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Schematic Review Of Oral Egg Albumin Protein – An Overview In Critically Ill Patient

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ABSTRACT:

Background: The share of ovalbumin, ovotransferrin, ovomucoid, ovoglobulins, ovomucin, and lysozymes are the main components of albumen protein. 12.5% (w/w) protein can be found in fresh egg whites. The principal proteins in egg white are albumen (water-soluble) and globular proteins (soluble in neutral dilute salt solutions). Biotin, niacin, and riboflavin are water-soluble vitamins that are present in substantial amounts in egg albumen. The major protein present in egg albumen is known as "Ovalbumin" and it is the only protein of egg albumen that contains free SH groups. Albumin is a natural plasma protein synthesized exclusively by the liver at a rate of 9 to 14 g/day in healthy individuals, with a median half-life of about 18 to 19 days. Albumin is catabolized in most organs of the body at a similar rate of about 9 to 14 g/day, by uptake into endocytotic vesicles on the endothelial surface; the final breakdown products are amino acids. Whatever the underlying mechanisms, hypoalbuminemia is associated with worse outcomes including increased complications and reduced short-term and longer-term survival in critically ill patients. Conclusion: Egg albumin has multiple physiological effects, including regulation of colloid osmotic pressure (COP), binding and transportation of various substances (for example, drugs, hormones) within the blood, antioxidant properties, nitric oxide modulation, and buffer capabilities, which may be of particular relevance in critically ill patients. It possesses antioxidant, antihypertensive, anti-cancerous properties. It can be used in critically ill patients with involvement of the liver, renal diseases, peripheral edema, cirrhosis, bacterial peritonitis, ascites, etc.

Keywords: Anticancer, Critical ill patients, Egg albumin, Ovalbumin

INTRODUCTION

The majority of egg albumen is water, which ranges approximately from 84% to 89%. Proteins constitute the major portion (10%–11%) of albumen primarily while other components, such as carbohydrates, lipids, and minerals, form a minor portion of albumen. The share of ovalbumin, ovotransferrin, ovomucoid, ovoglobulins, ovomucin, and lysozymes is 54%, 12%–13%, 11%, 2.0%, 1.5%–3.0%, and 3.5%, respectively, are the main components of albumen protein while ovastatin, ovoflavoproteins, and avidin are also present in small amounts. Peynaud (1984) reported that about 12.5% (w/w) protein can be found in fresh egg whites. The principal proteins in egg white are albumen (water-soluble) and globular proteins (soluble in neutral dilute salt solutions).

Biotin, niacin, and riboflavin are water-soluble vitamins that are present in substantial amounts in egg albumen. Minerals, such as sulfur, potassium, sodium, and chlorine, form the major portion while calcium, phosphorus, and magnesium are present in trace amounts in egg albumen. The major protein present in egg albumen is known as "Ovalbumin" and it is the only protein of egg albumen that contains free SH groups.

Albumin has multiple physiological effects[1], including regulation of colloid osmotic pressure (COP), binding and transportation of various substances (for example, drugs, hormones) within the blood, antioxidant properties, nitric oxide modulation, and buffer capabilities, which may be of particular relevance in critically ill patients. Albumin solutions have been used worldwide for the treatment of critically ill patients since they became commercially available in the 1940s. However, their use has become the subject of criticism and debate in more recent years. Importantly, all fluid solutions have potential benefits and drawbacks.

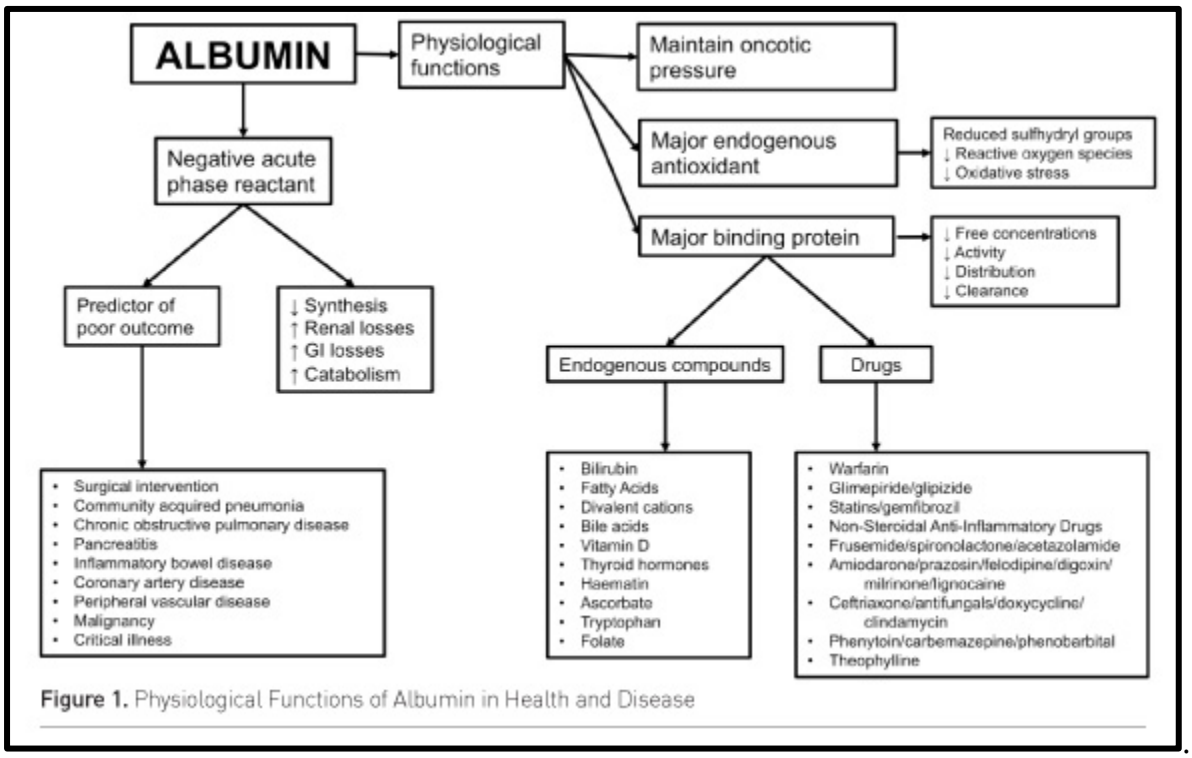


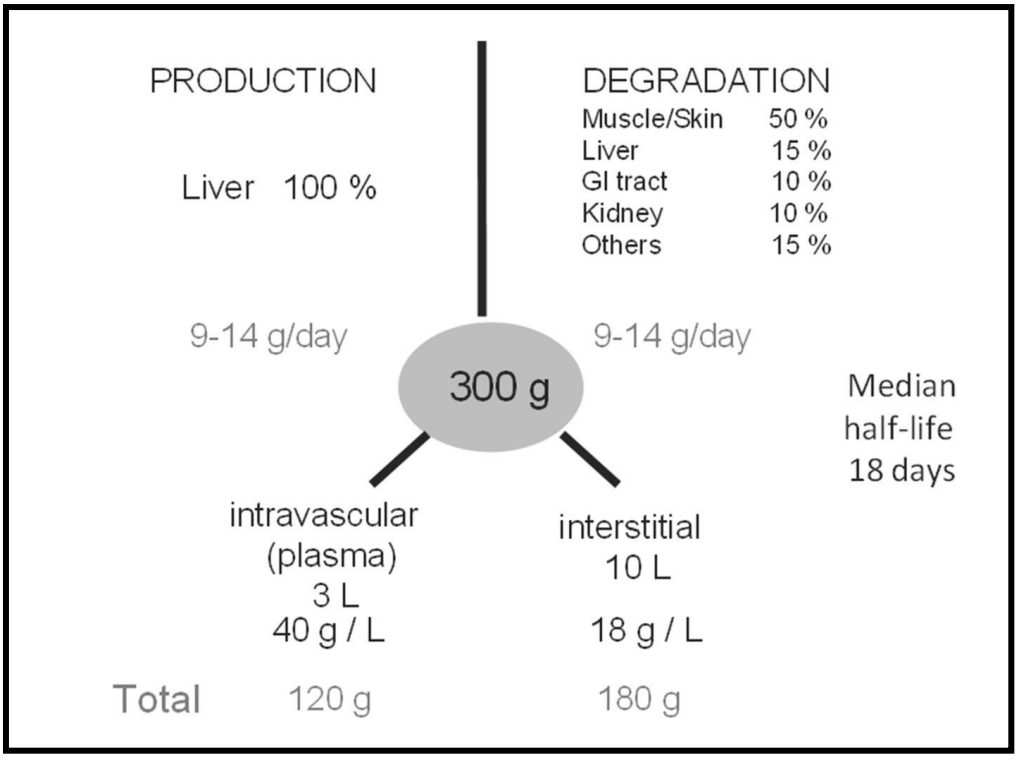
Figure 1. Physiological Functions of Albumin in Health and Disease

HISTORY

Albumin was one of the first human proteins to be isolated and extracted from plasma for clinical use. First crystallized in 1934, preparation was made available for clinical use in the 1940s [2,3]. Early successful use in multi-trauma and severely burned patients led to a rapid expansion of the so-called human albumin program in the USA[4], and albumin use spread from the military setting to civilian hospitals and into regular use in operating and emergency rooms around the world. The first commercially available preparations of intravenous human albumin solution were developed using the cold alcohol fractionation technique created by Edwin Joseph Cohn. Later developments and refinements in extraction and processing have resulted in increasingly pure solutions.[5]

PHYSIOLOGICAL PROPERTIES

Albumin is a natural plasma protein synthesized exclusively by the liver at a rate of 9 to 14 g/day in healthy individuals, with a median half-life of about 18 to 19 days (Figure 1)[6].Albumin is catabolized in most organs of the body at a similar rate of about 9 to 14 g/day, by uptake into endocytotic vesicles on the endothelial surface[7]; the final breakdown products are amino acids.



Effects of Hypoalbuminemia in the body

Hypoalbuminemia (generally defined as a serum albumin concentration ≤30 g/l)[8,9] is very common in critically ill patients, the main reasons probably being increased albumin losses from bleeding and via the gastrointestinal tract[10], increased capillary permeability leading to a redistribution from the intravascular to the interstitial space (previously called third-spacing)[11], and dilution from intravenous fluid administration Moreover, in some patients – particularly

older patients – baseline albumin levels may already be below as a result of poor nutritional status or altered liver function. Although animal models suggested that albumin synthesis may be reduced in critical illness[12], synthesis appears to be increased in critically ill humans[13].

Importantly, whatever the underlying mechanisms, hypoalbuminemia is associated with worse outcomes including increased complications[14,15,16,17] and reduced short-term [18,19, 20, 21, 22] and longer-term[23,24,25] survival in critically ill patients. In a meta-analysis of 90 cohort studies that had evaluated hypoalbuminemia as a prognostic biomarker in acutely ill patients, each 10 g/l decreases in serum albumin concentration were associated with a 137% increase in the odds of death, an 89% increase in morbidity, and a 71% increase in length of hospital stay. There is, therefore, a clear association between the albumin level and the severity of the result[26], it remains uncertain whether the effect of hypoalbuminemia on an outcome is a cause-effect relationship or whether hypoalbuminemia is rather a marker of serious disease.

LITERARY REVIEW ON CLINICAL TRIALS

Table 1. Biological activities of egg white and yolk proteins and the derived peptides

Protein		Biological activities	References
Egg white	Ovalbumin	Antioxidant activity	Huang et al. (2012)
		Antimicrobial activity	Pellegrini et al. (2004)
		Anticancer activity	Vis et al. (1998)
		Immunomodulatory activity	Fan et al. (2003); Goldberg et al. (2003); He et al. (2003); Rupa et al. (2015); Vidovic et al. (2002)
	Ovotransferrin	Antioxidant activity	Kim et al. (2012)
		Antihypertensive activity	Majumder and Wu (2010, 2011)
		Antimicrobial activity	Abdallah and Chahine (1999); Ibrahim et al. (2000); Moon et al.(2012)
		Anticancer activity	Ibrahim and Kiyono (2009); Lee et al. (2017a); Moon et al. (2012)

		Immunomodulatory activity	Huang et al. (2010); Lee et al. (2018); Majumder et al. (2013)
	Lysozyme	Antihypertensive activity	Yoshii et al. (2001)
		Antimicrobial activity	Hughey and Johnson (1987); Ibrahim et al. (1991, 1992, 1994)
		Anticancer activity	Das et al. (1992); Mahanta et al. (2015); Pacor et al. (1996, 1999)
		Immunomodulatory activity	Asakura et al. (1990); Ha et al. (2013); Sava (1996); Sugahara et al.(2000)
	Cystatin	Antimicrobial activity	Blankenvoorde et al. (1996)
		Anticancer activity	Cegnar et al. (2004); Muehlenweg et al. (2000); Premzl et al. (2001);
		Immunomodulatory activity	Kato et al. (2000); Verdot et al. (1996, 1999)
	Avidin	Antimicrobial activity	Korpela et al. (1984)
		Anticancer activity	Corti et al. (1998); Gasparri et al. (1999); Moro et al. (1997)
	Ovomucin	Antimicrobial activity	Kobayashi et al. (2004)
		Anticancer activity	Oguro et al. (2000); Ohami et al. (1993); Watanabe et al. (1998)

		Immunomodulatory activity	Sun et al. (2016); Tanizaki et al. (1997)

Effect of egg albumin on the nutritional status of CAPD patients.

On overviewing the literary review, many studies are conducted to evaluate the effect of oral administration of an egg albumin-based protein supplement on the nutritional status of CAPD patients. In this randomized, open-label, controlled clinical trial, 28 CAPD patients were allocated to a study (n = 13) or a control (n = 15) group. Both groups received conventional nutritional counseling; the study group received, additionally, an oral egg albumin-based supplement. During a 6-month follow-up, all patients had monthly clinical and biochemical evaluations and quarterly assessments of the adequacy of dialysis and nutrition. Serum albumin levels were not different between groups; however, a significant increase (baseline vs final) was observed in the study group (2.64+/-0.35 vs 3.05+/-0.72 g/dL) but not in the control group (2.66+/-0.56 vs 2.80+/-0.54 mg/dL). Calorie and protein intake increased more in the study group (calories 1331+/-432 vs 1872+/-698 kcal; proteins 1.0+/-0.3 vs 1.7+/-0.7 g/kg) than in the control group (calories 1423+/-410 vs 1567+/-381 kcal; proteins 1.0+/-0.4 vs 1.0+/-0.3 g/kg). Similarly, non-protein nitrogen appearance rate (nPNA) increased significantly more in the study (1.00+/-0.23 vs 1.18+/-0.35 g/kg/day) than in the control group (0.91+/-0.11 vs 0.97+/-0.14 g/kg/ day). Triceps skinfold thickness (TSF) and midarm muscle area (MAMA) displayed a nonsignificant trend to a greater increase in the study group (TSF 16.7+/-8.7 vs 18.3+/-10.7 mm; MAMA 23.8+/-6.2 vs 25.8+/-5.9 cm2) than in controls (TSF 16.4+/-5.7 vs 16.9+/-7.0 mm; MAMA 28.7+/-7.8 vs 30.0+/-7.9 cm2). At the end of follow-up, the frequency of patients with moderate or severe malnutrition decreased 6% in the control group and decreased 28% in the study group.

At the final evaluation, the most important predictors of serum albumin were the oral egg albumin-based supplement administration and protein intake ($p < 0.05$); secondary predictors ($p = 0.06$) were peritoneal transport rate and MAMA. In the study group, oral administration of the egg albumin-based supplement significantly improved serum albumin, calorie and protein intake, and nPNA, and, compared to controls, this maneuver was associated with a trend to increased anthropometric parameters and improved Subjective Global Assessment evaluation. Oral administration of the albumin supplement and protein intake were the most significant predictors of serum albumin at the end of follow-up. The oral supplement may be a safe, effective, and cheap method to improve nutritional status in peritoneal dialysis patients.

Antioxidant Activity

Egg yolk phosvitin has a metal-chelating effect (Castellani et al., 2004), and as a result, is a strong antioxidant. Furthermore, phosvitin oligophosphopeptides produced by tryptic hydrolysis of phosvitin demonstrate strong antioxidant activity in DPPH free-radical-scavenging assays and Caco-2 cells (Katayama et al., 2006; Xu et al., 2007). Sakanaka et al. (2004) reported that egg yolk protein hydrolysates display antioxidant activities in a

linoleic-acid oxidation system. One particular peptide resulting from the pepsin-mediated hydrolysis of crude egg white proteins was shown to have a strong antioxidant activity and high-radical-scavenging activity (Davalos et al., 2004). Ovalbumin–saccharide mixture has been reported to have stronger reducing power, greater DPPH-scavenging activity, and higher Trolox equivalent antioxidant capacity values than those of ovalbumin (Huang et al., 2012). Kim et al. 2012 reported that ovotransferrin from egg white protein has antioxidant properties and that this is further improved following hydrolysis by various enzymes.[27]

Antihypertensive Activity

The 3 peptides (IRW, IQW, and LKP) derived from thermolysin- and pepsin-mediated ovotransferrin hydrolysis are capable of exerting a strong inhibitory effect on angiotensin-converting enzyme (**ACE**) (Majumder and Wu 2010, 2011). In addition, Rao et al. (2012b) reported that a hydrolysate of hen egg-white lysozyme has potent ACE-inhibitory effects. Oligopeptides prepared from egg yolk protein were shown to suppress the development of hypertension in spontaneously hypertensive rats via inhibition of ACE activity (Yoshii et al., 2001).[28]

Antimicrobial Activity

The bacteriolytic activity of lysozyme, which is often used as a natural food preservative (Hughey and Johnson, 1987), involves hydrolysis of the β(1-4) linkage between N-acetylmuramic acid and N- acetylglucosamine of peptidoglycan. It is typically most effective against gram-positive bacteria; however, chemical modification has been shown to increase its antimicrobial action against gram-negative bacteria (Ibrahim et al., 1991, 1992, 1994). Enzymatic hydrolysis of lysozyme has been found to enhance its antibacterial activity by producing peptides. More specifically, peptides corresponding to amino acid residues (aa) 15–21, 98–108 (Mine et al., 2004), and 98–112 (Pellegrini et al., 2000) were shown to have antimicrobial activity against Escherichia coli and Staphylococcus aureus.[29]

Peptides resulting from enzymatic digestion of ovalbumin were found to be strongly active against Bacillus subtilis and to a lesser extent against gram-negative bacteria such as E. coli, Bordetella bronchiseptica, Pseudomonas aeruginosa, and Serratia marcescens (Pellegrini et al., 2004). Ovotransferrin, a member of the transferrin family, can bind iron and is thought to function as an iron scavenger, preventing iron utilization by microorganisms (Abdallah and Chahine, 1999). It has also been shown to have antibacterial activity against a wide range of bacteria, including Pseudomonas spp., E. coli, Streptococcus mutans (Valenti et al., 1983), S. aureus, Bacillus cereus (Abdallah and Chahine, 1999), Listeria monocytogenes, and Helicobacter pylori (Moon et al.,2012). Ovotransferrin antimicrobial peptide (OTAP)-92 consists of 92 aa located within the aa 109–200 region and has been shown to have antibacterial properties (Ibrahim et al., 2000). Under thermal stress, phosvitin from egg yolk exerts a bactericidal action against E. coli and S. aureus owing to an increase in its metal-chelating ability and high surface activity (Khan et al., 2000; Maet al., 2013). Furthermore, ovomucin (Kobayashi et al., 2004), cystatin (Blankenvoorde et al., 1996), avidin (Korpela et al., 1984), ovomacroglobulin (Miyagawa et al., 1991), and IgY (Kovacs-Nolan and Mine,

2004) have all demonstrated antimicrobial activities against food poisoning–associated bacteria.[30]

Anticancer Activities of Egg Proteins

Several studies have demonstrated the anti-cancer activities of egg proteins and associated peptides, and these can occur via a variety of mechanisms. Cystatin has been widely studied as an anticancer drug. It is known to inhibit the tumor-associated activity of intracellular cysteine proteases, possibly due to the presence of a urokinase-type plasminogen activator receptor binding site (Muehlenweg et al., 2000). Its ability to inhibit cysteine proteinases resulted in a reduction in tumor invasion ability and metastasis of Ras-transformed breast epithelial cells (Premzl et al., 2001). Cystatin has also been shown to be toxic toward MCF-10A neoT cells (Cegnar et al., 2004), and poly(lactide-co-glycolide) nanoparticles have been shown to improve the bioavailability and delivery of cystatin into tumor cells. Finally, Saleh et al. (2003) reported that purified egg white cystatin reduces the effects of cathepsins B and L, which have higher activity in gastric cancer tissues. Avidin has been used in a wide variety of applications in the life sciences and medicine, especially in the pre-targeting of cancer treatments. Avidin has a strong affinity for biotin and is highly thermostable and resistant to proteolysis by proteinase K (Hytonen et al., 2003). Moro et al. (1997) and Corti et al. (1998) studied the antitumor properties of avidin using avidin- biotinylated tumor necrosis factor-α (**TNF-α**). The addition of avidin was shown to increase the binding and persistence of TNF-α on tumor cells and increase the antitumor activity of TNF-α at least 5-fold, but importantly did not increase toxicity, as judged by as- sessing animal survival after treatment (Gasparri et al., 1999).[31]

Lysozyme has been shown to have cancer-preventive properties when administered to normal mice (Das et al., 1992), and can directly activate immune cells and increase tumor cell immunogenicity(Sava et al., 1989). Lysozyme coupled with monomethoxypolyethylene glycol (**mPEG**-lysozyme) reduces tumor growth and prevents lung metastasis. However, this causes it to lose its enzymatic action against the Micrococcus lysodeikticus cell wall, meaning that the effect of lysozyme on tumor growth is unrelated to immunoactive peptidoglycan production (Pacor et al., 1996). mPEG-lysozyme has also been shown to reduce the number of tumor cells in the synthesis and pre-mitotic phases of the cell cycle (Pacor et al., 1999).[32]

For resuscitation in heterogeneous groups of critically ill patients

Although albumin solutions were first introduced in the 1940s, the first RCT of albumin administration was only published some 30 years later in 1975 (Table 1). This early RCT, conducted in just 16 patients undergoing abdominal aortic surgery, compared the effects of intraoperative use of albumin solution with those of a sodium-rich fluid during surgery and showed that albumin infusion led to less extracellular fluid expansion[33]. Other relatively small studies followed so that by the time the Cochrane meta-analysis[34] was published in 1998 the average sample size of the 32 included studies was just 46 patients. Although the results of many studies take years to be published and to change clinical practice – if indeed they ever do

– this Cochrane report influenced practice rapidly around the world, especially in the UK where the use of albumin decreased by 40 to 45% in the 6 months after publication[35]. An Expert Working Party of the Committee on Safety of Medicines in the UK highlighted the thoughts of many in the medical community that there was an urgent need to conduct large multicenter RCTs to determine whether albumin administration did indeed worsen outcomes[36]. In 2004, the results of the Saline versus Albumin Fluid Evaluation (SAFE) RCT in almost 7,000 critically ill patients were published, showing that a 4% albumin solution was as safe as normal saline when used as a resuscitation fluid[37].

For resuscitation in patients with sepsis

Subgroup analysis of the SAFE study suggested there may be a benefit in patients with severe sepsis (35% of whom had septic shock), with an adjusted odds ratio for death of 0.71 (95% CI, 0.52 to 0.97; P = 0.03) for albumin compared with saline[38]. A subsequent meta-analysis that included 17 RCTs comparing albumin solutions with other fluids for fluid resuscitation in patients with sepsis reported that albumin use was associated with decreased mortality (odds ratio, 0.82; 95% CI, 0.67 to 1.0; P = 0.047)[39]. Guidelines currently suggest (grade 2C) that albumin use should be considered as a resuscitation fluid in patients with severe sepsis, particularly if those patients are not responding to crystalloid infusion[40,41], based on data from the meta-analysis[42] and preliminary data from a multicenter study in France that suggested a nonsignificant reduction in mortality in patients with septic shock who received albumin [43].

In the multicenter EARSS study in France, so far published only in abstract form, 798 patients with the septic shock of fewer than 6 hours duration were randomized to receive 100 ml of 20% albumin or 100 ml of 0.9% saline every 8 hours for 3 days. Almost all patients had severe hypoalbuminemia at study inclusion. There were no significant differences in mortality rates between the two groups (24.1 vs 26.3%)

In the ALBIOS study, conducted in 100 ICUs in Italy[44], 1,818 patients with severe sepsis or septic shock were randomized either to receive 300 ml of 20% albumin plus crystalloid or to receive crystalloid alone initially to achieve the target resuscitation goals of the early goal-directed therapy protocol used by Rivers and colleagues[45]. Over the subsequent 28 days, albumin infusions were adjusted to maintain serum albumin ≥30 g/l; crystalloid solutions were given when considered clinically indicated by the attending physician. More patients in the albumin group than in the crystalloid group reached the target mean arterial pressure within 6 hours after randomization (86% versus 82.5%, P = 0.04), and during the first 7 days the mean arterial pressure was higher and the net fluid balance lower in the albumin group than in the crystalloid group[46], despite similar amounts of fluid being administered to the two groups. There were, however, no overall differences in 28-day mortality rates (32% albumin vs 32% crystalloid; relative risk in the albumin group, 1.00; 95% CI, 0.87 to 1.14; P = 0.94) or 90-day mortality rates (41% albumin vs 44% crystalloid; relative risk, 0.94; 95% CI, 0.85 to 1.05; P = 0.29) between the groups. Of the 1,818 patients, 579 (31.8%) were randomized within 6 hours and 1,239 (68.2%) more than 6 hours after meeting the clinical criteria for severe sepsis; there were no significant differences in outcomes according to the interval between meeting clinical criteria and randomization. In the subgroup of patients with

septic shock at enrollment (n = 1,121), however, those who received albumin had significantly lower 90-day mortality rates than those who received saline (44% versus 50%; relative risk, 0.87; 95% CI, 0.77 to 0.99; P = 0.03).

Effect of albumin in Burn Patients:

In the triple-blind clinical trial, a total of 90 patients from Taleghani hospital, Ahvaz, Iran were selected and randomly divided into two groups based on the inclusion criteria. The intervention group was dressed in egg white formulation + silver sulfadiazine cream and the control group was treated with placebo + silver sulfadiazine cream. The burn wound healing process was evaluated on days 1, 7, and 15 by the Bates-Jensen wound assessment tool. The mean scores of wound healing were decreased (13.75±1.83) in the intervention group when compared to the control (21.51±5.7) on day 15 ($p<0.001$). The mean duration of wound healing, wound depth, edges, undermining, necrotic tissue, amount of necrosis, exudate type and amount, surrounding skin color, wound induration, peripheral edema, granulation, and epithelialization were significantly decreased in the intervention group in comparison with control ($p<0.001$). The findings of this research showed that egg whites formulation is an appropriate treatment for burn wound healing, reducing above-noted burn wounds' variables. It seems that this treatment, along with the common medicine, improves chronic wound recovery rate and patients' health status.[47]

For albumin replacement in patients with hypoalbuminemia

The effects of increasing albumin concentrations by giving exogenous albumin have also been investigated in the critically ill. A meta-analysis of nine prospective controlled trials on correcting hypoalbuminemia in acutely ill patients suggested that complication rates were reduced in patients who achieved serum albumin concentrations >30 g/l after albumin administration [5]. However, in a subgroup analysis of the SAFE study in patients with hypoalbuminemia, using a cutoff value of 25 g/l[48], there were no significant differences in outcomes in hypoalbuminemia patients and normoalbuminuric patients who received albumin. In a pilot RCT of 100 hypoalbuminemia critically ill patients who were randomized either to receive 300 ml of 20% albumin solution on the first day and then 200 ml/day if the serum albumin concentration remained <30 g/dl or to receive no albumin, Dubois, and colleagues reported that organ function (as assessed by change in the Sequential Organ Failure Assessment score) improved more in the albumin-treated patients (P = 0.03)[49]; these patients also had a less positive fluid balance (P =0.04). There was also a beneficial effect on cumulative calorie intake during the first week, suggesting that albumin may have helped decrease intestinal edema.

The effects of albumin administration may also depend on the simultaneous use of diuretics to prevent an albumin infusion-induced increase in hydrostatic pressure, which may increase (rather than decrease) edema formation. Some studies have suggested that the concurrent use of albumin may increase furosemide-induced diuresis in hypnotic patients with acute respiratory distress syndrome/acute lung injury[50,51] and cirrhosis-induced ascites[52], although not in all critically ill patients [53]; whether this strategy has any effect on patient-centered clinical outcomes is unclear.

Albumin in Cirrhosis and spontaneous bacterial peritonitis

In 1999 Sort and colleagues published the results of an RCT in 126 patients with cirrhosis and spontaneous bacterial peritonitis comparing treatment with intravenous cefotaxime or cefotaxime plus intravenous albumin for plasma volume expansion. Renal impairment developed in fewer patients in the patients who received albumin ($P = 0.002$) and these patients also had reduced hospital and 3-month mortality rates (both $P = 0.01$). A more recent RCT reported beneficial effects of albumin plus antibiotic on renal and circulatory function in 110 patients with cirrhosis and infections other than spontaneous bacterial peritonitis; treatment with albumin was an independent predictive factor of survival. A meta-analysis of 16 RCTs also suggested that albumin use was associated with a significant reduction in mortality (odds ratio, 0.46; 95% CI, 0.25 to 0.86) and renal impairment (odds ratio, 0.34; 95% CI, 0.15 to 0.75) in patients with cirrhosis and any infection. Two small RCTs have also demonstrated improved renal function in patients with cirrhosis and hepatorenal syndrome treated with albumin and terlipressin.[54,55,56,57]

Albumin for End-Stage Liver Disease

Albumin has been widely used in patients with cirrhosis in an attempt to improve circulatory and renal functions. The benefits of albumin infusions in preventing the deterioration in renal function associated with large-volume paracentesis, spontaneous bacterial peritonitis, and established hepatorenal syndrome in conjunction with a vasoconstrictor are well established. While some of these indications are supported by the results of randomized studies, others are based only on clinical experience and have not been proved in prospective studies. The paucity of well-designed trials, the high cost of albumin, the lack of a clear-cut survival benefit, and the fear of transmitting unknown infections make the use of albumin controversial. The recent development of the molecular adsorbent recirculating system, albumin dialysis, is an example of the capacity of albumin to act by mechanisms other than its oncotic effect. Efforts should be made to define the indications for albumin use, the dose required, and predictors of response, so that patients gain the maximum benefit from its administration.[58]

Patients with peripheral edema during their recovery phase

Albumin has usually been studied in humans as a plasma substitute for volume replacement. From this point of view, the volume effect in itself, when taking into account the different characteristics of the types of fluid considered, is identical for albumin, other forms of colloids, and crystalloids[59]. Nonetheless, at equal intravascular volumes, potential complications and advantages may depend on the different properties of the infused fluid. For example, when employing mainly crystalloids for volume replacement, the most important disadvantage is probably the greater amount of fluids to be infused to reach the same volume effect of albumin or other synthetic colloids, with a consequent increased risk of peripheral edema and weight gain. On the other hand, artificial colloids may alter coagulation, essentially because of absorption of the factor VII/von Willebrand factor complex, with consequently altered platelet aggregation, and may lead to an increased risk of developing acute renal failure, as recently observed.[60]

Along the same line of reasoning, the role of albumin, especially because of its oncotic properties, may gain even greater importance in the clinical phase that usually follows the acute phase of volume replacement and resuscitation, i.e., the recovery phase, in which, having obtained clinical stability in terms of hemodynamics and organ function, the clinical priority is normally elimination of the excessive fluid previously accumulated in the interstitial space during the resuscitation phase. The intravascular plasma concentration of albumin may be critical during the recovery phase, as it accounts for about 80% of the entire oncotic pressure of the intravascular space[61], as mentioned above. Moreover, the pathophysiological rationale for intravenous administration of albumin during this phase may be more solid than that for administration during the acute phase, as the increased permeability of the capillary barrier that usually characterizes the acute florid phase during volume, replacement tends to normalize. The albumin infused in this situation is, therefore, more likely to "remain" within the intravascular space than usually occurs during the acute phase. Unfortunately, no clear evidence from randomized clinical trials or other forms of large studies is currently available, probably because of the difficulty of designing studies to investigate such a heterogeneous issue. Nonetheless, in our opinion, the soundness of the biological and pathophysiological rationale may at least partially justify such an indication for albumin administration.

The following case report may help to elucidate this issue. A patient was admitted to our post-surgery ICU after he had been admitted for 7 days in a neurological ICU because of traumatic spinal shock. On admission, the patient appeared to be in an oedematous state, with peripheral edema and bilateral pleural effusion (despite a water restriction program applied a few days previously), hypotension, oligo-anuria, and systemic arterial hypoxia. The patient's plasma albumin concentration was 13 g/L. We interpreted the patient's clinical situation as a state of anasarca in great need of elimination of the excessive accumulated fluid, probably as a consequence of the volume necessarily administered during the acute phase of the hemodynamic shock. We, therefore, continued the strategy of water restriction, but we initiated albumin administration at the maximal dose usually employed in our institution, i.e., 60 g/day, in association with a low dose of dopamine, in an attempt to obtain a higher mean arterial pressure. Within the following few days, we were able to increase the plasma albumin concentration to about 25 g/L, and we observed a parallel increase in mean arterial pressure and a marked increase of diuresis, with the possibility of obtaining a negative daily fluid balance. In association with these improvements, respiratory function ameliorated, with a significant increase of the ratio of arterial oxygen partial pressure to inspiratory oxygen fraction (PaO_2/FiO_2).

CONCLUSION

On overlooking the properties and physiological activities of albumin, history, its uses and clinical trial conducted, it can be concluded that albumin has multiple physiological effects, including regulation of colloid osmotic pressure (COP), binding and transportation of various substances (for example, drugs, hormones) within the blood, antioxidant properties, nitric oxide modulation and buffer capabilities, which may be of particular relevance in critically ill patients. It possesses antioxidant, antihypertensive, anticancerous properties. It can be used in

critically ill patients with involvement of the liver, renal diseases, peripheral edema, cirrhosis, bacterial peritonitis, ascites, etc.

Research on egg protein-derived bioactive peptides has been progressed during the past decades. Enzymatic hydrolysis is the major technique to prepare bioactive peptides from egg protein. Quantitative structure-activity relationships-aided in silico prediction is increasingly applied as a promising tool for the efficient prediction of novel bioactive peptides. A number of bioactive peptides from egg proteins have been characterized for antioxidant, immunomodulatory, antihypertensive, antidiabetic, anticancer, and antimicrobial activities. Egg protein-derived peptides that can improve bone health have been reported as well. However, the molecular mechanisms of many peptides are not fully understood.

Thus, it can be judiciously said that in patients with acute and chronic illness serum albumin concentration is inversely related to the risk of death.

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