Elevations of Inflammatory and Procoagulant Biomarkers in Elderly Persons With Renal Insufficiency

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Background—Renal insufficiency has been associated with cardiovascular disease events and mortality in several prospective studies, but the mechanisms for the elevated risk are not clear. Little is known about the association of renal insufficiency with inflammatory and procoagulant markers, which are potential mediators for the cardiovascular risk of kidney disease.

Methods and Results—The cross-sectional association of renal insufficiency with 8 inflammatory and procoagulant factors was evaluated using baseline data from the Cardiovascular Health Study, a population-based cohort study of 5888 subjects aged ≥65 years. C-reactive protein, fibrinogen, factor VIIc, and factor VIIIc levels were measured in nearly all participants; interleukin-6, intercellular adhesion molecule-1, plasmin-antiplasmin complex, and D-dimer levels were measured in nearly half of participants. Renal insufficiency was defined as a serum creatinine level ≥1.3 mg/dL in women and ≥1.5 mg/dL in men. Multivariate linear regression was used to compare adjusted mean levels of each biomarker in persons with and without renal insufficiency after adjustment for other baseline characteristics. Renal insufficiency was present in 647 (11%) of Cardiovascular Health Study participants. After adjustment for baseline differences, levels of C-reactive protein, fibrinogen, interleukin-6, factor VIIc, factor VIIIc, plasmin-antiplasmin complex, and D-dimer were significantly greater among persons with renal insufficiency ($P<0.001$). In participants with clinical, subclinical, and no cardiovascular disease at baseline, the positive associations of renal insufficiency with these inflammatory and procoagulant markers were similar.

Conclusion—Renal insufficiency was independently associated with elevations in inflammatory and procoagulant biomarkers. These pathways may be important mediators leading to the increased cardiovascular risk of persons with kidney disease. **(*Circulation*. 2003;107:87-92.)**

Key Words: inflammation ■ coagulation ■ kidney ■ coronary disease

As defined by elevated serum creatinine levels, renal insufficiency has been associated with incident cardiovascular disease events and cardiovascular disease mortality in prospective studies.[1,2] The increased cardiovascular risk for persons with renal insufficiency is explained in part by the increased prevalence and severity of diabetes and hypertension. However, other renal mechanisms, such as elevated levels of homocysteine, lipoprotein(a), and triglycerides and reduced levels of HDL cholesterol, likely contribute to the increased cardiovascular risk in renal insufficiency.

Additional pathways that might mediate the association between renal dysfunction and cardiovascular risk are the inflammatory and coagulation cascades. Several studies have demonstrated that inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen, and soluble adhesion molecules are associated with increased cardiovascular risk in healthy populations.[3–6] In addition, markers of increased coagulability and fibrinolysis, such as factor VII, factor VIII, plasmin-antiplasmin complex (PAP), and D-dimer, have been associated with cardiovascular disease events.[7–9] In persons with end-stage renal disease (ESRD), CRP, IL-6, and fibrinogen are elevated and are predictors of subsequent mortality.[10,11] Furthermore, patients with ESRD and predialysis renal failure demonstrate activa-

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tion of both inflammatory and thrombosis pathways, indicating that these abnormalities are not entirely a consequence of renal replacement therapies.[12–14] Whether mild renal insufficiency is associated with activation of the inflammatory and coagulation cascades has not been well studied.

In the present study, we compared levels of 8 inflammatory and procoagulant biomarkers among elderly persons with and without renal insufficiency using data collected at baseline in the Cardiovascular Health Study (CHS). We hypothesized that renal insufficiency would be independently associated with activated inflammation and a procoagulant state.

Methods

Subjects and Design

The CHS is a prospective cohort study of risk factors for cardiovascular disease events in elderly men and women. Potential participants were sampled at random from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. They were invited to participate in CHS if they met the following inclusion criteria: (1) aged ≥65 years, (2) not institutionalized, (3) expected to remain in the current community for ≥3 years, and (4) gave informed consent without requiring a proxy respondent. Among those who met the eligibility requirements and were invited to participate, 57% enrolled in CHS. The initial 5201 participants were enrolled by June 1990; an additional 687 black participants were recruited and enrolled by June 1993. This study is a cross-sectional analysis using information obtained on enrollment into CHS.

The baseline examination included a medical history, physical examination, laboratory testing, and assessments of cardiovascular disease status. The study design, quality-control procedures, laboratory methods, and blood-pressure measurement procedures have been published previously.[15]

Measurements

The primary predictor variable for this analysis was the presence of renal insufficiency. In all but 80 of the enrollees, serum creatinine levels were measured at entry into CHS. In the present study, we defined renal insufficiency as a serum creatinine level ≥1.5 mg/dL in men and ≥1.3 mg/dL in women because these cutoffs were associated with increased adjusted mortality in CHS. We also estimated creatinine clearance levels using the Cockcroft-Gault equation.[16]

Other covariates included demographic variables [age, sex, race (white, black, other), and education level] and cardiovascular risk factors [history of diabetes and hypertension, systolic and diastolic blood pressures, smoking status (never, current, former), LDL and HDL cholesterol and triglyceride levels, alcohol intake, body mass index, and physical activity (kcal)]. Hypertension was defined at the baseline examination as either a physician's diagnosis of hypertension, the use of antihypertensive medications, or seated systolic blood pressure level ≥140 and/or diastolic blood pressure level ≥90. Diabetes was defined as the use of insulin, oral hypoglycemic medications, or a fasting glucose level ≥126 mg/dL. Cardiovascular disease status was defined as prevalent cardiovascular disease, subclinical cardiovascular disease, and no cardiovascular disease. Prevalent cardiovascular disease included a history of myocardial infarction, revascularization procedure, angina, or stroke. Among persons without prevalent cardiovascular disease, subclinical cardiovascular disease was defined as either an ankle-arm index <0.9, common carotid intima-media thickness >1.18 mm (the upper quintile in CHS), left ventricular hypertrophy [left ventricular mass index ≥100 g/(height in meters)^2 in women or ≥131 g/(height in meters)^2 in men], or left ventricular function considered borderline or abnormal on echocardiography.

The outcome variables for this study were the inflammatory and thrombotic markers measured on baseline plasma from CHS participants. CRP, fibrinogen, factor VII, and factor VIII levels were measured on baseline blood samples in nearly all CHS participants. IL-6, intercellular adhesion molecule-1 (ICAM-1), D-dimer, and PAP levels were measured only in subjects subsequently enrolled in the CHS Case-Cohort substudy (n=2454), whose selection was based on the presence or absence of prevalent coronary heart disease at baseline and the incidence of cardiovascular events during CHS follow-up. Subgroups of cases included those individuals with prevalent myocardial infarction at baseline (n=553); individuals without prevalent cardiovascular disease who had incident myocardial infarction (n=217), stroke (n=208), and angina (n=226); individuals with ≥2 infarcts on cerebral MRI (n=220); and a subset of individuals with one infarct on cerebral MRI (n=30).

The methods for drawing blood, handling and shipping samples, quality assurance, and assay performance have been previously described.[17] All assays were measured on plasma drawn in the morning and stored at −70°C. The specific assays used for each measure were as follows: fibrinogen: BBL Fibrometer, Becton-Dickerson[7,17]; factor VIIc and factor VIIIc: Coag-A-Mate, Organon Teknika[7,9,17]; soluble ICAM-1: R&D Systems; and IL-6: ultrasensitive ELISA, R&D Systems. CRP was measured using an ELISA developed by the CHS central blood laboratory. D-dimer was measured by ELISA using 2 monoclonal antibodies directed against nonoverlapping antigenic determinants that detect D-dimer from cross-linked fibrin but not D-monomer.[8] PAP was measured using a 2-site ELISA with murine monoclonal antibodies specific for PAP complex.[8]

Statistics

We initially compared demographic characteristics, cardiovascular risk factors, and cardiovascular disease prevalence among subjects with and without renal insufficiency using the t test and χ^2 tests where appropriate and the Kruskal-Wallis for variables not normally distributed. Multivariate linear regression was used to determine the independent association of renal insufficiency with each biomarker. The presence of renal insufficiency and other baseline characteristics were independent variables in these analyses, and the biomarkers were the dependent variables. We used a generalized linear model estimating procedure from SAS to determine the adjusted mean levels of each biomarker within categories of renal function.

In these analyses, a backward stepwise procedure was used to eliminate covariates that were not associated with the biological marker ($P<0.20$). We tested for statistical interactions with the participant's cardiovascular disease status at baseline for each measurement, and we repeated these analyses after stratification. We also tested for interactions of race and sex.

We used estimated creatinine clearance levels (>60 mL/min, 40 to 60 mL/min, and <40 mL/min)[16] to determine whether the biomarkers increased incrementally as renal function decreased. We tested for the presence of a statistical interaction with cardiovascular disease status and creatinine clearance. Where significant interactions were found (4 of 8 biomarkers), stratified data were presented. Two-sided probability values <0.05 were considered statistically significant.

The final step of our analysis was to determine the relative strength of association with renal insufficiency among the 8 biomarkers. We calculated correlation coefficients to determine variable relations among the biomarkers. The 8 biomarkers were initially forced into a logistic regression model and then sequentially eliminated ($P<0.05$) to identify those that remained significantly associated with renal insufficiency. We repeated this analysis as a step-forward analysis and the results were unchanged.

Results

Among the 5808 participants in CHS who had creatinine levels measured at entry, the proportions with renal insufficiency, as defined in this study, were 15.9% of men (n=394) and 7.6% of women (n=254). Those with renal insufficiency were, on average, older, less educated, and less physically active, were

TABLE 1. Baseline Characteristics of CHS Participants With and Without Renal Insufficiency

Characteristics	No Renal Insufficiency (n=5160)	Renal Insufficiency (n=648)	P
Age, y	73	76	<0.0001
Race			0.56
Black	769 (15)	107 (17)	
Other	33 (1)	4 (1)	
Female sex	3083 (60)	254 (39)	<0.0001
Education			0.002
<Grade 12	1463 (28)	226 (35)	
≥Grade 12 but <college	1895 (37)	213 (33)	
≥College	1789 (35)	205 (32)	
Creatinine clearance, mL/min	65	39	<0.0001
Diabetes	603 (12)	91 (14)	0.08
Hypertension	2935 (57)	463 (71)	<0.0001
Systolic blood pressure, mm Hg	139	144	<0.0001
Diastolic blood pressure, mm Hg	71	72	0.05
LDL cholesterol, mg/dL	130	129	0.60
HDL cholesterol, mg/dL	55	49	<0.0001
Triglycerides, mg/dL	138	154	<0.0001
Smoking status			0.30
Never	2409 (47)	282 (44)	
Former	2136 (41)	285 (44)	
Current	609 (12)	81 (13)	
Alcohol use, drinks/wk	3	2	0.02
Physical activity, kcal	1774	1274	<0.0001
Body mass index, kg/m^2	27	27	0.61
Prior cardiovascular disease*	1058 (21)	234 (36)	<0.0001
Subclinical cardiovascular disease†	1185 (23)	188 (29)	0.0006

Values are mean or n (%).

*Cardiovascular disease was defined as a history of myocardial infarction, revascularization procedure, angina, or stroke.

†Subclinical cardiovascular disease was defined as an ankle-arm index <0.9, common carotid intima-media thickness >1.18 mm, left ventricular hypertrophy, or left ventricular dysfunction, after excluding those with prevalent cardiovascular disease.

more likely to smoke, and used less alcohol than subjects without renal insufficiency (Table 1). The participants with renal insufficiency had higher blood pressures, higher triglyceride levels, and lower HDL cholesterol levels than persons without renal insufficiency. Those with renal insufficiency were also more likely to have both clinical and subclinical cardiovascular disease (Table 1).

Levels of the inflammatory markers CRP, IL-6, and fibrinogen were significantly higher in persons with renal insufficiency, whereas ICAM-1 levels were not significantly different in the 2 groups (Table 2). Higher procoagulant measures were also significantly associated with renal insufficiency: Factor VIIc, factor VIIIc, PAP, and D-dimer levels were all significantly higher in persons with renal insufficiency (Table 2). Only factor VII had a significant interaction with race and renal insufficiency. White persons with renal insufficiency had mean levels of factor VIIc 11% (95% confidence interval, 8% to 13%) higher than white persons without renal insufficiency, whereas black persons with renal insufficiency had mean levels 15% (95% confidence intervals, 10% to 20%) higher than black persons without renal insufficiency.

We repeated these multivariate analyses after stratifying by the participants' cardiovascular disease status (Table 3) and found a significant interaction of renal insufficiency and cardiovascular disease status only in predicting PAP levels ($P=0.001$). The association of higher PAP with renal insufficiency was strongest in persons with cardiovascular disease, but it was statistically significant and in the same direction in all 3 subgroups.

The 8 biomarkers were intercorrelated, but the strongest correlations were among the 3 inflammatory factors CRP, IL-6, and fibrinogen, with r values of 0.39, 0.46, and 0.50, respectively (all $P<0.001$). When all 8 biomarkers were entered into a multivariate logistic regression model with renal insufficiency as the outcome, only the procoagulant measures PAP, factor VIII, and factor VII remained significantly associated with renal

TABLE 2. Unadjusted and Adjusted Levels of Inflammatory and Procoagulant Biomarkers by the Presence of Renal Insufficiency in the Cardiovascular Health Study

	Unadjusted			Adjusted*		
Biomarker	No RI	RI	*P*	No RI	RI	P
CRP, mg/L	3.5±0.1 (n=5140)	5.1±0.3 (n=647)	<0.0001	4.4±0.2 (n=4936)	5.5±0.3 (n=608)	<0.0001
Fibrinogen, mg/dL	321.3±0.9 (n=5131)	344.5±2.8 (n=645)	<0.0001	331.7±2.0 (n=4926)	347.4±3.1 (n=607)	<0.0001
IL-6, pg/mL	2.4±0.1 (n=2103)	3.2±0.2 (n=262)	<0.0001	2.7±0.1 (n=2030)	3.1±0.2 (n=245)	0.007
ICAM-1, ng/mL	325.2±2.0 (n=1978)	343.3±5.8 (n=268)	0.002	329.9±4.6 (n=1905)	339.0±6.7 (n=252)	0.13
Factor VII, %	122.6±0.4 (n=5099)	130.3±1.4 (n=636)	<0.0001	114.4±0.8 (n=4896)	126.1±21.2 (n=597)	<0.0001
Factor VIII, %	120.4+0.5 (n=4525)	138.1±1.8 (n=582)	<0.0001	131.1±1.5 (n=4352)	144.9±2.0 (n=548)	<0.0001
PAP, nmol/L	6.1±0.1 (n=2240)	7.7±0.2 (n=291)	<0.0001	6.4±0.1 (n=2162)	7.7±0.2 (n=274)	<0.0001
D-dimer, ng/mL	242.6±11.8 (n=2218)	468.8±57.9 (n=289)	<0.0001	342.3±32.2 (n=2143)	501.0±47.2 (n=273)	0.0002

Data are presented as mean±SEM. RI indicates renal insufficiency.

*Adjusted for age, race, sex, education, history of diabetes, history of hypertension, systolic and diastolic blood pressure, LDL, HDL, triglycerides, smoking status, alcohol, physical activity in kilocalories, body mass index, and cardiovascular disease status.

insufficiency. In a second multivariate model that adjusted for baseline characteristics and the inflammatory markers (CRP, IL-6, and fibrinogen), fibrinogen had the strongest association with renal insufficiency ($P<0.001$); CRP and IL-6 were no longer statistically significant.

Levels of each biomarker increased significantly as renal function declined (Table 4). Levels of fibrinogen and CRP seemed to be elevated primarily in participants with estimated creatinine clearance <40 mL/min, whereas levels of IL-6 and factor VII seemed to have an inverse linear association with renal function. The association of creatinine clearance with levels of ICAM-1, factor VIII, PAP, and D-dimer varied by cardiovascular disease status (Table 4). Levels of factor VIII, PAP, and D-dimer were highest among persons with creatinine clearance <40 mL/min in all 3 strata and were somewhat elevated among those with a clearance of 40 to 60 mL/min compared with persons with clearance of >60 mL/min. Levels of ICAM-1 were highest in participants with creatinine clearance <40 mL/min only among persons with subclinical or no cardiovascular disease.

Discussion

Renal insufficiency was associated with increased levels of inflammatory and procoagulant biomarkers, including CRP, IL-6, fibrinogen, PAP, factor VII, factor VIII, and D-dimer. These elevations were apparent even among participants with no evidence of clinical or subclinical cardiovascular disease. Thus, inflammation and hypercoagulability seem to be present early in renal disease and could promote atherosclerosis and thrombosis. These mechanisms may in part explain the high incidence of cardiovascular events in patients with renal insufficiency and the high prevalence of cardiovascular disease among persons developing ESRD.

The association of renal insufficiency with these biomarkers could be caused either by their increased production, decreased clearance, or a combination of both mechanisms. Renal dysfunction may directly cause increases in inflammatory mediators via a mechanism of increasing oxidative stress that could lead to accumulation of advanced glycation end products. Levels of these oxidation products increase as glomerular filtration rate declines, which may cause monocyte activation and cytokine production.[18,19] Other studies have identified renal dysfunction as a state of activated coagulation due to the elevated D-dimer levels, which are not cleared by the kidney.[20,21] Although fibrinogen levels are thought to be primarily determined by fibrinogen synthesis, Lane and colleagues[22] found the metabolism and elimination of fibrinogen to be decreased in renal insufficiency and ESRD. The role of the kidney in the elimination of these biomarkers has not been established, nor

TABLE 3. Adjusted Levels of Inflammatory and Procoagulant Biomarkers by Presence of Renal Insufficiency and Stratified by Cardiovascular Disease Status

	Prevalent Disease			Subclinical Disease		
Biomarker	No RI†	RI	P	No RI	RI	P
CRP, mg/L	4.7±0.5 (n=1005)	5.8±0.7 (n=216)	0.04	4.2±0.3 (n=1138)	4.9±0.5 (n=177)	0.14
Fibrinogen, mg/dL	335.1±4.4 (n=1001)	352.1±6.2 (n=215)	0.002	330.8±3.7 (n=1134)	340.8±6.2 (n=177)	0.08
IL-6, pg/mL	2.3±0.5 (n=110)	2.8±0.6 (n=39)	0.29	2.5±0.2 (n=562)	3.1±0.3 (n=99)	0.05
ICAM-1, ng/mL	382.5±19.7 (n=118)	381.2±25.9 (n=42)	0.95	326.3±7.2 (n=559)	346.2±11.4 (n=104)	0.06
Factor VII, %	114.1±1.6 (n=975)	125.4±2.2 (n=206)	<0.0001	114.0±1.3 (n=1133)	124.6±2.2 (n=175)	<0.0001
Factor VIII, %	137.6±3.3 (n=869)	150.6±3.9 (n=196)	<0.0001	126.4±2.8 (n=950)	136.4±3.9 (n=157)	0.003
PAP, nmol/L	6.5±0.8 (n=118)	9.0±1.1 (n=41)	0.002	6.3±0.2 (n=608)	7.9±0.3 (n=112)	<0.0001
D-dimer, ng/mL	159.6±288.5 (n=117)	632.1±379.0 (n=42)	0.11	375.7±60.5 (n=601)	440.1±96.2 (n=111)	0.47

Data are presented as mean±SEM. RI indicates renal insufficiency. Data are adjusted for age, race, sex, education, history of diabetes, history of hypertension, systolic and diastolic blood pressures, LDL, HDL, triglycerides, smoking status, alcohol, physical activity in kilocalories, and body mass index.

TABLE 4. Adjusted Levels of Inflammatory and Procoagulant Biomarker Levels by Estimated Creatinine Clearance*

	Estimated Creatinine Clearance			
Biomarker	>60 mL/min	40–60 mL/min	<40 mL/min	*P**
Fibrinogen, mg/dL	330.7±2.2 (n=2787)	332.7±2.2 (n=2159)	346.8±3.3 (n=587)	<0.0001
CRP, mg/L	4.4±0.2 (n=2797)	4.3±0.2 (n=2160)	5.3±0.3 (n=587)	0.003
IL-6, pg/mL	2.5±0.1 (n=1149)	2.8±0.1 (n=873)	3.2±0.2 (n=253)	0.002
Factor VII, %	112.2±0.9 (n=2777)	117.4±0.9 (n=2138)	124.2±1.3 (n=578)	<0.0001
ICAM-1, ng/mL†				
Prevalent CV disease	383.5±23.6 (n=51)	382.6±22.9 (n=59)	379.9±26.0 (n=50)	0.99
Subclinical CV disease	322.8±8.5 (n=298)	332.1±8.6 (n=263)	342.2±12.1 (n=102)	0.32
Neither	322.1±6.2 (n=711)	324.0±6.4 (n=516)	336.9±9.7 (n=107)	0.31
Factor VIII, %†				
Prevalent CV disease	131.5±3.6 (n=436)	143.2±3.5 (n=448)	152.5±4.2 (n=181)	<0.0001
Subclinical CV disease	121.6±3.1 (n=500)	131.7±3.0 (n=456)	135.7±4.2 (n=151)	0.0002
Neither	128.3±2.3 (n=1472)	132.5±2.3 (n=1062)	149.9±3.3 (n=194)	<0.0001
PAP, nmol/L†				
Prevalent CV disease	6.1±1.0 (n=51)	6.4±1.0 (n=58)	8.5±1.1 (n=50)	0.05
Subclinical CV disease	5.9±0.2 (n=328)	6.8±0.3 (n=284)	8.1±0.4 (n=108)	<0.0001
Neither	5.8±0.2 (n=838)	6.1±0.2 (n=599)	7.1±0.3 (n=120)	<0.0001
D-dimer, ng/mL†				
Prevalent CV disease	147.6±343.0 (n=51)	109.0±334.5 (n=58)	689.5±376.9 (n=50)	0.14
Subclinical CV disease	338.3±71.0 (n=323)	409.1±72.3 (n=282)	469.4±102.7 (n=107)	0.46
Neither	268.1±25.5 (n=831)	271.6±26.3 (n=596)	393.0±40.2 (n=118)	0.004

Data are presented as mean±SEM. CV indicates cardiovascular. Data are adjusted for age, race, sex, education, history of diabetes, history of hypertension, systolic and diastolic blood pressures, LDL, HDL, triglycerides, smoking status, alcohol, physical activity in kilocalories, body mass index, and cardiovascular disease status.

**P* value for linear trend.

†Presented with stratification because of significant interactions between the creatinine clearance categories and cardiovascular disease status.

is it known whether mild to moderate renal insufficiency has an impact on their clearance.

Prior studies have found that all of these inflammatory and procoagulant biomarkers are elevated in persons with ESRD.[12,23] The inflammatory markers CRP and IL-6 are also independent risk factors for mortality in ESRD.[10,11,24] However, few studies have evaluated these biomarkers in persons with less severe kidney disease. Persons with predialysis renal failure (creatinine clearance <10 mL/min) had elevated levels of CRP, fibrinogen, and ICAM-1, and ICAM-1 was a strong predictor of their mortality.[13,14,25] In a sample of 382 hypertensive patients, Catena and colleagues[26] found renal insufficiency was associated with higher levels of fibrinogen and D-dimer. Smaller studies have found decreased renal function is correlated with fibrinogen, IL-6, and D-dimer, but they had inadequate power to determine the independence of these associations or the effect of prevalent cardiovascular disease.[20,27] Studies in persons with insulin resistance and diabetes found microalbuminuria was associated with increased fibrinogen levels.[28]

Although our findings in conjunction with prior studies seem to demonstrate that inflammatory and procoagulant biomarkers are elevated in persons with renal insufficiency, we cannot determine the direction of the association because of the cross-sectional design of our study. For example, activated inflammation could have caused both renal disease and hypercoagulability. An additional potential explanation for our findings is that renal insufficiency may be a marker for systemic atherosclerosis, which in turn is associated with inflammation and hypercoagulability. This possibility seems less likely, however, because we found the associations of these biomarkers with renal insufficiency to be independent of the participants' cardiovascular disease status and to be of similar magnitude among persons with prevalent, subclinical, and no cardiovascular disease. We did find statistical interactions for

TABLE 3. (Continued)

None		
No RI	RI	P
4.3±0.3 (n=2793)	5.6±0.5 (n=215)	0.0009
326.1±3.0 (n=2791)	343.1±4.9 (n=215)	<0.0001
2.6±0.2 (n=1358)	3.0±0.3 (n=107)	0.08
323.2±5.7 (n=1228)	331.4±9.3 (n=106)	0.33
116.0±1.2 (n=2788)	128.9±2.0 (n=216)	<0.0001
130.8±2.2 (n=2533)	146.9±3.2 (n=195)	<0.0001
6.0±0.2 (n=1436)	6.7±0.3 (n=121)	0.005
271.0±23.2 (n=1425)	404.7±38.4 (n=120)	<0.0001

cardiovascular disease status and creatinine clearance categories for the outcomes of ICAM-1, factor VIIIc, PAP, and D-dimer. However, within each category of cardiovascular disease status, the biomarkers seemed to be inversely related to renal function.

In addition to the cross-sectional design of our study, an important limitation was our reliance on serum creatinine levels to define renal insufficiency. More precise measures of renal function are very difficult to use in large epidemiological studies. For example, insulin or iothalamate clearances are invasive, cumbersome, and very expensive, and 24-hour urine collections are unreliable.[29] Several potential cutoffs for serum creatinine levels could have been used; we think that the cutoffs of $\geq$1.5 mg/dL in men and $\geq$1.3 mg/dL in women were appropriate for our study because they seemed to be the thresholds above which adjusted mortality increased in this cohort. A reasonable alternative to the Cockroft-Gault equation for estimating glomerular filtration rate is the Modification of Diet in Renal Disease (MDRD) formula, which may be more precise.[30] However, because this equation has not yet been validated against a reference standard in an elderly population, we decided to use the Cockroft-Gault equation, which is the most widely used estimator of renal function.

In summary, we found elderly persons with renal insufficiency to have elevated levels of all 8 of the inflammatory and procoagulant biomarkers tested. These pathways may be important mediators for the elevated cardiovascular risk observed in persons with renal disease. Future studies should prospectively evaluate the association of the inflammatory and coagulation pathways with renal dysfunction and should examine the reduction of inflammatory markers in persons with renal insufficiency as a potential intervention for cardiovascular prevention.

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