Reassessment of Albumin as a Nutritional Marker in Kidney Disease

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ABSTRACT

The decision by nephrologists, renal dietitians, federal agencies, health care payers, large dialysis organizations, and the research community to embrace serum albumin as an important index of nutrition and clinical performance is based on numerous misconceptions. Patients with analbuminemia are not malnourished and individuals with simple malnutrition are rarely hypoalbuminemic. With the possible exception of kwashiorkor, a rare nutritional state, serum albumin is an unreliable marker of nutritional status. Furthermore, nutritional supplementation has not been clearly shown to raise levels of serum albumin. The use of serum albumin as a quality care index is also problematic. It has encouraged a reflexive reliance on expensive and unproven interventions such as dietary supplements and may lead to adverse selection of healthier patients by health care providers. The authors offer a rationale for considering albumin as a marker of illness rather than nutrition. Viewed in this manner, hypoalbuminemia may offer an opportunity to improve patient well-being by identifying and treating the underlying disorder.

Kidney disease is closely associated with protein–calorie malnutrition. The World Health Organization defines malnutrition as "bad nourishment" characterized by "inadequate or excess intake of protein, energy, and micronutrients such as vitamins, and the frequent infections and disorders that result."[1] The definition implies that protein–calorie malnutrition (henceforth referred to as "malnutrition") will improve when missing nutrients are provided.

Serum albumin is the principal nutritional marker used to identify malnutrition in patients with chronic kidney disease (CKD). Through endorsements by nephrologists, renal dietitians, the research community, federal agencies, health care payers, and large dialysis organizations, it has also become a *de facto* index of clinical performance. The use of serum albumin as a nutritional and quality care marker involves the following assumptions: Serum albumin is a reliable index of malnutrition; because serum albumin is typically low in patients with CKD, these patients should be considered malnourished; replacing missing nutrients will raise low albumin levels; and, because hypoalbuminemia is strongly associated with mortality, replacing missing nutrients to raise albumin will also improve patient outcomes. This review expands on previous viewpoints[2] by critically examining these assumptions and offering an alternative vision to interpreting serum albumin.

DETERMINANTS OF SERUM ALBUMIN

General Population

Albumin is a negatively charged, water-soluble protein (molecular weight 65 kD) that is synthesized in the liver. Its functions include maintaining osmotic pressure and transporting a variety of circulating molecules.[3,4] Serum albumin levels are determined by rates of hepatic synthesis and secretion, exchanges between the intra- and extravascular compartments, lymphatic uptake, alterations in volume of distribution (including hemodilution), protein degradation, and body losses.

The two most influential factors regulating hepatic albumin synthesis are nutritional intake—specifically protein consumption—and illness.[5] Reduced protein consumption slows mRNA synthesis of albumin and results in lower serum levels,[3,6–11] although only in the setting of negligible dietary protein intake. Protein restriction also slows albumin degradation, although to a lesser degree than reductions in the synthesis rate.[3,12] Refeeding with amino acids or protein induces an immediate rise in albumin synthesis.[7,10]

It is also well established that albumin levels fall in patients with inflammatory disorders and other illnesses. Possible contributory mechanisms include downregulated production of albumin mRNA by the liver, leading to re-

duced synthesis,[13] and increased albumin catabolism[14] and vascular permeability.[15]

Patients with CKD

The factors regulating serum albumin are similar between individuals with and without CKD. Reduction in the glomerular filtration rate does not, in and of itself, predispose to hypoalbuminemia. Individuals with hypoalbuminemia and advanced CKD have plasma albumin half-lives and degradation rates similar to those of healthy individuals[16] and possibly even higher rates of albumin synthesis.[17] Dialysis patients also show similar rates of albumin synthesis and turnover.[17–19] However, conditions that often accompany CKD profoundly influence albumin synthesis. Among these are chronic metabolic acidosis[20] and inflammation from concurrent illnesses.[21] Therefore, apart from very rare circumstance in which dietary protein intake is minimal, hypoalbuminemia in CKD is driven primarily by nondietary factors.

IS SERUM ALBUMIN A USEFUL INDEX OF MALNUTRITION?

Origin of the Concept of Serum Albumin as a Nutritional Marker

Because glomerular hypofiltration does not directly influence albumin metabolism, it is instructive to consider clinical observations in populations without CKD to determine whether serum albumin is a reliable nutritional marker. Early findings in malnourished children from developing countries who manifest marasmus and kwashiorkor—two distinct states of malnutrition—offer important insights.

Marasmus is characterized by severe loss of lean and fat mass resulting from prolonged deficiency of both calories and protein.[22] Although individuals with marasmus typically manifest the skeletal appearance and apathetic, listless behavior indicative of starvation, their serum albumin levels remain normal.[23] This key observation suggests that malnutrition, even when life threatening, is not sufficient to cause hypoalbuminemia.

Kwashiorkor (a West African word meaning "the disease the child gets once the second one is born") was originally described in Jamaican children by Cicely Williams.[24] In many reports, the onset of kwashiorkor is linked to a diet extremely deficient or even absent in protein but adequate in carbohydrate-derived calories,[22,24–26] whereas in others, it is associated with a variety of conditions, including inflammation.[27–29] Its cardinal features include edema, dermatitis, and fatty liver in individuals who (despite their edema) are usually thin and underweight with spared subcutaneous fat stores.[22,30,31] In contrast to marasmus, serum albumin levels are usually low.[25,28,30,31] In fact, kwashiorkor is the only premoribund state of malnutrition in which serum albumin is low and is therefore the likely origin for the concept that serum albumin reflects nutritional status. This is a critical point, because kwashiorkor is often accompanied by infection and is rare in the Western industrialized world,[32] where dietary protein is plentiful. In fact, the primary nutritional derangement in CKD nowadays is due to the consumption of *excess* calories and protein. The dialysis population's rising body mass index (BMI) levels exemplify this, with the mean now approaching the "obesity" range (BMI ≥30; Table 1).

Serum Albumin and Malnutrition in the General Population

Anorexia nervosa offers a useful model through which to understand the relationship between malnutrition and serum albumin because patients with anorexia experience loss of lean and fat mass independent of manifestations of illness such as volume shifts, altered vascular permeability, or abnormal albumin loss.[33] These patients maintain serum albumin levels in the normal range, even when BMIs reach the low teens.[33–36] Only when health status approaches death does serum albumin actually fall.[34]

Additional insights are gleaned from the Minnesota Experiment.[37] Initiated in the early 1940s by Ancel Keys, this seminal study explored the biology and physiology of human starvation. Thirty-two healthy young men complied with a semistarvation diet (3200 kcal/d baseline

Table 1. Trends in serum albumin and BMI levels in the US ESRD population: 1996 through 2006

Parameter	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
BMI (kg/m²)											
mean ± SD	25.5 ± 6.6	25.6 ± 6.7	26.0 ± 6.9	26.5 ± 7.0	27.0 ± 7.0	27.2 ± 7.1	27.5 ± 7.2	27.6 ± 7.2	27.8 ± 7.3	28.2 ± 7.5	28.5 ± 7.6
median	24.4	24.6	24.9	25.3	25.8	25.8	26.1	26.3	26.4	26.7	27.1
25th percentile	21.1	21.2	21.5	21.8	22.2	22.4	22.5	22.7	22.8	23.0	23.2
75th percentile	28.7	28.9	29.4	29.8	30.5	30.6	31.0	31.2	31.4	31.9	32.3
Serum albumin (g/dl)											
mean ± SD	3.2 ± 0.7	3.2 ± 0.7	3.2 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	3.2 ± 0.7
median	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
25th percentile	2.8	2.8	2.8	2.7	2.7	2.7	2.7	2.7	2.6	2.7	2.7
75th percentile	3.7	3.7	3.7	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.7

Data courtesy of the US Renal Data System: USRDS 2008 Annual Data Report Special Data Request: Atlas of End-Stage Renal Disease in the United States, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2008.

to <1600 kcal/d) over a 24-wk period. By study's end, the participants' generally emaciated appearance and altered behavior—including lassitude, weakness, and reduced cognition—reflected profound malnutrition. However, whereas the mean BMI and lean and fat mass all dropped sharply, serum albumin levels fell only modestly (Table 2). In fact, serum albumin poorly reflected nutritional changes within individuals, having *increased* in eight participants and remained unchanged in one, despite similar weight loss. Whether acute illness or extracellular volume expansion, which was commonly documented, played a role in the reduction of serum albumin in the remaining participants was not addressed.

Serum Albumin and Malnutrition in CKD

The Modification of Diet in Renal Disease (MDRD) study restricted dietary protein intake to as little as 0.56 g/kg per d.[38] Despite this and concomitant reductions in spontaneous caloric consumption, serum albumin levels remained >4 mg/dl and unchanged from baseline. In fact, even more severe restriction of dietary protein (0.3 to 0.4 g/kg per d) and energy for extended periods did not cause reductions in serum albumin.[39–41]

In a number of observational studies, including those enrolling hemodialysis study patients (Hemodialysis [HEMO] trial), Kaysen *et al.*[42] determined that low serum albumin levels in dialysis patients are primarily associated with systemic inflammation, with little evidence impli-

cating inadequate nutrition as a causative factor. Studies that did find a relationship between serum albumin and diet all used normalized protein catabolic rate to estimate protein intake[43]; however, normalized protein catabolic rate does not measure caloric consumption and has a number of other important limitations.[44] Furthermore, the estimated amount of protein intake in all these studies *far* exceeds the amount typically associated with hypoalbuminemia.

In summary, a plethora of corroborative clinical evidence in the general population and in patients with CKD demonstrates that serum albumin is an insensitive indicator of malnutrition, possibly excepting the very rare circumstance of kwashiorkor-like states, and that even severe protein and caloric restriction do not cause serum albumin levels to fall.

CAN NUTRITIONAL INTERVENTIONS RAISE SERUM ALBUMIN LEVELS?

Although the assumption that hypoalbuminemia reflects a state of malnutrition is often accompanied by the corollary that nutritional interventions can raise serum albumin levels, the supportive evidence for this is inconsistent. Half of the handful of mostly unblinded, randomized studies testing the effects of oral nutritional supplements on serum albumin levels in dialysis patients found no statistical improvement, despite a susceptibil-

ity to bias favoring the study hypothesis (Table 3).

The effect of nutritional supplementation on serum albumin and mortality has been tested only in the French Intradialytic Nutrition Evaluation study (FineS). Patients were randomly assigned for 1 yr to intradialytic parenteral nutrition *versus* no treatment, although both arms were prescribed oral supplements for 2 yr. Two-year mortality was the primary end point, and serum albumin was a secondary one.[45] The intervention did not affect mortality rates, but serum albumin rose early in both groups (3.15 to 3.35 g/dl) and remained stable thereafter. Although the early rise in serum albumin may be construed as resulting from the nutritional intervention, a plausible alternative explanation involves the introduction of bias through the study's unblinded design that led to extranutritional interventions that reduced inflammation. In fact, study subjects' baseline characteristics more strongly suggest the presence of systemic inflammation rather than malnutrition, and early albumin changes were negatively correlated with changes in C-reactive protein ($r = -0.47$; $P < 0.001$). Therefore, on the basis of the available literature, there is insufficient evidence to conclude that nutritional supplementation raises serum albumin in CKD patients with hypoalbuminemia.

SERUM ALBUMIN AS A RESEARCH, CLINICAL, AND QUALITY CARE INDEX

Serum albumin is a commonly used research tool, being cited in more than one quarter of the scientific publications that include the terms "dialysis" and "nutrition." Widespread hypoalbuminemia in the dialysis population in the United States has been used to support the concept that malnutrition is the preeminent nutritional concern[46,47] despite evidence demonstrating that overnutrition, not malnutrition, now predominates (Table 1). Of note, the effect of excess adiposity on clinical outcomes remains controversial in CKD. Moreover, the severe degree

Table 2. The Minnesota Experiment[37]: Effects on body composition and serum albumin

Parameter	6-Mo Semistarvation Diet[a] (n = 32)	
	Baseline	End of Study
BMI (kg/m^2)	21.7 ± 1.7	16.4 ± 0.9
Body composition (kg)		
total weight (% of baseline)	69.4 ± 5.9 (100)	52.6 ± 4.0 (76)
"active" body mass (% of baseline)[b]	39.9 (100)	29.2 (73)
fat mass (% of baseline)	9.8 ± 4.2 (100)	3.1 ± 2.5 (32)
Serum albumin (g/dl)	4.3 ± 0.5	3.9 ± 0.5

[a]Mean ± SD (although no SD available for "active" body mass).
[b]"Active" body mass is total body weight less the sum of the fat, intracellular, and bone mineral weight; fat mass was measured on the basis of specific gravity.

Table 3. Effects of randomized oral nutritional interventions on serum albumin levels in dialysis patients

Study	N/Location/Dialysis Modality	Group Interventions	Study Length (wk)	BMI (kg/m²)	Serum Albumin (g/dl) Baseline	Serum Albumin (g/dl) End	Blinded Study?	Comments
Kuhlmann et al.,[62] 1999	22/Germany/HD	I₁: high-protein/energy diet; I₂: standard diet; I₃: low-protein/energy diet	12	I₁: 18; I₂: 22; I₃: 22	I₁: 4.14; I₂: 4.08; I₃: 4.19	I₁: 5.14; I₂: no change; I₃: no change (no significant change in any group)	No	Unclear how group assignments were performed
Eustace et al.,[63] 2000	47/United States/HD + PD	C: matched placebo; I: amino acid tablets	12	PD: C, 23; I, 24; HD: C, 25; I, 31	PD: C, 3.00; I, 3.43; HD: C, 3.47; I, 3.57	PD: C, +0.02; I, +0.04 (NS); HD: C, +0.04; I, +0.26 (P = 0.02)	Yes	NS effect on combined groups (P = 0.08)
Hiroshige et al.,[64] 2001	44/Japan/HD	C: matched placebo; I: amino acid granules	52	C: 18; I: 19	C: 3.27; I: 3.31	C: no increase; I: increase	Yes	Mean dialysis vintage 6 to 7 yr
Sharma et al.,[65] 2002	40/India/HD	C: dietary counseling; I₁: home-prepared supplement; I₂: commercial supplement	4	C: 17; I₁: 18; I₂: 17	C: 3.4 0; I₁: 3.40; I₂: 3.40	C: +0.1; I₁: +0.6; I₂: +0.5 (P < 0.001)	No	Patients with diabetes excluded
Kloppenberg et al.,[66] 2004	45/Netherlands/HD	C: regular-protein diet; I: high protein diet	80	C: 25; I: 24	C: 4.77; I: 4.19	No significant change in either group	No	Intervention also included high versus regular dialysis dosage
Akpele and Bailey,[67] 2004	40/United States/HD	C: dietary counseling; I: 1 to 2 supplement cans per day	29 (mean)	NA	C: 3.01; I: 3.11	C: +0.03/mo; I: −0.04/mo (P = 0.03)	No	
Gonzalez-Espinoza et al.,[68] 2005	28/Mexico/PD	C: usual care; I: oral protein supplement	24	C: 25; I: 23	C: 2.66; I: 2.40	C: +0.14; I: +0.41 (P < 0.05)	No	
Leon et al.,[69] 2006	180/United States/HD	C: usual care; I: strategies to lower dialysis/nutritional barriers	52	C: 28; I: 29	C: 3.40; I: 3.40	C: +0.06; I: +0.21 (P < 0.01)	No	Nonnutritional interventions also included

C, control arm; HD, hemodialysis; I, intervention arm; PD, peritoneal dialysis.

of hypoalbuminemia, as noted in Table 1, is greatly out of proportion to what is observed in malnourished states and calls into question its use in establishing a link between malnutrition and inflammation.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Nutrition advanced the field by recommending that serum albumin be measured routinely in long-term dialysis patients but mistakenly used it as a nutritional biomarker.[48] Data from the Minnesota Experiment was used as supportive evidence. The guidelines also focused on the inverse association between serum albumin and mortality and raised the possibility that nutritional interventions could improve mortality rates, while also acknowledging that inflammation could play a confounding role.

The Council on Renal Nutrition recommends serum albumin as one of a select number of objective data to help identify malnutrition. It is the third most common nutritional test used by renal dieticians, after weight and serum electrolytes.[49] Serum albumin has become the predominant nutritional marker, being included in >99% of dietary evaluations, as compared with <50% that use anthropometric measurements or the subjective global assessment.[49] The International Society of Renal Nutrition and Metabolism recently included serum albumin <3.8 g/dl as one of three biochemical diagnostic criteria for protein–energy wasting.[50]

The widespread use of serum albumin has led the US government to consider it as a quality care index. The Medicare ESRD Network Organizations Glossary suggests that albumin "may reflect the amount of protein intake in food."[51] In the Secretary of Health and Human Services 2004 Report to Congress on Medical Nutritional Therapy, serum albumin is reported as having "critical implications for dialysis patients if not carefully monitored."[49] The Centers for Medicare and Medicaid Services (CMS) End-Stage Renal Disease Quality Initiative offered incentive payments for reporting serum albumin as one of five quality measures[52]

but has since removed it.[53] The CMS 2007 Annual Performance Report: ESRD Clinical Performance Measures Project chose albumin as a mortality risk indicator in adult dialysis patients and based its albumin goal on previous National Kidney Foundation guidelines.[48] At least one large dialysis organization uses albumin as a quality indicator, and it may very well be adopted in the future by CMS and other payers to determine performance and influence value-based purchasing.

The use of serum albumin by either payers or large dialysis organizations as a measurement of nutrition and performance is fraught with problems. Among these is the unsubstantiated premise that nutritional supplementation reverses hypoalbuminemia, leading to unnecessary and costly care. Another important issue is that despite the clinician's best efforts, the cause(s) of hypoalbuminemia may never be identified and may not be modifiable. The clinician may therefore be forced to select adversely, or "cherry pick," his patient population to meet performance expectations. In addition, the index of performance for a particular clinician or dialysis facility may be falsely improved by the deaths of sicker patients who have lower albumin levels.

SERUM ALBUMIN: A CLINICAL INDEX OF ILLNESS

Whereas the relationship between serum albumin and malnutrition is unreliable,[2,54] the strong and robust inverse relationship between serum albumin and mortality does offer potential clinical value. The association was first described in 1990, when a serum albumin <4 g/dl was found to be inversely and progressively associated with increased risk for death in hemodialysis patients.[55] Three years later, Owen et al.[56] confirmed this observation. Although similar findings have subsequently been described in various populations with CKD, the relationship is highly unlikely to be causal, because even individuals who are born with a complete absence of circulating albumin (analbuminemia) manifest only minimal, if any, clinical symptoms.[57]

Moreover, acknowledging that an inverse association exists between albumin and mortality is one thing, but conflating it with death *from a nutritional derangement* is quite another.

Nevertheless, hypoalbuminemia may help to identify the rare CKD patient with extremely low protein intake (<0.3 g/kg per d in predialysis patients with CKD or 0.5 g/kg per d as a conservative estimate in dialysis patients) who would be amenable to nutritional therapy. Figure 1 offers an algorithm to assist clinicians in identifying such patients. However, the lack of an effect of nutritional supplementation on serum albumin levels or anthropometric findings inconsistent with a kwashiorkor-like state (*e.g.* obesity) makes it very unlikely that hypoalbuminemia reflects a nutritional problem.

Albumin's widespread use as a nutritional marker is understandable in light of the desire of clinicians for a convenient, widely applicable, easily interpretable, and accurate indicator of nutritional status. Unfortunately, no such indicator exists or probably will for the foreseeable future. This does not mean that serum albumin lacks utility. Although we have demonstrated that serum albumin is not a good nutritional index in the great majority of cases, it is a powerful way to detect underlying illness; that is, the higher the serum albumin, the more intact is overall health.

All too often, the presence of hypoalbuminemia automatically triggers the initiation of nutrition supplementation and nothing more. This strategy may delay identification of an underlying treatable disorder. Although the causes of hypoalbuminemia are protean, it is important for the clinician at least to establish a differential diagnosis. Mitch et al.[21] described a common pathway—the ubiquitin proteasome system—through which a number of CKD-related complications, including metabolic acidosis, reduced insulin action, higher angiotensin II levels, and inflammation, induce protein breakdown and muscle loss. The model of a common pathway is useful to consider when investigating hypoalbuminemia, especially in light of the estab-
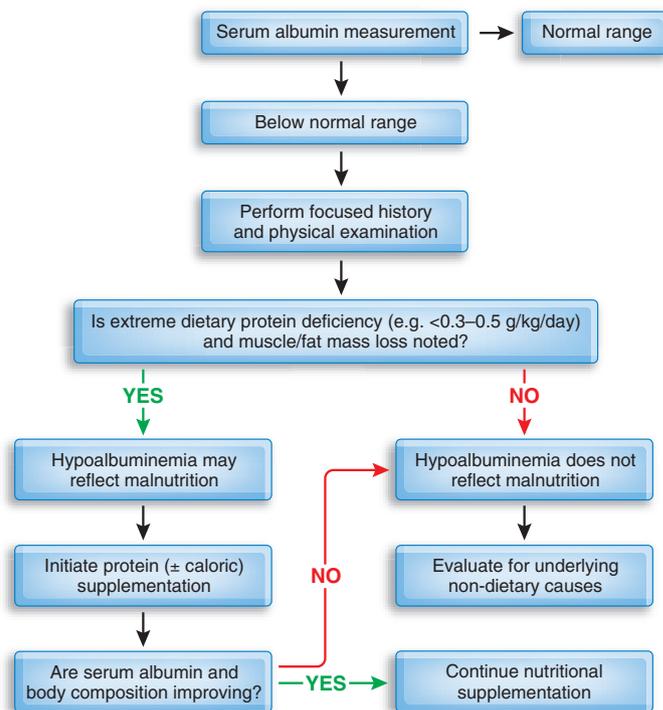
Figure 1. Clinical algorithm for interpreting serum albumin is shown.

lished association between inflammation and albumin synthesis.[42] An illness or inflammatory state can reduce serum albumin levels by suppressing synthesis, increasing catabolism and/or vascular permeability to albumin, or a combination of these.

Aside from obvious illnesses and inflammatory states, a number of specific causes should be considered in the workup of hypoalbuminemia, including dialysis access infections (*e.g.*, occult old arteriovenous graft infections[58] and tunneled dialysis catheters), dental or periodontal disease, *Helicobacter pylori* infection, diverticulitis, peripheral vascular disease, occult malignancies, and possibly insulin resistance. Although uremia and metabolic acidosis can lower serum albumin levels,[20,59] conclusive evidence demonstrating that reversing these pathologic states actually raises serum albumin levels is lacking.[60,61]

CONCLUSIONS

This article highlights the rationale for reconsidering albumin as a marker of illness rather than nutrition. Patients with analbuminemia are not malnourished, and individuals with simple malnutrition are rarely hypoalbuminemic. Furthermore, kwashiorkor, the only nutritional illness associated with hypoalbuminemia, is rarely observed in the United States and may itself be caused by underlying inflammatory conditions rather than malnutrition. Hence, the heavy reliance on serum albumin as a clinical and research nutritional tool in CKD is unwarranted, and the strategy of supplying expensive nutritional supplements as a reflexive first step in managing hypoalbuminemia should be discouraged. Nonetheless, the presence of hypoalbuminemia may offer health care providers the opportunity to improve patient well-being by identifying and treating underlying disorders. Because the cause of

hypoalbuminemia cannot always be reversed or even identified, the use of serum albumin as a quality performance measure should focus only on whether it triggers a search for underlying causes rather than on the albumin level itself.

DISCLOSURES

None

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