Inflammatory and Prothrombotic Markers and the Progression of Renal Disease in Elderly Individuals

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Abstract. Inflammatory and prothrombotic markers are elevated in individuals with mild to moderate renal disease. It was hypothesized that these markers may also be determinants of the progression of renal disease. The association of six markers—serum C-reactive protein (CRP), white blood cell (WBC) count, fibrinogen, factor VII, albumin, and hemoglobin—with subsequent elevations of creatinine and decline in estimated GFR in the Cardiovascular Health Study, a community-based cohort of elderly individuals, was analyzed. Linear regression was used to determine predictors of an annualized change in serum creatinine as the main outcome. Duration of follow-up was 7 yr for the original cohort and 4 yr for the more recently recruited black cohort. A total of 588 (12.7%) individuals had a decline in estimated GFR of at least 3 ml/min per yr per 1.73 m^2. Higher CRP ($P < 0.001$), WBC count ($P < 0.001$), fibrinogen ($P < 0.001$), and factor VII ($P < 0.001$) levels and lower albumin ($P < 0.001$) and hemoglobin levels ($P < 0.001$) were associated with a rise in creatinine, after adjusting for age. With additional adjustments for race, gender, baseline creatinine, systolic and diastolic BP, lipid levels, weight, and pack-years smoking, higher CRP, factor VII, fibrinogen, WBC count, and lower albumin and hemoglobin levels remained associated with a rise in creatinine. Similar results were found for decline in estimated GFR. The decline in GFR was greater with increasing number of inflammatory or prothrombotic markers that were above the median (below for hemoglobin and albumin). Inflammatory and prothrombotic markers are predictors for a change in kidney function in elderly individuals. Interventions that reduce inflammation might confer significant cardiovascular and renal benefits.

Patients with renal failure have a high prevalence of cardiovascular disease, and it has been proposed that atherosclerosis may promote the progression of renal disease in older individuals (1). Diamond *et al.* (2) proposed that mechanisms that result in atherosclerosis also cause glomerulosclerosis and that renal disease in atherosclerosis is not simply the result of ischemia from renal artery disease. In his model, glomerulosclerosis results from the influx and accumulation of inflammatory cells (monocytes and macrophages), with mesangial cells responding in a similar manner to vascular smooth muscle cells. If this hypothesis is correct, then renal disease and cardiovascular disease should share similar risk factors. In particular, inflammatory and prothrombotic factors, which are risk factors for atherosclerosis (3), might be important factors in the progression of renal disease. The relationship of inflammation to a subsequent loss of renal function has not been previously examined in a population-based sample.

We have previously found that inflammatory and prothrombotic markers are elevated in elderly individuals with mild to moderate renal insufficiency, a relationship that persisted after adjusting for the greater extent of atherosclerosis that is present in individuals with renal insufficiency (4). In a previous analysis of the Cardiovascular Health Study (CHS), Bleyer *et al.* (5) found that progression of renal disease after 4 yr was predicted by a low baseline serum albumin, which may be a marker of systemic inflammation. In the current analysis, we examine the relationship of inflammatory and prothrombotic

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markers with progression of renal insufficiency in elderly individuals.

Materials and Methods

Participants and Design

CHS is a prospective, longitudinal study of elderly community-dwelling adults. CHS participants were recruited from Medicare eligibility lists at four locations: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA (6). They were invited to participate when they were community-dwelling adults, were aged 65 or older, were free of cancer or other life-threatening diseases, expected to remain in the area for the next 3 yr, and were able to give informed consent without a proxy. Renal dysfunction did not exclude individuals from participating in CHS. The initial cohort was recruited in 1989 to 1990, and a second cohort of 687 blacks was recruited in 1992 to 1993, resulting in a total of 5888 participants.

The design and details of the initial examination were described previously (6). Baseline clinical and subclinical cardiovascular status was determined by a review of medical records and by electrocardiogram (ECG), echocardiography, carotid artery ultrasound, and ankle-arm index (AAI) (6–9). Prevalent cardiovascular disease (CVD) was defined as history of coronary heart disease (myocardial infarction, angina, bypass surgery, percutaneous coronary angioplasty, and use of nitrates), claudication, congestive heart failure, transient ischemic attack, or stroke (9).

Outcome

Creatinine was measured at baseline (study year 2), year 5, and year 9. Creatinine values in the years after baseline were adjusted for drift. The black cohort had creatinine measured at baseline (study year 5) and 4 yr later (study year 9). Baseline serum creatinine was missing on 80 (1.4%) participants. At least two creatinine values were available for 4620 individuals. As there was a different length of follow-up for the original and black cohorts, the average annual change in creatinine was determined by linear regression as the slope of the change in creatinine for each individual. The main outcome was change in creatinine. We also analyzed change in estimated GFR with the four-variable Modification of Diet in Renal Disease (MDRD) formula (10). As the mean change was small, to analyze a clinically relevant decrease in renal function, we dichotomized the annual change in GFR (annual decrease $\geq$3 ml/min per yr per 1.73 m^2). We chose this number on the basis of a previous study of change in renal function (11).

Exposures

Laboratory tests were performed after an 8- to 12-h fast. Detailed methods for blood drawing, quality assurance, and assay performance were described previously (8). Serum chemistries, including creatinine, were performed on the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY); the Olympus Demand System (Olympus, Lake Success, NY) was used for total and HDL cholesterol and triglycerides; LDL cholesterol was calculated by the Friedewald formula (12); fibrinogen was measured in a BBL fibrometer (Becton Dickinson, Cockeysville, MD); factor VII assay was performed using Coag-A-Mate (Organon Teknika); and C-reactive protein (CRP) was measured using an ELISA (13). The interassay coefficient of variation for CRP was 5.5%. The coefficients of variation were 3.25% for albumin, 3.09% for fibrinogen, and 5.31% for factor VII. Hemoglobin was measured in local hematology laboratories near each field center, with monitoring of internal and external quality assurance reports (13). The laboratory values used in these analyses were from the baseline visit.

Diabetes was defined as the use of insulin or oral hypoglycemic agents or a fasting glucose level $\geq$126 mg/dl. Impaired glucose tolerance was defined as a fasting glucose $>$110 but $<$126 mg/dl. Echocardiography was performed using a standardized procedure using a Toshiba SSH-160A machine recorded onto super-VHS tape and sent to the echocardiography reading center for review (14). Left ventricular ejection fraction (LVEF) was characterized as normal or abnormal. LVEF was available at baseline for the original cohort and at year 7 (2 yr after enrollment) for the black cohort. For the AAI, after 5 min of rest in the supine position, BP cuffs were applied to the right arm and both ankles. After identification of each artery using palpation or a Doppler stethoscope (8 MHz; Huntleigh Technology, Inc.), the BP was measured for each artery using a standard mercury manometer. The lowest ratio of AAI was used for these analyses. Major ECG variable abnormalities were based on Minnesota codes (15). The common carotid artery was evaluated by high-resolution B-mode ultrasonography to determine the maximal intimal-medial thickness (IMT) and the maximum stenosis (0, 1 to 24, 25 to 49, 50 to 74, 75 to 99, or 100%) as described previously (16).

Statistical Analyses

Differences in participant characteristics were compared with ANOVA using F test for continuous variables and χ^2 test for discrete variables; Bonferroni adjusted tests for significance were used for comparisons among groups. CRP and pack-years were compared using k-sample test of equality of medians as these variables are skewed. As inflammatory and thrombotic markers were the main variables of interest, the initial models evaluated the age-adjusted association of these variables (CRP, albumin, white blood cell [WBC] count, fibrinogen, factor VII, and hemoglobin) with creatinine rise or GFR decline. We log-transformed CRP to normalize its distribution. Factors associated with the annual change in creatinine or GFR were analyzed using linear regression. For the dichotomous outcomes, logistic regression was used. Multivariate models were examined after adjustment for inflammatory and thrombotic markers, age, gender, race (black, other), diabetes (normal, glucose intolerance, diabetes), AAI, LVEF, IMT, major ECG abnormalities, baseline creatinine, weight, systolic and diastolic BP, lipids, and pack-years smoking. AAI, baseline creatinine, logCRP, fibrinogen, albumin, factor VII, WBC count, hemoglobin, age, weight, BP, carotid IMT, and pack-years were examined as continuous variables. The GFR models did not include age, race, or gender as covariates as they are in the GFR formula. Residuals were plotted *versus* the predictor (inflammatory and procoagulant markers) to assess whether there was departure from linearity for these variables. As this analysis did not reveal departure from linearity, continuous variables were used. The initial models were examined using a backward stepwise procedure ($P = 0.10$ for removal and 0.05 for addition to the model) to determine important covariates for which to control. The final models did not use selection procedures. As the inflammatory and prothrombotic markers are correlated with each other (4), the addition of all of the inflammatory markers into the model at once could weaken the strength of the individual variables, despite an association of inflammation with a rise in creatinine or decline in GFR. We therefore examined combinations of inflammatory and prothrombotic markers in the multivariate analysis. In addition to individual markers, we analyzed whether the number (0 to 6) of abnormal markers (defined as above the median for CRP, fibrinogen, WBC count, and factor VII and below the median for albumin and hemoglobin) was associated with a decline in GFR.

Multivariate models considered different combinations of inflammatory and thrombotic markers, as the main independent variables, while adjusting for age, race, baseline creatinine, HDL, AAI, major ECG abnormalities, weight, diabetes (none, impaired fasting glucose, diabetes), systolic BP, and pack-years smoking. Adjustment for baseline creatinine did not affect the results of the association of inflammatory markers with the change in renal function but was included to adjust for regression to the mean. To control further for regression to the mean, we repeated analyses after stratifying for baseline creatinine. Interactions of the inflammatory markers with age, race, gender, and prevalent cardiovascular disease were examined.

STATA Statistical Software, Release 8.0 (Stata Corp., College Station, TX) was used for the analyses. Data are expressed as means and SD unless otherwise specified. $P < 0.05$ was considered statistically significant.

Results

A total of 4620 individuals had at least two creatinine measures and 2785 had three measures. The change in estimated GFR was normally distributed (Figure 1). A total of 588 (12.7%) individuals had a decrease in estimated GFR ≥3 ml/min per yr per 1.73 m^2. The characteristics of participants with and without a decrease in GFR are shown in Table 1. Compared with those with a stable GFR, individuals with a decrease in GFR were more likely to be older, to be black, and to have diabetes. CRP, fibrinogen, WBC count, systolic BP levels, and carotid IMT were higher, whereas albumin, hemoglobin, and AAI were lower in those whose GFR decreased. The baseline creatinine was lower in participants with a subsequent decline in GFR. A total of 390 (8.4%) individuals had an increase in estimated GFR ≥3 ml/min per yr per 1.73 m^2. Compared with those with a decline in GFR, these individuals were more likely to be male, had lower systolic BP and fibrinogen, and had higher albumin and hemoglobin levels (Table 1).

In age-adjusted analysis, the inflammatory and prothrombotic markers were associated with a rise in creatinine. The direction of association was consistent with inflammation, *i.e.*, higher WBC count and CRP, fibrinogen, and factor VII levels, and lower serum albumin and hemoglobin were significantly associated with a rise in creatinine (Table 2). Individually, each of the inflammatory variables remained associated with a rise in serum creatinine, after adjusting for significant noninflammatory variables (Table 2). The small β reflect that the creatinine did not change in most participants. The results were the same when estimated GFR was analyzed instead of creatinine. Table 3 shows the results for the combinations of inflammatory and prothrombotic markers in the multivariate analysis for rise in creatinine. As fibrinogen and logCRP were highly correlated (0.51 by Pearson correlation) and seemed to be similar in explaining the variance in the population, we chose the variable with the higher significance (CRP) and excluded fibrinogen from the multivariate models. The results for estimated GFR as a linear outcome were similar, except that CRP and WBC count were related to a decline in GFR but factor VII was not. In the logistic model for a decline of GFR of ≥3 ml/min per yr per 1.73 m^2, albumin (adjusted odds ratio [OR], 0.45 per 1 g/L increase; 95% confidence interval [CI], 0.32 to 0.64; $P < 0.001$), hemoglobin (adjusted OR, 0.82 per 1 g/dl increase; 95% CI, 0.76 to 0.89; $P < 0.001$), factor VII (adjusted OR, 0.95 per 10% increase; 95% CI, 0.92 to 0.99; $P = 0.008$), WBC count (adjusted OR, 1.06; 95% CI, 1.02 to 1.11; $P = 0.006$), and CRP (adjusted OR, 1.22 per 1 log mg/L increase; 95% CI, 1.11 to 1.35; $P < 0.001$) were significant in combination. In contrast to results for creatinine, a higher factor VII level was associated with a lower odds for a decrease in GFR. Tests for interaction of the inflammatory markers with age and gender were NS. However, there were significant interactions of race and prevalent CVD with the inflammatory markers (Table 4). The relationship of the inflammatory markers on change in creatinine seem to be stronger in blacks and in those with prevalent CVD. The relationship was also stronger in those with a higher baseline creatinine (Table 5). We found that the greater the number of inflammatory markers that were elevated, the more negative the β (slope) of the change in GFR (Figure 2).

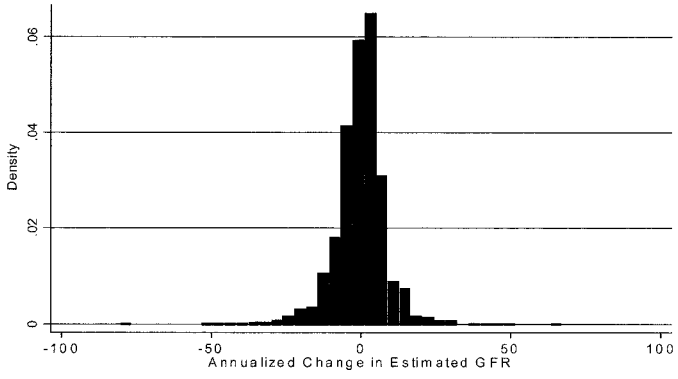

Figure 1. Annualized change in estimated GFR (ml/min per yr per 1.73 m^2).

Discussion

Renal insufficiency is associated with higher levels of inflammatory and prothrombotic markers, and this may be one of the explanations for the increased risk of cardiovascular disease among individuals with renal insufficiency (4,17). In this study, we found that markers of inflammation and thrombosis were also associated with a subsequent rise in serum creatinine and decline in estimated GFR. On the basis of the results from this study and previous studies (4,17), one may hypothesize a positive feedback loop, in which renal insufficiency leads to elevations of inflammatory markers, which then leads to progression of renal disease and further increases in inflammatory markers. The precise mechanisms through which inflammation would lead to a decline in renal function are not clear. Cytokines could act directly on the endothelium and mesangium of the glomerulus. Alternatively, the relationship of inflammatory and prothrombotic markers with progression of renal disease could be mediated through acceleration of atherosclerosis. Controlling for baseline subclinical atherosclerosis had only a small effect on the relationship between inflammatory markers and rise in creatinine, suggesting that the association was independent of systemic atherosclerosis. However, the associ-

Table 1. Characteristics of participants by change in estimated GFR (ml/min per year per 1.73 m^2)[a]

Variable	Decrease in GFR ≥3 ml/min per year per 1.73 m^2	Stable GFR	Increase in GFR ≥3 ml/min per year per 1.73 m^2	*P* Value[b]
N (%)	588 (12.7)	3642 (78.8)	390 (8.4)	
Age (SD)	72.8 (5.6)[d]	72.0 (5.0)	72.9 (5.5)[d]	0.0001
Race (black, %)	174 (29.6)[d,e]	381 (10.5)	43 (11.0)[c]	<0.0001
Gender (male, %)	196 (33.3)[d,e]	1522 (41.8)	202 (51.8)[c,d]	<0.0001
Risk factors				
Baseline creatinine (mean, SD)	0.88 (0.30)	1.05 (0.29)	1.12 (0.28)[c,d]	<0.0001
diabetes				
none (*n* [%])	374 (63.6)[d]	2702 (74.4)	264 (67.7)[d]	<0.0001
glucose intolerance	67 (11.4)	478 (13.2)	65 (16.7)	0.056
diabetes	147 (25.0)[d,e]	452 (12.4)	61 (15.6)[c]	<0.0001
prevalent CVD (*n* [%])	150 (25.5)	779 (21.4)	112 (28.7)[d]	0.0008
pack-years (median [5, 95])	1.8 (0, 70)[e]	1 (0, 64.5)	8 (0, 84)[c,d]	0.015
LDL (mg/dl)	127.6 (35.2)	130.7 (35.2)	128.1 (35.6)	0.08
HDL (mg/dl)	54.1 (15.4)	54.7 (15.8)	52.4 (14.4)[d]	0.013
triglycerides (mg/dl)	140.8 (75.0)	138.3 (7.5)	140.5 (71.7)	0.67
weight (lb)	162.4 (31.5)	160.1 (31.4)	160.0 (31.6)	0.26
systolic BP (mmHg)	141.2 (22.5)[d,e]	134.7 (21.0)	133.9 (20.3)[c]	<0.0001
diastolic BP (mmHg)	70.9 (11.8)	70.6 (11.0)	70.7 (11.1)	0.81
Inflammatory markers				
CRP (mg/L; median [5, 95])	2.3 (0.47, 17.7)[d,e]	1.8 (0.39, 10.5)	1.9 (0.37, 11.4)[c]	<.00001
fibrinogen (mg/dl; mean [SD])	335.0 (71.8)[d,e]	317.3 (61.4)	312.3 (63.9)[c]	<0.0001
albumin (g/dl; mean [SD])	3.93 (0.28)[d,e]	4.01 (0.29)	4.05 (0.29)[c]	<0.0001
hemoglobin (g/dl; mean [SD])	13.7 (1.33)[d,e]	14.1 (1.37)	14.3 (1.49)[c,d]	<0.0001
WBC count (1000/mm^3; mean [SD])	6.6 (3.0)[d]	6.2 (1.9)	6.3 (1.6)	<0.0001
factor VII (%; mean [SD])	123.1 (28.3)	124.2 (29.0)	121.4 (31.3)	0.16
Subclinical atherosclerosis				
carotid IMT (mm; mean [SD])	1.09 (0.22)[d]	1.04 (0.20)	1.08 (0.23)[d]	<0.0001
AAI (mean [SD])	1.04 (0.17)[d]	1.09 (0.16)	1.05 (0.19)[d]	<0.0001
Abnormal LVEF (*n* [%])	15 (2.6)	85 (2.4)	13 (3.4)	0.46
Maximum carotid stenosis (%)				0.015
0 (*n* [%])	123 (21.0)	908 (25.0)	75 (19.3)	
1–24	184 (31.4)	1143 (31.5)	106 (27.3)	
25–49	258 (44.0)	1.439 (39.7)	190 (49.0)	
50–74	19 (3.2)	104 (2.9)	15 (3.9)	
75–99	3 (0.5)	23 (0.6)	1 (0.3)	
100	0 (0)	10 (0.3)	1 (0.3)	
major ECG abnormalities (*n* [%])	177 (30.9)[d]	900 (25.5)	115 (30.3)	0.006

[a] CVD, cardiovascular disease; CRP, C-reactive protein; WBC, white blood cell; IMT, intimal-medial thickness; AAI, ankle-arm index; LVEF, left ventricular ejection fraction; ECG, electrocardiogram.

[b] The significance of the three groups based on ANOVA F test for continuous variables and χ^2 tests for discrete variables, except for pack-years smoking and CRP, which were compared using k-sample test of medians.

[c] Significantly different ($P < 0.05$) from the low estimated GFR group, using Bonferroni-adjusted test for significance.

[d] Significantly different ($P < 0.05$) from the stable estimated GFR group, using Bonferroni-adjusted test for significance (note: if one group is significantly different from the stable group, then it is implicit that the stable group is significantly different from that group).

[e] Significantly different ($P < 0.05$) from the high estimated GFR group, using Bonferroni-adjusted test for significance.

ation of inflammatory markers with change in renal function was greater in individuals with prevalent CVD.

Currently, the data on the relationship of inflammation and prothrombotic markers with progression in nonimmunologic renal disease are scant. In a recent analysis of the MDRD Study, Sarnak *et al.* (18) examined the association of CRP levels with decline in GFR. They did not find a significant association in either univariate or multivariate analysis. Our contrasting findings could be attributed to significantly different source populations. The subjects in MDRD primarily had polycystic kidney disease or primary glomerular disease but did not include diabetic nephropathy. The subjects in CHS

Table 2. Association of inflammatory and thrombotic markers with change in creatinine per year[a]

Variable	Age-Adjusted β (95% CI)[b]	*P* Value	Multivariate Adjusted (95% CI)[c]	*P* Value
logCRP (1 log mg/L)	0.006 (0.004 to 0.008)	<0.001	0.004 (0.001 to 0.006)	0.001
Albumin (1 g/dl)	−0.025 (−0.032 to 0.018)	<0.001	−0.026 (−0.032 to −0.017)	<0.001
Fibrinogen (50 mg/dl)	0.005 (0.004 to 0.007)	<0.001	0.004 (0.002 to 0.005)	<0.001
Factor VII (10%)	0.002 (0.001 to 0.002)	<0.001	0.002 (0.001 to 0.003)	<0.001
WBC count (1000/mm^3)	0.002 (0.001 to 0.003)	<0.001	0.001 (0.0003 to 0.002)	0.012
Hemoglobin (1 g/dl)	−0.005 (−0.007 to −0.004)	<0.001	−0.006 (−0.007 to −0.004)	<0.001

[a] CI, confidence interval.
[b] Each variable individually analyzed in linear model with age alone.
[c] Adjusted for baseline creatinine, HDL, AAI, major ECG abnormalities, age, race, weight, diabetes (none, impaired fasting glucose, diabetes), systolic BP, and pack-years smoking, without the other inflammatory or prothrombotic markers.

Table 3. Multivariate analysis of combinations of inflammatory markers with change in serum creatinine per year[a]

Model	β (95% CI)	*P* Value
CRP and albumin[a]		
logCRP (1 log mg/L)	0.003 (0.001 to 0.005)	0.010
albumin (1 g/dl)	−0.025 (−0.032 to −0.017)	<0.001
CRP and factor VII[a]		
logCRP	0.003 (0.0004 to 0.005)	0.023
factor VII (10%)	0.002 (0.001 to 0.002)	<0.001
CRP and hemoglobin[a]		
logCRP	0.003 (0.0003 to 0.005)	0.023
hemoglobin (1 g/dl)	−0.006 (−0.007 to −0.004)	<0.001
CRP and WBC count[a]		
logCRP	0.003 (0.001 to 0.005)	0.004
WBC count (1000/mm^3)	0.001 (−0.00005 to 0.0021)	0.063
CRP, albumin, and hemoglobin[a]		
logCRP	0.002 (−0.0001 to 0.004)	0.07
albumin	−0.020 (−0.027 to −0.012)	<0.001
hemoglobin	−0.005 (−0.006 to −0.003)	<0.001
CRP, albumin, and factor VII[a]		
logCRP	0.002 (−0.0006 to 0.004)	0.14
albumin	−0.025 (−0.033 to −0.018)	<0.001
factor VII	0.002 (0.001 to 0.003)	<0.001
CRP, hemoglobin, and factor VII[a]		
logCRP	0.002 (−0.0005 to 0.004)	0.12
hemoglobin	−0.005 (−0.007 to −0.004)	<0.001
factor VII	0.001 (0.001 to 0.002)	<0.001
CRP, albumin, hemoglobin, and factor VII[a]		
logCRP	0.001 (−0.001 to 0.003)	0.30
albumin	−0.021 (−0.028 to −0.013)	<0.001
hemoglobin	−0.004 (−0.006 to −0.002)	<0.001
factor VII	0.001 (0.0007 to 0.002)	<0.001

[a] Adjusted baseline creatinine, HDL, AAI, major ECG abnormalities, age, race, weight, diabetes (none, impaired fasting glucose, diabetes), systolic BP, and pack-years smoking.

were older, were representative of the general population, and had more vascular disease at baseline. Erlinger *et al.* (19) found in an analysis of National Health and Nutrition Examination Survey data that an elevated WBC count was predictive of ESRD or death. In a study of type 1 diabetes, Orchard *et al.* (20) found that an elevated WBC count was associated with progression from microalbuminuria to overt nephropathy, suggesting that inflammation may be important in the progression of early diabetic nephropathy. Although our study is limited to the elderly, that both of these studies found that an elevated

Table 4. Interactions of race and prevalent CVD with the inflammatory markers on change in serum creatinine

Variable	Nonblack		Black		Interaction *P* Value
	Age-Adjusted β (95% CI)	*P* Value	Age-Adjusted β (95% CI)	*P* Value	
logCRP (1 log mg/L)	0.005 (0.003 to 0.007)	<0.0005	0.011 (0.003 to 0.018)	0.004	0.056
Albumin (1 g/dl)	−0.019 (−0.026 to −0.012)	<0.0005	−0.049 (−0.075 to −0.023)	<0.0005	0.002
Fibrinogen (50 mg/dl)	0.004 (0.002 to 0.005)	<0.0005	0.007 (0.002 to 0.013)	0.011	0.105
Factor VII (10%)	0.002 (0.001 to 0.002)	<0.0005	0.006 (0.003 to 0.009)	<0.0005	<0.0005
WBC count (1000/mm^3)	0.002 (0.001 to 0.003)	0.002	0.003 (0.001 to 0.006)	0.012	0.100
Hemoglobin (1 g/dl)	−0.004 (−0.006 to −0.003)	<0.0005	−0.005 (−0.009 to −0.001)	0.016	0.481
	No History of CVD		History of CVD		
logCRP (1 log mg/L)	0.005 (0.003 to 0.007)	<0.0005	0.010 (0.004 to 0.016)	0.001	0.019
Albumin (1 g/dl)	−0.017 (−0.023 to −0.011)	<0.0005	−0.051 (−0.072 to −0.030)	<0.0005	<0.0005
Fibrinogen (50 mg/dl)	0.005 (0.003 to 0.006)	<0.0005	0.006 (0.001 to 0.010)	0.012	0.499
Factor VII (10%)	0.002 (0.001 to 0.002)	<0.0005	0.003 (0.0005 to 0.005)	0.016	0.224
WBC count (1000/mm^3)	0.001 (0.0004 to 0.002)	0.007	0.003 (0.0002 to 0.005)	0.033	0.231
Hemoglobin (1 g/dl)	−0.004 (−0.005 to −0.002)	<0.0005	−0.010 (−0.015 to −0.006)	<0.0005	<0.0005

Table 5. Interaction of baseline creatinine with the inflammatory markers and change in serum creatinine[a]

Variable	Low Baseline Creatinine Women: ≤0.8 Men: ≤1.1		Midbaseline Creatinine Women: 0.8–1.0 Men: 1.1–1.3		High Baseline Creatinine Women: >1.0 Men: >1.3		Interaction *P* Value
	Adjusted β	*P* Value	Adjusted β	*P* Value	Adjusted β	*P* Value	
logCRP (1 log mg/L)	0.002	0.07	0.002	0.08	0.010	0.02	<0.0005
Albumin (1 g/dl)	−0.010	0.002	−0.013	0.002	−0.061	<0.0005	<0.0005
Fibrinogen (50 mg/dl)	0.002	0.042	0.003	0.007	0.008	0.020	<0.0005
Factor VII (10%)	0.0006	0.10	0.001	0.003	0.006	<0.0005	<0.0005
WBC count (1000/mm^3)	0.002	0.005	0.0002	0.73	0.002	0.16	0.28
Hemoglobin (1 g/dl)	−0.002	0.004	−0.002	0.004	−0.018	<0.0005	<0.0005

[a] Adjusted for HDL, AAI, major ECG abnormalities, age, race, weight, diabetes (none, impaired fasting glucose, diabetes), systolic BP, and pack-years smoking.

WBC count is predictive of progression of renal disease suggests that inflammation may be an important mediator of progression in other groups. However, even if the findings were limited to elderly individuals, this would still be an important finding as the elderly make up the largest proportion of individuals with chronic kidney disease (21).

We found that several measures of inflammation and thrombosis were associated with an increased risk for a rise in serum creatinine. The data seemed to be strongest for the inflammatory markers, as we did not find consistent results across models for factor VII. Although anemia is a frequent complication of renal disease, our study suggests that it is also a predictor of a rise in creatinine, after adjusting for baseline creatinine levels. Our data are consistent with a recent study of predictors for progression of diabetic nephropathy in type 2 diabetes, which found that low hemoglobin levels predicted the doubling of serum creatinine (22), although this study did not control for inflammatory markers. In ESRD, a low hemoglobin level is associated with elevated CRP levels (23). This relationship is less clear in earlier renal disease. Although we considered a low hemoglobin level to be a marker of inflammation, the relationship with a rise in creatinine could be due to other reasons, such as changes in hemodynamics and renal perfusion. That anemia might directly affect renal function is supported by Silverberg *et al.* (24), who found that treatment of anemia in heart failure led to improvement in both cardiac and renal function. Lower serum albumin was also associated with a rise in creatinine; however, it is possible that low serum albumin reflects proteinuria rather than inflammation. Measurements of urine protein were not performed at baseline, so we are not able test whether proteinuria confounds the relationship between low serum albumin and decline in renal function. The degree of proteinuria has previously been shown to be an important predictor of the progression of renal disease (25,26). Of note, the strength of the association of these inflammatory markers varied. Why some of the inflammatory markers are stronger predictors than others of the rise in creatinine is not clear and should be studied further.

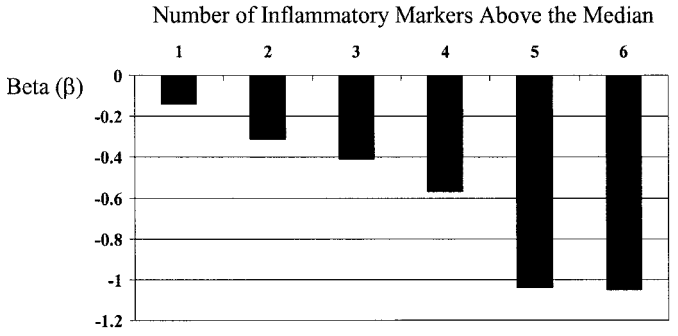

Figure 2. Slope of the change in estimated GFR by the number of elevated inflammatory markers (above the median for C reactive protein, fibrinogen, white blood cell count, and factor VII and below the median for albumin and hemoglobin). β are adjusted for HDL, ankle-arm index, major electrocardiogram abnormalities, age, race, weight, diabetes (none, impaired fasting glucose, diabetes), systolic BP, and pack-years smoking. There were 189 individuals with zero, 669 individuals with one, 1183 individuals with two, 1400 individuals with three, 1225 individuals with four, 767 individuals with five, and 235 individuals with six markers above the median. $P < 0.001$ for linear trend.

One of the strengths of the present study is that it is a population-based study and thus may be more generalizable to other elderly individuals. The cohort is well characterized, with the measurement of multiple inflammatory mediators and other cardiovascular risk factors. The inflammatory mediators were significant predictors of change in renal function even after controlling for other known predictors of progression, such as race, diabetes, and BP. A limitation of our study is that we do not have any direct measure of GFR. We used change in creatinine, which is relatively insensitive to small changes in renal function, as our outcome. Although we also use change in estimated GFR, the slope of change in estimated GFR is mainly due to change in serum creatinine and would also be insensitive to small changes in GFR. In addition, neither MDRD nor Cockcroft-Gault has been validated as a measure of change in GFR. Direct measures of renal function are not available in CHS because of the difficulties in acquiring these measures in large populations. We also do not have the ability to measure hemodynamic changes that could occur from CVD that would also affect kidney function. Improvement in hemodynamic factors could be one explanation for why those who had an improvement in GFR had a higher prevalence of CVD than those whose GFR did not change. Another possibility is that our results might represent, in part, regression to the mean. This can be a problem, irrespective of the measurement used to determine renal function (27). That the expected predictors for progression of kidney disease were also significant in our study supports a true association and provides external validity. In addition, the relationship of inflammatory markers with change in kidney function was greatest in those with a higher baseline serum creatinine, arguing against regression to the mean as an explanation of the results. Although the development of ESRD might have been an alternative outcome, follow-up was too short and renal disease and CVD seem to be competing risks, with most elderly individuals with an elevated creatinine in CHS dying before reaching ESRD (17,28). The relationship of inflammatory and prothrombotic markers with a rise in creatinine should be repeated in a younger cohort.

In summary, we found that inflammatory and prothrombotic markers were associated with a rise in serum creatinine. Efforts to understand and reduce the inflammatory state pharmacologically have the potential to decrease both the CVD associated with renal disease and the progression of renal disease.

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