interacts with nitric oxide, both endogenous and exogenous (to form nitrosoalbumin as described) as well as with a number of eicosanoids. These interactions provide further potential mechanisms for the role of HSA in the regulation of vascular tone, both in physiological and pathological conditions such as sepsis and cirrhosis [18].

Altered structure and function of albumin in cirrhosis

Advanced cirrhosis is characterized by a range of clinical manifestations including portal hypertension, ascites,

hepatic encephalopathy and increased risk of infection. In the setting of acute decompensation with a systemic inflammatory response, progression to acute-on-chronic liver failure with multiple organ dysfunction is common [34]. It may be expected that the reduced concentration of albumin seen in advanced cirrhosis due to impaired synthesis could impact on these clinical sequelae given its multifunctional properties. Indeed, recent findings indicate that immunosuppression in acutely decompensated cirrhosis is associated with the degree of hypoalbuminemia and this may be ameliorated by albumin replacement [30]. However, it is also abundantly clear that there are structural changes of albumin seen in cirrhosis, which are functionally and clinically significant [2, 35, 36]. This has led to the concept of "effective albumin concentration" whereby overall albumin function is not related just to the circulating level but to the amount of structurally intact or functional albumin [4, 37]. Several techniques for measuring the functional capacity of albumin have been described including electron paramagnetic resonance spectroscopy using labelled stearic acid to measure function at the fatty acid binding sites and assays for ischemia modified albumin (IMA), which reflect the binding affinity of cobalt at the metal binding domain [37, 38]. Patients with advanced cirrhosis and ACLF exhibit significantly reduced albumin function using these measures and this impaired functional capacity has been shown to correlate with disease severity [3, 35, 38]. Furthermore, the severity of albumin dysfunction may also have prognostic value with the ratio of IMA to total albumin (IMAR) found to be significantly higher in non-survivors with ACLF [3]. A recent study of 127 acutely decompensated cirrhotic patients reported significantly higher IMA and IMAR levels in patients with bacterial infection, further supporting the association of albumin and immune dysfunction in cirrhosis [39].

Albumin exists in three major fractions depending on the redox state. The majority is in a reduced non-oxidised form with a free thiol group at the cysteine-34 site. This site can be oxidised reversibly to human non-mercaptalbumin 1 (HNA1) or irreversibly oxidised to sulfinic or sulfonic acid to create the isoform known as non-mercaptalbumin 2 (HNA2) [7]. Increasing severity of liver failure has been associated with progressive increase in the fraction of HNA2. In a study of 67 patients with acutely decompensated cirrhosis, there were increased fractions of oxidised albumin, particularly levels of HNA2. This is associated with functional impairment reflected by a decreased binding capacity for dansylsarcosine, correlated with parameters of liver function. Furthermore, baseline HNA2 levels appear predictive of survival in patients with decompensated cirrhosis [2].

A further study analysing posttranscriptional structural changes of HSA in 168 patients with cirrhosis indicated significant reduction in the native, unchanged isoform in cirrhosis but identified at least seven isoforms with alterations at several sites including the Cys-34 residue. These altered isoforms were more abundant in cirrhosis and the increase in isoforms with structural changes along with the reduction in the native, structurally preserved isoform correlated with disease severity and may also predict survival. Interestingly, there were also strong associations seen between specific altered HSA isoforms and clinical complications of cirrhosis in hospitalised patients including ascites, renal impairment and bacterial infection which were independent of the severity of disease [1].

The clinical implications of altered structure and biologic functions of albumin in the setting of cirrhosis and ACLF are portrayed in Fig. 2. The mechanisms for the formation of these altered functionally impaired forms of albumin are unclear but may be related to the environment of increased inflammation and oxidative stress seen in advanced cirrhosis. In any case, these data further support the concept of effective albumin concentration and indicate that albumin dysfunction in cirrhosis is both pathophysiologically and prognostically important. In addition, improved understanding of albumin biology in chronic liver failure provides further insight into the potential therapeutic effects and mechanisms of action of HSA. Indeed, in a recent study of acutely decompensated cirrhosis, HSA infusion resulted in an increase in albumin concentration as well as a reduction in IMAR indicating improved albumin function. This was associated with improved renal function via modulation of functions attributable to albumin such as endothelial activation and oxidative stress [40]. Further studies are required to determine appropriate targets for therapy in terms of albumin concentration or function and the clinical implications of this.

Therapeutic uses of albumin in liver disease

Originally, it was thought that the benefits of albumin in patients with liver cirrhosis were due to its role as a volume expander. In recent years, this view has increasingly changed with a better knowledge of the pathophysiology of liver disease and the multifunctional properties of HSA leading to its proposed role for many indications in liver cirrhosis [41, 42]. Established and potential therapeutic indications for albumin with the attendant clinical benefits are summarised in Table 1.

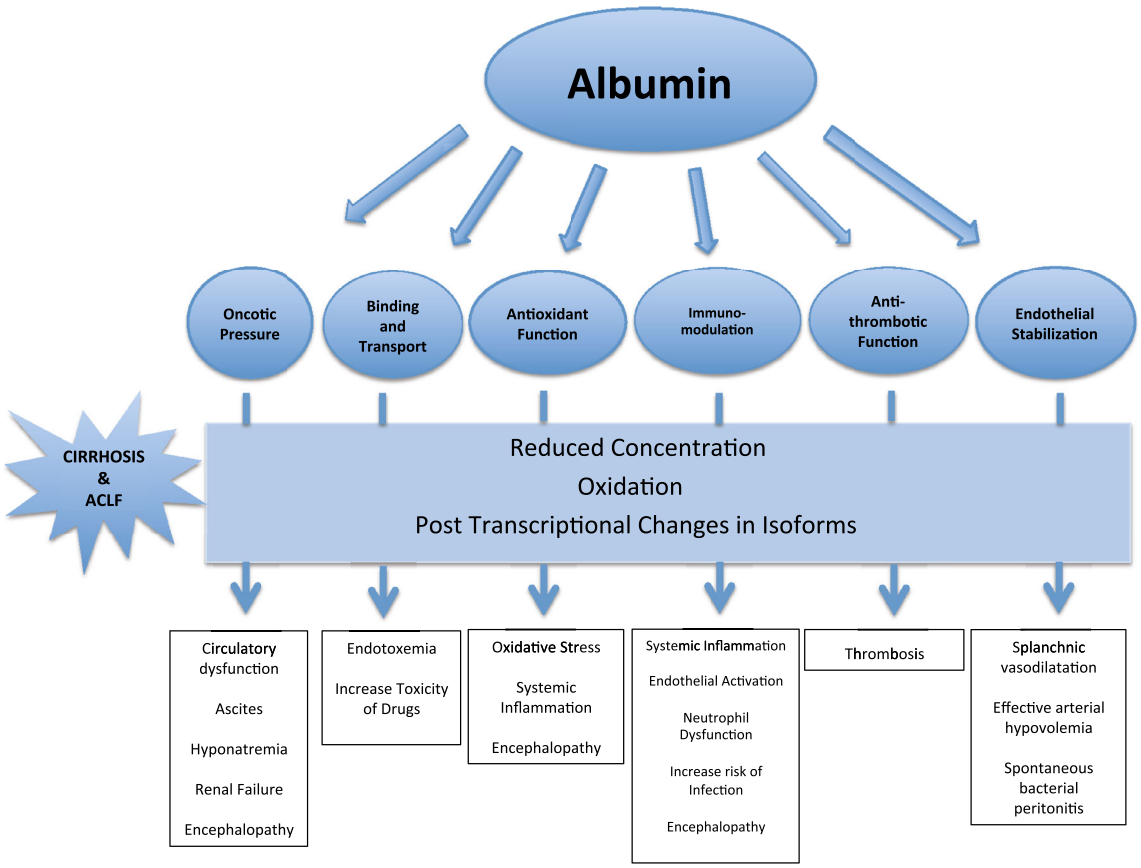

Fig. 2 Biologic effects of altered structure and function of albumin in liver disease. Albumin has multifunctional properties which are impaired in the setting of cirrhosis and ACLF due to reduced concentration and structure changes including irreversible oxidation and altered isoforms. This may contribute to a wide range of biologic effects and clinical complications as well as correlate with overall survival

Table 1 Currently established and potential future therapeutic indications for albumin in cirrhosis with their associated clinical benefits

Clinical Indications	Outcome
Established	
Paracentesis induced circulatory dysfunction	↓ hyponatraemia ↓ Acute Kidney Injury ↑ survival
Type-1 hepatorenal syndrome	↓ circulatory dysfunction ↑ renal perfusion ↑ survival
Spontaneous bacterial peritonitis	↓ hepatorenal syndrome ↓ circulatory dysfunction ↑ survival
Potential	
Non spontaneous bacterial peritonitis infection	↓ renal and circulatory dysfunction no change in survival
Hepatic encephalopathy	no change in hepatic encephalopathy ↑ survival

Prevention of paracentesis induced circulatory dysfunction (PICD)

Paracentesis induced circulatory dysfunction is a serious complication of liver cirrhosis that occurs following large volume paracentesis due to significant activation of the renin-angiotensin system leading to exacerbation of arteriolar vasodilatation with an insufficient associated cardiac response [43–45]. It is not spontaneously reversible and is associated with increased mortality related to acute renal failure [46]. Recent meta-analyses confirm that albumin administration in patients with ascites undergoing paracentesis significantly reduces development of PICD, hyponatremia, renal failure and risk of mortality compared with patients receiving either no or alternative volume expanders [47–49]. This reaffirms that the beneficial effects of HAS extend beyond its oncotic function.

Treatment of type-1 hepatorenal syndrome

Hepatorenal syndrome (HRS) is a severe and progressive functional renal failure occurring in patients with cirrhosis and ascites characterized by splanchnic arterial vasodilatation in association with cardiac dysfunction [50]. The resultant circulatory dysfunction with renin-angiotensin and sympathetic system activation causes renal hypoperfusion and organ dysfunction. Several studies have demonstrated that HSA, in combination with vasoconstrictors (especially vasopressin analogs such as terlipressin which preferentially target the splanchnic circulation), helps to reverse type-1 HRS with improvement in circulatory dysfunction and renal perfusion as well as survival. These benefits are much greater with combination therapy than terlipressin alone although treatment with albumin alone may be effective [51–53]. Recent data from a study of acutely decompensated cirrhotic patients with acute kidney injury treated with albumin infusion suggest possible mechanisms for this related to properties of albumin with improvement in renal blood flow autoregulation associated with endothelial stabilisation and reduced oxidative stress [40].

Prevention of type-1 hepatorenal syndrome in spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is a frequent infection in advanced cirrhosis, often complicated by type-1 HRS despite antibiotic therapy. This may be related to several factors including systemic inflammatory response, hepatic and cardiac circulatory dysfunction and renin-angiotensin and sympathetic system activation predisposing to subsequent renal and multiorgan dysfunction [18]. The role of HSA in the treatment of SBP, in addition to antibiotics, has been well established with several clinical studies and a recent meta-analysis demonstrating significantly reduced prevalence of HRS associated with improved cardiac and circulatory dysfunction as well as decreased mortality [53–56]. Similar benefits on systemic hemodynamics in patients with SBP were not reported with other plasma expanders, again highlighting the non-oncotic properties of albumin such as its effects on endothelial function [57]. The beneficial effects of HSA in patients at low risk of SBP-induced renal dysfunction and mortality (total bilirubin less than 4 mg/dl and creatinine less than 1 mg/dl) are less clear [54]. However, in the absence of further randomised trial data, guidelines continue to recommend the administration of HSA for all patients with SBP at a dose of 1.5 g/kg on day 1 and 1 g/kg on day 3 [41].

Treatment of bacterial infection

Bacterial infections are a common complication in cirrhotic patients, frequently precipitate acute-on-chronic liver failure and are associated with significant morbidity and mortality [34, 58–60]. Organ dysfunction such as HRS does occur in patients with bacterial infections other than SBP although with lower prevalence [18, 60]. There has been interest in the potential role of HSA in the management of patients with cirrhosis and non-SBP bacterial infections. A randomised controlled single-centre study of 110 cirrhotic patients hospitalized for non-SBP infections showed that a combination of antibiotics and HSA improved both renal and circulatory function [61]. Furthermore, in a subsequent multicentre randomised controlled trial, HSA infusion delayed the onset of renal failure but did not improve the overall incidence of renal failure [62]. Neither of these studies demonstrated clear advantage in terms of survival at 3 months, which could reflect lack of power or suboptimal patient selection. Whether particular subgroups, such as those at higher risk of renal impairment and death, may derive greater benefit as seen in patients with SBP is unclear. A study with a larger number of more advanced cirrhotic patients with non-SBP infections coordinated by the EASL Chronic Liver Failure Consortium is underway. Previous studies have used protocols similar to that established for the treatment of SBP (1.5 g/kg on day 1 and 1 g/kg on day 3). Based on recent data suggesting a serum albumin concentration less than 30 mg/dl predicts immunosuppression in acutely decompensated cirrhosis and that HSA helps restore immune competency, a further multicentre clinical trial is in development using an alternate strategy of HSA infusions to achieve a concentration above 30 mg/dl as a means of ameliorating immune dysfunction, preventing and treating infection in such patients (ATTIRE study, UKCRN ID 18450) [30].

Long-term administration in patients with cirrhosis and ascites

The potential role of regular long-term HSA in the management of cirrhotic patients with ascites has been proposed but data to evaluate this approach are limited. A previous small comparative study of 17 patients and an unblinded randomised trial of 100 patients suggested an improved prognosis with repeated albumin administration [63, 64]. Survival benefit was not confirmed in another randomised trial of 126 patients although albumin treatment appeared to improve resolution and prevent recurrence of ascites as well as reduce hospital stay and readmissions [65]. Further larger-scale studies to address this situation are ongoing.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a common complication of cirrhosis associated with hyperammonemia, inflammation, circulatory dysfunction and oxidative stress leading to astrocyte swelling and disturbed neurotransmission [66]. HAS may have a role in the treatment of HE via modification of these factors. A clinical study comparing plasma volume expansion with colloid or HSA in 15 patients with diuretic induced HE demonstrated improvement in circulatory function and plasma ammonia concentration in both groups but improvement in HE associated with reduction in oxidative stress markers only in patients treated with HSA [67]. This again highlights potential benefits of albumin beyond volume expansion. HSA for the treatment of acute HE was evaluated further in a multicentre, prospective, double-blind, randomized controlled study of 56 patients given HSA or saline. This study showed that HSA did not improve resolution of HE in hospital nor significant reduction in markers of circulatory dysfunction, oxidative stress and inflammation, putative mechanisms of action of albumin. However, there was a significant improvement in a secondary endpoint of 90-day survival following HSA infusion suggesting there may be a subgroup of patients with advanced cirrhosis who most benefit from this therapy [68].

Albumin dialysis

Extracorporeal liver support systems such as the molecular adsorbent recirculating system (MARS) using albumin dialysis and the Prometheus system using fractionated plasma separation and adsorption apply principles of albumin biology to provide detoxification by removal of protein-bound and water-soluble substances [69]. Such devices have been shown to improve systemic haemodynamics and reduce portal pressure in patients with ACLF and severe alcoholic hepatitis as well as improve severe HE in advanced cirrhosis and refractory pruritis in cholestatic liver disease [70]. In a large multicentre randomised trial of 189 patients with ACLF, treatment with MARS improved individual organ dysfunction but did not show any significant survival benefit [71]. Similarly, a randomised trial of 145 patients with ACLF treated with the Prometheus device or standard medical therapy did not improve survival [72]. MARS and Prometheus therapy has no effect on the irreversibly damaged and functionally impaired albumin (HNA2) seen in advanced cirrhosis with only transient improvements of the redox state of albumin or the milder reversibly oxidised albumin fraction (HNA1) [3, 73]. These observations may help explain the lack of benefit in terms of outcome and further illustrate the pathophysiological impact of structural and functional changes of albumin in cirrhosis.

Conclusions

Albumin is a multifunctional protein with a wide range of properties that may explain its clinical and therapeutic effects. Cirrhosis is characterised by hypoalbuminemia but also structural alterations including posttranscriptional changes and oxidative modification which are associated with functional impairment and correlate with worsening severity of disease. These changes appear pathophysiologically important in terms of clinical complications, represent potential prognostic biomarkers and provide mechanistic insights into the therapeutic benefits from albumin replacement. The concept of effective albumin concentration underlies our improved understanding of albumin biology and function in cirrhosis with future therapeutic goals potentially directed towards correcting albumin dysfunction rather than albumin levels.

Compliance with ethical standards

Conflict of interest Rosaria Spinella and Rohit Sawhney declare that they have no conflict of interest. Rajiv Jalan has served on the Scientific Advisory Board for Conatus Pharma, has received lecture fees from Gambro and has on-going research collaboration with Gambro, Grifols and is the Principal Investigator of an Industry sponsored study (Sequana Medical). He is also inventor for a drug, L-ornithine phenyl acetate (OCR-002), which UCL has licensed to Ocera Therapeutics. He is also the founder of the UCL spin-out company Yaqrit Ltd. and Cyberliver Ltd.

Ethical approval This article does not contain any studies with human participants or animals.

References

1. Domenicali M, Baldassarre M, Giannone FA, Naldi M, Mastroroberto M, Biselli M, Laggetta M, et al. Posttranscriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis. Hepatology. 2014;60:1851–1860.
2. Oettl K, Birner-Gruenberger R, Spindelboeck W, Stueger HP, Dorn L, Stadlbauer V, Putz-Bankuti C, et al. Oxidative albumin damage in chronic liver failure: relation to albumin binding capacity, liver dysfunction and survival. J Hepatol. 2013;59:978–983.
3. Jalan R, Schnurr K, Mookerjee RP, Sen S, Cheshire L, Hodges S, Muravsky V, et al. Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. Hepatology. 2009;50:555–564.
4. Jalan R, Bernardi M. Effective albumin concentration and cirrhosis mortality: from concept to reality. J Hepatol. 2013;59:918–920.
5. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathophysiology, Part III: albumin and disease states. JPEN J Parenter Enteral Nutr. 1991;15:476–483.
6. Caraceni P, Tufoni M, Bonavita ME. Clinical use of albumin. Blood Transfus. 2013;11(Suppl 4):s18–s25.
7. Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the

treatment of cirrhosis and its complications. Hepatology. 2013;58:1836–1846.
8. Evans TW. Review article: albumin as a drug–biological effects of albumin unrelated to oncotic pressure. Aliment Pharmacol Ther. 2002;16(Suppl 5):6–11.
9. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth. 2000;85:599–610.
10. Guizado TR. Analysis of the structure and dynamics of human serum albumin. J Mol Model. 2014;20:2450.
11. Sugio S, Kashima A, Mochizuki S, Noda M, Kobayashi K. Crystal structure of human serum albumin at 2.5 A resolution. Protein Eng. 1999;12:439–446.
12. Fasano M, Curry S, Terreno E, Galliano M, Fanali G, Narciso P, Notari S, et al. The extraordinary ligand binding properties of human serum albumin. IUBMB Life. 2005;57:787–796.
13. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. Mol Aspects Med. 2012;33:209–290.
14. Anraku M. Elucidation of the mechanism responsible for the oxidation of serum albumin and its application in treating oxidative stress-related diseases. Yakugaku zasshi. 2014;134:973–979.
15. Oettl K, Stauber RE. Physiological and pathological changes in the redox state of human serum albumin critically influence its binding properties. Br J Pharmacol. 2007;151:580–590.
16. He XM, Carter DC. Atomic structure and chemistry of human serum albumin. Nature. 1992;358:209–215.
17. Kragh-Hansen U, Chuang VTG, Otagiri M. Practical aspects of the ligand-binding and enzymatic properties of human serum albumin. Biol Pharm Bull. 2002;25:695–704.
18. Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol. 2014;61:396–407.
19. Quinlan GJ, Margarson MP, Mumby S, Evans TW, Gutteridge JM. Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion. Clin Sci (Lond). 1998;95:459–465.
20. Neuzil J, Stocker R. Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. J Biol Chem. 1994;269:16712–16719.
21. Cantin AM, Paquette B, Richter M, Larivee P. Albumin-mediated regulation of cellular glutathione and nuclear factor kappa B activation. Am J Respir Crit Care Med. 2000;162:1539–1546.
22. Bortoluzzi A, Ceolotto G, Gola E, Sticca A, Bova S, Morando F, Piano S, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology. 2013;57:266–276.
23. Keaney JF Jr, Simon DI, Stamler JS, Jaraki O, Scharfstein J, Vita JA, Loscalzo J. NO forms an adduct with serum albumin that has endothelium-derived relaxing factor-like properties. J Clin Investig. 1993;91:1582–1589.
24. Kim SB, Chi HS, Park JS, Hong CD, Yang WS. Effect of increasing serum albumin on plasma D-dimer, von Willebrand factor, and platelet aggregation in CAPD patients. Am J Kidney Dis. 1999;33:312–317.
25. Jaeschke H, Hasegawa T. Role of neutrophils in acute inflammatory liver injury. Liver Int. 2006;26:912–919.
26. Zhang W-J, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res. 2002;55:820–829.
27. Chen TA, Tsao YC, Chen A, Lo GH, Lin CK, Yu HC, Cheng LC, et al. Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis. Scand J Gastroenterol. 2009;44:619–625.
28. Mookerjee RP, Stadlbauer V, Lidder S, Wright GAK, Hodges SJ, Davies NA, Jalan R. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. Hepatology. 2007;46:831–840.
29. Stadlbauer V, Mookerjee RP, Wright GAK, Davies NA, Jurgens G, Hallstrom S, Jalan R. Role of Toll-like receptors 2, 4, and 9 in mediating neutrophil dysfunction in alcoholic hepatitis. Am J Physiol Gastrointest Liver Physiol. 2009;296:G15–G22.
30. O'Brien AJ, Fullerton JN, Massey KA, Auld G, Sewell G, James S, Newson J, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med. 2014;20:518–523.
31. Qiao R, Siflinger-Birnboim A, Lum H, Tiruppathi C, Malik AB. Albumin and Ricinus communis agglutinin decrease endothelial permeability via interactions with matrix. Am J Physiol. 1993;265:C439–C446.
32. Lang JD Jr, Figueroa M, Chumley P, Aslan M, Hurt J, Tarpey MM, Alvarez B, et al. Albumin and hydroxyethyl starch modulate oxidative inflammatory injury to vascular endothelium. Anesthesiology. 2004;100:51–58.
33. Garcia-Martinez R, Andreola F, Mehta G, Poulton K, Oria M, Jover M, Soeda J, et al. Immunomodulatory and antioxidant function of albumin stabilises the endothelium and improves survival in a rodent model of chronic liver failure. J Hepatol 2015;62:799-806.
34. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437.
35. Oettl K, Stadlbauer V, Petter F, Greilberger J, Putz-Bankuti C, Hallstrom S, Lackner C, et al. Oxidative damage of albumin in advanced liver disease. Biochim Biophys Acta. 2008;1782:469–473.
36. Klammt S, Brinkmann B, Mitzner S, Munzert E, Loock J, Stange J, Emmrich J, et al. Albumin binding capacity (ABiC) is reduced in commercially available human serum albumin preparations with stabilizers. Z Gastroenterol. 2001;39(Suppl 2):24–27.
37. Bhagavan NV, Lai EM, Rios PA, Yang J, Ortega-Lopez AM, Shinoda H, Honda SA, et al. Evaluation of human serum albumin cobalt binding assay for the assessment of myocardial ischemia and myocardial infarction. Clin Chem. 2003;49:581–585.
38. Klammt S, Mitzner SR, Stange J, Loock J, Heemann U, Emmrich J, Reisinger EC, et al. Improvement of impaired albumin binding capacity in acute-on-chronic liver failure by albumin dialysis. Liver Transplant. 2008;14:1333–9.
39. Giannone FA, Domenicali M, Baldassarre M, Bartoletti M, Naldi M, Laggetta M, Bertucci C, et al. Ischaemia-modified albumin: a marker of bacterial infection in hospitalized patients with cirrhosis. Liver Int 2015. doi:10.1111/liv.12860.
40. Garcia-Martinez R, Noiret L, Sen S, Mookerjee R, Jalan R. Albumin infusion improves renal blood flow autoregulation in patients with acute decompensation of cirrhosis and acute kidney injury. Liver Int 2015;35:335–343.
41. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53:397–417.
42. Runyon BA, Committee APG. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49:2087–2107.
43. Salo J, Gines A, Gines P, Piera C, Jimenez W, Guevara M, Fernandez-Esparrach G, et al. Effect of therapeutic paracentesis on plasma volume and transvascular escape rate of albumin in patients with cirrhosis. J Hepatol. 1997;27:645–653.
44. Ruiz-del-Arbol L, Monescillo A, Jimenez W, Garcia-Plaza A, Arroyo V, Rodes J. Paracentesis-induced circulatory dysfunction:

mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology. 1997;113:579–586.
45. Vila MC, Sola R, Molina L, Andreu M, Coll S, Gana J, Marquez J, et al. Hemodynamic changes in patients developing effective hypovolemia after total paracentesis. J Hepatol. 1998;28:639–645.
46. Kwok CS, Krupa L, Mahtani A, Kaye D, Rushbrook SM, Phillips MG, Gelson W. Albumin reduces paracentesis-induced circulatory dysfunction and reduces death and renal impairment among patients with cirrhosis and infection: a systematic review and meta-analysis. BioMed Res Int. 2013;2013:295153.
47. Gines P, Cardenas A. The management of ascites and hyponatremia in cirrhosis. Semin Liver Dis. 2008;28:43–58.
48. Salerno F, Guevara M, Bernardi M, Moreau R, Wong F, Angeli P, Garcia-Tsao G, et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int. 2010;30:937–947.
49. Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology. 2012;55:1172–1181.
50. Moller S, Henriksen JH. Cirrhotic cardiomyopathy. J Hepatol. 2010;53:179–190.
51. Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras D, Guevara M, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. Hepatology. 2002;36:941–948.
52. Neri S, Pulvirenti D, Malaguarnera M, Cosimo BM, Bertino G, Ignaccolo L, Siringo S, et al. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. Dig Dis Sci. 2008;53:830–835.
53. Martin-Llahi M, Pepin MN, Guevara M, Diaz F, Torre A, Monescillo A, Soriano G, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology. 2008;134:1352–1359.
54. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341:403–409.
55. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol. 2013;11:123–130.e121.
56. Fernandez J, Navasa M, Garcia-Pagan JC, G-Abraldes J, Jimenez W, Bosch J, Arroyo V. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. J Hepatol. 2004;41:384–390.
57. Fernandez J, Monteagudo J, Bargallo X, Jimenez W, Bosch J, Arroyo V, Navasa M. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology. 2005;42:627–634.
58. Fernandez J, Navasa M, Gomez J, Colmenero J, Vila J, Arroyo V, Rodes J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology. 2002;35:140–148.
59. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139:1246–1256.
60. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, et al. Bacterial infections in cirrhosis: a position statement based on the EASL special conference 2013. J Hepatol. 2014;60:1310–1324.
61. Guevara M, Terra C, Nazar A, Sola E, Fernandez J, Pavesi M, Arroyo V, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol. 2012;57:759–765.
62. Thevenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, Rudler M, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol. 2015;62:822–830.
63. Tarao K, Iwamura K. Influence of long-term administration of serum albumin on the prognosis of liver cirrhosis in man. Tokai J Exp Clin Med. 1983;8:71–78.
64. Romanelli R-G, La Villa G, Barletta G, Vizzutti F, Lanini F, Arena U, Boddi V, et al. Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. World J Gastroenterol. 2006;12:1403–1407.
65. Gentilini P, Casini-Raggi V, Di Fiore G, Romanelli RG, Buzzelli G, Pinzani M, La Villa G, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. J Hepatol. 1999;30:639–645.
66. Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol. 2015;62:437–447.
67. Jalan R, Kapoor D. Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid. Clin Sci. 2004;106:467–474.
68. Simon-Talero M, Garcia-Martinez R, Torrens M, Augustin S, Gomez S, Pereira G, Guevara M, et al. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. J Hepatol. 2013;59:1184–1192.
69. Nevens F, Laleman W. Artificial liver support devices as treatment option for liver failure. Best Pract Res Clin Gastroenterol. 2012;26:17–26.
70. Jalan R, Williams R. Improvement in cerebral perfusion after MARS therapy: further clues about the pathogenesis of hepatic encephalopathy? Liver Transplant. 2001;7:713–415.
71. Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, Saliba F, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013;57:1153–1162.
72. Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, Sarrazin C, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology. 2012;142:782–789.
73. Oettl K, Stadlbauer V, Krisper P, Stauber RE. Effect of extracorporeal liver support by molecular adsorbents recirculating system and Prometheus on redox state of albumin in acute-on-chronic liver failure. Ther Apher Dial. 2009;13:431–436.