Serum Albumin: Relationship to Inflammation and Nutrition

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ABSTRACT

Hypoalbuminemia is the result of the combined effects of inflammation and inadequate protein and caloric intake in patients with chronic disease such as chronic renal failure. Inflammation and malnutrition both reduce albumin concentration by decreasing its rate of synthesis, while inflammation alone is associated with a greater fractional catabolic rate (FCR) and, when extreme, increased transfer of albumin out of the vascular compartment. A vicious cascade of events ensues in which inflammation induces anorexia and reduces the effective use of dietary protein and energy intake and augments catabolism of the key somatic protein, albumin. Hypoalbuminemia is a powerful predictor of mortality in patients with chronic renal failure, and the major cause of death in this population is due to cardiovascular events. Inflammation is associated with vascular disease and likely causes injury to the vascular endothelium, and hypoalbuminemia as two separate expressions of the inflammatory process. Albumin has a myriad of important physiologic effects that are essential for normal health. However, simply administering albumin to critically ill patients with hypoalbuminemia has not been shown to improve survival or reduce morbidity. Thus the inference from these clinical studies suggests that the cause of hypoalbuminemia, rather than low albumin levels specifically, is responsible for morbidity and mortality.

Albumin levels are lower in dialysis patients than among the general population and are a powerful predictor of mortality (1), suggesting that either the cause of hypoalbuminemia or reduced albumin levels per se affect mortality. The prevalence of reduced albumin levels increases in patients well before the onset of end-stage renal disease (ESRD) (2). While this is ascribed to malnutrition, albumin levels remain virtually unchanged even in the presence of severe protein calorie malnutrition in otherwise healthy individuals until near terminal starvation (3). Thus low albumin levels suggest that a more complex etiology other than reduced protein intake alone may contribute to hypoalbuminemia.

Several processes control plasma albumin concentration, including the absolute rate of albumin synthesis, the fractional catabolic rate (FCR), albumin distribution between the vascular and extravascular compartments, and exogenous loss of albumin. The rate of albumin synthesis is affected by both nutrition (4) and inflammation, given that albumin is a negative acute phase protein. Plasma volume expansion can also dilute the plasma pool, resulting in lower albumin levels. The latter is particularly relevant to the situation of dialysis patients, who clearly have no control over salt and water excretion. However, dilution of the albumin pool is at least partially offset by an increase in the rate of albumin synthesis (5,6). Albumin levels are also decreased as a result of direct loss of protein from the body, such as in the nephrotic syndrome or during the dialysis procedure.

There are two potential sources of albumin loss that result directly from the dialysis process. Peritoneal dialysis can lead to extensive losses of albumin (7), overwhelming the effects of other variables. For example, in peritoneal dialysis patients, the effect of normalized protein catabolic rate (nPCR) on serum albumin concentration is undetectable statistically, while transperitoneal dialysis albumin loss and C-reactive protein (CRP) both strongly and independently predict albumin levels (8). In hemodialysis patients, loss of albumin across the dialyzer can be extensive, in our own experience in excess of 20 g in a single dialysis session after reprocessing many times with bleach (9), reducing albumin levels.

One of the adaptive responses that defend albumin mass when protein is restricted is that of a reduction in the FCR of albumin (4). When protein intake is reduced, the rate of albumin synthesis decreases and the serum albumin concentration decreases. Alterations in albumin FCR play an important role in sustaining albumin concentration during protein restriction (4,10). In this setting, as serum albumin levels decrease, so does the FCR, consistent with a regulated reduction in the half-life of the protein. This results in a positive correlation between serum albumin concentration and albumin FCR, tending to defend the albumin pool in the setting of starvation. In hemodialysis patients, there is no linear relationship between albumin levels and albumin FCR. However, if one adjusts for inflammation using the levels of acute

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phase proteins, an inverse relationship between albumin levels and albumin FCR can be demonstrated (11,12), suggesting that the lack of an association between albumin levels and albumin FCR is an effect of inflammation. Thus albumin FCR is greater than anticipated for a given albumin level.

The metabolism of albumin in a number of chronic wasting diseases is therefore not straightforward. For example, plasma protein composition, including serum albumin levels, and to a lesser extent muscle mass, are maintained at nearly normal levels in subjects with anorexia nervosa, in part by a reduction in resting energy expenditure (REE), total net protein catabolism, and also most likely due to a decrease in FCR (3,13). In contrast, patients with wasting and infection as a consequence of infection with human immunodeficiency virus (HIV) have an increased REE that is even more marked in the presence of diagnosed infection (14), as well as hypoalbuminemia. This is also true of patients with chronic lung disease (15) and cancer (16,17) and in patients with renal failure (18,19). Harty (20) noted that there was no relationship between REE and nutritional state among peritoneal dialysis patients and suggested that their inability to conserve energy appropriately may act as an additional risk factor contributing to malnutrition in this dialysis population.

Rats with an experimental model of sepsis develop hypoalbuminemia (21), but the absolute rate of albumin synthesis did not decrease. Instead, the fractional albumin synthesis rate increased, suggesting that the primary cause of hypoalbuminemia was an increase in albumin FCR. Other investigators also reported an increased rate of albumin synthesis in rat models of sepsis (22) or following endotoxin injection (23). Albumin synthesis has also been found to be increased in hypoalbuminemic patients following head trauma (24) and in hypoalbuminemic cancer patients (25). Thus the conclusion that trauma- or sepsis-induced hypoalbuminemia is caused by suppression of albumin synthesis does not describe the sole interaction between metabolic stress and albumin levels. An alteration in albumin distribution as well as an increase in albumin FCR clearly may play a determining role. Of interest is that despite the increase in albumin synthesis, levels of acute phase proteins and both the level and rate of synthesis of fibrinogen are also increased in these patients (24). Thus regardless of whether albumin concentration is reduced in the presence of either an increased or decreased rate of albumin synthesis, other risk factors associated with both inflammation and cardiovascular risk are increased.

Using nPCR as a measure of protein intake, we have shown that there is a positive correlation between nPCR and serum albumin concentration if controlled for CRP (26) or serum amyloid A (SAA) (27). The relationship between nPCR and albumin concentration in dialysis patients is nonlinear in a cross-sectional analysis (28) and increases in magnitude as nPCR declines. nPCR has an increasingly negative correlation with albumin at low nPCR values, but has little or no relationship with albumin concentration for higher nPCR values. For nPCR values greater than 1.2, there is little relationship between albumin concentration and nPCR (28) (Fig. 1), whereas

![Cross-sectional relationship between serum albumin concentration and both nPCR (g/kg/day) (left panel) and CRP level (mg/L; log transformed data) (right panel) in a single measurement in 1063 hemodialysis patients. Serum albumin concentration correlates independently with both CRP and nPCR for values of nPCR less than 1.0 g/kg/day and for CRP values greater than 13 mg/L. Serum albumin concentration does not correlate with nPCR for values greater than 1.0 g/kg/day nor with CRP for values less than 13 mg/L, leading to a plateau in the relationships.](image-url)
with a low nPCR, an increase of 0.1 g/kg/day was associated with an increase in albumin of 0.0278 g/dl (28). Thus albumin concentration in hemodialysis patients is affected in part by protein intake, but the presence of the effect as well as its magnitude depends on the quantity of protein intake.

The observation that serum albumin is a negative acute phase protein supports the contention that serum albumin concentration is a marker of inflammation. Hemodialysis patients with hypoalbuminemia have increased serum levels of CRP and other positive acute phase proteins and cytokines (29,30) when compared with normoalbuminemic patients. While albumin levels are independently associated with both nPCR and the level of these acute phase proteins, there is a stronger association between the level of acute phase proteins and albumin levels than with nPCR (26–28). Yeun et al. (30) found that CRP was a more powerful predictor of mortality for hemodialysis patients than hypoalbuminemia. After adjusting for CRP levels, low serum albumin lost its ability to predict mortality.

Several large cross-sectional studies have identified CRP as an independent risk factor of cardiac disease in both men and women (31–33). In the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study, CRP predicted future risk of coronary heart disease in healthy middle-aged men (34). In another study, the subpopulation of men who benefit from aspirin were those with elevated CRP levels (35). Thus serum CRP levels, and presumably systemic inflammation, are powerful predictors of cardiovascular risk both in the non-dialysis patient population and in our patients as well. CRP contributes significant risk of cardiovascular disease at values between 1 and 3 mg/L (36,37).

C-reactive protein levels are highly variable in individual dialysis patients (38). While the magnitude of variability in albumin levels is three orders of magnitude less than that of CRP or interleukin (IL)-6 because of the much greater range of serum concentrations that occur biologically for CRP, serum albumin concentration changes with each change in CRP and correlates with the temporally prevalent CRP value (Fig. 2). In a longitudinal study of albumin levels in 59 hemodialysis patients in which paired measurements of albumin synthesis were performed, those patients in whom serum albumin concentration declined by 0.3 g/dl for a period of more than 1 month exhibited a significant decrease in the rate of albumin synthesis as the cause for the decline in albumin levels and plasma albumin mass (39). The decrease in the rate of albumin synthesis was accompanied by a significant increase in CRP and all other acute phase proteins measured, but not a decrease in nPCR. Thus, while nPCR...
is clearly associated with albumin levels, especially when decreased to less than 1.0 g/k/day, changes in nPCR are less powerful in altering albumin levels. Measures of inflammation appear to have a greater effect.

In a longitudinal and cross-sectional analysis of the relationships between nPCR, CRP, and albumin concentration in a group of 1063 hemodialysis patients participating in the National Institutes of Health (NIH) Hemodialysis (HEMO) study, albumin correlated inversely with CRP for CRP greater than 13 mg/L in a cross-sectional analysis (Fig. 1). Longitudinal changes in serum albumin were also significantly associated with concurrent longitudinal changes in CRP (28). While CRP was associated with reduced albumin when increased to values greater than 13 mg/dL, lower levels of CRP are still associated with increased cardiovascular risk and may have little or no effect on the serum albumin concentration (33,37). Thus a normal albumin level does not imply that CRP levels are normal, and there is no activation of a systemic inflammatory response.

Similar to our previous studies (26,40), albumin concentration was independently associated with nutrition (nPCR) and inflammation (CRP). We postulate that inflammation is at least one potentiating factor in these patients that amplifies the effect of malnutrition on body composition by removing defense mechanisms that protect albumin pools during periods of reduced protein and caloric availability.

The studies mentioned thus far have demonstrated an important relationship between inflammation, nutrition, and serum albumin level, but have not established how these parameters lead to the high mortality in our dialysis and predialysis (chronic kidney disease) patients. It is known that atherosclerotic cardiovascular disease is the major cause of morbidity and mortality in patients with chronic renal failure undergoing renal replacement therapy (41–43). The reasons for the increased prevalence of atherosclerotic cardiovascular disease in the dialysis population is not well understood and may be due to factors such as an increased incidence of diabetes mellitus, hypertension, and hyperlipidemia. Oxidative stress and chronic inflammation have emerged as important cofactors for the development of endothelial dysfunction and atherogenesis (44). Stenvinkel et al. (45) have suggested that inflammation and nutrition may be key factors in the development of atherosclerosis. Malnourished dialysis patients as assessed by subjective global assessment and patients with elevated CRP levels had significantly greater carotid intima media thickness compared to well-nourished dialysis patients and those with normal CRP levels. Similar patients having an increased level of IL-6 also had increasing intima media thickness compared to similar patients having lower IL-6 levels (46), showing that inflammation was not only associated with incident vascular disease, but predicted progression of vascular injury.

**Hypoalbuminemia: Proxy or Cause of Mortality?**

The evolving concept presented in this review is that both inflammation and nutritional factors are responsible for low serum albumin concentration and are associated with increased mortality in the dialysis population. But is a low albumin concentration merely a serologic marker of inflammation superimposed on malnutrition, or does it contribute to accelerated mortality in patients with renal failure as well?

To understand whether a low albumin concentration is a surrogate marker or is responsible for increased mortality, it may be helpful to review the function of albumin. Albumin has five main functions: 1) maintenance of colloid osmotic pressure, 2) binding and transport, 3) free radical scavenging, 4) platelet function inhibition and antithrombotic effects, and 5) effects on vascular permeability.

Albumin is a single polypeptide consisting of 585 amino acids with a molecular weight of approximately 69 kDa. The total albumin pool is 4–5 g/kg body weight, of which 40–45% is in the intravascular space and other 60% is in the interstitial space. Because of its relatively low molecular weight relative to the other major intravascular proteins (immunoglobulins), albumin accounts for 75–80% of the colloid osmotic pressure of human plasma.

Another important function of albumin is its ability to bind various ligands at four major binding sites. These ligands include free fatty acids, calcium, certain steroid hormones, thyroxin, bilirubin, copper, and tryptophan. In addition, a number of drugs are bound to albumin, including aspirin, warfarin, sulfonamides, penicillin, digoxin, and nonsteroidal anti-inflammatory drugs (NSAIDs) (47).

Albumin is a major source of sulfhydryl groups, and these thiols scavenge free oxygen and nitrogen radicals and other toxins (48). This may be an important function in the setting of sepsis and shock. One potential mechanism for this salutary effect could be the ability of albumin to bind toxic lipid moieties, such as leukotoxin, that contribute to increased vascular permeability and shock.

In this context, the anticoagulant and antiatherothrombotic effects of albumin may be due to binding of nitric oxide (NO) free radicals. Hypoalbuminemia may affect blood viscosity (49) and endothelial cell function because of increased concentrations of free lysophosphatidylcholine (49), altering erythrocyte structure, or by inhibiting NO-mediated vascular relaxation (50,51). Albumin serves as a reservoir for NO, and thus hypoalbuminemia can directly lead to reduced arteriolar relaxation through this mechanism as well (52).

Is therapeutic “normalization” of albumin levels beneficial in ill patients with hypoalbuminemia? We found that infused albumin leaves the plasma compartment with an initial half-life of 4.5 ± 2.1 hours in hemodialysis patients, independent of serum albumin levels, so that within a 24-hour period, essentially all infused albumin has equilibrated with the interstitial pool. In critically ill and septic patients, the rate of albumin egress is even greater. Thus any benefit of infused albumin may be short-lived (53). In addition, in some clinical situations hypoalbuminemia occurs despite an increased rate of albumin synthesis (24), suggesting that delivery of greater quantities of albumin would be unlikely to have a significant impact on albumin concentrations or mass.

Administration of albumin has been found to be protective in animal models following hemorrhagic shock.
(54) or endotoxin infusion (55). In clinical studies, albumin infusions have been shown to be most helpful in the setting of hypovolemia (56–58). However, many of the studies investigating this question of whether albumin administration is salutary have been performed in the intensive care setting, and have generally not shown any significant benefit (59,60). In fact, a large meta-analysis of 30 randomized controlled trials studying the effects of albumin infusions by the Cochrane Injuries Group in 1998 actually demonstrated a higher mortality in critically ill patients treated with albumin infusions than in control groups (61).

Despite all of the important functions that albumin serves, hereditary analbuminemia is compatible with life. Rats with hereditary analbuminemia reproduce normally and have normal renal function and blood pressure (62,63). Rather than presenting as a disease, analbuminemia in humans is generally only found as an incidental laboratory finding. Thus it is likely the cause of hypoalbuminemia that is associated with morbidity and mortality rather than an effect of low albumin levels per se. The effects of inflammation on the vascular endothelium and on lipoprotein structure suggest that it is primarily the effect of inflammation on albumin levels that is responsible for much of the morbidity and mortality associated with hypoalbuminemia.

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