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One Year Serum Albumin is an Independent Predictor of Outcomes in Kidney Transplant Recipients

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Abstract

Objective—This research study was conducted to investigate whether serum albumin levels predict allograft/patient outcomes in the new era of transplant medicine and immunology.

Methods—The association of 1-year post transplant serum albumin and patient and graft outcomes was retrospectively analyzed in 500 kidney transplant recipients between 1998 and 2005. Albumin was used as a categorical and a continuous variable in univariate and multivariate Cox regression and Kaplan-Meier survival analyses.

Results—The average ($\pm$ SE) age at transplant was 47 ± 12 years. Patients were followed for 63.4 ± 28 months after transplant. There were 56 graft losses and 38 patient deaths. In univariate analysis, the following variables were associated with the composite endpoint of patient death or allograft loss: one-year serum albumin (HR 0.52, $p=0.0009$), one-year serum albumin < 4.0 g/dL (HR 1.81, $p=0.02$), one-year serum creatinine (HR 3.55, $p<0.00001$), ACE-I/ARB use (HR 1.61, $p=0.03$), a history of previous transplant (HR 1.54, $p=0.04$), months of dialysis before transplant (HR 1.01, $p=0.00003$), type of transplant (deceased donor HR 1.64, $p=0.02$) and acute rejection (HR 1.52, $p=0.0000003$). Of these, multivariable Cox regression analyses retained one-year serum albumin (HR 1.4, $p<0.0001$), serum creatinine (HR 2.7, $p<0.0001$) and acute rejection (HR 1.7, $p=0.02$) as significant predictors of patient/graft loss.

Conclusion—One-year serum albumin is an independent predictor of poor outcomes in the contemporary era of transplant medicine and immunosuppression. Further studies are needed to separate the role of this biomarker in inflammation and nutrition in kidney transplant recipients.

Keywords

albumin; kidney transplant; outcomes

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Introduction

Hypoalbuminemia has been associated with increased mortality in patients with acute illness as well as in the general population (1,2). Albumin is a serum protein that is synthesized in the liver, and its serum levels are regulated by synthesis and degradation. Degradation occurs throughout all tissues, but predominantly occurs in muscle, liver and kidneys (3). Albumin is thought to be a biomarker of both inflammation and nutritional status. In the CHOICE study, Parekh et al found hypoalbuminemia was a marker of inflammation and malnutrition in end stage renal disease (ESRD) patients (4). Those with the highest high sensitivity c-reactive protein (hsCRP) and the lowest serum albumin were four times more likely to have a sudden cardiac death event compared to those with the lowest hsCRP and highest serum albumin.

Inflammation may lead to hypoalbuminemia via decreased production, consumption and loss into the tissues through capillary leak (5). Lower serum albumin levels are frequently noted in the setting of acute illness and chronic inflammation (6). Notably, hypoalbuminemia is a predictor of poor outcomes in patients with chronic kidney disease (CKD) and ESRD (7-9). Furthermore, two studies from the nineties showed that serum albumin levels followed a bimodal pattern after transplantation and correlated with outcomes (10,11). Serum levels of albumin levels were lowest at three months and highest at one year post-transplant (10,11). However, with the advent of KDOQI and KDIGO clinical practice guidelines and recommendations standards of care have changed in the last five to ten years. Furthermore, novel induction and maintenance immunosuppressive protocols have changed the platform of immunosuppression after transplantation. We hypothesized that despite these modifications in care delivery, hypoalbuminemia remains an important negative predictor of outcomes in kidney and kidney pancreas transplant recipients. We tested this hypothesis by examining the effects of low serum albumin at one year on long-term outcomes in the contemporary era of transplant medicine and immunology.

Methods

Patients

To address this question adult kidney and kidney-pancreas transplant recipients from the University of Wisconsin who were transplanted between 1998 and 2005 were retrospectively analyzed. Recipients were selected if (1) they were 18 years or older, (2) the patient and graft (s) survived to one year and (3) a serum albumin was available at 1-year post transplant. We examined the effects of serum albumin as a continuous variable and as a categorical variable on patient and graft outcomes using correlation and logistic regression analyses; univariate and multivariate Cox regression analyses and Kaplan-Meier survival analyses.

Data Collection

Clinical information and laboratory data was collected at the time of transplantation, at one year after transplantation and at outcome. The data collected included age, gender, race, body mass index (BMI), cause of end-stage renal disease (ESRD) including diabetes mellitus (DM) type 1, DM type 2, hypertension (HTN), glomerular disease (GD), polycystic kidney disease (PKD) or other causes of ESRD, type of transplant: kidney-pancreas (KP), living donor kidney transplant (LDKT) or deceased donor kidney transplant (DDKT), acute rejection, retransplant status, length of pre-transplant dialysis, serum albumin at 1 year, MAP at 1 year and last visit, serum creatinine (Scr) at 1 year and last visit, urine protein to creatinine ratio (UPC) at 1 year and last visit and abbreviated MDRD estimated glomerular filtration rate (eGFR) (12) at 1 year and last visit. Records of induction immunosuppression (alemtuzumab, basiliximab, antithymocyte globulin, rituximab), immunosuppression at one year post-transplant including cyclosporine (CSA), tacrolimus (TAC), sirolimus (SRL), prednisone, mycophenolic acid

(MPA), azathioprine (AZA) and treatment of rejection were reviewed. Data on the use of statins, beta blockers and angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) at one year post transplant was collected. Data on glycosylated hemoglobin (Hgb A1C) and low density lipoprotein (LDL) cholesterol were collected at one year.

Measurement of serum albumin

Serum albumin levels were determined at the UWHC biochemistry core laboratories. Between 1998 and June 2000 the laboratory used a Roche Hitachi 747 with a Dade Dimension analyzer and the bromocresol purple method. Since July 2000 the analyzer has been changed to a Roche Modular System and the method to bromocresol green. The reference interval for adults is 3.9-5.0 mg/dL.

Statistical Analyses

Primary outcome was ESRD (death censored), death or the composite endpoint of death or ESRD. Patient survival was defined as time from transplantation to death or last follow-up. Graft loss was defined as initiation of dialysis or retransplantation. Correlation and logistic regression analyses were used to evaluate the association between 1-year serum albumin and outcomes. Univariate Cox regression analyses were performed to determine independent covariates affecting outcomes. These covariates included age, gender, race, BMI, cause of ESRD, type of transplant, times re-transplanted, length of pre-transplant dialysis, biochemical characteristics including Scr, UPC, Hgb A1C, LDL cholesterol, albumin, immunosuppressive regimen (induction and maintenance), use of statins, beta blockers and ACE-I or ARB at 1 year. Statistically significant variables were then entered into stepwise multivariable Cox regression analyses. Graft and patient survival rates were also modeled using Kaplan-Meier survival curves. Data analysis was performed using Microsoft Excel 2003, version 11.8012.6568 and MedCalc, version 9.3.0.0. A p-value of ≤ 0.05 was considered significant. All analyses were performed with the approval of the UW Hospital and Clinics Institutional Review Board.

Results

Baseline characteristics

Five hundred of the 1401 kidney and kidney pancreas transplants performed between 1998 and 2005 had available serum albumin levels at one year and were included in the analysis. The average time ($\pm$ SE) between transplant and last follow up was 63.4 ± 28 months. Table 1 represents the baseline characteristics of these patients. The average age was 47 ± 12 years. The majority was male (58%) and Caucasian (92%). The most common causes of ESRD included DM 1 (26%), GD (25%) and PKD (12%). The average length of time on dialysis was 18 ± 25 months, 14% of the patients were re-transplants and 25% were treated for 1 or more episodes of rejection. The majority of patients (49%) had received a DDKT. Basiliximab induction was most common (50%) followed by alemtuzumab (30%). Table 2 demonstrates the characteristics at one year. The average Scr at 1 year was 1.5 ± 0.5 mg/dL, with an average eGFR 52 ± 16 mL/min/1.73 m² and UPC 0.4 ± 0.9 g/g. Immunosuppression primarily consisted of prednisone (95%), MPA (88%) and calcineurin inhibitors (CSA 44% and TAC 42%) with only 9 % receiving SRL and 2% receiving AZA. Beta blocker and statin use were common, with 70% and 51% use respectively. Only 24% received an ACE-I or ARB. The average MAP at one year was $97 (\pm 13)$ mmHg.

Kidney function, albumin and outcomes

There were 52 graft losses (death censored) and 38 patient deaths. Causes of death included cardiovascular disease (11%), malignancies (21%), infection (16%) or unknown (25%). Spearman's Correlation analysis revealed a significant association between 1 year serum albumin < 4.0 and ESRD (Rho -0.17, 95% CI -0.27 to -0.7), death (Rho -0.16, 95% CI -0.16 to -0.6) and ESRD/death combined (Rho -0.25, 95% CI -0.3 to -0.15). Logistic regression analysis also confirmed the association between 1 year serum albumin < 4.0 and ESRD (OR 2, 95% CI 1.08-4), Death (OR 3.2, 95% CI 1.4-7.1) and ESRD/death (OR 2.8, 95% CI 1.6-4.7). We performed univariate regression analysis to determine factors associated with graft loss or death (Table 3). All variables from tables 1 and 2 were included. Albumin at 1 year was used both as a continuous variable and categorical variable with the cutoff of 4 g/dL. This value was chosen as it was the close to the mean, 4.0 (SD $\pm$ 0.02), in our population (Figure 1). These analyses showed that serum albumin at 1 year, serum albumin < 4.0 g/dL, Scr 1 year, ACE-I/ARB use at 1 year, acute rejection, DDKT, duration of pre-transplant dialysis and times re-transplanted were significantly associated with the combined endpoint of graft loss/patient death. The variables that remained significant in the multivariate analysis were serum albumin at 1 year (HR 1.7, 95% CI 1.07-2.79), Scr (HR 2.7, 95% CI 1.82-4.05) and acute rejection (HR 1.4, 95% CI 1.2-1.7).

To further evaluate the relationship of serum albumin with these variables, outcomes in patients with serum albumin < 4.0 g/dL were compared to those with a serum albumin $\geq$ 4.0 g/dL by combining Kaplan-Meier and Cox regression analyses (survival time from transplantation to outcome) and adjusting for acute rejection, 1 year Scr, transplant type, age, gender, ethnicity and CNI use (Figure 2). These studies confirmed that the composite endpoint of graft loss or patient death was significantly greater in patients with a serum albumin < 4.0 g/dL.

Discussion

Findings demonstrate a strong association between 1-year serum albumin levels and patient/graft survival in the contemporary era of transplant medicine and immunosuppression. The half-life of serum albumin is 20 days; hence it is readily impacted upon by inflammation and nutrition (5). Because renal transplant recipients are more prone to medical and surgical complications in the first year, the relationship between serum albumin and long-term outcomes after this time interval were evaluated. Patients are indeed considered more medically stable at this point (13-15). Notably, average serum albumin levels are the highest at twelve months post transplant confirming the near return to healthy and steady conditions (10,11).

Findings are consistent with previous reports (10,11). Guijarro et al found that serum albumin was an independent risk factor for death with each change in albumin by 1 g/dL (RR 0.26, 95% CI 0.16-0.44) among kidney transplants performed between 1976 and 1991 (10). They also found that hypoalbuminemia, defined as $\leq$ 3.5, was associated with reduced renal function. Of note, renal function was correlated with number of acute rejection episodes, but it does not appear that the number of acute rejections was independently associated with hypoalbuminemia. While populations were similar to in age, male gender and caucasian ethnicity predominance, the present study addressed a contemporary group of kidney transplant recipients with higher rates of LDKT (34% vs. 11.2%) and use of modern immunosuppressive therapy including induction therapy with antithymocyte globulin (ATG), rituximab, alemtuzumab and basiliximab as well as maintenance therapy at one year with MPA, CNIs and prednisone compared to azathioprine and prednisone alone.

Another study evaluated patient and graft outcomes in 232 kidney-pancreas transplant recipients from 1993 to 1997 (11). The study population was 91% Caucasian and had a mean age of 37.4 ($\pm$ 5.9) years. Induction was primarily with muromonab CD3 (OKT3) through 1996

followed by ATG. Maintenance immunosuppression was primarily based on Cyclosporine and Azathioprine which was replaced by MPA in the latter part of the study. The authors found that hypoalbuminemia defined as albumin ≤ 3.5 was associated with cytomegalovirus infection (RR 2.5, $p < 0.02$) and pancreas and kidney graft failure (RR 3.66, $p < 0.01$ and RR 2.41, $p < 0.05$, respectively). There was no statistically significant association between hypoalbuminemia and death rates, which may have been attributable to a smaller patient population ($N=232$) and shorter follow up (2.0 ± 1.3 years).

This study is limited by its single center retrospective nature. Due to its retrospective nature this analysis did not include c-reactive protein as a biomarker of inflammation as it is not routinely measured in the transplant population at this center. Also, the association of patient/graft outcomes with one-year serum albumin alone was without comparison to levels at other time points. These findings do add to the existing literature by demonstrating that a serum albumin of $< 4.0\text{g/dL}$ measured at one time point, one year, is associated with worsened outcomes. And this raises the question of whether improving nutrition status and reducing inflammation by the first year will lead to improved outcomes. It is interesting that changes in BMI within the first year did not correlate with serum albumin at one year and outcomes. This likely indicates the complex relationship between nutrition, inflammation and patient/graft outcomes in this population. It is also important to further define the role of albumin as a marker of outcomes in kidney transplant recipients. More specifically, does it work as a nutritional marker or as a marker of inflammation? This distinction is important as the interventions would likely be different. Prospective studies are needed to further evaluate and validate the results of this study. As this relationship is further elucidated, prospective, randomized trial could be performed to evaluate interventions, whether anti-inflammatory or nutritional in nature, on serum albumin and outcomes on graft and patient survival in kidney transplant recipients.

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References

1. Hermann FR, Safran C, Levkoff SE, et al. Serum Albumin Level on Admission as a Predictor of Death, Length of Stay, and Readmission. *Archives of Intern Medicine* 1992;152:125–130.
2. Philips A, Shaper AG, Whincup PH. Association between serum albumin and mortality from cardiovascular disease, cancer and other causes. *Lancet* 1989;2:1434–1436. [PubMed: 2574367]
3. Quinlan GJ, Martin GF, Evans TW. Albumin - Biochemical Properties and Therapeutic Potential. *Hepatology* 2005;41:1211–1219. [PubMed: 15915465]
4. Parekh RS, Plantinga LC, Kao WHL, et al. The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney International* 2008;74:1335–1342. [PubMed: 18769368]
5. Franch-Arcas G. The meaning of hypoalbuminaemia in clinical practice. *Clinical Nutrition* 2001;20:265–269. [PubMed: 11407875]
6. Kaysen GA, Chertow GM, Adhikarla R, et al. Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. *Kidney International* 2004;65:1408–1415. [PubMed: 15086482]
7. Menon V, Greene T, Wang X, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney International* 2005;68:766–772. [PubMed: 16014054]
8. Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. *Kidney International* 1993;44:115–119. [PubMed: 8355451]
9. Ayus JF, Achinger SG. At the peril of dialysis patients: ignoring the failed transplant. *Seminars in Dialysis* 2005;18:180–184. [PubMed: 15934958]

10. Guijarro C, Massy ZA, Wiederkehr MR, et al. Serum Albumin and Mortality After Renal Transplantation. *American Journal of Kidney Diseases* 1996;24:117–123. [PubMed: 8546125]
11. Becker BN, Becker YT, Heisey DM, et al. The impact of hypoalbuminemia in kidney-pancreas transplant recipients. *Transplantation* 1999;68:72–75. [PubMed: 10428270]
12. Levy AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of Internal Medicine* 2006;145:247–254. [PubMed: 16908915]
13. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of Mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *New England Journal of Medicine* 1999;341:1725–30. [PubMed: 10580071]
14. Djamali A, Kendzierski C, Brazy PC, et al. Disease progression and outcomes in chronic kidney disease and renal transplantation. *Kidney International* 2003;64:180–1807.
15. Kukla A, Adulla M, Pascual J, et al. CKD stage-to-stage progression in native and transplant kidney disease. *Nephrology Dialysis Transplant* 2008;23:693–700.

Figure 1. Relative Distribution of serum Albumin at 1 year

Relative frequency of serum albumin levels at one year post transplant in 500 kidney transplant recipients. The distribution was not Normal (Median = 4g/dL).

Figure 2. Kaplan-Meier for post transplant serum albumin

Kaplan-Meier survival analyses demonstrating the probability of patient or graft loss based on Median serum albumin levels (4 g/dL) in the patient population. Data was adjusted for age, gender, ethnicity, transplant type, use of calcineurin inhibitors, acute rejection and one year serum creatinine.

Table 1

Baseline characteristics

Characteristic	N
Female Gender (%)	209 ($\pm$ 42)
Age at time of transplant in years (SD)	47 ($\pm$ 12)
BMI* at transplant (SD)	26.80 ($\pm$ 5.1)
Pre-transplant time on dialysis in months (SD)	18 ($\pm$ 25)
Cause of ESRD** (%)	
Diabetes Mellitus Type 1	130 (26)
Glomerular Disease	125 (25)
Polycystic Kidney Disease	60 (12)
Diabetes Mellitus Type 2	52 (10)
Hypertension	41 (8)
Other	96 (19)
Type of transplant (%)	
Deceased Donor Kidney	245 (49)
Living Related Donor Kidney	171 (34)
Simultaneous Kidney-Pancreas	84 (17)
Number re-transplanted (%)	68 (14)
Number treated for acute rejection (%)	127 (25)
Induction agent (%)	
Basiliximab	250 (50)
Alemtuzumab	157 (31)
Anti-thymocyte globulin	51 (10)

* BMI = Body mass index

** ESRD = end stage renal disease

Table 2

Characteristics at one year

Characteristic	N
Serum creatinine (mg/dL) (SD)	1.5 ($\pm$ 0.5)
eGFR (ml/min/1.73m ²) (SD)	52 ($\pm$ 16)
Protein to creatinine ratio (g/g) (SD)	0.4 ($\pm$ 0.9)
Mean arterial pressure (mmHg) (SD)	97 ($\pm$ 13)
Maintenance immunosuppression (%)	
Prednisone	474 (95)
Mycophenolic acid	442 (88)
Azathioprine	9 (2)
Cyclosporine	218 (44)
Tacrolimus	209 (42)
Sirolimus	43 (9)
Beta-blocker (%)	348 (70)
ACE-I/ARB* (%)	212 (24)
HMG-CoA reductase inhibitors (%)	256 (51)

* ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 3

Stepwise Cox regression analyses for graft loss or death

Covariate	Univariate			Multivariate		
	P	HR	95% CI	P	HR	95% CI
ACE/ARB* 1 yr	0.03	1.61	1.04 to 2.51	-	-	-
Albumin 1 yr	0.0009	0.52	0.36 to 0.77	0.02	1.7	1.07 to 2.79
Albumin 1 yr < 4.0 g/dL	0.02	1.81	1.12 to 2.92	-	-	-
Acute Rejection	0.0000003	1.52	1.3 to 1.78	<0.0001	1.4	1.2 to 1.7
DDKT**	0.02	1.64	1.08 to 2.51	-	-	-
Time on dialysis (mo)	0.00003	1.01	1.01 to 1.02	-	-	-
Scr*** 1 yr (mg/dL)	<0.00001	3.55	2.47 to 5.1	<0.0001	2.7	1.82 to 4.05
Retransplant	0.04	1.54	1.03 to 2.31	-	-	-

* ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

** DDKT = deceased donor kidney transplant

*** Scr = serum creatinine