Cystatin C and Subclinical Brain Infarction

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Subclinical brain infarcts (SBI) are common in the elderly and are associated with covert neurologic and cognitive impairment. Although renal impairment is associated with accelerated cerebrovascular disease and an increased risk for clinically apparent brain infarct, few studies have examined the relationship between renal function and SBI, and these may have been limited by the inaccuracy of creatinine as a renal function marker. A cross-sectional study was performed among older adults in the Cardiovascular Health Study to examine associations between SBI and two serum markers of renal function: Serum creatinine (SCr) and cystatin C (CysC). Patients had cranial magnetic resonance imaging and renal markers measured in 1992 to 1993. Logistic regression was used to estimate the associations between renal function (estimated by 1/SCr and 1/CysC) and SBI, controlling for potential confounding factors. SBI were present in 789 (28.7%) of 2784 participants. A linear association with SBI was observed for 1/CysC (per 1-SD decrement; odds ratio [OR] 1.20; 95% confidence interval [CI] 1.09 to 1.32; $P < 0.001$) but not for 1/SCr (OR 1.08; 95% CI 0.98 to 1.19; $P = 0.14$), for which a quadratic U-shaped association was suggested ($P = 0.004$). In a model with both markers, 1/CysC was linearly associated with SBI (OR 1.26; $P < 0.001$), whereas 1/SCr was not (OR 1.06; $P = 0.3$). The prevalence of SBI was directly associated with quintile of CysC, whereas the association between SCr and SBI was U-shaped, with greater prevalence at high and low levels. Compared with creatinine, CysC, a novel marker of renal function, has a stronger and more direct association with SBI in the elderly.

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Subclinical brain infarcts (SBI) are radiographically defined lesions consistent with infarcts in individuals without a clinical history of stroke. Previous studies have reported a high prevalence of these infarcts among the elderly and an association with increased neurologic and cognitive morbidity (1–7). Traditional vascular risk factors including advanced age and elevated BP have been identified as contributing to the risk for SBI. However, the contribution of "nontraditional" vascular risk factors has not been well characterized. Impaired renal function is increasingly being recognized as an important and highly prevalent vascular risk factor associated with an increased risk for cerebrovascular disease. Previous reports have found both renal insufficiency and ESRD to be associated with an increased risk for clinical stroke (8–12) and subclinical carotid artery atherosclerosis (13–19). Consequently, the estimated 8 million individuals in the United States with decreased renal function may also be at increased risk for SBI and its associated morbidity.

The few investigations that have examined this association either have been small single-center studies (20) or have used serum creatinine (SCr) as a marker of renal insufficiency (7,21). However, SCr is an insensitive serum marker of renal function, especially in detecting mild to moderate renal dysfunction in the elderly. Levels of SCr are influenced by muscle mass, which may be reduced in elderly patients, especially those with infarct-related morbidity or with high levels of comorbid risk factors. Cystatin C (CysC), a cysteine proteinase inhibitor that is constitutively expressed in all nucleated cells, has been proposed as an alternative and more accurate renal function marker. Previous studies have suggested that CysC levels are independent of muscle mass and are more strongly correlated with renal function compared with levels of creatinine (22). However, a recent study suggested that CysC levels may be determined by certain nonrenal factors, such as microinflammation, (23), which itself may contribute to vascular risk. Therefore, one might expect CysC to be a strong direct correlate of SBI risk because of its relationship to both renal and nonrenal

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factors. We therefore analyzed the cross-sectional association between CysC and SBI in a large population of community-dwelling older adults, using data from the Cardiovascular Health Study (CHS). We hypothesized a direct association between CysC and the prevalence of SBI and compared this with the association between creatinine and SBI.

Materials and Methods

Study Population: CHS

The design of the CHS has been described previously (24). Briefly, the study participants consisted of 5888 individuals who were aged 65 and older and selected at random from Medicare eligibility lists in four U.S. communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. A total of 5201 participants were recruited in 1989 to 1990, and an additional 687 black participants were recruited in 1992 to 1993. Participants were followed annually for cardiovascular and cerebrovascular disease events. All participants gave informed consent to participate, and all research was performed in adherence to the Declaration of Helsinki principles.

Because our analysis focused on SBI, individuals with a history of stroke or transient ischemic attack (TIA) were excluded. Previous stroke or TIA was defined as a self-reported or adjudicated history of stroke/TIA that occurred before enrollment in CHS and/or an adjudicated stroke or TIA, as determined by the Cerebrovascular Disease Adjudication Committee (25), that occurred between the date of enrollment and the date of brain imaging.

Cranial Imaging

All of the 5477 CHS participants who were alive at the 1992 to 1993 visit were invited to receive a cranial magnetic resonance imaging (MRI) to assess for cerebral vascular disease (26). Of these, a total of 3660 CHS participants received cranial MRI. Participants who received an MRI were generally healthier than those who did not, as reportedly previously (27). Cranial MRI was performed according to a previously described standard protocol (26). All images were read centrally by experienced neuroradiologists who were unaware of participants' clinical information (including renal function measurements). A brain infarct was defined radiographically as a lesion with abnormal signal in a vascular distribution and no mass effect, according to standardized criteria described previously (1). For the purposes of this analysis, an SBI was defined as an infarct-like lesion ≥3 mm in a participant without a previous stroke or TIA. In a pilot study, the intra- and inter-reader reliability for detection of infarcts of this size was high (κ = 0.71 and κ = 0.78, respectively) (26).

Data Collection

SCr and serum CysC, measured from serum collected in 1992 to 1993, were used for this cross-sectional analysis. SCr measurements were performed using a colorimetric assay. Mean coefficient of variation (CV) on monthly controls was 1.94% (range 1.16 to 3.9%). CysC was measured with a particle-enhanced immunonephelometric assay using the BNII nephelometer (Dade Behring, Inc, Deerfield, Illinois). Intraassay CV ranged from 2.0 to 2.8%, and interassay CV ranged from 2.3 to 3.1%. Estimated GFR was computed using the abbreviated Modification of Diet in Renal Disease formula (28). BP was measured twice in the seated position, and the two measurements were averaged. Measures of muscle strength included (*1*) grip strength in the dominant hand, assessed with a hand-held Jamar A dynamometer, and (*2*) the time required to walk 15 feet at a participant's usual pace. Comorbid conditions that were assessed in the same year as the renal function measures were used in this analysis. Hypertension was defined as a systolic BP ≥140, diastolic BP ≥90, or use of antihypertensive medications in a person with a self-reported history of hypertension. Diabetes was defined as a fasting glucose ≥126 mg/dl or use of insulin or hypoglycemic medication. Coronary heart disease was defined as a history of angina, myocardial infarction, coronary angioplasty, or coronary artery bypass surgery. The use of aspirin and other medications within the preceding 2 wk was assessed at each annual clinic visit; for the purposes of this analysis, previous aspirin use was defined as reported use at any clinic visit preceding the cranial MRI.

Statistical Analyses

Baseline covariates, stratified by gender, were compared among participants with and without one or more SBI using the χ^2 test or the *t* test. Spearman rank correlations were computed between CysC and other continuous covariates. Multivariate logistic regression was used to determine the association between each marker of renal function and odds of one or more SBI. We adjusted *a priori* for factors that might plausibly confound the association between renal function and SBI: Age, race, gender, weight, height, diabetes, systolic and diastolic BP, use of antihypertensive medications, smoking, and aspirin use. Because the relationship between SCr and renal function differs between men and women, it was hypothesized *a priori* that the relationship between SCr and the odds of SBI may also differ by gender. Hence, a separate analysis was performed for each gender. The multivariate association between CysC and SBI was also estimated among subgroups defined by level of SCr to determine whether this association was stronger among those with higher or lower SCr levels.

In an exploratory analysis, we also adjusted for factors that might plausibly mediate or explain the association between renal function and SBI, considering three sets of factors: (*1*) Inflammatory markers and lipids (C-reactive protein [CRP], fibrinogen, factor VII, and total cholesterol), (*2*) prevalent clinical cardiac disease (coronary heart disease and atrial fibrillation), and (*3*) subclinical carotid artery disease (intima-media thickness and severity of stenosis) (29). In addition, we assessed whether the association of renal impairment and SBI differed by infarct location (subcortical *versus* cortical). In the analysis of cortical infarcts, participants with only subcortical or posterior infarcts were excluded; likewise, in the analysis of subcortical infarcts, those with only cortical or posterior infarcts were excluded. Participants with both cortical and subcortical infarcts were included in both analyses.

Because both SCr and CysC are inversely related to renal function and typically have a highly skewed distribution in an unselected population, both variables were transformed to their inverse (1/SCr and 1/CysC) before inclusion in regression models. Graphic evaluation of these transformed variables confirmed their Gaussian distribution. To compare the magnitude of the associations of each serum marker with SBI, we standardized the scale of each variable (1/SCr and 1/CysC) by dividing each measurement by the variable's SD. We initially tested linear forms of these continuous variables in the regression models; however, exploratory analyses were performed to investigate their correct functional forms.

To explore further the appropriate functional form of each renal function variable, we plotted the adjusted prevalence of SBI for each gender-specific quintile of SCr or CysC. For comparison, the prevalence of SBI for each gender-specific quintile of estimated GFR was also plotted. The Wald test of quintiles of renal function variables as a linear term was used to test for trend. Global goodness-of-fit testing of all logistic models was performed with the Hosmer-Lemeshow test (30). Effect modification by gender, age, race, diabetes, hypertension, and inflammatory/thrombotic markers was assessed using standard techniques. All statistical analyses were performed with Stata Intercooled v7.0 (Stata Corp., College Station, TX).

Results

Study Population

Of the 3660 CHS participants who received a cranial MRI in 1992 to 1994, 338 (9.2%) had a self-reported or adjudicated stroke or TIA before MRI imaging and were excluded from this analysis. Of the remaining 3322 participants, 370 (11.1%) had their MRI before study year 5 (when measurements of CysC were performed) and were also excluded. A total of 2784 (94.3%) of the remaining patients had complete measurements of both CysC and SCr during the same study year as their MRI imaging and formed the final study population.

The prevalence of SBI was 28.1% ($n = 473$) among women and 28.7% ($n = 316$) among men (Table 1). Compared with women without SBI, those with at least one SBI were older; had higher CysC, SCr, and BP; and were more likely to have hypertension. Similar differences in baseline characteristics were also found among men with and without SBI (Table 1); in addition, men with SBI had lower body mass index and were more likely to have prevalent coronary disease than men without SBI. Participants with SBI also took longer to walk 15 feet and (among men) had weaker grip strength. SCr values ranged from 0.5 to 3.3 mg/dl among women and 0.7 to 3.1 mg/dl among men. CysC values ranged from 0.61 to 3.19 mg/L among women and 0.51 to 2.91 mg/L among men. CysC was weakly correlated with inflammatory and thrombotic markers: CRP ($r = 0.15$), fibrinogen ($r = 0.15$), and factor VII ($r = 0.11$).

Association between CysC and SBI

When considered as a continuous variable, 1/CysC was associated with the odds of SBI (Table 2). In an unadjusted model, a 1-SD decrement in 1/CysC (indicating a relative increment in CysC) was associated with 27% greater odds of SBI. Adjustment for potential confounders (age, gender, race, weight, height, diabetes, BP, use of aspirin and antihypertensive medications, and smoking) attenuated this association somewhat (adjusted odds ratio [OR] per 1-SD decrement 1.20).

The association of 1/CysC and SBI was similar among men and women and did not differ significantly by age, race, diabetes, hypertension, or prevalent coronary disease ($P > 0.3$ for all pairwise tests of interaction). The prevalence of SBI, adjusted for age, gender, race, weight, height, BP, diabetes, antihypertensive medication, and aspirin use, increased in a graded manner with higher levels of CysC ($P < 0.001$ for test for trend; Figure 1A).

Association between Creatinine and SBI

In contrast, the association between 1/SCr and SBI was more modest (Table 2), with a 1-SD decrement conferring a nonsignificant 8% greater odds of infarct after adjustment for potential confounders ($P = 0.13$). Further exploration suggested a quadratic relationship between 1/SCr and SBI, with increased odds at both high and low values ($P = 0.006$ for test of quadratic term). When the relationship between 1/SCr and SBI was examined among men and women separately (Table 2), there was

Table 1. Baseline characteristics of study participants, by gender and presence of SBI on cranial MRI[a]

Covariate	Women ($n = 1684$; n [%] or Mean [SD])			Men ($n = 1100$; n [%] or Mean [SD])		
	≥1 Infarcts ($n = 473$)	No Infarcts ($n = 1211$)	P	≥1 Infarcts ($n = 316$)	No infarcts ($n = 784$)	P
Age (yr)	75.5 (4.9)	74.4 (4.8)	<0.001	76.4 (5.6)	75.0 (4.9)	<0.001
Race			0.6			0.6
black	79 (16.7%)	214 (17.7%)		47 (14.9%)	127 (16.2%)	
white/other	394 (83.3%)	997 (82.3%)		269 (85.1%)	657 (83.8%)	
Hypertension	311 (65.6%)	705 (58.2%)	0.005	186 (58.9%)	413 (52.7%)	0.06
SBP (mmHg)	138.4 (22.6)	134.0 (20.0)	<0.001	135.1 (20.7)	133.3 (19.9)	0.2
DBP (mmHg)	71.1 (10.9)	69.6 (10.4)	0.009	73.0 (11.2)	71.8 (10.3)	0.1
BMI (kg/m^2)	26.9 (5.1)	26.9 (5.1)	0.9	25.9 (3.5)	26.7 (3.7)	0.007
Diabetes	54 (11.4%)	146 (12.1%)	0.7	49 (15.5%)	123 (15.7%)	0.9
Coronary heart disease	84 (17.8%)	173 (14.3%)	0.08	96 (30.4%)	174 (22.2%)	0.004
Atrial fibrillation	8 (1.7%)	22 (1.8%)	0.9	11 (3.5%)	27 (3.5%)	0.9
Smoking status			0.3			0.08
current	256 (54.1%)	672 (55.5%)		81 (25.6%)	233 (29.7%)	
former	164 (34.6%)	434 (35.8%)		196 (62.0%)	485 (61.9%)	
never	53 (11.2%)	105 (8.7%)		39 (12.3%)	66 (8.5%)	
Aspirin use before MRI	36 (7.6%)	81 (6.7%)	0.5	35 (11.1%)	68 (8.7%)	0.2
SCr (mg/dl)	0.96 (0.20)	0.94 (0.20)	0.05	1.25 (0.31)	1.19 (0.31)	0.001
CysC (mg/L)	1.10 (0.29)	1.05 (0.26)	0.004	1.20 (0.34)	1.11 (0.26)	<0.001
Estimated GFR (abbreviated MDRD formula [28])	70.4 (18.6)	71.7 (17.2)	0.2	69.0 (19.1)	72.7 (17.5)	0.004
Time to walk 15 feet (s)	6.3 (0.2)	5.5 (0.1)	<0.001	5.5 (0.1)	5.0 (0.1)	<0.001
Grip strength (kg)	22.5 (0.2)	21.9 (0.3)	0.1	35.8 (0.5)	37.7 (0.3)	0.001

[a]SBI, subclinical brain infarct; MRI, magnetic resonance imaging; SBP, systolic BP; DBP, diastolic BP; BMI, body mas index; SCr, serum creatinine; CysC, cystatin C; MDRD, Modification of Diet in Renal Disease. See Materials and Methods for definitions of comorbid conditions.

Table 2. Association of CysC and SCr with MRI-defined SBI, by gender[a]

Renal Function Marker	Adjustment Variables	OR of SBI (per 1-SD Decrement[b]; 95% CI)		
		All (n = 2784)	Women (n = 1684)	Men (n = 1100)
1/CysC	Unadjusted	1.27 (1.17 to 1.38)	1.24 (1.11 to 1.38)	1.33 (1.16 to 1.53)
	Partially adjusted[b]	1.24 (1.13 to 1.36)	1.19 (1.06 to 1.34)	1.31 (1.13 to 1.52)
	Fully adjusted[c]	1.20 (1.09 to 1.32)	1.16 (1.02 to 1.31)	1.25 (1.08 to 1.46)
1/SCr	Unadjusted	1.10 (1.02 to 1.20)[e]	1.07 (0.95 to 1.19)[e]	1.33 (1.11 to 1.60)[e]
	Partially adjusted[b]	1.10 (0.99 to 1.21)[e]	1.03 (0.92 to 1.16)[e]	1.28 (1.06 to 1.55)[e]
	Fully adjusted[c]	1.08 (0.98 to 1.19)[e]	1.02 (0.91 to 1.15)	1.23 (1.01 to 1.50)

[a]OR, odds ratio; CI, confidence interval.
[b]Equivalent to a relative increase in CysC or SCr.
[c]Adjusted for age, gender, race, weight, and height.
[d]Adjusted for all variables above in addition to diabetes, smoking, SBP and DBP, use of antihypertensive medications, and aspirin use.
[e]A quadratic or U-shaped relationship between 1/SCr and SBI is suggested ($P < 0.05$ for test of quadratic term).

no linear association between 1/SCr and infarct among women (per 1-SD change, OR 1.02), but the linear association was statistically significant among men, with a 23% increased risk per 1-SD decrement. The test for interaction showed a nonsignificant trend toward a differential association of 1/SCr and infarct between men and women ($P = 0.14$). In addition, a U-shaped relationship between SCr quintile and prevalence of SBI was estimated (Figure 1B), with higher prevalence at both high and low levels of SCr ($P = 0.2$ for linear trend). When a creatinine-based prediction equation for GFR (the abbreviated Modification of Diet in Renal Disease formula [28]) was used as an estimate of renal function, a U-shaped association with SBI prevalence was also observed (Figure 1C).

Simultaneous Associations of Creatinine and CysC with SBI

Adding 1/SCr (as a quadratic term) to a model that already contained 1/CysC and the same adjustment covariates described above did not improve the prediction of SBI among the entire cohort ($P = 0.1$ for likelihood ratio test), but adding 1/CysC to a model with 1/SCr (the latter variable modeled as a quadratic term) did significantly improve the prediction of SBI ($P = 0.002$). In a model that contained both renal function markers together, 1/CysC was still linearly associated with SBI (per 1-SD change, OR 1.26; 95% CI 1.11 to 1.42), whereas 1/SCr was not (OR 1.08; 95% CI 0.94 to 1.22).

Association of CysC and SBI Stratified by Baseline Creatinine

The association between 1/CysC and SBI was determined in subgroups defined by levels of SCr (Table 3). After adjustment for potential confounders, 1/CysC was linearly associated with SBI among participants with SCr levels in the second to fourth quintiles of distribution (0.8 to 1.0 mg/dl in women and 1.0 to 1.3 mg/dl in men), with higher CysC associated with a greater odds of SBI in these subgroups. In contrast, when the association of 1/SCr and SBI was examined in subgroups defined by levels of CysC, an inverse association with SBI was observed among participants with CysC levels in the first and second quintiles, with higher levels of SCr being associated with *lower* odds of SBI in these subgroups (Table 4).

Influence of Mediating Factors and Infarct Location

In an exploratory analysis, we adjusted for additional factors that might plausibly mediate the association between renal impairment and SBI. The association between 1/CysC and SBI was not appreciably changed after adjustment for inflammatory factors and cholesterol (OR 1.17), and there was no effect modification by these factors (tests for interaction, $P > 0.3$). The association with SBI was also not appreciably changed after adjustment for prevalent clinical cardiac disease (coronary disease and atrial fibrillation, OR 1.19) or measures of subclinical carotid atherosclerosis (intima-media thickness and stenosis, OR 1.19). We also explored whether the association between renal impairment and SBI differed according to location of infarct (cortical *versus* subcortical). A total of 696 participants had one or more subcortical infarcts, and 70 participants had one or more cortical infarcts. The OR for 1/CysC and subclinical infarct were similar for both cortical (1-SD decrement OR 1.15; 95% CI 0.94 to 1.41) and subcortical locations (OR 1.21; 95% CI 1.10 to 1.33).

Discussion

In a population of community-dwelling older adults without previous stroke or TIA, higher levels of CysC, a novel marker of renal function, were associated with higher odds of MRI-defined SBI. This association persisted after adjustment for other potential correlates of SBI: Age, gender, height and weight, BP, diabetes, smoking, and use of aspirin. Even among participants with SCr levels typically considered in the "normal range" (0.8 to 1.0 mg/dl in women and 1.0 to 1.3 mg/dl in men), higher CysC was still associated with a greater prevalence of SBI. In contrast, the association between SCr and SBI was more complex, with increased prevalence at both high and low levels of SCr. A similar U-shaped association with SBI was observed when estimated GFR using the creatinine-based formula of Levey *et al.* (28) was used as an estimate of renal function. These findings are similar to those of our previous report on renal function markers and incident cardiovascular mortality and morbidity, in which CysC was a stronger and more direct predictor than SCr (31).

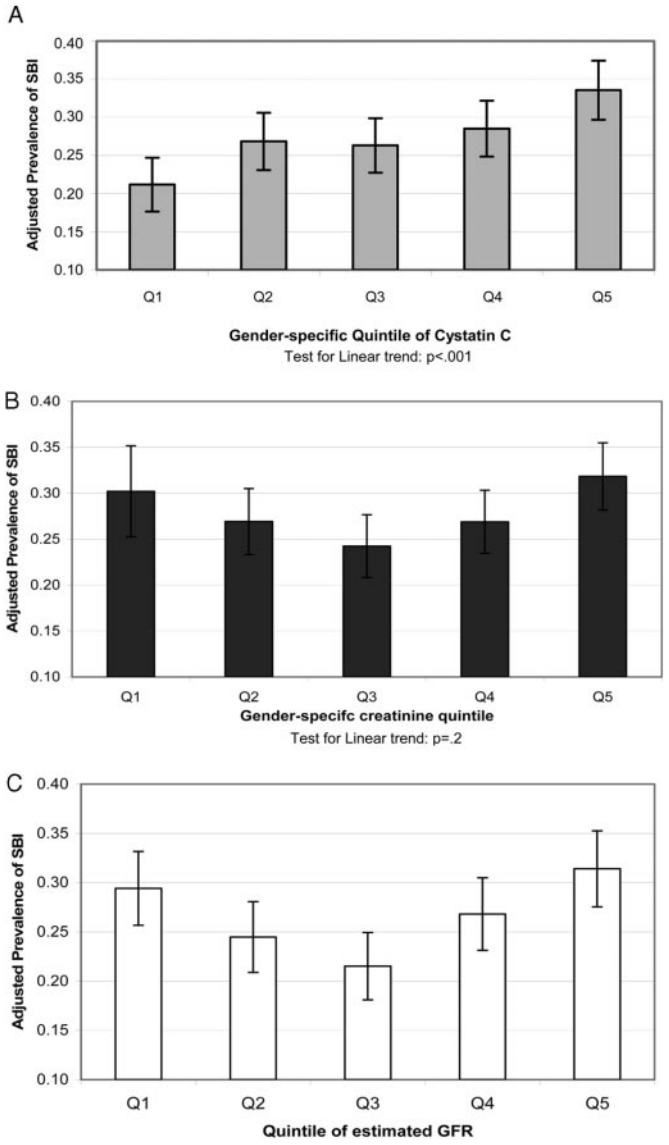

Figure 1. Prevalence of subclinical brain infarct (SBI), by gender-specific quintiles of cystatin C (A), creatinine (B), and estimated GFR (C). SCr (mg/dl) gender-specific quintile cutoff points are as follows: Women 0.5 to 0.7, 0.8, 0.9, 1.0, and 1.1 to 3.3; men 0.7 to 0.9, 1.0, 1.1, 1.2 to 1.3, and 1.4 to 3.1. CysC (mg/L) gender-specific quintile cutoff points are as follows: Women 0.61 to 0.86, 0.87 to 0.95, 0.96 to 1.05, 1.06 to 1.21, and 1.22 to 3.19; men 0.51 to 0.91, 0.92 to 1.01, 1.02 to 1.12, 1.13 to 1.27, and 1.28 to 2.91.

Table 3. Association between CysC and SBI, by quintile of SCr

Quintile of SCr	OR[a] (95% CI) per 1-SD Decrement in 1/CysC[b]
1	1.01 (0.74 to 1.38)
2	1.39 (1.04 to 1.85)
3	1.28 (0.97 to 1.68)
4	1.56 (1.15 to 2.19)
5	1.10 (0.87 to 1.38)

[a]Adjusted for age, gender, race, weight, height, diabetes, smoking, SBP and DBP, use of antihypertensive medications, and aspirin use.
[b]Equivalent to a relative increase in CysC.

Table 4. Association between SCr and SBI, by quintile of CysC

Quintile of CysC	OR[a] (95% CI) per 1-SD Decrement in 1/SCr[b]
1	0.74 (0.56 to 0.97)
2	0.77 (0.58 to 1.03)
3	0.88 (0.64 to 1.20)
4	1.30 (0.93 to 1.81)
5	1.07 (0.84 to 1.37)[d]

[a]Adjusted for age, gender, race, weight, height, diabetes, smoking, SBP and DBP, use of antihypertensive medications, and aspirin use.
[b]Equivalent to a relative increase in creatinine.
[c]Quadratic relationship between 1/SCr and SBI suggested ($P = 0.04$ for test of quadratic term).

CysC and SCr as Markers of Renal Function

The nonlinear association of SCr with SBI may be explained by the influence on SCr levels of creatinine generation, which is determined largely by muscle mass. In our study, surrogate markers of muscle mass (body mass index) and muscle strength (timed walk and grip strength) tended to be lower in participants with SBI, perhaps as a result of infarct-related morbidity. A lower relative muscle mass among those with SBI could result in an apparent association between low SCr and higher odds of these infarcts. In contrast, levels of CysC have been reported to be independent of muscle mass, and it has been suggested that CysC is a more accurate marker of GFR (22).

However, a recent cross-sectional study of 8000 community-based subjects suggested that factors other than renal filtration may influence levels of CysC (23). In that study, CysC was moderately correlated ($r = 0.29$) with CRP, and this correlation persisted after adjustment for creatinine clearance (CrCl) as estimated from 24-h urine collections. The authors suggested that CysC levels might be influenced by the severity of underlying inflammation (itself a putative vascular risk factor) and not simply by renal filtration function. However, in our study, correlations between CysC and inflammatory markers such as CRP and fibrinogen were weak ($r = 0.11$ to 0.15). In addition, the direct association between 1/CysC and SBI was still observed after adjustment for inflammatory markers, and the association did not vary across levels of CRP or fibrinogen. It therefore seems unlikely that levels of inflammation explain the observation of CysC with SBI, although in the absence of gold standard measures of renal function, we cannot completely exclude the influence of such nonrenal factors.

Renal Impairment and SBI

Recent studies have found that unrecognized SBI is exceedingly common among the elderly, with a frequency approximately five times that of clinical stroke (4,7). Reports from CHS and other large community-based studies have found that in-

dividuals with SBI have a higher frequency of cognitive impairment (1,6), dementia (6), fine motor defects (1), and subsequent acute clinical stroke (2,3,5), after adjustment for other potential risk factors. Factors that are associated with risk for coronary disease and clinical stroke, such as advanced age and elevated BP, were also found to be associated with risk for SBI.

In a previous single-center study by Kobayashi *et al.* (20), patients with chronic kidney disease and a CrCl <40 ml/min per 1.73 m^2 had a prevalence of SBI nearly three-fold that of controls; in contrast, patients with documented kidney disease but with CrCl >40 ml/min per 1.73 m^2 had no increase in SBI prevalence. In a previous study from CHS, SCr was one of several predictors of incident SBI among a subset of CHS participants who were free of infarct at their first MRI and who underwent repeat MRI (7). Creatinine was also one of several significant correlates of silent lacunar (small subcortical) infarcts among CHS participants in a cross-sectional analysis (21). In these CHS studies, the risk for SBI was appreciably greater among those with SCr >1.3 mg/dl; measurements of CysC were not available for CHS participants at the time of these reports. Our results extend the findings of these earlier studies, and suggest that, to the extent that CysC is an accurate marker of renal function, the relationship between renal function and SBI may be linear, with a greater prevalence of SBI in association with modest differences in CysC levels.

The factors that mediate the association between markers of renal impairment and SBI are unclear. Patients with renal insufficiency may have more severe atherosclerosis of the carotid arteries, even after adjustment for other vascular risk factors (18,19), which could contribute to a higher risk for SBI. However, after adjustment for markers of carotid atherosclerosis (stenosis and intima-media thickness), the association between CysC and SBI was attenuated only modestly, suggesting that other factors may explain this association. Most of the SBI in this study were small and subcortical in location (1); these types of infarcts are believed to arise from ischemia as a result of disease of small intracerebral arteries rather than large-vessel atherosclerosis. Hypertension is a common risk factor for small-vessel disease in the kidney and has also been associated with SBI (1,4) and therefore could confound the association between renal function and SBI. However, after adjustment for BP and antihypertensive medications, the association between CysC and SBI persisted, and this association was observed among participants without hypertension. This suggests that the association is not fully explained by these common underlying conditions, although differences in long-term BP or in end-organ susceptibility to hypertension between those with and without renal impairment could at least partly explain our results.

Limitations and Strengths

Limitations of this study include the cross-sectional design, in which the temporal relationship between renal impairment and SBI cannot be determined. Another limitation is that measurements of urinary protein excretion were not available on the study population at the time of MRI. Because many causes of chronic renal impairment also result in elevated protein excretion, it is possible that a true association between proteinuria and SBI explains the apparent effect of lower renal function in this study. CHS participants who completed cranial MRI were generally healthier than those who did not complete such imaging (27); therefore, the results obtained from this analysis may not be fully generalizable to all CHS participants or to the general population of older adults. However, the community-based, multicenter design of the study allows for greater generalizability of results than clinic-based or hospital-based studies.

Other strengths of this study include the large study population and high frequency of SBI, which provided sufficient power to detect moderately sized associations between markers of renal insufficiency and infarct. CHS collected extensive data on clinical and subclinical comorbidities, which allowed for adjustment for potential confounding or mediating factors. All participants received MRI using standardized techniques and interpretation by centralized readers who were blinded to participants' renal function, which minimized the biased misclassification of infarct status.

Conclusion

The results of this community-based study demonstrate for the first time that CysC, a marker of renal function, is directly associated with a higher prevalence of SBI, even after adjustment for other factors that potentially are associated with infarction. Although we cannot exclude all factors other than renal filtration function that influence this association, the results do provide further evidence for a link between renal impairment and subclinical vascular disease of the brain. Given the high prevalence of renal disease and the poor prognosis associated with SBI, future research should focus on potentially modifiable factors that mediate this association.

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A full listing of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

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