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Inflammatory biomarkers and decline in kidney function in the elderly: the Cardiovascular Health Study

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Abstract

Background. Cross-sectional studies have demonstrated a consistent and linear association between circulating inflammatory markers and kidney function. The objective of this study was to determine whether elevated markers of inflammation are independently associated with longitudinal kidney function decline.

Methods. This study included 4128 subjects from the Cardiovascular Health Study. Cystatin C was measured at baseline, 3 years later and 7 years later; eligible subjects had at least two measures. Cystatin C-based estimated glomerular filtration rate ($eGFR_{cysC}$) was estimated, and rapid kidney function decline was defined as an annual loss of $eGFR_{cysC}$ >3 mL/min/1.73 m^2. Predictors included ten inflammatory and procoagulant biomarkers: C-reactive protein, interleukin-6, intercellular adhesion molecule-1, white blood cell count, fibrinogen, factor VII, factor VIII, D-dimer, plasmin-antiplasmin complex and serum albumin.

Results. During the study, 1059 subjects (26%) had a rapid decline in kidney function. In contrast to the other nine inflammatory or procoagulant biomarkers, serum albumin had a consistent and inverse association with rapid kidney function decline [final adjusted logistic regression model: 1.14-fold increased odds (95% CI 1.06–1.23) of rapid decline per standard deviation lower albumin]. The lowest quartile of albumin had an odds ratio of 1.55 (95% CI 1.23–1.96) for rapid decline compared with the highest quartile. These associations persisted after adjusting the albumin models for CRP, IL-6 and fibrinogen.

Conclusions. In contrast to nine other inflammatory and procoagulant markers, only lower baseline levels of serum albumin were consistently associated with a rapid decline in kidney function, as measured by cystatin C-based eGFR.

Keywords: cystatin C; inflammation; inflammatory biomarkers; kidney

Introduction

Prior studies using creatinine-based estimated glomerular filtration rate ($eGFR_{creat}$) found associations between kidney function and multiple markers of inflammation only in subjects with chronic kidney disease (CKD; $eGFR_{creat}$ < 60 mL/min/1.73 m^2) [1,2]. However, using cystatin C, a marker of kidney function that is more sensitive for small changes in glomerular filtration rate, associations between kidney function and markers of inflammation and procoagulation were demonstrated in elderly subjects with $eGFR_{creat}$ ≥60 mL/min/1.73 m^2 [3]. These cross-sectional studies suggest that inflammatory markers may predict kidney function decline.

In support of this hypothesis, two studies using longitudinal measures of $eGFR_{creat}$ found that several baseline markers of inflammation and procoagulation, including C-reactive protein (CRP), fibrinogen and serum albumin, were associated with more rapid declines in $eGFR_{creat}$ [4,5]. However, serum creatinine and creatinine-based measures of eGFR are less reliable on subjects with $eGFR_{creat}$ >60 mL/min/1.73 m^2, and may not demonstrate the true association between inflammation and kidney function decline in subjects with early kidney disease [6,7]. This may be true even in subjects with CKD, given that a longitudinal analysis from the MDRD study showed no association between CRP and iothalamate GFR decline [8].

Cystatin C, a measure of kidney function that is particularly sensitive to early changes in kidney function, may be helpful in evaluating the association between inflammation and kidney function decline over a broad range of kidney function. The present analysis used longitudinal data from the Cardiovascular Health Study (CHS) to evaluate the association between baseline inflammatory and procoagulant biomarkers and the progression of kidney disease over time, measured by cystatin C-based eGFR.

Methods

Participants

The CHS is a prospective cohort study of 5201 participants enrolled in 1989–90, with an additional 687 black subjects enrolled in 1992–93. The participants were randomly sampled from Medicare eligibility lists in Sacramento, CA; Washington County, MD; Forsyth County, NC; and Allegheny County, PA. Eligible individuals were aged ≥65 years, able to give informed consent and expected to remain in the area for ≥3 years. The 5888 enrolled participants had interviews and laboratory measurements performed at the enrolment visit, 3 years after baseline and 7 years after baseline. A total of 4128 participants had at least two measurements of serum creatinine and cystatin C and were included in the analysis. The study was approved by institutional review boards at each centre, and all study participants gave informed consent.

Kidney function

Blood samples were drawn at the initial visit after an overnight fast and stored at −70°C using standardized protocols. Cystatin C was measured using a BN II nephelometer on plasma specimens (N Latex Cystatin C; Dade Behring, Deerfield, IL, USA) [9]. The assay range was 0.195–7.330 mg/L, with the reference range for young, healthy individuals reported as 0.53–0.95 mg/L. Intra-assay coefficients of variation (CVs) range from 2.0 to 2.8% and inter-assay CVs range from 2.3 to 3.1%. Cystatin C-based eGFR was calculated using the equation $GFR = 76.7 \times (\text{cystatin C})^{-1.18}$, from a study recently published by Stevens *et al.* [10]. Rapid kidney function decline was defined as an $eGFR_{cysC}$ loss of >3 mL/min/1.73 m^2/year; this threshold was chosen based on its established use in prior studies [4,11]. As a comparison, a >4% rise in cystatin C (highest quartile) was also used as an alternative threshold for rapid kidney function decline.

Serum creatinine levels were measured using colorimetry with an Ektachem 700 analyser (Eastman Kodak, Rochester, NY, USA). Values were calibrated to the Cleveland Clinic Laboratory using NHANES III data [12]. Creatinine-based estimated GFR was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) equation [13]. Chronic kidney disease was defined as $eGFR_{creat}$ <60 mL/min/1.73 m^2 [7].

Inflammatory and procoagulant markers

CRP was measured with an enzyme-linked immunosorbent assay (ELISA) developed in the CHS laboratory; the analytical CV was 5.1% [14]. Interleukin-6 (IL-6) was measured by ELISA (R&D Systems, Minneapolis, MN, USA). The laboratory analytical CV for this assay was 6.3%. White blood cell (WBC) counts were measured in local laboratories near each field centre, with monitoring of quality assurance [15]. Serum albumin levels were measured with the Ektachem 700 analyser (Eastman Kodak). In the African American cohort, the average change of serum albumin levels over follow-up was slightly larger than expected due to laboratory drift; these values were adjusted using the equation (measured albumin − 0.06). Factor VII levels were measured with the Coag-A-Mate X2 (Organon Teknika, Durham, NC, USA) with a mean monthly CV of 5.31%. Fibrinogen was measured using a BBL fibrometer (Becton Dickinson, Bedford, MA, USA) with a mean monthly CV of 3.09%.

ICAM-1, factor VIII, D-dimer and plasmin-antiplasmin complex (PAP) levels were available only in subsets of the cohort [16,17]. Intercellular adhesion molecule-1 (ICAM-1) was measured by ELISA (R&D Systems, Minneapolis, MN, USA); analytical CV was 5.0%. Baseline measurements of ICAM-1 in the original cohort were measured as part of a case–control study involving 2000 subjects. ICAM-1 was also measured in one-third of African American subjects randomly selected at baseline. Factor VIII levels were measured with the Coag-A-Mate X2 (Organon Teknika) with a mean monthly CV of 9.67%. Factor VIII was measured in the original CHS cohort, and not in the African American cohort ($N = 3670$). D-dimer and PAP were measured with ELISA assays [17]. D-dimer and PAP levels were measured in CHS subjects as part of several nested studies (1) 1500 subjects who were randomly selected from the original cohort, (2) a random selection of one-third of the African American cohort and (3) 2800 subjects from three different case–control studies. All available subjects with baseline D-dimer ($N = 1628$), PAP ($N = 1659$) or ICAM-1 levels ($N = 1409$) and at least two values of cystatin C measured were included in this analysis.

Table 1. Baseline characteristics in the CHS study, by rapid kidney function decline

	Cystatin C eGFR decline Mean ± SD, median [IQR] or % (*N*)		
	<3 mL/min/year ($n = 3069$)	≥3 mL/min/year ($n = 1059$)	*P*-value
Age	72 (5)	73 (5)	<0.001
Gender (female)	1906 (62%)	646 (61%)	0.524
Race (black)	391 (13%)	184 (17%)	0.001
BMI (kg/m^2)	26.7 (4.5)	26.8 (4.8)	0.734
Diabetes	383 (13%)	203 (19%)	<0.001
Hypertension	1670 (55%)	687 (65%)	<0.001
LDL (mg/dL)	131 (35)	130 (36)	0.402
HDL (mg/dL)	55 (16)	55 (16)	0.493
Triglycerides (mg/dL)	121 [93, 164]	118 [91, 163]	0.232
CRP (mg/L)*	2.40 [1.24, 4.12]	2.37 [1.21, 4.39]	0.900
IL-6 (pg/mL)*	1.56 [1.08, 2.38]	1.64 [1.16, 2.39]	0.095
ICAM-1 (ng/mL)*	322 (87)	320 (83)	0.746
WBC count (cells × 10^9/L)*	6.2 (2.1)	6.3 (1.9)	0.364
Fibrinogen (mg/dL)*	320 (64)	318 (63)	0.602
Factor VII (%)*	125 (29)	124 (30)	0.275
Factor VIII (%)*	121 (37)	121 (37)	0.777
Albumin (g/dL)*	4.01 (0.28)	3.97 (0.29)	<0.001
D-dimer (ng/mL)*	132 [86, 213]	144 [96, 231]	0.019
PAP (nmol/L)*	5.9 (2.7)	6.1 (2.4)	0.360
Cystatin C (mg/L)	1.04 (0.26)	0.96 (0.22)	<0.001
Cystatin C-based eGFR (mL/min/1.73 m^2)	77 (18)	85 (21)	<0.001

Decline in cystatin C-based eGFR defined as ≥3 mL/min/year; ICAM-1 = intercellular adhesion molecule-1; PAP = plasmin-antiplasmin complex.

Covariates

Participant history including demographics (age, gender, race), comorbid conditions (diabetes, hypertension), alcohol history, smoking history and use of antihypertensive medications was obtained at the enrolment visit. Body mass index (BMI) was calculated using weight (kg) divided by height (m^2). Hypertension was defined from two-seated measurements at the initial study visit (average systolic blood pressure >140 mmHg or diastolic pressure >90 mmHg) or by the current use of antihypertensive medications. Diabetes was defined as a fasting blood glucose ≥126 mg/dL or by the use of insulin or oral hypoglycaemic agents. Other prevalent diseases were defined using participant responses and confirmed by medical record review and findings from the baseline physical examination [18].

High-density lipoprotein cholesterol (HDL) and glucose levels were measured from fasting serum samples with the Olympus Demand System (Olympus, Lake Success, NY, USA). Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation [19]. While urinary albumin was not available at baseline, spot urinary albumin was collected in 3057 subjects at the Year 7 visit and was measured using an Array 360 CE Analyzer (Beckman Instruments, Fullerton, CA, USA). Spot urinary creatinine was measured with the Ektachem 700 analyser (Eastman Kodak). Macroalbuminuria was defined as an albumin–creatinine ratio >300 mg/g.

Statistical analysis

Baseline characteristics were described as mean, median or percent values. Multiple logistic regression models were performed using an $eGFR_{cysC}$ decline of >3 mL/min/ 1.73 m^2/year as the dichotomized outcome. Each of the ten biomarkers was used as the primary predictor, modelled per standard deviation (SD) of the biomarker. Covariates from Table 1 were entered into the models based on their potential role as confounders due to their association with both kidney disease and inflammation. Covariates that changed the odds ratio of the models by 5% or greater or covariates that were significantly associated with $eGFR_{cysC}$ decline were included in the final adjusted models. Given that ICAM-1, D-dimer and PAP were

Table 2. Associations of biomarkers (per standard deviation) with decline in cystatin C-based eGFR using logistic regression

Biomarker	*N*	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
C-reactive protein (per SD = 7.74)	4113	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)	0.99 (0.92, 1.07)
Interleukin-6 (per SD = 1.82)	3813	1.04 (0.97, 1.11)	1.01 (0.94, 1.08)	0.99 (0.92, 1.07)
ICAM-1 (per SD = 85.59)	1409	0.98 (0.87, 1.10)	1.00 (0.89, 1.13)	0.98 (0.86, 1.11)
White blood cell count (per SD = 2.02)	4113	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	0.99 (0.93, 1.07)
Fibrinogen (per SD = 63.44)	4107	0.98 (0.92, 1.06)	0.95 (0.89, 1.03)	0.94 (0.87, 1.01)
Factor VII (per SD = 29.25)	4082	0.96 (0.89, 1.03)	0.99 (0.92, 1.08)	0.97 (0.89, 1.05)
Factor VIII (per SD = 36.75)	3670	1.00 (0.92, 1.08)	0.97 (0.89, 1.04)	0.94 (0.86, 1.01)
D-Dimer (per SD = 448)	1628	1.00 (0.90, 1.12)	0.95 (0.84, 1.09)	0.94 (0.83, 1.07)
PAP (per SD = 2.59)	1659	1.04 (0.93, 1.16)	0.98 (0.87, 1.10)	0.98 (0.87, 1.10)
Albumin (per SD = −0.29)	4125	1.15 (1.06, 1.23)†	1.11 (1.04, 1.20)†	1.14 (1.06, 1.23)†

†$P < 0.05$.
Decline in cystatin C-based eGFR defined as >3 mL/min/year; ICAM-1 = intercellular adhesion molecule-1; PAP = plasmin-antiplasmin complex
*Adjusted for age, gender and race.
**Adjusted for age, gender, race, hypertension, diabetes, smoking, LDL, HDL, prevalent coronary heart disease and prevalent congestive heart failure.

taken from subjects who were not randomly selected, these biomarkers were adjusted for incidence density sampling. In separate analyses, models with serum albumin as the primary predictor were adjusted for baseline CRP, IL-6 and fibrinogen; serum albumin models were also repeated after excluding subjects with a Year 7 urinary albumin–creatinine ratio >300 mg/g. Logistic regression models were conducted subsequently modelling quartiles of each biomarker as the predictor variables.

We created separate linear regression models using each of the ten biomarkers to predict the average annual change in $eGFR_{cysC}$ using the estimated slope from available $eGFR_{cysC}$ values for each individual. Due to non-parametric distributions, CRP, IL-6 and D-dimer were logarithmically transformed in these analyses. We next evaluated the associations of serum C-reactive protein, fibrinogen and albumin levels with decline in kidney function modelled as a continuous variable in linear regression models. Because of the potential concern that diabetes and hypertension might have a residual confounding or bias on the analyses, these models were conducted both in the overall cohort and within subgroups defined by the presence or absence of diabetes and hypertension, respectively. The test of trend was used to determine whether the rate of decline in kidney function differed incrementally across the quartiles of each biomarker. To determine whether the association between inflammation and kidney function decline differed by the presence or absence of these comorbidities, we tested for an interaction using a cross-product covariate in the multivariate model.

Overall, a *P*-value < 0.05 was considered statistically significant, with a $P < 0.2$ designated as significant for interactions. The S-Plus (release 6.1, Insightful Inc., Seattle, WA, USA) and SPSS statistical software (release 15.0.1, SPSS Inc., Chicago, IL, USA) were used for the analyses.

Results

The participants of the CHS had an average age of 72 years, with 62% of the cohort female and 14% African American. The mean cystatin C concentration in the cohort was 1.02 ± 0.25 mg/L, with a mean cystatin C-based eGFR of 79 ± 19 mL/min/1.73 m^2. On average, those who had rapid kidney function decline during the study were more likely to be older, African American, and to have diabetes and hypertension (Table 1). The mean baseline levels of all ten biomarkers by rapid kidney function decline are included in Table 1. During the study, the mean decline of cystatin C-based eGFR was 1.83 ± 2.59 mL/min/1.73 m^2. Overall, 803 subjects (20%) had CKD at baseline, and 1059 subjects (26%) met the criteria for rapid kidney function decline.

When the 10 baseline inflammatory or procoagulant biomarkers were used as continuous predictor variables per standard deviation, only lower baseline serum albumin was associated with rapid kidney function decline (Table 2). Each standard deviation lower baseline level of serum albumin increased the odds of rapid kidney function decline by 14% (95% CI 6–23%; $P < 0.001$). Logistic regression analyses in which the models were adjusted for baseline $eGFR_{cysC}$ were not significantly different from the results in Table 2 (data not shown). Lower serum albumin levels were associated with significant increases in the odds of kidney function decline in analyses restricted to subjects without CKD [adjusted OR 1.14 (1.05, 1.23), $P < 0.05$ for both]. In subjects with CKD, the odds ratios for albumin and rapid decline were larger than in subjects without CKD, but not statistically significant [adjusted OR 1.21 (0.97, 1.51)].

Each biomarker was also categorized into quartiles in an attempt to identify threshold effects in the association with rapid kidney function decline. Even at the highest quartile of each biomarker, there was no association between the other nine inflammatory and procoagulant biomarkers and rapid kidney function decline. In contrast, compared to subjects with an albumin >4.2 g/dL, those in the quartile with serum albumin <3.8 g/dL had a significant 1.6-fold odds of rapid decline in $eGFR_{cysC}$ ($P < 0.05$).

After exclusion of the 96 subjects with Year 7 urinary albumin–creatinine ratio >300 mg/g, the odds ratio of the adjusted model remained significant [OR 1.10 (1.01–1.22) per 1 SD lower albumin; $P < 0.05$]. A second sensitivity analysis, adjusting for CRP, IL-6 and fibrinogen to control for systemic inflammation, demonstrated no attenuation in the association of serum albumin with rapid kidney function decline [OR 1.17 (1.09–1.27) per 1 SD lower albumin; $P < 0.05$].

Baseline levels of each biomarker per standard deviation were evaluated as predictors of the continuous change in $eGFR_{cysC}$ using linear regression. Similar to above, only lower albumin was associated with a decline in $eGFR_{cysC}$. Each 1 standard deviation lower albumin was associated with a 0.21 mL/min/1.73 m^2/year decline (95% CI 0.13–0.29; $P < 0.05$).

We compared the adjusted associations of quartiles of serum CRP, fibrinogen and albumin with kidney function decline using linear regression, overall and after stratification by diabetes and hypertension (Table 3). Neither CRP

Table 3. Adjusted associations of CRP, fibrinogen and albumin with longitudinal decline in kidney function, overall and stratified by diabetes and hypertension

	Overall	Adjusted** mean (SD)		Adjusted*** mean (SD)	
Biomarker	Adjusted* mean (SD)	No diabetes	Diabetes	No hypertension	Hypertension
CRP quartiles					
<1.24	−1.88 (2.62)	−1.68 (2.54)	−2.24 (2.83)	−1.63 (2.47)	−2.09 (2.70)
1.24–2.39	−1.76 (2.58)	−1.80 (2.43)	−2.29 (4.28)	−1.64 (2.42)	−1.84 (2.70)
2.40–4.19	−1.71 (2.59)	−1.62 (2.46)	−2.23 (3.57)	−1.67 (2.70)	−2.12 (2.59)
> 4.19	−1.94 (2.63)	−1.78 (2.44)	−2.77 (3.56)	−1.45 (2.25)	−1.90 (2.85)
P-value for trend	*0.27*	*0.60*	*0.26*	*0.95*	*0.64*
Fibrinogen quartiles					
<275	−1.93 (2.63)	−1.83 (2.44)	−2.58 (3.53)	−1.46 (2.36)	−1.85 (2.50)
275–311	−1.68 (2.57)	−1.76 (2.54)	−2.35 (3.37)	−1.52 (2.62)	−2.07 (2.71)
312–361	−1.84 (2.58)	−1.62 (2.30)	−2.04 (3.59)	−1.74 (2.34)	−2.07 (2.92)
>361	−1.84 (2.60)	−1.67 (2.43)	−2.90 (3.50)	−1.66 (2.46)	−1.98 (2.71)
P-value for trend	*0.64*	*0.62*	*0.26*	*0.86*	*0.79*
Albumin quartiles					
>4.20	−1.52 (2.61)	−1.51 (2.42)	−1.57 (3.42)	−1.31 (2.44)	−1.68 (2.71)
4.01–4.20	−1.69 (2.59)	−1.69 (2.41)	−1.75 (3.43)	−1.51 (2.45)	−1.81 (2.68)
3.81–4.00	−1.92 (2.58)	−1.79 (2.42)	−2.77 (3.42)	−1.72 (2.42)	−2.08 (2.68)
<3.81	−2.11 (2.58)	−1.87 (2.42)	−3.56 (3.44)	−1.71 (2.44)	−2.42 (2.71)
P-value for trend	*<0.001*	*0.01*	*<0.001*	*0.02*	*<0.001*

*Adjusted for age, gender, race, hypertension, diabetes, smoking, LDL, HDL, prevalent coronary heart disease and prevalent heart failure.
**Adjusted for age, gender, race, hypertension, smoking, LDL, HDL, prevalent coronary heart disease and prevalent heart failure.
***Adjusted for age, gender, race, diabetes, smoking, LDL, HDL, prevalent coronary heart disease and prevalent heart failure.

nor fibrinogen quartiles demonstrated a significant trend in their association with kidney function decline in the overall cohort, or in subgroups defined by diabetes or hypertension. In contrast, lower quartiles of serum albumin levels were associated with progressively larger rates of kidney function decline in the overall cohort (P for trend < 0.001). Although present in the subgroups without diabetes and without hypertension, these associations were stronger in the subgroup with diabetes (P for interaction < 0.001) and the subgroup with hypertension (P for interaction $= 0.11$).

Discussion

In both unadjusted and adjusted logistic regression models, our analysis demonstrated that among ten inflammatory and procoagulant markers, only lower serum albumin levels had a significant association with a rapid decline in $eGFR_{cysC}$. These results were consistent when decline in kidney function was modelled as a dichotomous outcome using logistic regression or as a linear endpoint using linear regression models. Lower quartiles of serum albumin were associated with steadily worsening rates of kidney decline, and this association was particularly strong in participants with diabetes. Concurrent adjustment for CRP, IL-6 and fibrinogen levels did not alter the association between lower serum albumin and faster rates of kidney function decline, nor did the exclusion of subjects with macroalbuminuria at the end of follow-up.

The lack of consistent association between the inflammatory and procoagulant biomarkers with progression of kidney disease using cystatin C was an unexpected finding, as prior cross-sectional studies had shown strong associations. Using baseline data from the CHS, we previously found an association of cystatin C with both CRP and fibrinogen [20]. In a cross-sectional analysis from the Health ABC cohort, our group also demonstrated a direct relationship of cystatin C with CRP, IL-6, tumour necrosis factor-alpha (TNF-α) and two soluble receptors of TNF-α, even among persons with an estimated GFR >60 mL/min/1.73 m^2 [3]. Combining the strong cross-sectional results with these null longitudinal results suggest that impaired kidney function leads to elevations in inflammatory markers, rather than the converse. Another possibility is that inflammation does predict progression of kidney disease, just not in this population. By selecting elderly subjects without advanced kidney disease, this population could be relatively resistant to the effects of inflammation on kidney disease progression.

The major positive finding was the consistently strong and inverse association of serum albumin with kidney disease progression in our study. In general, serum albumin levels are reflective of three key systemic processes: chronic inflammation, general nutritional status and loss of serum albumin through heavy proteinuria. In this study, the association between serum albumin and kidney function decline appeared to be independent of CRP, IL-6 and fibrinogen levels. In addition, after exclusion of subjects with macroalbuminuria at the Year 7 visit, the association between albumin and kidney function remained significant. Therefore, mechanisms other than inflammation and proteinuria, such as early changes in nutritional status, may be a potential mediator in the relationship of serum albumin with kidney function decline. Interestingly, this association was significantly stronger among participants with diabetes in this cohort. As a manifestation of nutritional status and overall health, serum albumin levels may be particularly important in persons with diabetes.

Our findings appear to be in contrast to studies demonstrating an association between baseline markers of

inflammation and progression of kidney disease using creatinine-based measures of kidney function [4,5]. In the same cohort studied here, Fried *et al.* found that elevations in CRP, WBC count, fibrinogen and factor VII were associated with a significant rise in serum creatinine using linear regression, and CRP, WBC count and factor VII all independently predicted an $eGFR_{creat}$ decline of >3 mL/min/1.73 m^2. Our results suggest that inflammation does not lead to progression of kidney disease, and an eGFR equation using cystatin C—a more reliable marker for kidney function than creatinine, especially when $eGFR_{creat}$ >60—captures the true association more accurately than serum creatinine [21,22]. Our findings are consistent with a prior analysis from the MDRD study, in which CRP was not associated with declines in iothalamate-based GFR, a more accurate measure of kidney function than $eGFR_{creat}$ [8].

There are several limitations to our study. Firstly, while cystatin C is a sensitive marker of kidney function, we did not have a gold standard for kidney function available, such as iothalamate clearance. Secondly, given the negative findings of the other nine biomarkers in our study, it is possible that the association of serum albumin with kidney function decline may be due to chance alone. Because of the association between inflammation and cardiovascular mortality, it is also possible that subjects with the highest levels of inflammatory markers died before their kidney function could decline, leading to these null findings. Since albumin is one of the strongest predictors of poor outcomes, the association between albumin and kidney decline may have persisted despite survival bias, while weaker associations between inflammatory markers and kidney decline may have been eliminated [23]. Finally, although multiple serum measurements of inflammatory markers were not performed, it is likely that significant within-subject variability in the measurements exists. While such variability could have generated enough noise to obscure a significant association, single baseline measurements of multiple inflammatory markers have previously been associated with an increased longitudinal risk of coronary heart disease [24,25]. In addition, cross-sectional analyses found strong associations between single baseline measurements of inflammatory markers and markers of kidney function [1–3]. These findings support the use of single biomarker measurements as meaningful predictors of important outcomes.

An additional limitation of this study is shared by all evaluations using filtration markers, such as creatinine and cystatin C, to estimate kidney function in the elderly. No adequately powered studies have measured GFR directly using an exogenous filtration marker in this population, and few studies have measured GFR in non-diabetics without CKD. Therefore, we unfortunately must extrapolate from filtration marker research studies conducted in CKD patients, who are usually middle-aged, to the general population and to the elderly; this underlying bias limits our effectiveness both as clinicians and as researchers. Future studies should measure GFR directly in elderly persons to optimize GFR estimation in research and in practice.

Future research should also focus on the mechanisms for the uniquely strong association between serum albumin and progression of kidney disease. Firstly, it is important to confirm these findings with data from other studies, and to validate them in younger and more ethnically diverse populations. In addition, our negative findings of inflammation and kidney disease progression may not be valid in individuals that are more susceptible to the effects of a proinflammatory state. Future studies in this field could refine the possible association between inflammation and kidney disease progression by using genetic approaches to identify those groups most at risk of the adverse effects of inflammation, including progression of CKD.

In summary, our analysis demonstrated a strong and inverse association between serum albumin levels and progression of kidney disease, measured by cystatin C-based eGFR. In contrast, none of the other inflammatory and procoagulant biomarkers were associated with declines in $eGFR_{cysC}$. These results suggest that serum markers of inflammation may not mediate the progression of kidney disease in the elderly, and that serum albumin associations with declining eGFR may reflect factors other than inflammation.

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Conflict of interest statement. None declared.

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Combined cyclosporine and prednisolone therapy in adult patients with the first relapse of minimal-change nephrotic syndrome

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Abstract

Background. Although minimal-change nephrotic syndrome (MCNS) is highly steroid-responsive, some patients show frequent relapses, necessitating administration of repeated courses of prednisolone (PSL) at high doses. The adverse effects of long-term PSL treatment include osteoporosis, infection, diabetes, cataract, etc., most of which are serious. It is therefore necessary to establish useful strategies to reduce the PSL dose.

Methods. Patients with the first relapse of MCNS were randomly assigned to two groups, namely, the CyA (AUC 1700–2000 ng/ml) + PSL (0.8 mg/kg/day) group ($n = 26$) and the PSL alone (PSL) (1.0 mg/kg/day) group ($n = 26$), and the clinical characteristics were compared between the two groups. All patients used C2 for CyA monitoring.

Results. A significant decrease of the urinary protein excretion ($P = 0.02$) and serum total cholesterol ($P = 0.003$) was observed at 2 weeks from the first relapse in the CyA + PSL group. The increase in the serum total protein ($P = 0.03$) and serum albumin ($P = 0.007$) as compared with that in the PSL group was also observed in the CyA + PSL group at this time-point. The time to remission in the CyA + PSL group was shorter than that in the PSL group ($P = 0.006$).

Conclusion. It was possible to obtain early remission and reduce the PSL dose with combined CyA and PSL therapy in patients with MCNS.

Keywords: cyclosporine; minimal-change nephrotic syndrome; relapse