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Research Paper

# Hypoalbuminaemia – A Marker of Cardiovascular Disease in Patients with Chronic Kidney Disease Stages II - IV

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD) patients. Serum albumin, a negative acute-phase reactant and marker for underlying inflammation and/or malnutrition, is an independent predictor of CVD and mortality in CKD VI patients. Such an association in patients with less severe CKD is not well established.

We conducted a cross sectional study of all CKD II - IV patients attending the nephrology clinic (N=376; mean age: 57±17 years; GFR: 47±20 mL/min/1.73m2; females 48%; blacks 15%; diabetics 27%; hypertensive 79%). Laboratory and clinical data including risk factors and evidence of CVD were obtained at the point of the most recent visit. The association between risk factors and CVD was evaluated by logistic regression. In the simple logistic regression model, age (p<0.0001), sex (P= 0.02), hypertension (P<0.0001), diabetes (P<.0001), dyslipidemia (p=.01), and serum albumin (p<.0001) were found to be statistically significant. Serum albumin was found to be an independent predictor (p=0.04) of CVD by multiple logistic regression analysis using the above risk factor variables.

In conclusion: a) hypoalbuminaemia is an independent predictor of CVD in early CKD stages; b) hypoalbuminaemia may be used to identify the population at higher risk for CVD.

Key words: Hypoalbuminaemia, cardiovascular disease, chronic kidney disease patients, cross sectional study

## INTRODUCTION

400,000 Americans have ESRD and over 300,000 of these patients are on maintenance dialysis (1). CVD is the leading cause of morbidity and mortality in these patients accounting for more than 40% of hospitalizations and almost 50% of deaths (1, 2). This death rate attributed to CVD is 10-20 times that in the general population, stratified for age, race and gender (3).

An estimated 8 million patients have chronic kidney disease of at least stage III (as defined by an estimated glomerular filtration rate [GFR] of less than 60 ml per minute per 1.73 $m^2$ of body surface area) (4). These patients are not on dialysis. However, the prevalence of CVD in these patients has been shown to be significantly higher than the general population (5, 6).

The high burden of CVD in these patients can not be explained just by the high prevalence of traditional risk factors like hypertension (HTN), diabetes (DM), Dyslipidemia (DLP) and advanced age. Of late, novel risk factors like malnutrition and inflammatory state have been implicated in maintenance dialysis patients (CKD stage VI). This association is not well established in patients with less severe CKD. Here we evaluated association between serum albumin, a negative acute-phase reactant and marker of inflammation and/or malnutrition and CVD in patients with CKD stages II to IV.

## METHODS

### STUDY DESIGN

This is a cross sectional study of all CKD stage II-IV (n= 376) patients attending nephrology clinic of a community hospital. Excluded from initial sample of 583 patients were those with CKD stage I, V and those with missing albumin values or CVD data. Patients with a previous history of dialysis and/or renal transplant were also excluded.

### DATA COLLECTION

Data of age, sex, race, DM, HTN, serum chemistries and CVD were collected from office charts and from the most recent visit. All names and identifiers

were removed before any analysis of data was performed. Serum chemistries included blood urea nitrogen (BUN), serum creatinine, serum albumin, electrolytes, calcium (Ca), phosphorus (PO4), uric acid, lipids and hemoglobin. CVD included angina pectoris, myocardial infarction (MI), coronary artery disease (CAD), left ventricular hypertrophy (LVH) and heart failure (HF) as per history.

## RENAL FUNCTI0N

We used the abbreviated Modification of diet in Renal Disease (MDRD) equation to estimate the GFR (7, 8). Creatinine value on last visit was used to calculate MDRD eGFR. The formula is as below:

186 x (Creat / 88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black)

## OUTCOMES AND COVARIATES

Outcomes were measured in form of prevalence of CVD as defined above. Potential confounders selected based on prior studies and clinical relevance, including age, sex, HTN, DM and DLP were used in final model.

## STATISTICAL ANALYSIS

Results were expressed as mean ± SD for continuous variables, and as percentages for categorical data. The association between potential risk factors and CVD was evaluated by logistic regression model. Simple logistic regression models were used to evaluate associations of traditional and novel risk factors for CVD. To evaluate the independent effect of serum albumin on CVD, a multiple logistic regression model was used. All variables known to be associated with CVD involving all traditional risk factors like sex, age, DM, HTN, DLP were put in final multiple logistic regression model to remove confounding effects. Results were reported as p values and Odds Ratios with 95% confidence intervals. All analyses were conducted with the use of STATVIEW software.

# RESULTS

The patients included 52% male and 48% female, 85% white and 15% black and mean age was 57 years. The majority of patients (79%) had HTN and 27% had DM. CVD was prevalent in 35% of patients. A total of 62% were on angiotensin converting enzyme inhibitors (ACE-i), 30% on beta blockers and 53% on statins (Table 1). Laboratory data is shown in Table 2. All variables evaluated using simple logistic regression were significant except serum cholesterol (Table 3). The effects of BUN, serum creatinine, calcium, phosphorus, uric acid, and hemoglobin values on CVD were accounted by the GFR status. Multivariate analysis showed that GFR, serum albumin concentration, age, male sex and presence of DM were the independent predictors of CVD in the earlier stages of CKD (Table 4).

**Table 1:** Characteristics of patients with CKD stage II to IV excluding patient with history of renal transplant or maintenance dialysis.

| Variable | Value |
|---|---|
| Age (years) | 57±17 |
| Sex | 48% Female,<br>52% Male |
| Race | 15% Black,<br>85% White |
| Diabetes | 27% |
| Hypertension | 79% |
| Cardiovascular disease | 35% |
| ACEi/ ARB | 62% |
| Beta blockers | 40% |
| Statins | 53% |

**Table 2:** Laboratory data of the study patients with CKD stage II to IV including serum chemistries.

| Parameter | Mean ± SD |
|---|---|
| MDRD GFR (mL/min/1.73m$^2$): | 47 ± 20 |
| BUN (mg/dL): | 28 ± 16 |
| S. Creatinine (mg/dL): | 1.6 ± 0.7 |
| S. Calcium (mg/dL): | 9.4 ± 0.5 |
| S. Phosphorus (mg/dL): | 3.6 ± 0.6 |
| S. Albumin (g/dL): | 4.1 ± 0.5 |
| S. Uric Acid (mg/dL): | 7.0 ± 2.3 |
| S. Cholesterol (mg/dL): | 188 ± 43 |
| S. Triglycerides (mg/dL): | 169 ± 136 |
| S. hemoglobin (g/dL): | 13.2±1.8 |

**Table 3:** Univariate Logistic Regression Analysis evaluating association of risk factors with CVD.

| Variable | Exp (coef.) | P Value |
|---|---|---|
| Age: | 1.065 | 0.0100 |
| Sex (M): | 1.689 | 0.0170 |
| Race (W): | 0.489 | 0.0140 |
| HTN: | 5.422 | 0.0001 |
| DM: | 3.849 | 0.0001 |
| S. Phosphorus | 1.609 | 0.0063 |
| S. Uric Acid: | 1.287 | 0.0001 |
| GFR: | 0.952 | 0.0001 |
| S. Hemoglobin: | 0.740 | 0.0001 |
| S. Calcium | 0.539 | 0.0041 |
| S. Albumin: | 0.376 | 0.0001 |
| S. Cholesterol: | 0.997 | 0.3377 |

**Table 4:** Multivariate Logistic Regression Analysis evaluating independent effects of risk factors with CVD.

| Variable | P Value | Exp (Coef.) | OR (95% CI) |
|---|---|---|---|
| Age: | 0.0001 | 1.043 | (1.023-1.063) |
| Sex (M): | 0.0280 | 1.788 | (1.065-3.002) |
| HTN: | 0.0714 | 2.127 | (0.936-4.833) |
| DM: | 0.0012 | 2.472 | (1.430-4.273) |
| GFR: | 0.0004 | 0.976 | (0.961-0.992) |
| S. Albumin: | 0.0365 | 0.554 | (0.391-0.962) |

# DISCUSSION

The majority of patients with CKD have severe manifestations of CVD by the time they need mainte-

nance dialysis. This suggests that the damage to the cardiovascular system starts quite early in the time course of progressive chronic kidney disease. Indeed over the last few years, it has been well recognized that CKD patients in the predialysis stage are at increased risk of CVD and its complications. This has led to a rapidly growing interest in the relation between kidney disease and the risk of CVD and is the focus of several recent studies. These studies have shown that the association of CKD to CVD is independent of any traditional risk factors (9-12). The National Kidney Foundation, American Heart Association and the Seventh Joint National Committee on Prevention, Detection, Evaluation & Treatment of High Blood Pressure have classified the presence of CKD as a cardiovascular risk factor (9, 13, 14). These findings led to the evaluation of novel cardiovascular risk factors like chronic inflammation and malnutrition as predictors of the CVD in chronic kidney disease. This multifactorial disease introduces new challenges in predicting and treating patients early in course of CKD to positively alter patient outcome.

There is definitely a high prevalence of traditional risk factors like HTN, DM and DLP in chronic kidney disease patients (15-20), but this alone cannot explain the existing high burden of CVD in this population (21-24). There appears to be a close link between CVD, malnutrion and inflammation in ESRD patients (25, 26). Hypoalbuminemia, a marker of malnutrition and underlying inflammation has come up as a powerful predictor of mortality in patients with ESRD (27-30) and also a significant predictor for the occurrence of de novo vascular events in this population (27). In a recent study C-reactive protein and low albumin has been shown to be the predictor of morbidity and mortality in CKD 3-5 patients in Spain (31). Our study extends this finding to patients with more preserved renal function in American population.

Our hypothesis that serum albumin is a significant risk factor for cardiovascular disease in CKD patients is highlighted by our results on 376 patients with CKD II to IV in whom low serum albumin was significantly associated with CVD irrespective of traditional risk factors like age, sex, HTN, DM and DLP in multivariate analysis.

Beddhu et al (32) showed association between serum albumin level and CVD in chronic hemodialysis patients. An association between serum albumin and cardiovascular mortality has been reported by several studies. Owen et al (33) demonstrated that hypoalbuminemia was a strong predictor of mortality in dialysis patients. Kalantar-Zadeh et al (34) also showed higher mortality in dialysis patients with lower albumin. Many recent studies showed serial measurement of serum albumin can even better predict chronic inflammation and clinical events (35-37). Looking at the results of all these studies it is clear that hypoalbuminemia is adversely associated with CVD in ESRD. Stenvinkel et al. (38) were first to demonstrate that patients in predialysis chronic renal failure with carotid plaque has lower serum albumin level. Nobuhiko et al demonstrated that even in predialytic phase of chronic renal failure, hypoalbuminemia is an excellent reflection of CVD (39). Our study concludes that this is true even in patients with less severe kidney dysfunction. So serum albumin can be a helpful predictor of CVD at early stage of CKD and this patient population needs focused attention because early detection and intervention can provide better outcome.

Available data suggests interrelationship between hypoalbuminemia, inflammation, malnutrition and atherosclerosis in patients with kidney failure (38, 40). In some studies the relation between hypoalbuminemia and CVD is the reflection of inflammation induced malnutrition. The underlying mechanism behind this includes appetite suppression and increased catabolism by inflammatory cytokines (38). Cai and colleagues have implied serum albumin as potential scavenger of free radicals. Decrease in serum albumin level would lead to decrease antioxidant capacity and favor the noxious effects of oxidative stress on a variety of tissues, including the arterial vessel wall (41). These data suggest that hypoalbuminaemia can be more appropriately viewed as a composite marker which reflects malnutrition as well as increased acute phase inflammation, considering that albumin is also a negative acute phase reactant (38, 42-45).

Our study has several limitations. This was a retrospective chart review. Patients were not followed over time, so causal relationships cannot be established. We have not used serum albumin as a time dependent covariate which may have led to an even more reliable prediction of CVD. In addition, many of our patients were on medications that have protective effects on cardiovascular disease. Another important limitation is the lack of consistent measurements of other inflammatory markers such as CRP, whose importance as a predictor of CVD has been shown by others (46). Hypoalbuminemia is a non specific marker of a micro inflammatory state, and is seen in other diseases such as systemic lupus, rheumatoid arthritis, other connective tissue diseases, liver disease, malnutrition from other causes, and does not just represent cardiovascular disease. In addition, data on food intake, basal energy expenditure (BEE), and total daily energy expenditure (TEE) were not available for analysis that may have provided a better understanding of nutritional status in these patients.

Our study concludes that hypoalbuminemia is a strong risk factor for CVD, probably in context of the complex syndrome of malnutrition, inflammation and oxidative stress in patients with CKD. In order to reduce cardiovascular mortality, nutritional, anti-inflammatory and antioxidant intervention will need to be assessed in more randomized control trials. Statins and ACE inhibitors have been shown to have anti-inflammatory effects (47, 48). Recent studies have shown beneficial effects of statins on CVD outcome in CKD patients (49-51). But it is unclear whether the benefit is due to lipid lowering effect, an anti inflammatory effect or both.

## Conflict of Interest

The authors have declared that no conflict of interest exists.

## References


1. Renal Data System. USRDS 2003 annual data report: atlas of end-stage renal disease in the United States. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003.
2. Locatelli F, Marcelli D, Conte F et al. Cardiovascular disease in chronic renal failure: the challenge continures. Registro Lombardo Dialisi e Trapianto. Nephrol Dial Transplant 2000; 15 (Suppl 5): 69-80.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kideny Dis 1998; 32 (Suppl 3): S112-119.
4. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survery. Am J Kidney Dis 2003; 41: 1-12.
5. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community based cohort with mild renal insufficiency. Kidney Int. 1999; 56: 2214-19.
6. Shilpak MG, Fried LF, Crump C et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. Kidney Int. 2003; 62: 997-1004.
7. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130: 461-470.
8. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000; 11: 155A-155A.
9. Sarnak MJ, Levey AS, Schoolweth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003; 108: 2154-2169.
10. Shilpak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. J Am Coll Cardiol 2001; 38: 705-
11. Shulman NB, Ford CE, Hall WD, et al. The Hypertension Detection and Follow-up Program Group. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function results from the Hypertension Detection and Follow-up Program. Hypertension. 1989 May;13(5 Suppl):I80-93.
12. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001; 134: 62
13. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-2572.
14. Kidney Disease Outcome Quality Initiative. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kideny Dis 2002; 39(suppl 2): S1-S24.
15. Linder A, Charea B, Sherrard DJ, et al. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med. 1974; :290-701.
16. Junger P, Massy ZA, Khoa TN, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dial Transplant 1997; 12: 2597-2602.
17. Herzog CA, Ma JZ, Collins AJ. Poor long term survival after acute myocardial infarction among patients on long term dialysis. N Engl J Med 1998; 339: 799-805.
18. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephron. 1999; 10: 1606-1615.
19. D'Elia JA, Weinrauch LA, Gleason RE, et al. Application of the ambulatory 24-hour electrocardiogram in the prediction of cardiac death in dialysis patients. Arch Intern Med. 1988; 148: 2381-2385.
20. Aronow Ws. Usefulness of serum creatinine as a marker for coronary events in elderly patients with either systemic hypertension or diabetes mellitus. Am J Cardiol. 1991; 68: 678-679.
21. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis. 2003; 36: S24-30.
22. Danesh J, Collins R, Peto R. Lipoprotein (a) and coronary heart disease. Meta-analysis of prospective studies. Circulation. 2000; 102: 1082-5.
23. Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, et al. Lipoprotein (a) levels and risk of coronary heart disease in men. The Lipid Research Clinics Coronary Primary Prevention Trial. JAMA. 1994; 271: 999-1003.
24. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997; 336: 973-9.
25. Bergstrom J, Lindholm B: Malnutrition, cardiac disease, and mortality: An integrated point of view. Am J Kidney Dis 1998; 32: 834-841.
26. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999; 55: 648-658.
27. Foley RN, Parfrey PS, Harnett JD, et al. Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. J Am Soc Nephrol 1996; 7: 728-736.
28. Owen WF, Lew NL, Liu Y, et al. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. N Engl J Med. 1993; 329: 1001-1006.
29. Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. Kidney Int 1993; 44: 115-119.
30. Avram MM, Mittman N, Bonomini L, et al. Markers for survival in dialysis: A seven-year prospective study. Am J Kidney Dis 1995; 26: 209-219.
31. Soriano S, González L, et al. C-reactive protein and low albumin are predictors of morbidity and cardiovascular events in chronic kidney disease (CKD) 3-5 patients. Clinical nephrology 2007; 67(6):352-7.

32. Beddhu S, Kaysen GA, Yan G, Sarnak M, Agodoa L, Ornt D, Cheung AK, HEMO Study Group. Association of serum albumin and atherosclerosis in chronic hemodialysis patients. Am J Kidney Dis 2002; 40: 721-727.
33. Owen WFJr, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. N Engl J Med 1993; 329: 1001-1006.
34. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N et al. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant 2005; 20: 1880-1888.
35. Kaysen GA, Dubin JA, Muller HG, Rosales L, Levin NW, Mitch WE, HEMO study group. Inflammation and reduced albumin systhesis associated with stable decline in serum albumin in hemodialysis patients. Kidney Int 2004; 65: 1408-1415.
36. Nacimiento MM, Pecoits-Filho R, Qureshi AR et al. The prognostic impact of fluctuating levels of C-reactive protein in Brazilian haemodialysis patients: a prospective study. Nephrol Dial Transplant 2004; 19: 2803-2809.
37. Tsirpanlis G, Bagos P, Ioannou D et al. Exploring inflammation in hemodialysis patients: persistent and superimposed inflammation. A longitudinal study. Kidney Blood Press Res 2004; 27: 63-70.
38. Stevinkel P, Heimburger O, Paultre F et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 1999; 55: 1899-1911.
39. Nobuhiko Joki, Hiroki Hase, Yuri Tanaka et al. Relationship between serum albumin level before initiating haemodialysis and angiographic severity of coronary atherosclerosis in end-stage renal disease. Nephrol Dial Transplant 2006; 21(6): 1633-1639.
40. Kalantar-Zadeh K, Kopple JD, Block G, et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 2001; 38: 1251-1263.
41. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000; 87: 840-844.
42. Mitch WE. Malnutrition: a frequent misdiagnosis for hemodialysis patients. J Clin Invest 2002; 110: 437-439.
43. Kaysen GA. Biological basis of hypoalbuminemia in ESRD. J Am Soc Nephrol 1998; 9: 2368-2376.
44. Kaysen GA, Dubin JA, Muller HG, Rosales LM, Levin NW. The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients. The HEMO Study Group. Kidney Int 2000; 58: 346-352.
45. Kaysen GA, Chertow GM, Adhikarla R, Young B, Ronco C, Levin NW. Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. Kidney Int 2001; 60: 333-340.
46. Himmelfarb J, Stenvinkel P, Ikizler TA, and Hakim RM: The elephant of uremia: oxidative stress as a unifying concept of cardiovascular disease in uremia. Kidney Int 2002; 62: 1524-1538.
47. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. Sem Dial 2002; 15: 329-337.
48. Wanner C, Metzger T. C-reactive protein - a marker for all-cause and cardiovascular mortality in haemodialysis patients. Nephrol Dial Transplant 2002; 17(Supply 8): 29-32.
49. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet 2003; 361(9364): 1149-58.
50. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360(9326): 7-22.
51. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004; 110(12): 1557-63.