Serum Albumin as Predictor of Nutritional Status in Patients with ESRD

Thiane Gama-Axelsson, Olof Heimbürger, Peter Stenvinkel, Peter Bárány, Bengt Lindholm, and Abdul Rashid Qureshi

Summary

Background and objectives Serum albumin is a widely used biomarker of nutritional status in patients with CKD; however, its usefulness is debated. This study investigated serum albumin and its correlation with several markers of nutritional status in incident and prevalent dialysis patients.

Design, setting, participants, & measurements In a cross-sectional study, serum albumin (bromocresol purple), and other biochemical (serum creatinine), clinical (subjective global assessment [SGA]), anthropometric (handgrip strength; skinfold thicknesses), and densitometry (dual-energy x-ray absorptiometry) markers of nutritional status were assessed in 458 incident (61% male; mean age, 54 ± 13 years; GFR, 6.6 ± 0.3 ml/min per 1.73 m²; recruited 1994–2010) and 383 prevalent (56% male; mean age, 62 ± 14 years; recruited 1989–2004) dialysis patients.

Results In incident patients, serum albumin was correlated with age ($\beta = -0.15; P < 0.001$), diabetes ($\beta = -0.30; P < 0.001$), high-sensitivity C-reactive protein ($\beta = -0.37; P < 0.001$), and urinary albumin excretion ($\beta = -0.38; P < 0.001$) but less so with poor nutritional status (SGA score $> 1$, $\beta = -0.19; P < 0.001$). In prevalent patients, serum albumin was correlated with age ($\beta = -0.15; P < 0.001$), high-sensitivity C-reactive protein ($\beta = -0.30; P < 0.001$), diabetes ($\beta = -0.31; P < 0.001$), and SGA score $> 1$ ($\beta = -0.16; P < 0.001$). In predicting nutritional status assessed by SGA and other markers, adding serum albumin to models that included age, sex, diabetes, and cardiovascular disease did not significantly increase explanatory power.

Conclusions In incident and prevalent dialysis patients, serum albumin correlates poorly with several markers of nutritional status. Thus, its value as a reliable marker of nutritional status in patients with ESRD is limited.

Introduction

Biochemical analyses are routinely used to assess and monitor nutritional status in patients with CKD. However, none of the currently favored biochemical nutritional markers have been demonstrated to accurately reflect nutritional status in CKD (1–3).

Nevertheless, serum albumin is still being widely used for research purposes and, in the clinical setting, as a biomarker of nutritional status (4). In patients with CKD, factors such as overhydration and protein loss into urine and dialysate reduce serum albumin concentrations. Also limiting the usefulness of serum albumin as a nutritional marker are counter-regulatory mechanisms. In the short term, protein deficiency decreases the rate of albumin synthesis (5), but over time compensation occurs through a decrease in albumin breakdown and a shift of albumin from the extravascular to the intravascular space.

Among numerous complications of CKD, progressive loss of body protein mass and energy reserves is one of the most typical and detrimental. This loss has been termed protein-energy wasting (PEW) (6). It is more common in patients with advanced stages of CKD and may affect 18%–75% of patients with ESRD (6–8). PEW is to a large extent caused by inadequate nutritional intake leading to malnutrition; still, increased catabolism that is due to chronic low-grade inflammation and leads to wasting seems to be of equal importance (6,9). According to the definition of PEW (6), patients could have PEW and not necessarily be undernourished. There is considerable overlap among poor nutritional status, malnutrition (representing mainly chronic undernutrition), and PEW; however, these terms have different definitions and meanings and should not be used interchangeably (10).

No single marker can be regarded as ideal to assess nutritional status (11), especially not in patients with CKD, in whom various metabolic alterations and other confounding factors, such as fluid overload, are common. However, subjective global assessment (SGA), anthropometry, and dual-energy x-ray absorptiometry (DEXA) are widely used methods to assess nutritional status in patients with CKD and also are recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (11,12). Furthermore, SGA was found to be an appropriate tool for cross-sectional assessment of nutritional status in a study of patients with CKD (13).
Because albumin has a fairly long half-life and is present in large quantities (14), the effect of a temporarily decreased protein intake on concentrations of albumin is also limited (15). Instead, serum albumin is more likely to be influenced by its role as an acute phase reactant. Thus, low serum albumin levels in dialysis patients are strongly associated with inflammation (16). Because of the continuing controversy and the widespread use of serum albumin as a biomarker of nutritional status in patients with CKD, we investigated serum albumin and its correlation with several biomarkers of nutritional status in cross-sectional cohorts of incident and prevalent dialysis patients.

Materials and Methods

Patients and Study Design

This is a cross-sectional study of data from two independent cohorts coordinated at the Department of Renal Medicine, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden: incident dialysis patients who were investigated just before or in conjunction with start of dialysis therapy (17) and prevalent patients who, at different time periods, had been undergoing peritoneal dialysis (18) or hemodialysis (19,20) for more than 3 months in the Stockholm/Uppsala area. Exclusion criteria were current hospitalization, clinical signs of infection, or acute vasculitis at the time of enrollment or within 3 weeks before that date, as well as unwillingness to participate in the study or inability to give informed consent. Patients were categorized according to CKD status on the day of inclusion as incident dialysis patients (n=458; 61% male; mean age, 54±13 years; GFR, 6.6±2.3 ml/min) or prevalent dialysis patients (n=383; hemodialysis, n=347; peritoneal dialysis, n=36; 56% male; mean age, 62±14 years). Each patient’s medical chart was reviewed to extract data on underlying cause of CKD, cardiovascular disease (CVD) history, and diabetes mellitus.

The study protocols were approved by the Ethics Committee of Karolinska Institutet Hospital and Uppsala University Hospital. Informed consent was obtained from all patients before their inclusion in the study.

Anthropometric Evaluation

Body weight, body mass index (BMI; in kg/m²), and anthropometric measurements were obtained on a dialysis day in the prevalent dialysis patients (immediately after the dialysis session for the prevalent hemodialysis patients), and, for the incident dialysis patients, at the time of or within 1 week of blood sample collection, and fat mass and lean body mass (LBM) were assessed from these data according to the method of Durnin et al. (21). Fat mass was assessed by using four skinfold thicknesses (biceps, triceps, subscapular, and suprailliac), measured with a conventional skinfold caliper (Cambridge Scientific Instruments, Cambridge, MD). In addition, LBM was measured in incident dialysis patients by DEXA using the DPX-L device (Lunar Corp., Madison, WI). Handgrip strength was measured in both the dominant and nondominant hands by using a Harpenden Handgrip Dynamometer (Yamar, Jackson, MI). Each measurement was repeated three times for each arm, and the highest value for each arm was noted. For our analysis, we used the dominant arm for handgrip strength because fistulas were usually placed in the nondominant arm.

Laboratory Analysis

Blood samples were collected in the morning before the dialysis session. The plasma was separated within 30 minutes, and samples were kept frozen at ~70°C if not analyzed immediately. Concentrations of high-sensitivity C-reactive protein (hsCRP; high-sensitivity nephelometry assay), serum creatinine, and serum albumin (bromocresol purple) were measured by routine methods at the Department of Laboratory Medicine, Karolinska University Hospital, Huddinge. Inflammation status was defined as CRP level <10 mg/L (noninflamed) and CRP >10 mg/L (inflamed). GFR was estimated in incident dialysis patients by the mean of urinary creatinine and urea clearances during a 24-hour urine collection.

Nutritional Status Assessment

Nutritional status was assessed using the SGA score (22). The SGA has been validated in patients with CKD and consists of six components: three subjective, patient-performed assessments on the rate of the history of weight loss, incidence of poor appetite, and incidence of vomiting and three evaluator-performed assessments that subjectively grade muscle wasting, the presence of edema, and the loss of subcutaneous fat. On the basis of these assessments, each patient received a nutritional status score: 1 = normal nutritional status, 2 = mild malnutrition, 3 = moderate malnutrition, and 4 = severe malnutrition. For this study, poor nutritional status was defined as an SGA score >1; a score of 1 indicates normal nutritional status.

Statistical Analyses

All variables are expressed as mean ± SD or as median (10th and 90th percentiles), unless otherwise indicated. Statistical significance was set at the level of P<0.05. Multivariate logistic regression analyses were used to study the relative associations of selected markers with serum albumin. A determinant of serum albumin was analyzed using linear multivariate regression analysis. All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics

The studied population consisted of 841 patients (458 incident and 383 prevalent dialysis patients). Demographic, clinical, and important biochemical characteristics are presented in Table 1. Briefly, the incident dialysis patients comprised 61% men (average age, 54±13 years); 30% of patients had diabetes, and 35% had a history of CVD. The prevalent dialysis group comprised 56% men (average age, 62±14 years); 22% of patients had diabetes and 63% had a history of CVD. Serum albumin level was significantly lower in incident than in prevalent dialysis patients (33.0±6.0 versus 34.6±4.6 g/L; P<0.001).

Clinical Correlates of Serum Albumin Concentration

The results of multiple regression models predicting serum albumin (g/L) in both incident dialysis and prevalent dialysis patients are shown in Tables 2 and 3. Briefly, in incident dialysis patients, multivariate analysis that included age, sex, hsCRP, presence of diabetes mellitus,
Table 1. Clinical characteristics, anthropometric measurements, and biochemical markers of nutritional and inflammatory status in incident and prevalent patients undergoing dialysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Dialysis Group (n=458)</th>
<th>Prevalent Dialysis Group (n=383)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (yr)</td>
<td>54±13</td>
<td>62±14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>men (%)</td>
<td>61</td>
<td>56</td>
<td>0.21</td>
</tr>
<tr>
<td>diabetes mellitus (%)</td>
<td>30</td>
<td>22</td>
<td>0.01</td>
</tr>
<tr>
<td>cardiovascular disease (%)</td>
<td>35</td>
<td>63</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>6±3</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>hemoglobin (g/L)</td>
<td>104±14</td>
<td>110±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>urinary albumin excretion (mg/24 hr)</td>
<td>1981 (797–3741)</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>Nutritional variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA score &gt;1 (%)</td>
<td>31</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>serum albumin (g/L)</td>
<td>33.0±6.0</td>
<td>34.6±4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>body mass index (kg/m²)</td>
<td>24.6±4.3</td>
<td>23.7±4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>handgrip strength (% of control)</td>
<td>77±25</td>
<td>45±28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>serum creatinine (µmol/L)</td>
<td>722±242</td>
<td>766±223</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Inflammation variable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>9 (1.1–4.8)</td>
<td>10 (5.5–20.0)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median (25th–75th percentile), or percentage. Handgrip strength was normalized with the measurements from healthy persons. ND, not determined; SGA, subjective global assessment; hsCRP, high-sensitivity C-reactive protein.

Table 2. Multiple regression models for serum albumin in incident dialysis patients (n=458)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude [β (P Value)] (r²=0.01)</th>
<th>Model 1 [β (P Value)] (r²=0.09)</th>
<th>Model 2 [β (P Value)] (r²=0.17)</th>
<th>Model 3 [β (P Value)] (r²=0.16)</th>
<th>Model 4 [β (P Value)] (r²=0.32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.12 (0.02)</td>
<td>−0.06 (0.27)</td>
<td>−0.02 (0.61)</td>
<td>−0.03 (0.60)</td>
<td>−0.10 (0.08)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.01 (0.78)</td>
<td>0.05 (0.27)</td>
<td>0.05 (0.26)</td>
<td>0.10 (0.02)</td>
<td>0.13 (0.02)</td>
</tr>
<tr>
<td>hsCRP</td>
<td>−0.30 (0.001)</td>
<td>−0.29 (0.001)</td>
<td>−0.25 (0.001)</td>
<td>−0.10 (0.07)</td>
<td>−0.18 (0.004)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−0.30 (0.001)</td>
<td>−0.30 (0.001)</td>
<td>−0.30 (0.001)</td>
<td>−0.18 (0.004)</td>
<td>−0.42 (0.001)</td>
</tr>
<tr>
<td>CVD</td>
<td>−0.02 (0.70)</td>
<td>−0.03 (0.60)</td>
<td>−0.01 (0.79)</td>
<td>−0.19 (0.001)</td>
<td>−0.42 (0.001)</td>
</tr>
<tr>
<td>SGA score &gt; 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/24 hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; SGA, subjective global assessment. SGA>1 denotes poor nutritional status according to SGA.

CVD, clinical signs and symptoms indicating a poor nutritional status (defined as SGA score >1), and urinary albumin excretion rate showed that serum albumin was significantly correlated with female sex (β=−0.13; P=0.02), diabetes mellitus (β=−0.18; P=0.004), SGA score >1 (β=−0.19; P=0.001), and, especially, urinary albumin excretion (β=−0.42; P=0.001). In prevalent dialysis patients, and after adjustment for age, sex, hsCRP, presence of diabetes mellitus, CVD, and poor nutritional status (SGA score >1), serum albumin was associated with age (β=−0.14; P=0.05), hsCRP (β=−0.34; P=0.001), diabetes mellitus (β=−0.11; P=0.04), and SGA score >1 (β=−0.14; P=0.003).

Effect of Inflammation

Figure 1 shows that serum albumin levels among patients with normal nutritional status did not differ between inflamed and noninflamed patients; this was true among both incident and prevalent patients. However, patients with poor nutritional status—both incident and prevalent—who were also inflamed had a significantly lower serum albumin level (P<0.001) than noninflamed patients (Figure 1). We separately analyzed the patients who were not inflamed and found that in the noninflamed incident dialysis group, both LBM and handgrip strength, but not albumin, were significantly lower in patients with a poor nutritional status (SGA score >1) (data not shown). In the noninflamed prevalent dialysis patients, those with a poor nutritional status (SGA score >1) were older and had significantly lower fat mass, lower LBM, and lower serum albumin levels (35.0±4.5 versus 36.6±3.2 g/L; P<0.05); handgrip strength did not differ. However, after adjustment for age, sex, and diabetes mellitus, the difference in serum albumin levels...
between patients with normal and those with poor nutritional status was no longer significant (data not shown).

**Effect of Urinary Albumin Loss**

In Figure 2, incident dialysis patients were divided by inflammation state and albuminuria, as well as by serum albumin levels. Albuminuria was a strong predictor of serum albumin levels in both inflamed and noninflamed patients. Using receiver-operating characteristic curve (ROC) analysis, the areas under the curve for serum albumin (g/L) as a predictor of SGA score >1 were 0.62 in the incident dialysis patients (albumin explained only 12% of the variation in SGA) and 0.64 in the prevalent dialysis patients (albumin explained 14% of the variation).

**Bivariate Correlations between Serum Albumin and Other Markers of Nutritional Status**

Table 3. Multiple regression models for serum albumin in prevalent dialysis patients (n=383)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude [β (P Value)] (r²=0.03)</th>
<th>Model 1 [β (P Value)] (r²=0.04)</th>
<th>Model 2 [β (P Value)] (r²=0.19)</th>
<th>Model 3 [β (P Value)] (r²=0.21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.18 (0.009)*</td>
<td>-0.12 (0.009)*</td>
<td>-0.15 (0.002)*</td>
<td>-0.14 (0.005)*</td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td>0.12 (0.01)*</td>
<td>0.06 (0.2)</td>
<td>0.03 (0.48)</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-0.35 (0.001)*</td>
<td>-0.36 (0.001)*</td>
<td>-0.34 (0.001)*</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>-0.13 (0.009)*</td>
<td>-0.11 (0.04)*</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td>-0.06 (0.18)</td>
<td>-0.06 (0.19)</td>
<td>-0.14 (0.003)*</td>
</tr>
<tr>
<td>SGA score &gt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; SGA, subjective global assessment. SGA score >1 denotes poor nutritional status according to SGA.

*Statistically significant result: β (P value).
The crude unadjusted associations (in incident and prevalent patients, respectively) between albumin and handgrip strength ($r^2=0.02$ and $0.08$), LBM estimated by anthropometrics ($r^2=0.005$ and $0.01$), LBM estimated by DEXA (only in incident patients; $r^2=0.006$), and BMI ($r^2=0.003$ and $-0.0003$) were very weak.

Relative Contributions of Factors Explaining the Variation of Nutritional Status

In a separate analysis, we analyzed how well combinations of different factors (clinical and demographic data and different nutritional markers) could predict the variation of the different estimates of nutritional status (SGA, handgrip strength, LBM, and BMI), along with the added value of also using information on serum albumin (Figure 3).

The traditional clinical factors (age, sex, and presence of diabetes mellitus and CVD) could explain $0.05$–$0.52$ of the variation in different estimates of nutritional status (SGA, handgrip strength, LBM, and BMI) among the incident dialysis patients; addition of serum albumin in the model did not increase the explanatory power (pseudo $r/r^2=0.05$–$0.53$) (Figure 3A). When all the investigated measures of nutritional status (including serum albumin) were included in the model, the explanatory power increased to $0.13$–$0.77$ for the different estimates of nutritional status.

Similarly, in the prevalent dialysis patients, the traditional clinical factors (age, sex, presence of diabetes mellitus, and CVD) could explain $0.02$–$0.47$ of the variation in the different estimates of nutritional status (SGA, handgrip strength, LBM calculated with anthropometrics, and BMI). Again, the addition of serum albumin in the model did not increase the explanatory power, which remained $0.02$–$0.47$ for the different nutritional markers (Figure 3B). When all

Discussion

Although serum albumin is still a widely used biomarker for nutritional status in CKD (4) and has a strong association with a poor outcome (23,24), its usefulness as a nutritional marker has been challenged (4). In a cohort study, we investigated serum albumin and its correlation with several markers of nutritional state in both incident and prevalent dialysis patients.

In incident dialysis patients with residual renal function, urinary albumin was the strongest predictor of serum albumin levels. However, after adjustments for age, sex, hsCRP, diabetes mellitus, and CVD, an SGA score $\geq 1$ (indicating presence of poor nutritional status) was independently but, compared with other predictors, relatively weakly associated with low serum albumin levels in both groups.

It has traditionally been assumed that serum albumin is an indicator of nutritional status, and serum albumin is predominantly low in patients with CKD. Thus, it has been considered a supported sign of malnourishment. However, the effect of a decreased protein intake on concentrations of serum albumin is limited by albumin’s considerable half-life (up to 20 days) and abundance (14). Thus, even in extreme cases of malnutrition, such as marasmus and anorexia nervosa, serum albumin levels remain normal (25). Furthermore, results from the Minnesota study (15) show that after induced, prolonged starvation in healthy volunteers, with participants showing multiple signs of
malnutrition, serum albumin levels changed only slightly. Given these findings, as well as the study showing that healthy individuals and patients with CKD have a similar plasma albumin degradation rate (26), it would be surprising if malnutrition was the main factor influencing serum albumin in CKD. Indeed, patients with CKD commonly have comorbid conditions, fluid overload, and low-grade inflammation, all of which are known to affect serum albumin concentrations (27).

Supporting this interpretation, our study did not reveal strong association between nutritional status and serum albumin in incident or prevalent dialysis patients. Whereas serum albumin was a weak predictor of nutritional status defined by SGA score, associations between serum albumin and other markers of nutritional status, such as handgrip strength and LBM, were even weaker. Our data showing this clear lack of value of serum albumin as a predictor of nutritional status (Figure 3, A and B) correspond to and extend previous results reported by us (28) and others (29) showing that serum albumin is a poor predictor of nutritional status in dialysis patients. The current results support views expressed by
Friedman and Fadem (4) that there is a “rationale for reconsidering albumin as a marker of illness rather than nutrition.”

In the current study, the lack of predictive power of nutritional status by serum albumin levels among the incident dialysis patients may be partly explained by the strong negative correlations between serum albumin with urinary albumin losses, and with hsCRP. Inflammation, usually assessed with hsCRP in patients with CKD, is well described as associated with PEW (9,17), and there are also putative causal pathways linking low serum albumin and inflammation (20). Indeed, studies (1,24) have shown that inflammation is consistently associated with low levels of serum albumin in uremia. Although our findings underline the limited value of serum albumin as a predictor of nutritional status in incident and prevalent dialysis patients, they also underscore the massive importance of urinary albumin loss for circulating albumin levels in incident dialysis patients with residual renal function. This may be of more general importance, as Warnaock et al. (30) found that increased albuminuria is an independent risk factor for all-cause mortality in a prospective observational study consisting of 17,393 healthy participants.

Our study has many limitations. First, patients in the prevalent dialysis group were older than the incident dialysis patients, which probably explains differences in hsCRP and handgrip strength. Second, the study design by its nature precludes inferring causalities. Third, residual renal function and urinary albumin were not evaluated in prevalent dialysis patients; however, most of them were anuric. Fourth, the prevalent dialysis patients were included from different biomedical cohorts. Fifth, although overhydration may influence some of our findings, we did not include a marker of fluid status. Finally, although our findings did not support the value of serum albumin as a marker of nutritional status, we did not assess serum albumin as a marker of PEW; this, from a conceptual aspect, could be questionable considering that a low serum albumin level is a readily usable criterion for PEW classification.

In summary, among incident and prevalent dialysis patients, serum albumin correlates poorly with several markers of nutritional status; thus, its value as a reliable marker of nutritional status in patients with ESRD is limited.

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Disclosures
B.L. is employed by Baxter Healthcare Corporation. P.S. is a member of the scientific advisory board of Gambro AB. None of the other authors declare any conflicts of interest.

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