The Use and Misuse of Serum Albumin as a Nutritional Marker in Kidney Disease

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Nutritional status refers to the composite quantitative and qualitative assessment of visceral and somatic (muscle) protein stores and energy balance (1,2). Evaluating nutritional status is a critical component of physiologic health and fundamental to identifying protein-energy wasting (PEW), a condition highly prevalent and strongly correlated with increased morbidity and mortality in patients with kidney disease (3). Improved recognition of this common condition and effective interventions remain the holy grail of nutritional management of patients with kidney disease, especially those on maintenance dialysis.

Assessment of protein and energy nutritional status is a broad and complex topic. A clinically meaningful assessment of nutritional status should be able to identify and risk stratify patients with PEW, distinguishing the causes and consequences of both PEW and the underlying disease states that lead to PEW, and finally determine whether there is a possibility of benefit from nutritional interventions (4). Therefore, no single parameter is likely to adequately phenotype this comorbid state, and a comprehensive assessment of protein and energy nutritional status requires several different measurements (5).

Despite the obvious need for multiple markers, clinicians and researchers have continuously searched for a single marker that would fulfill all the requirements mentioned. Among these markers, serum albumin has been, by far, the most extensively studied serum protein in patients with advanced kidney disease on maintenance dialysis. Serum albumin robustly associates with death and hospitalization, is easily and reproducibly measured, and responds to appropriate interventions (6). Despite these advantages, serum albumin is also one the most highly criticized nutritional markers (7).

In this issue of CJASN, Gama-Axelsson et al. (8) report their findings regarding the predictive value of serum albumin as a nutritional marker in a large and well-phenotyped cohort of incident and prevalent maintenance dialysis patients. Their results show that serum albumin was significantly correlated with diabetes mellitus (DM), subjective global assessment (SGA) score >1, indicative of abnormal nutritional status, and urinary albumin excretion in incident dialysis patients. In prevalent dialysis patients, serum albumin was associated with age, C-reactive protein, DM, and SGA >1. They further go on to examine the diagnostic value of serum albumin as a nutritional marker using receiver operating curve (ROC) analysis using SGA, handgrip strength, lean body mass (LBM), and body mass index (BMI) as gold standards. In these analyses, addition of serum albumin to a standard model including clinical and demographic variables had no appreciable impact for explaining the variability in SGA, handgrip strength, LBM, and BMI. Based on these findings, the investigators conclude that serum albumin correlates poorly with several markers of nutritional status, and thus its value as a reliable marker of nutritional status in ESRD patients is limited. This particular study has multiple strengths including but not limited to a large patient cohort, detailed nutritional and clinical phenotyping, and thorough analysis.

The study also has important clinical and research implications. Most importantly, these data, along with other published studies, should guide clinicians and researchers on how to avoid misuse of serum albumin as a nutritional marker in incident and prevalent maintenance dialysis patients. For example, serum albumin has limited diagnostic ability for assessment of body composition, i.e., LBM and fat mass content, and physical functioning because it does not explain the variability in LBM, BMI, or hand grip strength. Similarly, serum albumin had little diagnostic value in identifying poor nutritional status by SGA in this study, which is largely based on the subjective assessment of body composition. Whereas this might seem discouraging, it is important to remember that overall nutritional status is a reflection of both visceral protein concentrations and somatic protein stores, and biomarkers reflecting the status of each compartment are not always tightly correlated. As a result, some of these findings might be anticipated, because serum albumin is a visceral protein, and body composition reflects somatic protein stores. Further, under physiologic stress, such as inflammation, these two compartments often have competing roles with visceral protein production often increasing at the expense of breakdown of somatic proteins, the latter to provide substrate for hepatic protein synthesis (9). Therefore, attempting to use a biomarker (i.e., serum albumin) alone to assess a distinct nutritional compartment without a direct biologic link may misdiagnose this condition of that
particular biomarker and should be avoided in both clinical and research settings. Accordingly, the incremental value of a biomarker is more readily recognized when used for appropriate indications.

Another important lesson one can learn from this study is how to use statistical methods to answer clinical and research questions. This issue is especially important for biomarker studies where a number of different approaches have been used. Whereas both regression analysis and C-statistics are used to assess the association and diagnostic ability in this study, respectively, their meaning and clinical applicability are not adequately discussed. For example, multiple logistic regression analysis indicated that serum albumin concentrations are associated with multiple factors, which is quite expected given the complex biology of this protein (vide infra). The observation that SGA is significantly associated with serum albumin after adjustment for multiple other factors attests to the latter’s utility as a useful nutritional marker in complex settings, a conclusion not necessarily appreciated by the authors. On the other hand, the area under the curve (AUC-ROC curve (C-statistics) measures the probability of a marker to correctly rank order any two randomly selected patients: one experiencing the outcome of interest, such as wasting or malnutrition, and one who does not (10). It has been estimated that extremely robust associations between biomarker levels and the outcome of interest, with minimal overlap in the distribution, are required to substantially improve the AUC. Because nutritional status is determined by a variety of physiologic processes, it is unrealistic to expect any single biomarker to perfectly discriminate between well-nourished and malnourished subjects, especially when the gold standard for comparison is ill-defined, as is the case in the study by Gama-Axelsson et al. Given its versatility, the AUC-ROC curve is also often extended to the prediction of future events. However, observations, primarily from the cardiovascular and AKI literature (11), suggest that change in the AUC-ROC may be a relatively insensitive metric to assess the incremental predictive ability of a marker relative to established predictors.

What, if any, then, is the value of serum albumin in clinical and research settings in patients with kidney disease? To answer this question, it is important to understand albumin’s complex biology and how its serum concentrations are determined. The concentration of serum albumin is the net result of its synthesis, breakdown, volume of distribution, and exchange between intra- and extravascular spaces, as well as losses (12). Albumin is a highly watersoluble protein, located mainly in the extracellular space. Albumin is synthesized in the liver and secreted into the bloodstream, where it is rapidly equilibrated and has a half-life of approximately 20 days. Equilibration between intra- and extravascular albumin pools is slower than within the intravascular space, varying from 7 to 10 days, depending on the tissue. Dietary protein intake (DPI) has a direct influence on serum albumin concentrations, and inadequate DPI is characterized by a decrease in the rate of albumin synthesis (13), which may have little impact on serum albumin levels in the short term. Numerically small, albeit clinically significant alterations in serum albumin levels can occur over time in certain conditions where low DPI is maintained. Yet in stark contrast to decreased DPI, numerous underlying conditions and diseases, such as hepatic and inflammatory disorders, which cause a decrease in albumin synthesis and increase in albumin breakdown, can cause/lead to profound hypoalbuminemia (14,15). Decreased albumin synthesis from liver failure and from albumin losses via the gastrointestinal tract, kidney, or from tissue injuries such as wounds, burns, and peritonitis, can also lead to hypoalbuminemia.

Given the multifactorial determinants of serum albumin, it remains to be one of the most sensitive screening tools available, which largely explains its widespread use in both clinical and research arenas. Serum albumin also possesses the unique characteristic of a robust and gradual predictive power in almost every disease state, including advanced kidney disease (16,17). For example, levels <2.5 g/dl have been associated with a risk of death 20 times higher compared with a reference level of 4.0–4.5 g/dl in hemodialysis patients, and levels of 3.5–4.0 g/dl (considered to be within the normal range) were associated with doubling the risk of death (18,19). However, much like serum creatinine, the standard test for screening for CKD, it provides little information about the complex nature of the problem if existent. In the setting of low serum albumin, it is quite obvious that the subject is suffering from the disease, and the appropriate approach should be to further evaluate the individual with additional tools. This could be as simple as a thorough physical exam or some other more sophisticated biochemical or nutritional marker such as serum prealbumin, dual-energy x-ray absorptiometry or magnetic resonance imaging (6). This complementary approach will allow not only the assessment of the overall nutritional status, but also will give clues regarding the etiology of the condition that have lead to observed abnormalities. The response to a targeted therapy can then be monitored again by changes in serum albumin concentrations or a combination of markers thereof.

The ease of its measurement, its limited cost, its reproducibility, and its consistent response to interventions make serum albumin one of the most efficient screening tools for assessment of nutritional status in ESRD patients. However, its potential (mis)use as a diagnostic marker, especially in comparison to unsuitable standards, makes it equally inefficient tool for assessment of nutritional status and should be avoided.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.