Biological Basis of Hypoalbuminemia in ESRD

GEORGE A. KAYSEN
Division of Nephrology, Department of Medicine, University of California Davis; and the Department of Veteran's Affairs Northern California Health Care System, Pleasant Hill, California.

Abstract. Hypoalbuminemia is associated with mortality in patients with end-stage renal disease (ESRD) maintained either on peritoneal dialysis (PD) or hemodialysis (HD). Serum albumin concentration is determined by its rate of synthesis, by the catabolic rate constant (the fraction of the vascular pool catabolized per unit time), by external losses, and by redistribution from the vascular to the extravascular space. Hypoalbuminemia in dialysis patients is primarily a consequence of reduced albumin synthesis rate in both HD and PD patients, and in the case of PD patents, of tranperitoneal albumin losses as well. Continuous ambulatory peritoneal dialysis patients are able to increase albumin synthesis to replace losses. Thus, ESRD does not directly suppress albumin synthesis. The rate of albumin synthesis is inversely proportional to the serum concentration of one potential acute phase protein (α2 macro-globulin), and albumin concentration is inversely proportional to that of either C-reactive protein or serum amyloid A in both HD and PD patients. The cause of decreased albumin synthesis is primarily a response to inflammation (the acute phase response), although it is possible that inadequate nutrition may also contribute. The cause of the inflammatory response is not immediately evident. There is no evidence that shifts of albumin to the extravascular space or that dilution of the plasma by volume expansion plays any role in causing hypoalbuminemia in ESRD patients.

Hypoalbuminemia is the strongest independent risk factor for death in hemodialysis patients (1,2) or those being treated with continuous ambulatory peritoneal dialysis (CAPD) (3,4) even when hypoalbuminemia occurs before initiation of dialysis (5). To understand the relationship between mortality and albumin levels, it is important to understand both the effects of hypoalbuminemia and the processes that lead to low albumin levels.

A change in the concentration of any protein in plasma is a consequence of a change in its rate of synthesis, in its rate of catabolism, the development of or change in rate of external losses, or a change in the distribution volume of the protein. As will be discussed below, albumin levels are reduced in part by a decrease in the rate of albumin synthesis in dialysis patients and in part because of external losses, either through the hemodialyzer as a consequence of reuse (6) or through losses across the peritoneal membrane in peritoneal dialysis (PD) patients. Decreased synthesis may be a result of reduced protein intake, the inflammatory response, or a combination of these processes. Any of the processes that tend to reduce albumin levels potentially can produce both morbidity and mortality.

Approximately 50% of plasma protein is albumin. Because of its low molecular weight, albumin contributes greatly to supporting plasma colloid osmotic pressure—oncotic pressure (π)—and acts as a high-capacity binding protein for free fatty acids and divalent cations (7). Albumin also binds other biologically relevant lipophilic molecules, such as steroid hormones and bilirubin (7). 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 BP (8,9). Hypoalbuminemia may affect blood viscosity (10) or endothelial cell function as a consequence of increased concentration of free lysophosphatidylcholine-altering erythrocyte structure (10) or by inhibiting nitric oxide-mediated vascular relaxation (11,12). Because albumin serves as a reservoir for nitric oxide, hypoalbuminemia can directly lead to reduced arteriolar relaxation through this mechanism as well (13). Although hypoalbuminemia may be potentially injurious by the above mechanisms, the observation that hereditary analbuminemia imparts little in the way of decreased viability supports a hypothesis that it is the cause of reduced albumin concentration that is responsible for morbidity and mortality in patients with acquired hypoalbuminemia rather than hypoalbuminemia itself.

It has been proposed that the primary cause of hypoalbuminemia is malnutrition (14–16), which itself is proposed to be a consequence of inadequate dialysis (17). However, hypoalbuminemia from protein malnutrition alone in the absence of renal failure is uncommon in adults. Oral nutritional supplementation has not been strikingly effective in normalizing albumin levels in hypoalbuminemic dialysis patients, although interdialytic parenteral nutrition has been somewhat more effective in some studies (18). In contrast, kwashiorkor responds quite easily when adequate protein is provided.

Recently, evidence has accumulated in our laboratory (19–21) and elsewhere (22–25) suggesting that inflammation, either alone or in combination with malnutrition, plays a significant,
and perhaps a controlling role in causing hypoalbuminemia in hemodialysis patients. This effect of inflammation would not be expected to respond to nutritional supplementation and may help to explain both the failure of hypoalbuminemia in dialysis patients to be reversed by nutritional supplementation, as well as to explain the high mortality rate associated with hypoalbuminemia in these patients.

**Albumin Homeostasis**

Albumin is synthesized exclusively in the liver, at a rate of between 12 and 15 g/d (7), and is catabolized by the vascular endothelium throughout the body with a half-life of approximately 16 d (26–28). Total albumin mass is approximately 4.5 g/kg body wt. Between 40 and 50% of the albumin pool is normally found in the plasma compartment (29,30). The rest is distributed in interstitial spaces throughout the body, mostly in muscle and skin. Plasma albumin concentration may be decreased because of dilution of the plasma pool during plasma volume expansion, as a result of redistribution of the albumin pool from plasma into interstitial compartments as occurs following burns or during sepsis (31), as a consequence of a decrease in the rate of albumin synthesis, as a result of increased albumin catabolic rate or as a consequence of the development of external albumin losses; into the urine or gut, or into dialysate, or transcutaneously in the case of trauma or burns. I will review factors that regulate these processes and identify which changes are responsible for hypoalbuminemia in dialysis patients.

**Albumin Synthesis**

The rate of albumin synthesis is regulated in part by availability of amino acids (7,32). Because of this relationship, plasma albumin concentration has been used as a clinical marker of nutritional status. However, the rate of albumin synthesis responds more to acute changes in dietary protein (33,34) than to general (chronic) nutritional status. When severely malnourished animals or people are re-fed, the rate of albumin synthesis increases promptly, even though total body protein stores are still severely depleted (35). This very short-term regulation appears to be at the posttranscriptional level of initiation of protein synthesis (36). In addition to being modulated by dietary protein, albumin (37) is a negative acute phase reactive protein (37). The acute phase response is initiated by cytokines and signal a cascade of events within hepatocytes (38,39). Synthesis of positive acute phase reactant proteins, including fibrinogen, C-reactive protein (CRP), α2-macroglobulin, serum amyloid A (SAA), and lipoprotein (a), is stimulated (40–43), and synthesis of negative acute phase reactive proteins—frequently used as nutritional markers (albumin [19], prealbumin [44]), apo A-I [45])—is suppressed. During the acute phase response, the concentration of positive acute phase reactive proteins is increased in plasma, whereas that of albumin is reduced. The presence of severe protein malnutrition may prevent the increase in synthesis of acute phase proteins even after an appropriate stimulus (46,47).

Prealbumin (transthyretin, also called thyroid binding globulin) and transferrin are also reduced in response to protein malnutrition and, like albumin, have also been used in nutritional evaluation. Because prealbumin levels change more rapidly than albumin levels, it has been proposed by some that measurement of this protein replace that of albumin for nutritional surveillance (48). However, the plasma concentration of none of these proteins is simply a reflection of nutritional status, because these, like albumin, are negative acute phase proteins and subject to the same limitations. Hepatic transferrin gene expression is also subject to iron stores (49) and to oncotic pressure (50), adding a further level of complexity to interpreting plasma levels of this protein.

**Albumin Catabolism**

Albumin is catabolized through a first-order process at sites distributed throughout the vascular endothelium or in a compartment in rapid equilibrium with the plasma compartment (26–28). When plasma albumin concentration is decreased, the absolute rate of albumin catabolism would be expected to decrease simply because the concentration of albumin having access to the catabolic sites is decreased. The fractional rate of catabolism (FCR) of a plasma protein is the fraction of the vascular pool catabolized per unit time. In the case of a protein that is catabolized by a first-order process, a change in the FCR is a consequence of a change in the catabolic rate constant and suggests regulation of plasma protein concentration by regulation of protein catabolic rate. In most conditions in which albumin concentration is decreased (malnutrition, for example) (34), the FCR of albumin is also reduced. When albumin concentration is increased, the FCR increases, suggesting that regulation of albumin concentration in plasma takes place in part by regulation of albumin FCR. This form of catabolic control dampens the effect of either increases or decreases in the rate of albumin synthesis and protects the albumin pool when the rate of albumin synthesis is decreased.

**Albumin Metabolism in ESRD**

Albumin levels are normally greater in men than women (Figure 1, right panel) and decrease with advancing age (left panel). Although the majority of patients on dialysis have albumin values that fall within the normal range (Figure 1), many have albumin levels that fall below normal, and both the gender-based and age-based variance that normally occurs is effaced (20). When patients with otherwise normal renal function lose albumin in the urine, they respond by increasing the rate of albumin synthesis (Figure 2, left panel) (51), although frequently this response is inadequate to normalize serum albumin concentration. Similarly, patients on PD also increase albumin synthetic rate in response to external losses (Figure 2, right panel), but albumin pools are preserved to a much greater extent than in nephrotic patients having the same albumin losses (Figure 2, right panel). The level of renal function also does not impair the ability of proteinuric rats from also increasing albumin synthesis rate (53) or increasing hepatic albumin mRNA in response to external losses (54). Thus, renal failure per se does not produce a gross defect in the capacity of patients or animals from having a normal rate of albumin.
Figure 1. (Left Panel) Relationship between age and serum albumin levels in healthy control subjects (filled circles; $r = 0.428; P = 0.0005$) and in patients on hemodialysis (open dotted circles; $r = 0.124; P = 0.233$). (Right Panel) Serum albumin concentration in healthy male (■) and female (□) control subjects. This difference is no longer present in hemodialysis patients (data not shown). Albumin was measured using bromcresol green dye binding. The figure shows data on hemodialysis patients taken from reference 20. *$P = 0.005$.

Figure 2. (Left Panel) Relationship between the rate of albumin synthesis and external albumin loss in continuous ambulatory peritoneal dialysis (CAPD) patients (filled circles; $r = 0.743; P < 0.01$; from reference 52) and patients with otherwise normal renal function and the nephrotic syndrome (open dotted boxes; $r = 0.585; P < 0.01$; from reference 51). (Right Panel) Relationship between serum albumin concentration in CAPD patients ($r = 0.744; P < 0.001$) and nephrotic patients ($r = 0.503; P < 0.05$). Symbols are the same as in the left panel. The lower serum albumin concentration in the nephrotic patients is a result of increased fractional rate of albumin catabolism in this group.

synthesis, or from responding to external losses of albumin with an appropriate increase in the rate of albumin synthesis (52). Hypoalbuminemia is therefore caused by a process other than renal failure. The cause of hypoalbuminemia needs to be specifically established in patients having this biochemical abnormality. Renal failure per se is not responsible.

The normal decline in albumin FCR that occurs during hypoalbuminemia is intact in patients on CAPD, but in the nephrotic syndrome albumin FCR increases as serum albumin concentration falls, contributing the lower-than-expected serum albumin concentration in nephrotic patients (55). Nevertheless, the normal mechanism that supports albumin levels in
hypoalbuminemic states remains intact in dialysis patients. A disorder in albumin FCR does not contribute to hypoalbuminemia in these patients (19,21).

We found that the proximate cause of hypoalbuminemia (≥3.5 g/dl) in hemodialysis patients was a reduced rate of albumin synthesis compared with hemodialysis patients having a normal serum albumin concentration (≥4.0 g/dl) (19). Albumin FCR was reduced in the hypoalbuminemic group just as in hypoalbuminemic CAPD patients (56). Distribution of albumin between the vascular and extravascular pool were the same in hemodialysis (20) and PD patients (52), and in healthy subjects regardless of serum albumin concentration. Neither plasma volume expansion nor redistribution of albumin out of the plasma compartment played any role at all in contributing to hypoalbuminemia in dialysis patients. Therefore, we must turn our attention to potential processes causing a decrease in the rate of albumin synthesis to establish a mechanism for hypoalbuminemia in this population.

Malnutrition causes decreased albumin synthesis (7,32-34,36) and is a potential cause of reduced albumin synthesis, decreased albumin levels, and increased morbidity and mortality in any chronically ill population, including those with ESRD. Malnutrition has been clearly documented in this patient population (14-16), and it has been generally assumed that hypoalbuminemia in this population is purely nutritionally based, primarily as a consequence of reduced albumin synthesis.

It is proposed that dietary protein intake and calorie intake should be between 1 and 1.2 g/kg and 35 kcal/kg per d, respectively, in patients on hemodialysis (57,58), a value greater than the 1 g/kg protein intake recommended for the rest of the population, and generally more protein than most hemodialysis patients consume. Because insufficient dialysis can lead to anorexia (59), it has been postulated that inadequate dialysis leads to poor nutritional intake followed by the development of hypoalbuminemia. Albumin levels may be increased after increased dialysis dose (60). It is suggested that optimal dialysis include the use of biocompatible membranes to deliver Kv/V > 1.4 (urea reduction ratio > 65%) (61).

Were protein malnutrition the only cause of hypoalbuminemia in the dialysis patient population, one would expect that nutritional supplementation would be effective in restoring albumin pools (14,16). However, oral nutritional supplementation does not reverse hypoalbuminemia in this patient population (62–64). Intradialytic parenteral nutrition is also either ineffective (65,66) or only slowly effective (67) in repair of hypoalbuminemia of hemodialysis patients. The lack of prompt success of nutritional intervention, and especially of enteral nutritional intervention in correcting hypoalbuminemia, suggests that non-nutritional factors may contribute to or be responsible for reduced albumin concentration in a fraction of hypoalbuminemic dialysis.

We measured the rate of albumin synthesis in a small group of hypoalbuminemic hemodialysis patients, and could find no difference in nutritional factors (19). However, we did find that the levels of acute phase proteins were increased, suggesting that inflammation and not malnutrition was the primary cause of reduced albumin synthesis in this small group of patients.

Further supporting a hypothesis that the inflammatory response plays a role in establishing albumin levels in hemodialysis patients, presumably by suppressing albumin synthetic rate, Bergström et al. reported in preliminary studies that plasma CRP concentration was the most powerful predictor of serum albumin, and was a better predictor of death in 1 yr than albumin concentration (23). When albumin levels were statistically corrected for CRP, albumin lost its value in predicting death. We found that both CRP and another acute phase protein, SAA, predicted albumin concentration in a group of 79 hemodialysis patients by using multiple regression analysis (20) (Figure 3, left panel).

Lymphokines, tumor necrosis factor-α, and interleukin-1 (IL-1) (68), as well as a group of acute phase reactive proteins (25,69) (α1 acid glycoprotein, ceruloplasmin, and C4 complement component), have been found to be increased in hemodialysis patients compared to other patients with chronic renal failure. Cytokine levels were also recently reported to correlate with albumin levels in hemodialysis patients, as well as with weight loss (24), and cytokine levels, like albumin, predicted survival (22).

External Albumin Losses During Dialysis
Kaplan et al. reported that reuse of a specific type of dialyzer (Fresenius 80A) with bleach causes increased protein losses during dialysis and contributes to hypoalbuminemia (6). We also found that albumin losses increased with reuse using these dialyzers and this technique, to as much as 20 g in a single dialysis treatment. However, the mechanism of hypoalbuminemia—reduced synthesis—suggests that the relationship between albumin losses and hypoalbuminemia in hemodialysis patients is more complex than simply albumin loss alone in hemodialysis patients. Loss of albumin across the PD membrane has a statistically significant effect on serum albumin levels in patients maintained on this modality (52,70,71) (Figure 2, right panel). We found that the response among individual CAPD patients to this external loss was an increase in the rate of albumin synthesis (52), similar to what occurs in nephrotic patients in response to urinary loss (51,55,72,73) (Figure 2).

Unlike patients on hemodialysis, transperitoneal losses of albumin are a consequence of a biological event within the dialysis patient that could potentially be a result of peritoneal inflammation and not a separate variable. This, however, is not the case. We found that although transperitoneal albumin loss and the levels of the acute phase protein CRP each strongly controlled serum albumin levels in PD patients (Figure 3, right panel), the two variables were statistically independent (70). Furthermore, there was also no relationship between serum levels of either CRP or SAA and transperitoneal albumin losses, whether expressed either as grams per day or as peritoneal clearance of albumin (to account for the lower serum albumin levels in patients with high loss rates) (Figure 4). These findings are consistent with the observation that albumin synthesis increases in CAPD patients in response to transperitoneal albumin loss (52), a process that should be suppressed if inflammation were responsible for peritoneal losses of albumin.
Han et al. (71) also found that CAPD patients with albumin concentrations ≤ 3.5 g/dl had higher dialysate albumin losses and higher CRP levels (17.5 versus 2.5 μg/ml) than those with albumin > 3.5 g/dl. Weekly Kt/V and PCR did not differ between the two groups, suggesting that differences in dialysis adequacy and in protein catabolic rate were of less importance than albumin losses and a measure of inflammation in predicting albumin levels in CAPD patients and that the two principal variables are external losses and the presence of an inflammatory response.

Recently, Han et al. (71) reported the results of a cross-sectional study of 106 CAPD patients and found that in those with serum albumin < 3.5 g/dl, serum CRP was significantly greater. By stepwise regression, they found that multiple risk factors independently correlated with albumin concentration, including CRP, dialysate albumin, and nutritional parameters (lean body mass, blood urea nitrogen, PCR). These data are quite similar to our own cross-sectional study on albumin levels in hemodialysis patients (20), although the peritoneal losses of albumin were much greater than the transdialyzer albumin losses that we have found during hemodialysis. Thus, a body of data are accumulating suggesting that the acute phase response plays an important role in causing hypoalbuminemia in dialysis patients. This would help to explain the relative resistance of these patients to nutritional intervention. The cause of the inflammatory response, however, has not been identified. There is evidence that dialysis with nonbiocompatible membranes may be one cause of cytokine activation.

**Potential Source of Inflammation**

Bioincompatible membranes, such as cuprophane, activate white cells (74), complement (75), and can even exert effects.

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**Figure 3.** Relationship between 3-mo average serum albumin concentration and C-reactive protein (CRP) concentration in hemodialysis patients (left panel; \( r = 0.490; P < 0.001 \); from reference 20) and between 3-mo average albumin concentration and CRP in peritoneal dialysis patients (right panel; \( r = 0.436; P < 0.016 \); from reference 70).

**Figure 4.** Relationship between the levels of serum amyloid A (open inverted triangles; \( r^2 = 0.0002, \) NS) and transperitoneal albumin clearance (Peritoneal albumin loss \( \times \) Day \( ^{-1} \)/Serum albumin concentration) and CRP concentration (filled circles; \( r^2 = 0.0035, \) NS) and transperitoneal albumin clearance in PD patients (from reference 70).
on residual renal function (76). Activation of cytokines has also been found to occur after dialysis with cuprophan (77) in contrast to biocompatible membranes (78,79). Reuse technique and numbers of reuse also may contribute to the interaction of blood with dialyzer (6,19), leading to changes in protein loss and possible changes in the acute phase response.

Honkanen et al. also found a very rapid and similar increase in IL-1β and SAA during 240 min of dialysis with cuprophan, cellulose acetate, and polymethylmethacrylate (80), the latter two being biocompatible membranes. Plasma IL-6 (77) and IL-1β (80) levels may increase during dialysis, and dialysis can also prime blood lymphocytes to release IL-1, IL-2 (81), and tumor necrosis factor-α (82). Indeed, cytokine production occurs even during in vitro dialysis of whole blood (83). Dialysis may even alter blood mononuclear cells in such a manner to make them respond more vigorously to subsequent exposure to endotoxin (84).

We were unable to find any increase in expression for genes encoding several cytokines in circulating mononuclear cells collected from a small number of hemodialysis patients with high CRP levels, and others also have not been able to identify circulating mononuclear cells as a potential source for stimulating infection in hemodialysis patients (85).

It is clearly possible that inflammation may be a consequence of unrecognized clinical infection. This possibility must be excluded in any dialysis patient who develops hypoalbuminemia.

Another potential way in which dialysis can change albumin levels is by loss of albumin across the dialysis membrane. Clearly, transperitoneal albumin losses contribute to reduced albumin levels in CAPD patients (52,70,71). Significant amounts of albumin (up to 20 g per treatment) can be lost across the hemodialysis dialysis membrane after extensive reuse, especially when polysulfone dialyzers are reused with bleach (6,19), suggesting that dialyzer membrane choice and both reuse number and technique may be partly responsible for deranged albumin homeostasis in hemodialysis patients (86).

The rate of albumin catabolism decreases both in hypoalbuminemic hemodialysis patients as well as in CAPD patients. In addition, the FCR of albumin also decreases as albumin concentration falls in both hemodialysis and CAPD patients, representing preservation of the normal relationship between FCR and serum albumin concentration. Preservation of this normal relationship will serve to support albumin concentration when other factors (decreased synthesis and loss across the hemodialysis or peritoneal membrane) favor a decreasing level of albumin in blood.

Redistribution of the albumin pool from the vascular to the extravascular space plays no role in the development of hypoalbuminemia in either the hemodialysis or CAPD patient population. If anything, the fraction of albumin found in the extravascular pool decreases slightly in hypoalbuminemic CAPD patients.

Synthesis of acute phase reactive proteins, like that of albumin, is also impeded by protein malnutrition (46,47) even following an appropriate inflammatory stimulus. Thus, the absence of an increase in the plasma levels of acute phase reactive proteins does not in itself prove that albumin synthesis is not in part inhibited as a component of the inflammatory response. Cytokine release, however, is unimpeded in protein calorie malnourished states (87). Thus, measurement of cytokine levels may provide greater insight into an inflammatory process than direct measurement of acute phase reactant proteins alone.

Kaizu et al. (24) found that dialysis membrane properties were one factor that predicted serum IL-6 level in their patients. They reported that predialysis IL-6 levels predicted not only albumin levels, but also nutritional status measured anthropometrically. Their findings suggested that inflammation might be associated with malnutrition. This association would not be surprising, since cytokines suppress appetite (88,89), cause loss of adipose tissue directly (90), and also make more severe the loss of tissue mass during periods of reduced nutritional intake (91). These observations would thus provide a more complex inter-relationship between inflammation and both hypoalbuminemia and reduced tissue mass in this patient population. First, increased cytokine levels would alter both plasma composition and body morphometry consistent with what is observed during pure uncomplicated calorie malnutrition. Second, increased levels of cytokines would directly suppress appetite and reduce calorie intake.

Exposure of blood to dialysis membranes, however, does not explain variability within the dialysis population. The majority of hemodialysis patients have serum CRP and SAA levels within the normal range. Furthermore, the acute phase response also plays an important role in establishing albumin levels in CAPD patients (70,71). Indeed, in our own patient population we found that CRP and SAA levels were significantly greater in PD patients than in hemodialysis patients (unpublished observations). Exposure of the peritoneal membrane to plasticizers found in dialysate may be one source of inflammation in this population. Another potential source is the transperitoneal access. Furthermore, the distribution of CRP and SAA values within the hemodialysis patient population is highly skewed, suggesting that patient-specific processes, such as the type of vascular access, unrecognized infections, or variable responses to the dialyzers used, may play a role as well.

Thus, hypoalbuminemia in the ESRD population is a consequence primarily of reduced albumin synthetic rate. There is evidence for activation of the acute phase response in many hypoalbuminemic dialysis patients, suggesting that one important mechanism responsible for decreased albumin synthesis is inflammation, a known cause of suppression of albumin gene transcription. The cause of inflammation is not clearly defined, but is likely to be multifactorial. Protein malnutrition may also contribute importantly to suppression of albumin synthetic rate in some patients. In addition to reduced albumin synthetic rate, external albumin losses also contribute to hypoalbuminemia. This is more important in peritoneal dialysis patients than in hemodialysis patients; however, with extensive dialyzer reuse with bleach, losses of albumin across the hemodialysis membrane may also be significant. There is no evidence that either maldistribution of the albumin pools or increased albumin FCR...
is of significance in causing hypoalbuminemia in ESRD patients.

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