Relationship Between C-Reactive Protein, Albumin, and Cardiovascular Disease in Patients With Chronic Kidney Disease

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● **Background:** C-Reactive protein (CRP) level is elevated in kidney failure and may be related to malnutrition and cardiovascular disease (CVD). Data are limited regarding relationships between CRP levels and glomerular filtration rate (GFR), nutritional indices, and CVD in patients with earlier stages of kidney disease. **Methods:** CRP was assayed from samples from the Modification of Diet in Renal Disease (MDRD) Study (n = 801). CRP distributions were compared between the MDRD Study and National Health and Nutrition Examination Survey (NHANES; 1999 to 2000). Associations between CRP level and GFR, nutritional indices, serum albumin levels, and CVD risk factors were examined in the MDRD Study. **Results:** Geometric means of CRP, adjusted for age and sex, were similar in NHANES (0.23 mg/dL) and the MDRD Study (0.22 mg/dL). In the MDRD Study, CRP level was related directly to measures of body fat and CVD risk factors, inversely with serum albumin level and energy intake, and unrelated to GFR. In multivariable analysis adjusting for other determinants of serum albumin level, high CRP level (>0.6 mg/dL) was associated with a 0.07-g/dL (0.7-g/L; 95% confidence interval [CI], 0.03 to 0.12) lower mean serum albumin level. After adjusting for traditional CVD risk factors, the odds of CVD were 1.73 (95% CI, 1.07 to 2.78) times greater in subjects with a high CRP level. **Conclusion:** GFR level does not appear to influence CRP level in the earlier stages of chronic kidney disease. CRP levels are independently associated with serum albumin level and CVD prevalence. Inflammation may be involved in the pathophysiological state of malnutrition and CVD in the earlier stages of predominantly nondiabetic kidney disease. *Am J Kidney Dis* 42:44-52.
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INDEX WORDS: C-reactive protein (CRP); glomerular filtration rate (GFR); albumin; cardiovascular disease (CVD).

IN PATIENTS WITH kidney failure (defined as the requirement for kidney replacement therapy), there appears to be a close pathophysiological link between cardiovascular disease (CVD), malnutrition, and inflammation.[1,2] Levels of C-reactive protein (CRP), a surrogate marker of inflammation, are elevated in kidney failure,[3-5] and CRP is a powerful risk factor for the development of CVD.[6-8] A low level of serum albumin, a marker of nutritional status, is also a strong predictor of morbidity and mortality in patients with kidney failure.[9-11] Accumulating evidence suggests that the hypoalbuminemia of kidney failure in part may be a consequence of activation of the acute-phase response and may represent a chronic inflammatory state.[12-14]

Thus, there appears to be a complex interplay between the atherosclerotic disease process, nutritional status, and activation of the inflammatory response in kidney failure.[15] Although data suggest that malnutrition and CVD are early events in the spectrum of chronic kidney disease,[16,17] relatively few studies have attempted to examine the relationship between inflammation, malnutrition, and CVD in patients during earlier stages of chronic kidney disease.

The objectives of this cross-sectional study are 3-fold: (1) to characterize levels of CRP, a marker of inflammation, in a large group of subjects with reduced glomerular filtration rate (GFR) from the randomized cohort of the Modification of Diet in Renal Disease (MDRD) Study and compare them with values from a population sample derived from the National Health and Nutrition Examination Survey (NHANES; 1999 to 2000); (2) to investigate the relationship between CRP level and indicators of nutritional intake and

status; and (3) to investigate the relationship between CRP level and prevalent CVD.

METHODS

Details of the MDRD study have been published previously.[18] In brief, it was a randomized, controlled trial of 840 patients with predominantly nondiabetic kidney disease and reduced GFR, conducted between 1988 and 1993, to study the effects of dietary protein restriction and strict blood pressure control on the progression of kidney disease. All patients entering baseline had mean arterial pressures of 125 mm Hg or less, were 18 to 70 years of age, and had chronic kidney disease with serum creatinine levels of 1.4 to 7.0 mg/dL (123.76 to 618.8 μmol/L) for men and 1.2 to 7.0 mg/dL (106.08 to 618.8 μmol/L) for women. Exclusion criteria were history of insulin-requiring diabetes, class III or IV congestive heart failure, renal artery stenosis, kidney transplantation, or frequent hospitalizations. Five hundred eighty-five patients with a baseline GFR of 25 to 55 mL/min/ 1.73 m^2 were randomly assigned to study A, and 255 patients with a baseline GFR of 13 to 24 mL/min/1.73 m^2 were randomly assigned to study B. Participants from studies A and B were combined for the analyses presented here.

Fasting serum samples were drawn at baseline from 804 participants in the MDRD Study (560 participants in study A, 244 participants in study B) and stored for future analyses. Samples were allowed to clot at room temperature for a maximum of 2 hours and were spun down, and serum was decanted and stored at −70°C. Frozen samples underwent 2 freeze-thaw cycles before being assayed for CRP (n = 801). High-sensitivity CRP was measured using a Dade Behring BN II nephelometer (Dade Behring, Deerfield, IL) by means of particle-enhanced technology. CRP assays were performed at the University of Washington (Seattle, WA). The detection limit of this method is 0.01 mg/dL, with interrun coefficients of variation for the low- and high-quality control samples of 3.5% and 3.0%, respectively. CRP data from the NHANES sample were obtained from the NHANES (1999 to 2000) public data release file.[19] CRP measurements from the NHANES also were performed at the University of Washington using the same high-sensitivity assay.[19] Levels of serum leptin, insulin, lipoprotein(a) [Lp(a)],[20] homocysteine (Hcy), and B vitamins also were measured using frozen samples, and Hcy, CRP, and leptin recently have been evaluated as risk factors for the progression of chronic kidney disease in the MDRD Study.[21,22]

Other relevant clinical and biochemical variables were measured at each center as described in previous reports.[23] GFR was assessed by means of kidney clearance of iodine 125 I–labelled iothalamate after subcutaneous injection. Level of proteinuria (grams per day of protein) was estimated from 24-hour urine samples. Serum albumin was measured by dye binding using bromocresol green reagents and an Astra 8 analyzer (Beckman Instruments, Brea, CA). Body mass index (BMI; (body weight [kg])/(height [m]))[2], percentage of body fat, and skinfold thickness were measured at month 2 of baseline, as described previously.[24] Nutritional status measures were estimated from data collected by trained dieticians during the first 2 weeks after study enrollment.[25] Dietary energy and protein intake were assessed from dietary diaries. A history of coronary heart disease, cerebrovascular disease, and peripheral vascular disease was obtained through patient self-report or review of hospital records.

Statistical Analyses

Comparison of CRP levels in the MDRD Study and NHANES samples. A total of 9,965 people participated in the NHANES 1999 to 2000 survey. The public release data set accessed for this analysis contained data from 8,344 participants. We restricted the NHANES sample to the same age limits as in the MDRD Study cohort; therefore, the final sample size was 3,744. Because CRP levels were skewed in both data sets, geometric means (antilogarithms of transformed means) and SEs were used for comparison of CRP levels between the MDRD Study and NHANES sample and for graphical representation of data. Comparison of geometric means was also performed after adjustment for age and sex. An interaction between study (MDRD versus NHANES) and age group also was evaluated.

Baseline characteristics of the MDRD Study sample by CRP level. The MDRD Study sample was divided into 2 groups based on CRP level (>0.6 versus ≤0.6 mg/dL). The 0.6-mg/dL cutoff value for CRP has been used previously in studies of dialysis patients, patients with reduced GFRs, and subjects in the general population, and levels greater than this cutoff value have been shown to be predictive of CVD events in longitudinal studies.[8,26,27] Summary statistics are presented as percentages for categorical data, mean ± SD for approximately normally distributed continuous variables, and medians and interquartile range for skewed continuous variables. Differences between groups were tested using chi-square test, Student's *t*-test, and Mann-Whitney test, as appropriate.

Relationship between CRP and serum albumin levels. A multivariable linear regression model was used to examine the association of albumin level (as the dependent variable) and CRP level, categorized into high (>0.6 mg/dL) and low (≤0.6 mg/dL), after adjusting for age, sex, BMI, GFR, proteinuria, cholesterol level, daily protein intake, and history of diabetes. We chose albumin level as an indicator of nutritional status because it has been used extensively as a marker of malnutrition in the dialysis population.[28,29] However, we acknowledge that albumin levels also may partially reflect the acute-phase response. Variables used for adjustment were forced into the multivariable model and chosen a priori based on previous studies as potential confounders in the relationship between albumin and CRP levels.[13,30-32]

Relationship between CRP level and CVD. The Mann-Whitney test was used to compare CRP levels in patients with and without a history of CVD. A composite outcome for CVD was computed from a history of coronary artery disease, cerebrovascular disease, or peripheral vascular disease. A logistic regression model was used to test the association of the composite CVD outcome and CRP level, categorized into high versus low (as defined), after adjusting for effects of other well-recognized CVD risk factors. These included age, sex, diabetes, smoking, total cholesterol level, and systolic blood pressure, all of which were forced into the model as a priori covariates. To evaluate for possible confounding by albumin level in the relationship between CVD
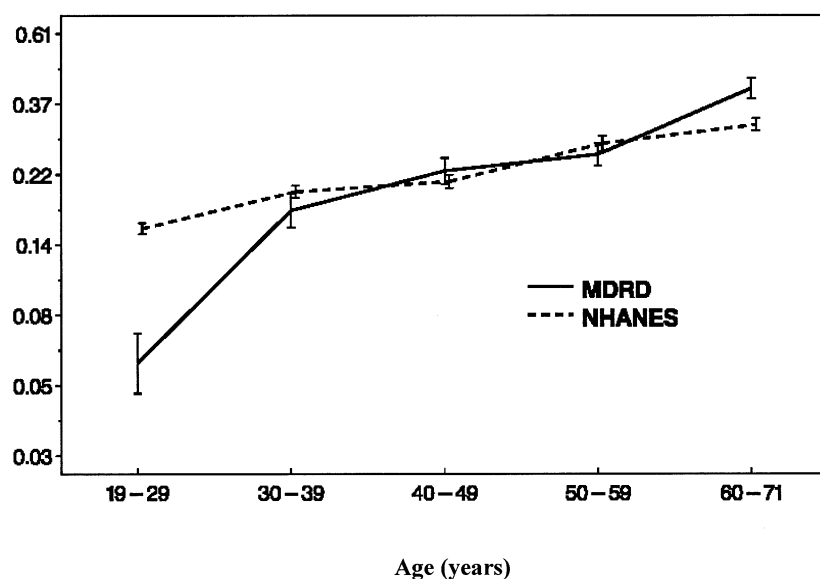
Fig 1. Geometric means (with error bars representing SEs) of CRP levels by decade of age and controlling for sex were compared between subjects from the MDRD Study randomized cohort (n = 801) and a general population sample derived from the NHANES from 1999 to 2000 (n = 3,744).

and CRP level, regression analysis was repeated after adding albumin level to the covariates listed. Multivariable analysis was also repeated with albumin level in the model, but excluding CRP level.

RESULTS

Mean age of the 801 participants of the MDRD Study randomized cohort included in this study was 52 ± 12 (SD) years. Sixty percent were men, and the prevalence of non–insulin-dependent diabetes was 5%. Minimum and maximum GFRs were 12 to 55 mL/min/1.73 m², with a mean GFR of 32.7 ± 12.0 mL/min/1.73 m². Frozen samples were not available for 39 of the original 840 participants in the MDRD Study. There was no difference in age, sex, BMI, percentage of body fat, albumin level, and prevalence of diabetes or CVD between the 39 patients excluded from the study and the 801 patients included in the study.

Comparison of CRP Levels in the MDRD Study and NHANES Samples

Figure 1 describes the distribution of the geometric mean of CRP levels by age and controlling for sex in the MDRD Study and a subset of the NHANES 1999 to 2000 populations. Mean age was 43 ± 16 (SD) years in the NHANES data set and 52 ± 12 years in the MDRD Study. CRP levels increased with age in both the MDRD Study and NHANES. Geometric means of CRP

were similar between the MDRD Study and the NHANES sample except in the youngest (19 to 29 years) age group, in which mean CRP level was lower in the MDRD Study. Overall, unadjusted geometric means of CRP levels were similar in the NHANES (0.22 mg/dL) and MDRD Study (0.25 mg/dL) samples. Overall geometric means of CRP adjusted for age and sex, two factors known to influence CRP levels, also were similar in the 2 groups (NHANES, 0.23 mg/dL; 95% confidence interval [CI], 0.21 to 0.25; MDRD Study, 0.22 mg/dL; 95% CI, 0.22 to 0.23; $P = 0.9$). The prevalence of high CRP levels, defined as CRP level greater than 0.6 mg/dL, was 24% in the NHANES and 26% in the MDRD Study samples. There was a significant interaction between age group and study (MDRD versus NHANES; $P < 0.001$) with level of CRP.

Characteristics of MDRD Study Sample by CRP Level

Table 1 lists characteristics of MDRD Study subjects according to CRP level. Subjects with higher CRP levels were older and more likely to have non–insulin-dependent diabetes. Neither GFR nor proteinuria differed between the high- and low-CRP groups. The correlation between GFR and CRP level was 0.06 ($P = 0.09$).

Measures of body fat, such as BMI and percent-

Table 1.   Characteristics of the MDRD Study Sample by CRP Level

	Low CRP ($\leq$0.6 mg/dL) (N = 593)	High CRP ($>$0.6 mg/dL) (N = 208)
Demographic factors		
Age (y)	50.3 $\pm$ 12.6	56.1 $\pm$ 10.4*
Men (%)	65	48*
White (%)	86	84
Diabetes (%)	3	11*
Current smoker (%)	9	11
Kidney disease factors		
GFR (mL/min/1.73 m^2)	32.4 $\pm$ 12.4	33.3 $\pm$ 11.1
Proteinuria (g/d)	0.3 (1.5)	0.3 (1.1)
Kidney disease category (%)		
Glomerular disease	32	29
Polycystic kidney disease	26	15
Other	42	56
Nutritional factors		
BMI (kg/m^2)	26.4 $\pm$ 7.6	29.4 $\pm$ 4.7*
Body Fat (%)	29.0 $\pm$ 6.9	34.1 $\pm$ 6.8*
Biceps skinfold (mm)	7.8 $\pm$ 4.6	11.4 $\pm$ 6.8*
Subscapular skinfold (mm)	18.4 $\pm$ 7.1	22.0 $\pm$ 7.3*
Protein intake (g/kg/d)	1.03 $\pm$ 0.3	1.06 $\pm$ 0.3
Energy intake (kcal/kg/d)	26.8 $\pm$ 7.6	24.9 $\pm$ 7.0*
Albumin (g/dL)	4.1 $\pm$ 0.4	3.9 $\pm$ 0.3*
Transferrin (mg/dL)	273.0 $\pm$ 45.0	276.1 $\pm$ 47.9
Vitamin B$_6$ (ng/mL)	9.8 (8.2)	7.3 (5.8)*
Vitamin B$_{12}$ (pg/mL)	554.1 (259.4)	583.9 (311.1)*
Folic acid (ng/mL)	2.3 (1.7)	2.2 (1.8)
Hcy (mg/L)	2.4 (1.1)	2.1 (0.9)*
Leptin (ng/mL)	8.1 (11.7)	13.8 (23.4)*
Insulin (μU/mL)	10.0 (8.0)	12.0 (10.5)*
CVD factors		
Systolic blood pressure (mm Hg)	130.8 $\pm$ 17.0	135.3 $\pm$ 18.9*
Diastolic blood pressure (mm Hg)	81.4 $\pm$ 10.0	80.1 $\pm$ 10.2
Total cholesterol (mg/dL)	214.3 $\pm$ 43.9	224.0 $\pm$ 49.6*
Triglycerides (mg/dL)	133.5 (107.0)	150.0 (134.0)*
Low-density lipoprotein cholesterol (mg/dL)	145.5 $\pm$ 40.3	153.4 $\pm$ 44.8*
High-density lipoprotein cholesterol (mg/dL)	40.3 $\pm$ 13.8	38.7 $\pm$ 15.3
Lp(a) (nmol/L)	28.8 (65.9)	43.1 (80.7)*
White blood cells (1,000/μL)	6.3 $\pm$ 1.6	7.3 $\pm$ 2.0*
History of CVD (%)	11	19*

NOTE. Values expressed as mean $\pm$SD or median (interquartile range). To convert serum albumin in g/dL to g/L, multiply by 10; serum creatinine in mg/dL to μmol/L, multiply by 88.4; transferrin in mg/dL to g/L, multiply by 0.01; vitamin B$_6$ in ng/mL to nmol/L, multiply by 4.046; vitamin B$_{12}$ in pg/mL to pmol/L, multiply by 0.738; folate in ng/mL to nmoL/L, multiply by 2.266; Hcy in mg/L to μmol/L, multiply by 7.397; insulin in μU/L to pmol/L, multiply by 6.945; total, high-density lipoprotein, and low-density lipoprotein cholesterol in mg/dL to mmol/L, multiply by 0.0259; white blood cells from 10^3/μL to 10^9/L, multiply by 1.

*$P < 0.05$.

age of body fat, were higher in subjects with greater CRP levels. Patients with higher CRP levels had lower daily caloric intakes, lower serum mean albumin levels, and lower vitamin B$_6$ levels.

Both CVD and CVD risk factors were more prevalent among patients with high CRP levels. Systolic blood pressure and levels of total choles-terol, triglycerides, and Lp(a) were significantly greater in the high-CRP group.

Relationship Between CRP and Serum Albumin Levels

In multivariable linear regression analysis, af-ter adjusting for age, sex, BMI, GFR, protein-uria, cholesterol level, daily protein intake, and

Table 2. Multivariable Regression Analysis for Association Between Serum Albumin and CRP Levels in the MDRD Study

	Regression Coefficients (95% CI)	P
Constant	4.347 (4.172, 4.523)	<0.001
Age (y)	−0.005 (−0.007, −0.003)	<0.001
Sex (women v men)	−0.162 (−0.205, −0.119)	<0.001
Proteinuria (g/d)	−0.126 (−0.139, −0.112)	<0.001
Total cholesterol (mg/dL)	0.001 (0.000, 0.001)	0.001
CRP ≤0.6 v >0.6 mg/dL	−0.07 (−0.123, −0.025)	0.003
GFR (mL/min/1.73 m^2)	−0.001 (−0.002, 0.001)	0.63
BMI (kg/m^2)	0.001 (−0.004, 0.005)	0.85
Daily protein intake (g/kg/d)	0.005 (−0.069, 0.06)	0.89
Diabetes	0.03 (−0.064, 0.125)	0.52

NOTE. To convert serum albumin in g/dL to g/L, multiply by 10; total cholesterol in mg/dL to mmol/L, multiply by 0.0259.

diabetes, high CRP level (CRP > 0.6 mg/dL) was associated with 0.07-g/dL (0.7-g/L) lower mean albumin levels compared with low CRP (CRP ≤ 0.6 mg/dL; Table 2).

Relationship Between CRP Level and CVD

Median CRP level was higher (P < 0.001) in subjects with a history of CVD (n = 104; CRP, 0.46 mg/dL) compared with those without CVD (n = 697; CRP, 0.22 mg/dL). In multivariable logistic regression analysis, the odds of CVD were 1.73 times greater in patients with high CRP levels (>0.6 mg/dL) than those with low CRP levels (≤0.6 mg/dL; Table 3). When albumin level was forced into the model, it was not significantly associated with CVD (odds ratio [OR] for 1-g/dL increase in albumin level, 1.59; 95% CI, 0.81 to 3.13), and the odds of CVD for high versus low CRP changed to 1.78 (95% CI,

Table 3. Multivariable Regression Analysis for Association Between CVD and CRP Levels in the MDRD Study

	OR (95% CI)
Age	1.09 (1.06-1.11)
Sex (women v men)	0.38 (0.22-0.64)
CRP ≤0.6 v >0.6 mg/dL	1.73 (1.07-2.78)
Systolic blood pressure (mm Hg)	1.00 (0.99-1.01)
Total cholesterol (mg/dL)	1.00 (1.00-1.01)
Current smoker	1.45 (0.70-3.02)
Diabetes	1.45 (0.66-3.18)

NOTE. CI excluding 1.0 implies statistical significance at the 5% level. CVD is the composite outcome of coronary artery disease or peripheral vascular disease or cerebrovascular disease. To convert total cholesterol in mg/dL to mmol/L, multiply by 0.0259.

1.01 to 2.89). Albumin level was not significantly associated with CVD even after CRP level was excluded from the model (OR for 1-g/dL increase in albumin level, 1.48; 95% CI, 0.76 to 2.88).

DISCUSSION

In summary, in this large group of subjects with reduced GFR, CRP levels approximate those in the general population. As in patients with kidney failure, there appears to be an association between CRP level with both nutritional indices and CVD. However, GFR level does not appear to be related to CRP level in the MDRD Study randomized cohort.

There is increased inflammatory activity with concomitant activation of the acute-phase response in patients on dialysis therapy.[4,33,34] Levels of CRP, an acute-phase protein, are elevated in patients on dialysis therapy.[3,5] It has been suggested that the dialysis process itself may be responsible in part for inducing the acute-phase reaction seen in kidney failure. Several mechanisms have been postulated to explain this phenomenon,[35] including induction of cytokine release by interaction of mononuclear cells with particular types of dialysis membranes,[36] dialysate contaminated by bacterial products,[37]and subclinical arteriovenous graft infection or occult infections elsewhere.[38,39] There are limited data on CRP levels in the earlier stages of chronic kidney disease.

Our results show that CRP levels in the MDRD Study, adjusted for age and sex, approximate levels from a general population sample derived from the NHANES 1999 to 2000 data set. How-

ever, we noted that the relationship of CRP level with age was different in the 2 studies. That is, CRP levels were slightly greater in older MDRD subjects and lower in younger MDRD subjects in comparison to the NHANES sample. The reason for this difference is not entirely clear. One potential explanation is there may be differences in other factors that influence CRP levels, and these factors differ in the various age subgroups of the MDRD and NHANES samples.

The prevalence of high CRP level, defined as CRP level greater than 0.6 mg/dL, also was similar in both populations, and there was no relationship between level of CRP and GFR in univariate analysis in the MDRD cohort. The lack of association between level of CRP and GFR is consistent with another study of subjects with reduced kidney function. In a cohort of 66 patients with a mean creatinine clearance (C_{Cr}) of 32 mL/min (0.53 mL/s), high-sensitivity CRP levels did not correlate with either proteinuria or C_{Cr}.[8] A study of 109 predialysis patients (mean GFR, 7 ± 1 mL/min) also was consistent with our data by showing similar serum creatinine and urea levels between patients with a CRP level of 10 mg/L or greater and those with a CRP level less than 10 mg/L.[15]

In contrast to our findings, Panichi et al[40] noted greater CRP levels in patients with a C_{Cr} less than 20 mL/min (0.33 mL/s) (mean CRP, 7.4 ± 6.3 mg/L) compared with those with a C_{Cr} greater than 20 mL/min (mean CRP, 2.76 ± 4.35 mg/L) in 102 patients with a mean C_{Cr} of 52 ± 37 mL/min (0.87 ± 0.62 mL/s). Similarly, a cross-sectional analysis of data from the Cardiovascular Health Study found an association between kidney function and several inflammatory markers, including CRP level.[41] Of note in the first study, approximately 12% of subjects had diabetic nephropathy and an unknown percentage had a history of CVD, and the Cardiovascular Health Study cohort consisted of subjects aged 65 years or older. We are unable to definitively explain the inconsistencies in results, but a few possibilities include the following. First, studies have used assays with varying sensitivities to CRP, potentially resulting in discrepancies between results. Second, differences in comorbidity of the populations may have a role. For example, it is well recognized that the prevalence of CVD increases as GFR declines[42]; therefore,

in populations with additional comorbid conditions, such as diabetes, as well as both clinical and subclinical CVD, CRP level, which may track with the presence of CVD, could increase as GFR declines. Conversely, in a healthier population with a low prevalence of clinical and subclinical CVD, such as the MDRD Study, the relationship between CRP level and GFR may be less evident.

One potential consequence of the systemic inflammatory response in kidney failure is the development of malnutrition. Cytokines impact on nutritional status by inducing anorexia and reduced food intake, as well as by modulating protein catabolic rate.[43] Accumulating evidence suggests an association between acute-phase proteins that are indicators of inflammation and markers of malnutrition in kidney failure.[13,15,30,44] Data from the Hemodialysis Study showed that serum albumin concentrations over time were negatively associated with corresponding levels of several acute-phase proteins, including $\alpha1$-acid glycoprotein, ceruloplasmin, transferrin, and CRP.[31] Thus, markers of inflammation and malnutrition appear to be closely linked in kidney failure.

In our sample of patients with reduced GFR, CRP level was an independent, albeit weak, determinant of serum albumin level. This finding is consistent with a study of subjects with reduced GFR in which greater baseline CRP levels correlated inversely with serum albumin levels and were predictive of albumin level decline at 1 year of follow-up.[8] In combination, these data support the hypothesis that the protein-energy malnutrition and anorexia of uremia may be part of a malnutrition inflammation complex mediated by cytokines,[45] and that this process begins in subjects with reduced GFR.

However, we acknowledge that serum albumin level may both reflect nutritional status and be a negative acute-phase reactant. Therefore, it is difficult to ascertain whether the relationship between CRP and albumin level is caused by an association between inflammation and malnutrition or an association between one marker of inflammation and another marker of inflammation. That CRP level is inversely related to energy intake and the relationship between CRP and albumin levels is partly attenuated by adjustment for other factors, including nutritional indi-

ces, is consistent with the possibility that both processes may be contributory.

It was recently recognized that CRP level is associated with indicators of subclinical atherosclerosis such as carotid artery intima media thickness and carotid plaque in predialysis patients[15] and is a risk factor for myocardial infarction[26] and mortality from CVD in dialysis patients.[2,7] Our data show that CRP level is also associated with CVD risk factors such as systolic blood pressure and cholesterol, triglyceride, and Lp(a) levels in subjects with less advanced kidney disease with a wide range of reduced GFR. CRP is also independently associated with prevalent CVD in this population.

In our sample, serum albumin level was not significantly associated with CVD and did not confound the association of CRP level with CVD. One potential interpretation of this finding is that hypoalbuminemia is not an intermediary in the path between inflammation and CVD. Rather, inflammation may result in CVD and decreased albumin levels through parallel processes. Furthermore, the relationship between decreased albumin levels and CVD may not be appreciated in a relatively healthy population with a low prevalence of both malnutrition and CVD, such as the MDRD Study.

There are 3 potential limitations of our study. First, because of its cross-sectional nature, this study is limited in terms of deriving mechanistic conclusions; however, results of this study are hypothesis generating and provide insights into the relationship between inflammation, albumin level, and CVD in subjects with reduced GFR.

Second, frozen samples were used for the measurement of CRP. However, there is a precedent for using frozen stored samples to analyze CRP, and CRP appears to be stable despite extended storage[46-49] and up to 4 freeze-thaw cycles.[49] Furthermore, relationships between CRP levels and other factors were consistent with those described previously. For example, CRP level directly correlated with markers of body fat[50,51] and other markers of inflammation, such as white blood cells and Lp(a).[52] In addition, CRP level correlated inversely with vitamin B_6 level.[53] Finally, CRP levels were higher in subjects with CVD.[8]

The third potential limitation relates to CRP being measured at 1 point in time. The stability of CRP over time in subjects with a reduced GFR is unknown. CRP levels are known to fluctuate in subjects in the general population[54]; however, there appears to be a close correlation between readings in the same person, with some individuals having consistently greater values than others.[8,49] Furthermore, single baseline measurements have been associated with cardiovascular outcomes in several studies.[5,6] Therefore, although levels measured at 1 point in time are not optimal, they are likely to reflect general inflammatory status.

The generalizability of this study is limited because the MDRD randomized cohort is relatively young and has only a few subjects with diabetes or advanced atherosclerosis compared with the population of patients with chronic kidney disease with a similar range of GFR.[55] However, this limitation also is a strength because the low prevalence of CVD decreases the confounding effect of CVD on the relationship between CRP with level of kidney function and CRP with nutritional indices.

In conclusion, kidney function per se does not appear to influence CRP levels in patients with reduced GFR. As in kidney failure, higher CRP levels are independently associated with lower albumin levels and the presence of CVD. Inflammatory processes may have a role in the development of both malnutrition and CVD in the earlier stages of kidney disease.

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