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Role of albumin in diseases associated with severe systemic inflammation: Pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis

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ABSTRACT

The metabolism of albumin in inflammatory states such as sepsis or major surgery is complex and still not well characterized. Nevertheless, in inflammatory states, albumin synthesis has been observed to increase. By contrast, in decompensated cirrhosis, a disease characterized by systemic inflammation, albumin synthesis by the liver may decrease to 30% to 50% of normal values. Furthermore, in these conditions, there are high capillary leakage and altered albumin kinetics. The discussion regarding the effect of exogenous albumin administration on intravascular volume in inflammatory states should therefore address albumin turnover. To add complexity to our understanding of the effects of albumin, there are many data indicating that the therapeutic action of albumin is mediated not only through the impact on plasma volume expansion but also through a modulatory effect on inflammation and oxidative stress. All these characteristics are relevant to diseases associated with systemic inflammation including sepsis and decompensated cirrhosis.

1. Introduction

Albumin is a medium size molecule with a molecular weight of 66 to 69 kDa and is the most abundant protein in human plasma (40 g/L of a total of 70 g/L). Synthesized exclusively in the liver, albumin plays an important role in a number of physiological mechanisms including the regulation of osmotic pressure. Furthermore, albumin is a carrier of poorly water-soluble molecules such as hormones, cholesterol, calcium, iron, bilirubin, free fatty acids, and drugs [1,2]. Albumin's role in other mechanisms, including the endothelial glycocalyx and the maintenance of vascular barrier competence, are not as well understood but are likely to be important, particularly in patients with increased capillary leakage [2,3].

Albumin synthesis is decreased in malnutrition and liver dysfunction [4]. Increased microvascular permeability is observed in inflammatory states, including sepsis [5]. This alters the distribution of albumin between intravascular and extravascular compartments, and consequently, serum albumin concentration decreases in many critically ill patients, with low serum albumin concentrations less than 35 g/L being reported in 30% to 50% of critically ill patients [5–7]. Importantly, hypoalbuminemia is associated with higher mortality rates. Reinhardt et al [7] reported 25% mortality after 30 days of a serum albumin concentration less than 34 g/L, yet mortality increased to 62% when the serum albumin concentration dropped to 20 g/L or less during hospitalization [8].

There continues to be controversy surrounding the use of colloids in fluid therapy. The selection and use of resuscitation fluids is based on physiological principles, yet clinical practice is determined largely by clinician preference and thus exists with notable regional variation. Human serum albumin is considered to be the standard colloidal resuscitation fluid because of it is responsible for 75% of the plasma oncotic pressure. Therefore, administration of albumin can increase circulating volume and, as a result, widely used as a plasma volume replacement. The

Abbreviations: AD, acute decompensation; ACLF, acute-on chronic liver failure; CO, cardiac output; CRP, C-reactive protein; FSR, fractional synthesis rate; GFR, glomerular filtration rate; HRS, hepatorenal syndrome; HNMA, human nonmercapto albumin; HMA, human mercapto albumin; ICU, intensive care unit; LCFA, low-chain fatty acid; MAP, mean arterial pressure; NO, nitric oxide; PICD, paracentesis-induced circulatory dysfunction; PAMPs, pathogen-associated molecular patterns; PGE2, prostaglandin E2; RCTs, randomized clinical trials; RNS, reactive nitrogen species; ROS, reactive oxygen species; TER, transcapillary escape rate.

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multifunctional nature of albumin means that it acts in various capacities such as a major extracellular antioxidant, buffer, immunomodulatory, and detoxifying agent, and also serves as a major transporter in plasma [9].

The aim of this study is to review albumin metabolism in critically ill patients, particularly in those with sepsis, the recent clinical trials on albumin use, and its use for treating systemic inflammation in decompensated cirrhosis.

2. Albumin metabolism in critical illness

Hypoalbuminemia may be acute or chronic. One important effect of very low albumin concentrations is general edema. In healthy subjects, approximately 8 g of albumin is synthesized in the liver daily, corresponding to 3% of the total exchangeable albumin pool. Albumin synthesis takes around 30 minutes, and the turnover time is about 30 days [10,11]. Albumin is derived from prealbumin, whereby albumin is released when the correct tertiary structure is configured and albumin is then secreted out of the hepatocyte.

2.1. Distribution of intravascular and extravascular albumin

In healthy adult subjects, the fractional synthesis rate (FSR) of albumin is 5% to 8%/24 h (Fig. 1)—corresponding to 8 g/24 h, or 3 %/24 h of the total exchangeable pool—thus giving an absolute synthesis rate of 120 mg/kg per 24 hours.

Albumin is distributed throughout the entire extracellular space, with 40% (120 g) located in plasma and 60% (180 g) in the extravascular space. The total time for equilibration is 2 to 4 days. The exchange rate between plasma and the extravascular space is measured by the transcapillary escape rate (TER), which is on average 4% to 5% per hour (of intravascular albumin) [12]. Albumin's TER is measured by the disappearance rate of (I)-labeled albumin from plasma as determined by scintillography of repeated samples. The distribution of albumin between plasma and the interstitial fluid compartment makes albumin kinetics complicated, particularly when capillary permeability is altered. This was illustrated by Fleck et al [5] in their classic publication describing patients with septic shock and postoperative patients after cardiac surgery. In both conditions, an elevated TER of 10% to 15% per hour for patients of both conditions returned to normal over several days in patients with sepsis, whereas the return to normal was not reported for the cardiac surgery patients. Although the increased capillary leakage in trauma and sepsis patients is well known, its precise quantification is difficult to determine. The recirculation from the interstitial space back to the bloodstream through the lymphatic vessels is well described [12], but the temporal pattern in relation to surgical trauma is not well characterized. For example, Norberg et al [13] demonstrated that a reduction in serum albumin concentration already began during general anesthesia initiation and the initial phase of major cancer surgery, but TER did not differ by the second postoperative day compared with the preoperative day. The reduction in serum albumin concentration was most certainly multifactorial and related to factors such as concomitant administration of intravenous fluids, general anesthesia, epidural block, and change in plasma volume, and most likely due to a change in capillary permeability. The estimation of TER poses difficulties, as circulatory stability is essential for reliable measurements. This is true during surgery as well as in sepsis, and in particular in septic shock. In situations where capillary leakage seems to persist over several days, albumin kinetics are even less well characterized. Therefore, although the albumin synthesis rate is increased, an increased albumin leakage may result in significant hypoalbuminemia.

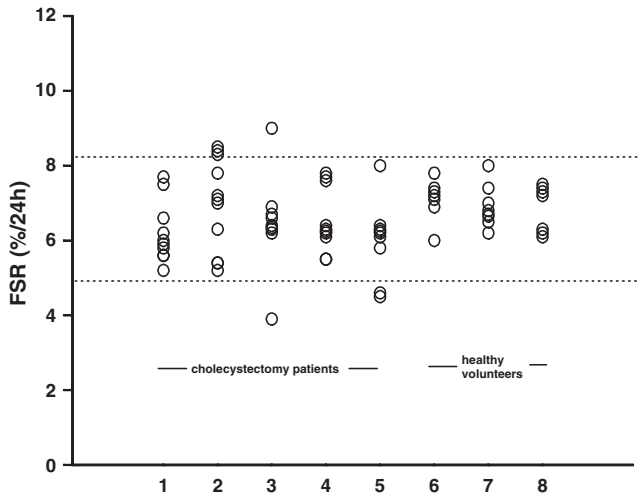

Fig. 1. Fractional synthesis rate of albumin measured by ^{13}C leucine or d5-phenylalanine in healthy subjects as volunteers or undergoing elective laparoscopic cholecystectomy. Aggregated data from several sources [11,14–17].

In a stable healthy individual, the absolute albumin synthesis rate is 100 to 150 mg/kg per 24 hours, with an equivalent degradation rate [11,14–17]. This corresponds to an albumin turnover time of 30 days if the total albumin pool is 300 g as postulated [12]. Others have reported similar albumin half-lives of healthy subjects using ^{131}I-albumin [12,18]. However, accurate data measuring albumin degradation in humans is limited.

2.2. Albumin synthesis in pathology: the role of systemic inflammation

Hypoalbuminemia is common in medical practice and is not necessarily equivalent to a low absolute albumin synthesis rate. In chronic liver disease with cirrhosis and an impaired ability for protein synthesis, the absolute albumin synthesis rate is decreased by 30% to 50% compared with normal values [19]. By contrast, in acute nephrosis, the fractional and absolute albumin synthesis rates are very high in an effort to compensate for the extensive urinary losses [20].

Critical illness is often associated with systemic inflammation, and the albumin synthesis rate has been reported to increase under these conditions. A number of studies have demonstrated that the absolute albumin synthesis rate is increased despite a low plasma concentration [11,14,21]. For critically ill patients, the FSR of albumin is very high (15%-20%/24 h) and, unlike healthy subjects undergoing elective cholecystectomy, is nonresponsive to exogenous recombinant growth hormone [15,16]. This suggests that the level of albumin synthesis in critically ill subjects is under maximal stimulation. In acute inflammatory states, the stimulation upon the FSR is 50% to 100% in excess of the normal rate, similar to what is seen in healthy subjects given an endotoxin challenge or in patients with acute cholecystitis [14,16]. However, after major abdominal surgery, postoperative absolute synthesis rate was no different from preoperative rates [22]. Interpretation of these data is impeded by the fact that postoperative measurements are most often performed in patients with a severe underlying disease and possible comorbidities. Other investigators, using a constant infusion of ^{13}C-leucine for quantitative measurements, report a postoperative FSR of 12% to 15% in patients after major cancer surgery [23,24].

2.3. Mechanism of action of albumin in sepsis

Besides its action as a plasma volume expander, albumin has many other functions related to its capacity to bind endogenous and exogenous water-insoluble substances (ie, bilirubin, hormones, fatty acids, bile salts, and drugs) and transport them to the site of action or disposal [9,25–29] (Fig. 2). Among these substances, proinflammatory molecules and mediators of inflammation deserve more attention [30–33]. For example, albumin binds lipopolysaccharide, lipoteichoic acid, and peptidoglycan. Given the abundance of albumin and the lower relative cell activation capacity of pathogen-associated molecular patterns