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Opinion paper

The clinical significance of hypoalbuminaemia

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SUMMARY

Albumin is a relatively small molecule with a radius of 7.5 nm and a molecular weight of 65 kDa. It is the most abundant protein in plasma, accounting for 60–75% of its oncotic pressure. Its concentration in plasma is merely one static measurement reflecting a dynamic and complex system of albumin physiology, and is the net result of several different processes, one or more of which may become deranged by disease or its treatment. It is also unsurprising that hypoalbuminaemia has proved to be an indicator of morbidity and mortality risk since the underlying conditions which cause it, including protein energy malnutrition, crystalloid overload, inflammation, and liver dysfunction are themselves risk factors. In some cases, its underlying cause may require treatment but mostly it is just a parameter to be monitored and used as one measure of clinical progress or deterioration. While malnutrition, associated with a low protein intake, may be a contributory cause of hypoalbuminaemia, in the absence of inflammation and/or dilution with crystalloid its development in response to malnutrition alone is slow compared with the rapid change caused by inflammatory redistribution or dilution with crystalloids. Other significant causes include liver dysfunction and serous losses. These causal factors may occur singly or in combination in any particular case. Treatment is that of the underlying causes and associated conditions such as a low plasma volume, not of hypoalbuminaemia *per se*.

1. Introduction

Albumin is a relatively small molecule composed of 585 amino acids, with a radius of 7.5 nm and a molecular weight of 65 kDa [1] and is the most abundant protein in plasma, accounting for 60–75% of its oncotic pressure. This contribution is greater than anticipated because of the Gibbs-Donnan equilibrium, which predicts that a difference in the concentration of less diffusible charged molecules such as albumin on either side of a semipermeable membrane inhibits the migration of small diffusible ions [2,3]. The distribution of extracellular fluid between the intravascular and extravascular compartments described by Starling's law indicates that the flux of fluid from the intravascular to the extravascular space is inversely related to capillary oncotic pressure as long as other factors in the equation remain constant [4].

The serum albumin concentration is merely one static measurement reflecting a dynamic and complex system of albumin physiology, and is the net result of several different processes, one or more of which may become deranged by disease. Early studies in malnourished children with hypoalbuminaemia and oedema (Kwashiorkor) led to its use as a specific marker of malnutrition [5–7], but we now know that hypoalbuminaemia has several possible causes which may occur singly or in combination. It is also unsurprising that it has proved to be an indicator of morbidity and mortality risk [8,9], since the underlying conditions which cause it,

Abbreviations: CRP, C-reactive protein; ESPEN, European Society for Clinical Nutrition and Metabolism; GLIM, Global Leadership Initiative on Malnutrition; RCT, randomised clinical trial.

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including malnutrition, are themselves risk factors [10]. In fact, in many cases of Kwashiorkor in children hypoalbuminaemia is likely due to underlying inflammatory conditions like infection as well as poor protein intake. In some cases, the underlying cause of hypoalbuminaemia may require treatment but mostly it is just a parameter to be monitored and used as one measure of clinical progress or deterioration.

2. Synthesis and function of albumin

In health, albumin is synthesised in the liver from amino acids at a rate of 12–25 g/day or 12–200 mg/kg body weight/day, a rate governed by the colloid osmotic pressure surrounding the hepatocytes rather than the serum albumin concentration *per se* [11,12]. Its production and concentration in plasma may, therefore, be reduced by liver disease or by a diminished supply of precursor amino acids, as in malnutrition and Kwashiorkor [6]. In health, approximately 140 g albumin is contained in plasma and 165 g in the interstitial fluid [11], with a serum albumin concentration of 35–45 g/l. The exchangeable albumin pool is 3.5–5 g/kg body weight, and 6–10% of the plasma albumin pool undergoes degradation each day [11].

Besides contributing to plasma colloid oncotic pressure, albumin is a high capacity, low affinity transport protein for many substances, such as thyroid hormones, calcium and fatty acids. It binds unconjugated bilirubin so that hypoalbuminaemia increases the risk of kernicterus in infants with unconjugated hyperbilirubinaemia. Salicylates, which displace bilirubin from albumin, can have a similar effect. Many drugs are bound to albumin and a decrease in albumin concentration can have pharmacokinetic consequences, e.g., increasing the concentration of free drug and with it the risk of toxicity. Albumin also has an important antioxidative role.

While malnutrition, associated with a low protein intake, may be a contributory cause of hypoalbuminaemia, it is important to remember that, even in severe cases of anorexia nervosa [13], the serum albumin concentration is usually normal, and in other causes of starvation, it is often normal until the terminal stages, unless malnutrition is accompanied by some inflammatory condition. The half-life of albumin is 17–19 days, and although it has a high total catabolic rate in comparison with other plasma proteins, because of its abundance it has a low fractional catabolic rate [14,15]. Hence, in the absence of inflammation, the development of hypoalbuminaemia in response to malnutrition alone is slow compared with the rapid change which takes place in response to inflammatory redistribution or dilution with crystalloids.

3. The interstitium and transcapillary escape of albumin: inflammation

Under normal circumstances, albumin does not distribute freely within the interstitial space. Its distribution is affected by the state of hydration of the interstitial hyaluron glycosaminoglycan and collagen gel matrix [16]. The physical space occupied by this interstitial matrix partially excludes albumin distribution, and the state of hydration of this matrix is proportional to the space available for the distribution of albumin within its molecular structure [17,18]. Changes in the function of this network and its compliance can affect the flow of albumin through the system, alter its distribution and, hence, its concentration in the circulation, facilitating the formation of oedema [17,18]. At a normal plasma volume, the interstitial space behaves as a low compliance system, so that small changes in interstitial volume or capillary filtration rate cause a steep rise in interstitial pressure, thereby resisting capillary filtration and oedema formation. If the interstitial volume is expanded by 20–50% then the space becomes a low compliance system with low pressure, allowing oedema to form more readily [17–19]. Since hyaluron is responsible for part of the albumin exclusion in the interstitial matrix, it is possible that the washout of the interstitial hyaluron contributes to the increase in interstitial space available for albumin [20].

In health, albumin escapes from the circulation through the capillary membrane into the interstitial space at a rate of 5%/h. This increases to 15%/h with inflammation or injury, due to local tissue damage and to the general effects of proinflammatory cytokines on capillary permeability [21,22]. Escaped albumin is returned to the circulation via the lymphatic system. When the albumin escape rate increases or lymphatic return is impaired due to disease, the serum albumin concentration tends to fall. Different organs also have greater or lesser rates of albumin escape rate. That in the liver, for example is higher than in skin or muscle. The whole-body value, therefore, reflects an average of the different tissues. A low serum albumin concentration may be a useful marker of inflammation, falling inversely as other inflammatory indicators such as C-reactive protein (CRP) rise [10,23–25]. These changes in albumin escape rate not only cause a fall in serum albumin concentration but may also contribute to the drop in circulating plasma volume associated with acute trauma and sepsis. The speed of these physical changes in distribution also explains why they have a more rapid and profound effect on albumin concentration than any metabolic causes e.g. protein-energy malnutrition.

4. Dilution by crystalloid infusions

One of the most common influences on the serum albumin concentration in hospital practice is that of dilution with intravenous crystalloids [26]. It falls and rises according to fluid gain or loss with far greater rapidity than can be explained by nutritional or metabolic causes. We infused 2 L of 0.9% saline over 1 h into normal subjects and measured its effects over the subsequent 6 h [27,28]. After 6 h, only 40% of the infused saline had been excreted, reflecting the inherently sluggish excretion of salt even in normal physiology. The serum albumin concentration, having fallen, due to dilution, by 20% at the end of the infusion, was still 15% below baseline after 6 h. The reverse process was noted by Starker and colleagues [29], who demonstrated, in critically ill patients receiving parenteral nutrition, a rise in serum albumin and a good outcome among those able to excrete an excess salt and water load, whereas among those who retained fluid there was a fall in serum albumin, associated with a worse prognosis. We showed, in similar patients referred for parenteral nutrition, a rise in serum albumin of 1 g/l for every 1 L of negative fluid balance as they excreted the excess salt and water retained after all the crystalloid received during the acute phase of their illness [30]. We also showed that excess perioperative fluid administration, causing fluid retention, adversely affects surgical outcome in patients undergoing colonic surgery [31], since confirmed by others [32,33], another example of the underlying cause being the risk factor rather than hypoalbuminaemia *per se*.

Both starvation and the response to illness or injury are associated not only with a reduction in cell mass, but also with a relative expansion of the extracellular fluid volume and an impaired ability to excrete an excess salt and water load [34–36]. This makes such patients particularly vulnerable to fluid overload. The return of the ability to excrete excess sodium and water heralds recovery, leading Moore to coin the terms ‘the sodium retention phase’ and ‘the sodium diuresis phase’ of injury [36]. In those patients with complications, however, spontaneous sodium diuresis is delayed, the retained fluid exacerbates hypoalbuminaemia, and oedema persists. Administered crystalloids cause a further cumulative

retention of sodium and water and further dilution of the serum albumin. A low serum albumin concentration, therefore, may not only be a result of redistribution due to inflammation, but also of dilution from fluid infusions [17,18,37].

It is often assumed erroneously that salt and water retention with oedema is innocuous and that patients soon excrete any excess which has been administered. There is increasing evidence, however, to suggest that excess salt and water is associated with inhibition of gastrointestinal function, pulmonary complications, immobility and prolonged recovery [38–43]. As outlined above, Starker and colleagues [39] showed that fluid retention, associated with intravenous feeding in malnourished surgical patients, was associated with dilutional hypoalbuminaemia and a worse outcome than in those able to excrete any fluid excess and to raise their serum albumin. As Sitges-Serra's group has shown, prevention is better than cure in this situation, since the use of low volume/low sodium feeds in such patients avoids fluid overload, dilution of albumin and postoperative complications [40,44].

These studies emphasise the role of dilution in causing hypoalbuminaemia and the fact that salt and water overload rather than hypoalbuminaemia is the risk factor. They also remind us that in all patients referred for nutritional support, as much care should be taken over fluid balance assessment and the sodium and water content of the feed as other aspects of the prescription. They highlight that, in the post-acute phase of illness, clinical and functional improvement is often associated with weight loss as the accumulated excess of salt and water is cleared and that a rise in the serum albumin concentration is a secondary effect of this process.

5. External losses

In certain diseases, albumin may be lost externally faster than it can be synthesised, thereby causing a reduced serum albumin concentration, often accompanied by oedema. This occurs in nephrotic syndrome, protein losing enteropathy, and where there are large areas of inflamed serous surfaces as in burns or exfoliative dermatitis [12].

6. Therapeutic significance of hypoalbuminaemia

Since hypoalbuminaemia is a non-specific consequence of the various factors described above, its diagnostic and therapeutic implications are those of its underlying causes and associated conditions.

Hypoalbuminaemia is not a specific nutritional marker, since it is possible to die of starvation with a normal serum albumin concentration. On the other hand, if inflammatory disease is present, the serum albumin concentration falls in proportion to the severity and time span of that disease. It is not surprising, therefore, that there is a good correlation between a low serum albumin concentration and poorer outcome [45,46], as shown in many of the so-called 'predictive nutritional indices' [47]. This does not imply that simply raising the serum albumin concentration by albumin infusion will improve outcome. Indeed, the opposite may be true [48,49].

The treatment of patients with hypoalbuminaemia in the post-acute phase of illness should be addressed to its one or more causes, i. e. liver dysfunction, protein malnutrition, inflammation with redistribution, dilution by crystalloids, and external losses. It is also crucial to assess plasma volume as this may be increased, normal or decreased in the presence of hypoalbuminaemia. This can be done by the bedside by noting the jugular venous level above the clavicle, firstly with the patient at 45° and then as they are lowered gradually to the recumbent position. If the jugular vein does not fill when the patient is lowered below 45° then hypovolaemia may be inferred. As long as this persists and renal perfusion remains inadequate, the patient will be unable to excrete an excess salt and water load and clear their oedema. The most logical treatment, which we have found extremely effective, is to infuse small volumes of 20% salt poor albumin which raises the plasma oncotic pressure, expands the intravascular volume without increasing the salt and water overload, improves renal perfusion and causes a salt and water diuresis. If the venous level is raised above the clavicle with the patient at 45°, then salt and water restriction with or without diuretics is appropriate.

7. Treatment of hypovolaemia with albumin infusions in the acute phase

Although trying to raise the serum albumin concentration with 4–5% albumin infusion is largely ineffective, its use in acute hypovolaemia is more controversial. It has been argued, not unreasonably, that the use of albumin infusions for the treatment of circulatory hypovolaemia in acute illness is unjustified because of its rapid leakage from the circulation [50,51]. Plasma substitutes such as gelatins, which normally have a shorter half-life than albumin in the circulation, may have a longer half-life in acute illness and injury [52], and are generally to be preferred for volume expansion in the acute phase. Alternatives are crystalloid or a combination of crystalloid and colloid. The relative effectiveness of these used separately or in combination is much debated [49,50,53–56] and outside the scope of this review. The primary concern is to maintain the intravascular volume and preserve the circulation, rather than to address the albumin concentration [57]. On the other hand, profound falls in serum albumin concentration, as Guyton showed [58], may predispose to systemic and pulmonary oedema unless excessive administration of salt and water is avoided. Albumin solutions are still in widespread use in paediatric practice for the treatment of conditions such as shock in meningococcal septicaemia and have proved effective in some adult conditions, including spontaneous bacterial peritonitis associated with liver cirrhosis [59]. This area, therefore, requires much more careful thought and study before dogmatic conclusions can be reached.

A systematic review on the use of human albumin infusions in critically ill patients included 30 randomised clinical trials (RCTs) with 1419 participants and showed that for every 17 critically ill patients treated with albumin there was one additional death [49]. However, that review was found to have several limitations including the fact that most of the RCTs included were designed to assess the effects of various fluids on physiological variables, and not to assess mortality [50]. The study with the highest excess mortality due to albumin [48] showed that this was predominantly due to cardiopulmonary failure which may have been due to over expansion of the intravascular volume as the protocol (albumin) group received higher volumes of fluid than the control (crystalloid) group [50]. Moreover, participants in eight of the 30 RCTs received albumin infusions for the treatment of hypoalbuminaemia [49], an indication that very few clinicians would consider nowadays [50]. A large RCT of nearly 7000 participants did not show any difference in outcomes between 4% albumin and 0.9% saline for intravascular fluid resuscitation [60]. It has been recommended that albumin should not be used for patients with traumatic brain injury (greater risk of mortality) [60] and those undergoing cardiac surgery with cardiopulmonary bypass [61]. In the latter situation, although the use of albumin attenuated hypervolaemia caused by crystalloid administration, albumin was not associated with any beneficial effect on any of the clinical end points, including the incidence of organ dysfunction [62]. The use of albumin in sepsis and septic shock remains controversial as although it reduces the

requirement of administered fluid volumes, effects on mortality and other clinically relevant outcomes remain inconclusive [63]. Nevertheless, a recent meta-analysis of eight studies with 5124 patients with sepsis and 3482 with septic shock showed that when compared with crystalloids, although resuscitation with albumin did not significantly reduce 28-day or 90-day mortality in patients with sepsis, it resulted in a significant reduction in 90-day mortality in patients with septic shock (OR 0.89, 95% CI 0.74–0.99, p = 0.04) [64]. In addition, although the use 4–5% albumin did not have a significant effect (OR 0.89, 95% CI 0.68–1.15, p = 0.37), the use of 20% albumin significantly reduced 90-day mortality in patients with septic shock when compared with crystalloids (OR 0.81, 95% CI 0.67–0.98, p = 0.03) [64]. Although statistical heterogeneity was low, the marginal significance suggests that further large-scale, well-conducted studies are warranted.

However, albumin may have an important role for some patients who are acutely ill [63]. Use of albumin can avoid circulatory dysfunction after large volume paracentesis [65] and it is beneficial in hepatic decompensation due to spontaneous bacterial peritonitis [66].

8. Treatment of redistributional hypoalbuminaemia

Treatment of redistributional hypoalbuminaemia in acute inflammatory conditions or in malignant disease should be directed to its cause, i. e., draining the abscess, treating with antibiotics, removing the cancer, or using anti-inflammatory drugs. Once the cause has been resolved, the albumin concentration will return to normal with time and adequate nutrition. However, the fall in serum albumin concentration in response to inflammation can last several weeks and may not be restored to normal for a while after resolution of the stress response.

9. Hypoalbuminaemia and nutritional support

Hypoalbuminaemia may be a feature of liver disease and/or malnutrition but it is specific to neither. Unless there is severe prior malnutrition, hypoalbuminaemia in the acute phase of illness has no nutritional or metabolic component. Indeed, albumin turnover may be increased, with acceleration of both synthesis and breakdown. Since albumin has a metabolic half-life of 17–19 days, one would expect any metabolic change, e.g. due to malnutrition or nutritional support to have a rather slow effect compared with changes brought about by dilution and redistribution.

In our study of fractured femur patients [67], we showed that both well-nourished and undernourished patients had a fall in serum albumin concentration acutely, associated with injury, surgery, and dilution with crystalloids, so that albumin concentration had no nutritional discriminatory value during the first few days. However, in the normally nourished or moderately undernourished patients the concentration returned spontaneously to normal over ten days, whereas, in the severely malnourished group such recovery was markedly delayed. Moreover, overnight supplementary nasogastric tube feeding in the latter group restored the recovery rate to that of the other two groups demonstrating a nutritional component to this biochemical change. An isolated measurement of serum albumin concentration may, therefore, be of little value as a nutritional marker, although serial values may reveal a nutritional dimension. Hypoalbuminaemia is a prognostic marker for adverse outcome [8,9,46,68], but it does not predict response to nutritional support [46] nor does the serum albumin concentration increase in the short-term in response to nutritional support [68]. Hence, although hypoalbuminaemia has been included in diagnostic criteria in the Global Leadership Initiative on Malnutrition (GLIM) consensus [69] and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for nutrition in surgical patients [70,71], it is more because it indicates the severity of inflammation and acute disease rather than malnutrition *per se*. A recent Delphi approach by the GLIM group on the assessment of inflammation in malnutrition has, by strong consensus, suggested that the serum albumin concentration lacks validity for the diagnosis of malnutrition in the setting of inflammatory conditions [25]. The use of CRP concentration is recommended as a marker of inflammation to support confirmation of the burden of disease or inflammation criterion in diagnosis of malnutrition using the GLIM criteria [25].

The effect of changes in liver function is also an important consideration since this may be impaired not only in primary liver disease but also with sepsis or the complications of disease and its treatment. In this situation albumin synthesis will clearly be affected. External losses in the nephrotic syndrome, from protein losing enteropathy or from wounds may also exceed the synthetic capacity of the liver. In all these cases protein and energy intake should be optimised and the underlying disease addressed.

10. Conclusion

Although hypoalbuminaemia may have a nutritional component especially in the presence of protein deficiency, it is mainly a manifestation of other factors such as inflammation, dilution, liver dysfunction, and serous losses, which often occur in combination. Treatment is that of the underlying causes and associated conditions, not of hypoalbuminaemia *per se*. Albumin infusions, especially those of the 20% solution may have a role in the treatment of intravascular hypovolaemia in the presence of interstitial fluid overload in the post-acute phase of illness and in the resuscitation of patients with septic shock.

Author contributions

Both authors contributed equally to all aspects of this paper and have approved the final submission.

Conflict of interest

None of the authors has a direct conflict of interest to declare. DNL has received an unrestricted educational grant from B. Braun for unrelated work. He has also received speaker's honoraria for unrelated work from Abbott, Nestlé and Corza.

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Data sharing

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Ethical statement

As this was a review, ethical approval was not necessary.

Use of generative artificial intelligence

None.

Declaration of Generative AI and AI-assisted technologies in the writing process

None.

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