Hypoalbuminemia, Cardiac Morbidity, and Mortality in End-Stage Renal Disease[1,2]

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ABSTRACT

A cohort of 432 ESRD (261 hemodialysis and 171 peritoneal dialysis) patients was followed up prospectively for an average of 41 months. Baseline and annual demographic, clinical, and echocardiographic assessments were performed, as well as serial clinical and laboratory tests measured monthly while patients were on dialysis therapy. Among hemodialysis patients, after adjustment was made for age, diabetes, and ischemic heart disease, as well as hemoglobin and blood pressure levels measured serially, a 10-g/L fall in mean serum albumin level was independently associated with the the development of *de novo* (relative risk (RR), 2.22; $P = 0.001$) and recurrent cardiac failure (RR, 3.84; $P = 0.003$), *de novo* (RR, 5.29; $P = 0.001$) and recurrent ischemic heart disease (RR, 4.24; $P = 0.005$), cardiac mortality (RR, 5.60; $P = 0.001$), and overall mortality (RR, 4.33; $P < 0.001$). Among peritoneal dialysis patients, a 10-g/L fall in mean serum albumin level was independently associated with the progression of left ventricular dilation as seen on follow-up echocardiography (β, 13.4 mL/m^2; $P = 0.014$), the development of *de novo* cardiac failure (RR, 4.16; $P = 0.003$), and overall mortality (RR, 2.06; $P < 0.001$). Hypoalbuminemia, a major adverse prognostic factor in dialysis patients, is strongly associated with cardiac disease.

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Dialysis patients have an age-adjusted death rate that is estimated to be four to five times that of the general population (1). A considerable proportion of this excess mortality can be explained by the high baseline prevalence of nonrenal comorbid conditions, such as diabetes mellitus and cardiovascular disease, among patients starting ESRD therapy (2–6). In recent years, there has been a growing realization that factors associated with chronic uremia, which are unrelated to baseline comorbid illnesses, may be causes, or markers, of poor outcome in dialysis patients (7–15). In particular, hypoalbuminemia, probably a reflection of malnutrition, has emerged as a very strong predictor of early demise in chronic dialysis patients (7–10).

Malnutrition is common in ESRD patients (16–19). It is unclear how malnutrition ultimately leads to death in these patients. Common sense alone would suggest that the major risk factor for death (hypoalbuminemia) and the largest cause of death (cardiac disease) in these patients might be connected. We recently completed a prospective study of a cohort of 433 patients followed up from the initiation of ESRD therapy for periods of up to 10 yr (20,21). In this article, we report a strong association between hypoalbuminemia, cardiac morbidity, and mortality in ESRD patients.

METHODS

Patients

This prospective cohort study was initiated in the Royal Victoria Hospital, Montreal, Quebec, in 1982, in the Health Sciences Centre, St John's, Newfoundland, in 1984, and in the Grace Hospital, St. John's, Newfoundland, in 1985. Patients were eligible for entry to the study if (*1*) they survived for 6 months, and (2) if they had a technically satisfactory echocardiogram within a year of starting renal replacement therapy. Patient recruitment ended in June 1991. The mean patient follow-up period was 41 months.

Of the 518 patients who survived at least 6 months from the start of ESRD therapy, a cohort of 433 (83.6% of those eligible) entered the study. One study patient was treated only with renal transplantation. Eighty-five patients were excluded for the following reasons: failure to obtain a technically adequate echocardiogram within 1 yr of starting therapy (71 patients), initiation of therapy elsewhere (seven patients), misplaced charts (five patients), or refusal to participate (two patients).

Data Collection

At baseline and at yearly intervals thereafter, a clinical assessment was undertaken to detect the presence of cardio-

vascular disease. The data collected at monthly intervals included blood pressure, hemoglobin and serum albumin levels, and interdialytic weight gain in hemodialysis patients. Blood pressure and blood tests were carried out immediately before dialysis in hemodialysis patients. In patients with patent arteriovenous fistulae or grafts, blood pressure levels were measured in the contralateral arm while the patient was in a seated position. The blood pressure and bloodwork recorded were single values taken at the start of each month. At yearly intervals, all changes related to renal replacement therapy, blood transfusions, use of recombinant human erythropoietin, antihypertensive and cardiac medication use, admissions to hospital, and autopsy notes were recorded. Baseline and annual echocardiography were performed using M-mode and two-dimensional ultrasonography. Left ventricular (LV) mass index was calculated according to the Penn convention (22). LV cavity volume was calculated by the formula of Pombo *et al.* (23) The initial echocardiogram was performed (mean ± SD) 3 ± 4 months (median, 0 months) after the initiation of ESRD therapy. Two hundred ninety-eight patients remained alive or untransplanted in the study at 1 year. Two hundred seventy-five patients had a repeat echocardiogram at a median interval of 13 months after the initial study. This patient subset was almost identical to the parent group of 433 patients, with no statistically significant differences in terms of baseline clinical and echocardiographic parameters (Table 1)

TABLE 1. Patient characteristics: All patients (N = 432), and patients who had serial echocardiograms (N = 275)[a]

Data	All Patients	Patients with Serial Echocardiograms[b]
Baseline Data		
Age (yr)	51 ± 17	54 ± 15
Male/Female (%)	64/36	63/37
Diabetes Mellitus (%)	27	27
Renal Disease (%):		
Glomerulonephritis	31	30
Diabetic nephropathy	20	18
Tubulointerstitial	11	12
Genetic	7	8
Nephrosclerosis	7	8
Other	18	19
Unknown	7	7
Hypertension >10 yr (%)	29	32
Ischemic Heart Disease (%)	22	25
Cardiac Failure (%)	31	33
Baseline Echocardiogram (%):		
Normal left ventricle	15	13
Concentric LV hypertrophy	39	42
LV dilation	27	27
Systolic dysfunction	18	18
Serial Data		
Mean Arterial BP (mm Hg)	101 ± 11	101 ± 11
Serum Albumin (g/L)	37 ± 5	37 ± 5
Hemoglobin (g/L)	89 ± 15	90 ± 16

[a] Continuous variables are expressed as mean ± SD. Column totals may not equal 100% because of rounding error. LV, left ventricular; BP, blood pressure.
[b] There were no statistically significant differences between the two groups.

Definitions

Mean arterial blood pressure: diastolic blood pressure + 1/3(systolic blood pressure −diastolic blood pressure).

Coronary artery disease: previous history of myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal angioplasty.

Angina pectoris: precordial chest pain, precipitated by exertion or stress and relieved by rest or nitrate therapy.

Ischemic heart disease: coronary artery disease or angina pectoris.

Cardiac failure: dyspnea in addition to two of the following conditions— raised jugular venous pressure, bibasalar crackles, pulmonary venous hypertension, or interstitial edema on chest X-ray, requiring hospitalization or extra ultrafiltration.

De novo cardiac failure: cardiac failure while on dialysis therapy in a patient without a history of cardiac failure at baseline.

Recurrent cardiac failure: cardiac failure while on dialysis therapy in a patient with a history of cardiac failure at baseline.

De novo ischemic heart disease: admission for ischemic heart disease while on dialysis therapy in a patient without a history of ischemic heart disease at baseline.

Recurrent ischemic heart disease: admission for ischemic heart disease while on dialysis therapy in a patient with a history of ischemic heart disease at baseline.

Echocardiographic systolic dysfunction: fractional shortening ≤25%.

LV dilation: LV cavity volume >90 mL/m^2 (23), no systolic dysfunction.

LV hypertrophy: LV mass index >131 g/m^2 in males, >100 g/m^2 in women (24).

Concentric LV hypertrophy: LV hypertrophy with normal cavity volume (25), and no systolic dysfunction.

Normal left ventricle: absence of hypertrophy, dilation, and systolic dysfunction.

Predominant mode of dialysis therapy: >50% of total dialysis time on a particular mode of dialysis (peritoneal dialysis or hemodialysis).

Cardiac death: cause of death recorded as "myocardial infarction," "sudden death," or "other cardiac cause".

Analysis

Normally distributed continuous variables were compared using t tests or analysis of variance. Categorical variables were compared using chi-squared analysis. All statistical tests are two-tailed with a P value less than 0.05 indicating statistical significance. All multivariate analyses incorporated a stepping procedure, and were performed using BMDP software (26).

Echocardiographic Outcomes. Mean serum albumin, hemoglobin, and mean arterial blood pressure levels were calculated from the monthly values measured between the first and second echocardiogram. The association between the mean serum albumin level observed during this time interval and the progression of concentric LV hypertrophy was determined by using multiple linear regression. In this

model, the change in LV mass between the first and second echocardiogram was the dependent variable. The analysis of factors related to the progression of concentric LV hypertrophy was confined to subjects with concentric LV hypertrophy at baseline, and used the following model: Δmass index(g/m^2) = constant + β_1Age(yr) + β_2Diabetes(0/1) + β_3Ischemic heart disease(0/1) + β_4Mean arterial blood pressure(mm Hg) + β_5Mean hemoglobin(g/L) + β_6Mean serum albumin(g/L). The indicators 0 and 1 code for "no" and "yes," respectively. To assess the association between mean serum albumin levels and the progression of LV dilation, the change in cavity volume was the dependent variable, in subjects with LV dilation on baseline echocardiography, using otherwise identical covariates. A similar analytic strategy, in which the change in fractional shortening was the dependent variable, was used to assess the association between hypoalbuminemia and the progression of systolic dysfunction. There were too few subjects with normal left ventricles on baseline echocardiography to assess the association between hypoalbuminemia and the development of abnormalities in initially normal left ventricles.

Clinical Outcomes. The clinical outcomes studied were time to ischemic heart disease, cardiac failure, death, cardiac death, and noncardiac death. Transplantation or reaching final follow-up were censoring events for mortality analyses. Transplantation, reaching final follow-up, and death were censoring events for the other clinical events. The association between serum albumin level and these clinical outcomes was assessed by Cox regression analysis using four different models:

In Model I, baseline serum albumin, hemoglobin, and mean arterial blood pressure levels were used as covariates, as well as age, the presence or absence of ischemic heart disease, and diabetes mellitus at baseline. All study patients were included in Model I.

Model II used only patients with baseline and follow-up echocardiograms; serum albumin, hemoglobin, and mean arterial blood pressure levels were averaged between the first and second echocardiogram. These data were then used to predict the clinical outcomes that developed after the second echocardiogram.

In Model III, serum albumin, hemoglobin, and mean arterial blood pressure levels were averaged up to the development of the clinical outcome of interest. For example, for the ischemic heart disease outcome, the first 12 monthly serum albumin measurements (and hemoglobin and blood pressure levels) would be averaged for a subject who developed ischemic heart disease after 1 yr. For a subject who never developed ischemic heart disease during 25 months of follow-up, the values entered would be those obtained from averaging the first 25 monthly serum albumin, hemoglobin, and blood pressure levels. All study patients were included in Model III.

In Model IV, time-dependent means were used. These were obtained by multiplying the mean values obtained in Model III by the natural logarithm of the duration of time to the event or final follow-up. Such a procedure controls for the natural variation with time of covariates like mean serum albumin, hemoglobin, and mean arterial blood pressure (27). All study patients were included in Model IV.

RESULTS

Patient Characteristics

The clinical and demographic characteristics of the patient cohort at the time of patient entry are shown in Table 1. The cohort was almost entirely Caucasian. Subjects who had a follow-up echocardiogram were almost identical to the parent group. Hemodialysis and peritoneal dialysis were the predominant mode of dialysis therapy in 60.5% and 39.5% of subjects, respectively. Compared with hemodialysis patients (Table 2), peritoneal dialysis patients were more likely ($P < 0.05$) to be female, diabetic, have ischemic heart disease and cardiac failure at baseline, to be less anemic, and to have low mean serum albumin levels while on dialysis therapy.

Patients were divided into four groups of approximately similar size according to the time period in which dialysis therapy was initiated: 1982 to 1984 (20.3%), 1985 to 1986 (17.3%), 1987 to 1988 (27.5%), and 1989 to 1991 (34.9%). There were no differences in mean serum albumin level (36.9 ± 4.1, 37.5 ± 4.1, 36.7 ± 5.0, and 36.9 ± 4.5 g/L, respectively; $P = 0.69$) according to time period of entry into the study. Similarly, there was no relationship between the mean serum albumin level and the time spent on dialysis therapy: the mean serum albumin level was 37.1 ± 4.6 in those who spent ≤1 yr on dialysis ($N = 104$), 36.8 ± 4.2 g/L in those who spent 1 to ≤2 yr on dialysis ($N = 127$), 36.1 ± 5.1 g/L in those who spent 2 to ≤3 yr on dialysis ($N = 75$), and 37.5 ± 4.3 g/L in those who spent >3 yr on dialysis ($N = 119$, $P = 0.21$). The latter analysis suggests that mean serum albumin levels did not vary directly as a function of time spent on dialysis therapy.

One third of patients had mean serum albumin levels less than 36.0 g/L, one third between 36.0 g/L and 39.0 g/L, and one third had levels greater than 39.0 g/L. The characteristics of patients in the different tertiles of mean serum albumin are shown in Table 3. Patients with lower albumin levels while on dialysis therapy had adverse prognostic features at baseline—older age ($P = 0.0002$), diabetes ($P = 0.0005$), ischemic heart disease ($P = 0.02$), and more LV dilation ($P = 0.03$).

Outcomes

Echocardiographic and clinical outcomes are shown in Table 4. Two hundred fifty-nine subjects had evaluable serial echocardiograms. On follow-up echocardiography, the mean LV mass index was 171 ± 58 g/m^2, cavity volume 91 ± 43 mL/m^2, and fractional shortening 31 ± 9%. Only 35 had normal left ventricles on follow-up. Concentric hypertrophy was present in 39.4%, LV dilation in 25.1%, and systolic dysfunction in 22%. A total of 143 of 432 (33%) patients developed cardiac failure during the study, of which 50.3% were *de novo* episodes. A total of 86 patients were admitted because of ischemic heart disease, of which 44% were *de novo* episodes. The overall median survival time for the patient cohort was 50 months. There were 137 deaths while on dialysis therapy, attributed to the following causes: myocardial infarction, 9.5%; sudden

TABLE 2. Comparison of hemodialysis (N = 261) and peritoneal dialysis patients (N = 171)[a]

Data	Hemodialysis	PD	P
Baseline Data			
Age (yr)	51 ± 19	51 ± 16	0.95
Male/Female (%)	68/32	59/41	0.052
Diabetes Mellitus (%)	23	33	0.018
Renal Disease (%):			
Glomerulonephritis	29	35	
Diabetic nephropathy	16	26	
Tubulointerstitial	12	9	
Genetic	10	3	
Nephrosclerosis	6	7	
Other	20	14	
Unknown	7	6	
Hypertension >10 yr (%)	29	21	0.064
Ischemic Heart Disease (%)	19	27	0.043
Cardiac Failure (%)	26	39	0.003
Baseline Echocardiogram (%):			
Normal left ventricle	16	15	Reference
Concentric LV hypertrophy	41	39	0.90
LV dilation	29	27	0.84
Systolic dysfunction	14	18	0.37
Serial Data			
Mean Arterial BP (mm Hg)	102 ± 11	101 ± 11	0.35
Serum Albumin (g/L)	39 ± 4	35 ± 5	<0.0001
Hemoglobin (g/L)	84 ± 14	96 ± 15	<0.0001

[a] Continuous variables are expressed as mean ± SD. Column totals may not equal 100% because of rounding error. PD, peritoneal dialysis; LV, left ventricular.

TABLE 3. Patient characteristics according to tertile of mean serum albumin level[a]

Data	≤36 g/L	36 to 39 g/L	>39 g/L	P for Trend
Baseline Data				
Age (yr)	54 ± 17	53 ± 16	46 ± 16	0.0002
Male/Female (%)	57/41	69/31	68/32	0.10
Diabetic (%)	34	27	14	0.0005
Hypertension >10 yr (%)	30	31	26	0.64
Ischemic Heart Disease (%)	26	25	13	0.02
Cardiac Failure (%)	34	35	22	0.06
Baseline Echocardiogram (%):				
Normal	13	13	22	Reference category
Concentric LVH	42	40	40	0.18
LV dilation	29	35	22	0.03
Systolic dysfunction	17	13	16	0.35
Serial Data				
Hemoglobin (g/L)	89 ± 17	88 ± 14	89 ± 15	0.91
MAP (mm Hg)	100 ± 11	101 ± 11	102 ± 10	0.19

[a] Continuous variables are expressed as mean ± SD. Column totals may not equal 100% because of rounding error. LVH, left ventricular hypertrophy; LV, left ventricular; MAP, mean arterial blood pressure.

death, 27.0%; other cardiac cause, 12.4%; other vascular cause, 10.2%; infection, 13.9%; withdrawal of dialysis, 12.4%; and other causes, 14.6%. The causes of death were similar in patients with mean serum albumin levels ≤36 g/L, 36 to 39 g/L, and >39 g/L (data not shown).

Prognostic Associations of Serum Albumin Level

Total Group. On bivariate analysis (Table 4), low mean serum albumin levels while on dialysis therapy were associated with *de novo* cardiac failure ($P = 0.005$), *de novo* ischemic heart disease ($P = 0.009$), overall mortality ($P < 0.0001$), cardiac mortality ($P = 0.0003$), and noncardiac mortality ($P < 0.0001$) while on dialysis therapy.

Using multiple linear regression (Table 5), low mean serum albumin levels were associated with the progression of LV dilation between baseline and follow-up echocardiography ($\beta = 11.6$ mL/m^2 per 10 g/L fall in mean serum albumin level, $P = 0.037$), independently of age, diabetes mellitus, and ischemic heart disease at baseline, as well as mean hemoglobin and mean arterial blood pressure levels measured while on dialysis therapy. In otherwise similar models, baseline serum albumin levels had no association with the progression of concentric LV hypertrophy, LV dilation, or systolic dysfunction (data not shown).

Using Cox's regression analysis, each 10 g/L decrement in baseline serum albumin was independently associated ($P < 0.05$) with *de novo* cardiac failure (RR, 1.54), all-cause mortality (RR, 1.35), and cardiac mortality (RR, 1.66) (Table 6, Model I). Similarly, falling serum albumin levels in the interval between echocardiograms were independently associated ($P < 0.05$) with the development of *de novo* ischemic heart disease (RR, 4.98), *de novo* cardiac failure (RR, 2.30), all-cause mortality (RR, 2.43), cardiac mortality (RR,

TABLE 5. Multiple linear regression analysis to assess the independent association between the progression of baseline echocardiographic abnormalities and each 10-g/L fall in mean serum albumin level[a]

Outcome—Progression of:	β Coefficient	P
Concentric LVH (Δmass index in g/m^2)	Not associated	Not associated
LV Dilation (Δcavity volume in mL/m^2)	11.6	0.037
Systolic Dysfunction (Δfractional shortening in %)	Not associated	Not associated

[a] In each analysis, the dependent variable was the change in echocardiographic parameter between baseline and follow-up echocardiography. For example, for patients with concentric LV hypertrophy at baseline, the model is: Δmass index(g/m^2) = constant + β_1Age (yr) + β_2Diabetes(0/1) + β_3Ischemic heart disease(0/1) + β_4Mean arterial blood pressure (mm Hg) + β_5Mean hemoglobin(g/L) + β_6Mean serum albumin(g/L). The indicators 0 and 1 code for no and yes, respectively.

TABLE 4. Echocardiographic and clinical outcomes and associated mean serum albumin levels

Outcome	No. of Events/No. at Risk	Albumin (g/L)	P
Diagnosis on Follow-Up Echo			
Normal	35/259 (14%)	38 ± 6	
Concentric LV hypertrophy[a]	102/259 (39%)	37 ± 4	0.55
LV dilatation[a]	65/259 (25%)	37 ± 5	0.49
Systolic dysfunction[a]	57/259 (22%)	38 ± 8	0.85
De Novo Cardiac Failure[b]			
No	227/299 (76%)	37 ± 4	
Yes	72/299 (24%)	36 ± 4	0.005
Recurrent Cardiac Failure[c]			
No	62/133 (47%)	37 ± 4	
Yes	71/133 (53%)	35 ± 4	0.096
De Novo Ischemic Heart Disease[b]			
No	297/337 (88%)	37 ± 5	
Yes	40/337 (12%)	35 ± 5	0.009
Recurrent Ischemic Heart Disease[c]			
No	49/95 (52%)	36 ± 5	
Yes	46/95 (48%)	36 ± 5	0.91
Death			
No	295/432 (68%)	38 ± 4	
Yes	137/432 (32%)	35 ± 4	<0.0001
Cardiac Death			
No	365/432 (84%)	37 ± 5	
Yes	67/432 (16%)	35 ± 4	0.0003
Noncardiac Death			
No	362/432 (84%)	37 ± 4	
Yes	70/432 (16%)	35 ± 5	<0.0001

[a] Normal left ventricle was used as reference category for each analysis.
[b] Analysis is confined to subjects without the condition at baseline.
[c] Analysis is confined to subjects with the condition at baseline.

TABLE 6. Cox regression analysis: association between serum albumin and clinical end points (expressed as the effect of a 10-g/L fall) in the combined group of hemodialysis and peritoneal dialysis patients[a]

Outcome	Model I[b]		Model II[c]		Model III[d]		Model IV[e]	
	Relative Risk	P	Relative Risk	P	Relative Risk	P	Relative Risk	P
Ischemic Heart Disease								
De novo	NA	NA	4.98	0.011	2.22	0.037	1.49	<0.001
Recurrent	NA	NA	NA	NA	NA	NA	1.25	0.052
Cardiac Failure								
De novo	1.54	0.017	2.30	0.038	1.82	0.007	1.30	0.007
Recurrent	NA	NA	NA	NA	NA	NA	1.44	<0.001
Mortality								
All-cause	1.35	0.039	2.43	<0.001	2.19	<0.001	1.11	<0.001
Cardiac	1.66	0.008	2.68	0.001	2.68	0.001	1.24	<0.001
Noncardiac	NA	NA	2.08	0.038	2.08	0.038	1.14	0.032

[a] NA, not associated.
[b] In Model I, the association of baseline serum albumin has been adjusted for age, diabetes mellitus at baseline, and ischemic heart disease (excluded for the outcomes of *de novo* and recurrent ischemic heart disease) at baseline, as well as baseline hemoglobin and mean arterial blood pressure levels. All patients were included in these analyses.
[c] In Model II, only patients who had baseline and follow-up echocardiograms were included. Mean serum albumin, hemoglobin, and mean arterial blood pressure levels were averaged up to the second echocardiogram. Only outcomes occurring after the second echocardiogram were analyzed. The other covariates were baseline age, diabetes mellitus, and ischemic heart disease (excluded for the outcomes *de novo* and recurrent ischemic heart disease).
[d] In Model III, the association of mean serum albumin while on dialysis therapy before each event has been adjusted for age, diabetes mellitus at baseline, and ischemic heart disease (excluded for the outcomes of *de novo* and recurrent ischemic heart disease) at baseline, as well as mean hemoglobin and mean arterial blood pressure levels. All patients were included in these analyses.
[e] In Model IV, mean serum albumin, hemoglobin, and mean arterial blood pressure before each event have been entered as time-dependent covariates, given as the (mean of given variable) (natural logarithm of follow-up time). The other covariates were baseline age, diabetes mellitus, and ischemic heart disease (excluded for the outcomes of *de novo* and recurrent ischemic heart disease). All patients were included in these analyses.

2.68), and noncardiac mortality (RR, 2.08) in the time period after the second echocardiogram (Table 6, Model II). In similar models applied to all subjects, low mean serum albumin levels were independently associated ($P < 0.05$) with *de novo* ischemic heart disease (RR, 2.22), *de novo* cardiac failure (RR, 1.82), all-cause mortality (RR, 2.19), cardiac mortality (RR, 2.68), and noncardiac mortality (RR, 2.08) (Table 6, Model III). When mean blood pressure and laboratory parameters were considered as time-dependent covariates, hypoalbuminemia was independently associated ($P < 0.05$) with *de novo* ischemic heart disease (RR, 1.49), *de novo* cardiac failure (RR, 1.30), recurrent cardiac failure (RR, 1.44), all-cause mortality (RR, 1.11), cardiac mortality (RR, 1.24), and noncardiac mortality (RR, 1.14); the association with recurrent ischemic heart disease was of borderline statistical significance (RR, 1.25, $P = 0.052$) (Table 6, Model IV).

Hemodialysis Patients. Using multiple regression analysis, mean albumin levels between first and second echocardiogram had no association with the progression of any of the echocardiographic abnormalities (data not shown). Using Cox's regression modeling, each 10 g/L fall in mean serum albumin was associated with *de novo* cardiac failure (adjusted RR, 2.22), recurrent cardiac failure (adjusted RR, 3.84), *de novo* ischemic heart disease (adjusted RR, 5.29), recurrent ischemic heart disease (adjusted RR, 4.24), cardiac mortality (adjusted RR, 5.60), noncardiac mortality (adjusted RR, 3.58) and overall mortality (adjusted RR, 4.33) (Table 7). Adding interdialytic weight gain as a covariate had no impact on the outcomes observed.

Peritoneal Dialysis Patients. Using multiple regression analysis, mean albumin levels between first and second echocardiogram were associated with the progression of LV dilation ($\beta = 13.4$ mL/m^2 per 10 g/L decrement in mean serum albumin, $P = 0.01$), but were not associated with the progression of concentric LV hypertrophy or systolic dysfunction (data not shown). Using Cox's regression modeling, each 10 g/L fall in mean serum albumin was associated with *de novo* cardiac failure (adjusted RR, 4.16), noncardiac mortality (adjusted RR, 3.52), and overall mortality (adjusted RR, 2.06) (Table 7).

DISCUSSION

In this study, the mean serum albumin level while on dialysis therapy was the variable that was most predictive of death or survival, even after controlling for baseline comorbidity. The association with mortality was seen in both hemodialysis and peritoneal dialysis patients. Similar findings have been reported by several other investigators, both in hemodialysis patients (7–9) and peritoneal dialysis patients (10).

TABLE 7. Association between mean serum albumin and clinical outcomes (expressed as the effect of a 10-g/L fall), analyzed separately in hemodialysis (N = 261) and peritoneal dialysis (N = 171) patients[a]

Outcome	Hemodialysis		Peritoneal Dialysis	
	Relative Risk	P	Relative Risk	P
Ischemic Heart Disease				
De novo	5.29	0.001	NA	NA
Recurrent	4.24	0.005	NA	NA
Cardiac Failure				
De novo	2.22	0.001	4.16	0.003
Recurrent	3.84	0.003	NA	NA
Mortality				
All-cause	4.33	<0.001	2.06	<0.001
Cardiac	5.60	0.001	NA	NA
Noncardiac	3.58	<0.001	3.52	<0.001

[a] The association of mean serum albumin while on dialysis therapy before each event has been adjusted for age, diabetes mellitus at baseline, and ischemic heart disease (excluded for the outcomes of *de novo* and recurrent ischemic heart disease) at baseline, as well as mean hemoglobin and mean arterial blood pressure levels. NA, not associated.

Hypoalbuminemia was associated with both cardiac and noncardiac mortality in hemodialysis patients. A relationship with noncardiac mortality was seen in peritoneal dialysis patients. It is unclear whether the lack of association with cardiac mortality in peritoneal dialysis patients reflects inadequate patient and event numbers, a consequence of subgroup analysis.

The adverse impact of hypoalbuminemia may have been partly mediated by cardiac dysfunction. Hypoalbuminemia was independently associated with echocardiographic abnormalities, *de novo* cardiac failure, recurrent cardiac failure, *de novo* ischemic heart disease, and recurrent ischemic heart disease. The analyses shown strongly suggest that low serum albumin levels came before these adverse events, and not *vice versa*. Preliminary reports from other investigators suggest an independent association between hypoalbuminemia and cardiac mortality (28).

The biological basis of a possible adverse effect of hypoalbuminemia on cardiac structure and function is unclear. In this study, cardiac failure was the major condition leading to death, predating 65% of all deaths (21). Cardiac failure in ESRD patients probably results primarily from cardiac ischemia and/or cardiomyopathy, although it is often impossible to distinguish inherent cardiac dysfunction from simple fluid overload on a clinical basis. Even with these limitations, it was clear, at least in this study, that clinically-defined "cardiac failure" was associated with a very poor prognosis.

Ischemic Heart Disease

We observed a very strong relationship between hypoalbuminemia and ischemic heart disease in this study. In the cohort without ischemic disease at baseline, the temporal association between hypoalbuminemia and the subsequent occurrence of ischemic disease suggests that hypoalbuminemia is an important predisposing risk factor. How hypoalbuminemia could cause ischemic heart disease is unclear, but some speculative mechanisms are suggested.

(1) Low Albumin Levels Lead to a Hypercoagulable State? In elderly, nonuremic patients, malnutrition is associated with heparin cofactor II and antithrombin III deficiency, which attenuate the ability to inhibit thrombin generation (29). It is interesting that low serum albumin levels were the single most predictive factor of graft thrombosis in the Canadian Hemodialysis Morbidity Study, leading to speculation that low oncotic pressure associated with hypoalbuminemia leads to a hypercoagulable state, as in the nephrotic syndrome (5).

(2) Low Albumin Levels Reflect More Severe Uremia: Uremia Leads to Atherogenesis? Quantitative and qualitative lipid abnormalities are common in ESRD patients, and probably influence prognosis (30–44). The contribution of malnutrition and low serum albumin levels to these abnormalities is unclear. In this study, the inverse association between serum albumin levels and ischemic heart disease was independent of total cholesterol levels. It is a matter of controversy whether uremia *per se* leads to a state of accelerated atherogenesis (45). There is some evidence that uremia leads to chronic endothelial cell dysfunction (46–48). The association between hypoalbuminemia and ischemic heart disease could be a surrogate marker for a more severe uremic state. Uremia and its treatment may result in a chronic, low-grade inflammatory state. There is accumulating evidence that inflammation may play a major role in atheroma formation in nonuremic populations (49). It is interesting that *Helicobacter pylori*, *Chlamydia pneumoniae* and cytomegalovirus infections have been associated with an excess incidence of coronary artery disease in nonuremic patients (50–52). It is well known that low serum albumin levels may be a response to inflammation, independent of protein intake. Whether such mechanisms may explain the recently reported excessive mortality seen with proinflammatory, bioincompatible hemodialysis membranes (53) is unknown.

(3) Low Albumin Levels are Associated with Other Nutritional Deficiencies that Lead to Ischemic Heart Disease? Recent evidence suggests that hyperhomocysteinemia is a risk factor for atherothrombotic cardiovascular disease in the general (54) and ESRD populations (55). Homocysteine levels are markedly elevated in chronic renal failure (56). In the general population, dietary deficiencies of pyridoxine, folic acid, pyridoxal 5'-phosphate, and vitamin B_{12} are

thought to be the major determinants of high plasma homocysteine levels (57).

Cardiomyopathy

Malnutrition can have pronounced effects on cardiac structure and function in nonuremic individuals. For example, "brown atrophy" of the heart was seen in autopsy studies of individuals who died of starvation in the Warsaw ghetto in World War II (58). Low cardiac output, cardiac fibrosis, fatty infiltration, and myofibrillar atrophy leading to frank cardiac failure have been seen in individuals with kwashiorkor (59–61). Both cardiac atrophy and cardiac hypertrophy (62) are seen in marasmus. The diets of many ESRD patients show certain similarities to those that result in kwashiorkor (inadequate protein intake with adequate caloric intake) and marasmus (inadequate intake of both protein and calories). In this study, serial albumin levels were inversely associated with the progression of LV dilation, especially in peritoneal dialysis patients. The vast majority of ESRD patients already have LV abnormalities at the time that they begin dialysis therapy (20). Very large numbers of patients with long-term follow-up would be needed to show that low albumin levels predate the development of LV abnormalities in patients free of LV abnormalities at baseline, although such an epidemiological design would be superior to that presented here. We have previously reported that patients with normal LV structure and function at the time of inception of dialysis are much more likely to have higher baseline serum albumin levels (adjusted odds ratios, 2.0 per 10 g/L; $P = 0.005$) (20).

Study Limitations

This study began in 1982, long before the quantification of dialysis techniques had reached their current level of sophistication. As such, the importance of factors such as adequacy of dialysis, blood volume expansion, fistula flow rates, and nutritional intake were not formally assessed. It has been shown that the association between hypoalbuminemia and mortality is independent of dialysis intensity (8). Some of the end points studied, such as ischemic heart disease and cardiac failure, are defined on a clinical basis. It is known that coronary artery stenosis and ischemic heart disease do not always coexist in ESRD patients (63). It was not feasible to perform routine coronary arteriography in this study. This is probably unavoidable in a large-scale epidemiological study like this one. Similarly, it must be recognized that correlation does not imply causation. Formal randomized, controlled clinical trials will be required to define the real impact of malnutrition on cardiac morbidity and mortality in ESRD patients.

Conclusions

Hypoalbuminemia is a major mortality marker in ESRD patients. Cardiac disease may be a major cause of this mortality.

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