Chronic Kidney Disease Is Associated With White Matter Hyperintensity Volume
The Northern Manhattan Study (NOMAS)

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Background and Purpose—White matter hyperintensities have been associated with increased risk of stroke, cognitive decline, and dementia. Chronic kidney disease is a risk factor for vascular disease and has been associated with inflammation and endothelial dysfunction, which have been implicated in the pathogenesis of white matter hyperintensities. Few studies have explored the relationship between chronic kidney disease and white matter hyperintensities.

Methods—The Northern Manhattan Study is a prospective, community-based cohort of which a subset of stroke-free participants underwent MRIs. MRIs were analyzed quantitatively for white matter hyperintensities volume, which was log-transformed to yield a normal distribution (log-white matter hyperintensity volume). Kidney function was modeled using serum creatinine, the Cockcroft-Gault formula for creatinine clearance, and the Modification of Diet in Renal Disease formula for estimated glomerular filtration rate. Creatinine clearance and estimated glomerular filtration rate were trichotomized to 15 to 60 mL/min, 60 to 90 mL/min, and >90 mL/min (reference). Linear regression was used to measure the association between kidney function and log-white matter hyperintensity volume adjusting for age, gender, race–ethnicity, education, cardiac disease, diabetes, homocysteine, and hypertension.

Results—Baseline data were available on 615 subjects (mean age 70 years, 60% women, 18% whites, 21% blacks, 62% Hispanics). In multivariate analysis, creatinine clearance 15 to 60 mL/min was associated with increased log-white matter hyperintensity volume ($\beta 0.322; 95\% CI, 0.095 to 0.550$) as was estimated glomerular filtration rate 15 to 60 mL/min ($\beta 0.322; 95\% CI, 0.080 to 0.564$). Serum creatinine, per 1-mg/dL increase, was also positively associated with log-white matter hyperintensity volume ($\beta 1.479; 95\% CI, 1.067 to 2.050$).

Conclusions—The association between moderate–severe chronic kidney disease and white matter hyperintensity volume highlights the growing importance of kidney disease as a possible determinant of cerebrovascular disease and/or as a marker of microangiopathy. (Stroke. 2007;38:3121-3126.)

Key Words: chronic kidney failure • leukoaraiosis • magnetic resonance imaging

White matter hyperintensities (WMH) are often incidentally discovered on T2-weighted MRI. However, it is becoming increasingly evident that WMH are not simply benign, age-related phenomena. Although the underlying pathological mechanisms are incompletely understood, they are at least partly mediated by vascular dysfunction as suggested by clinical studies showing an association with hypertension,1,2 diabetes,3 history of cardiac disease,3 and total homocysteine (tHcy)4,5 as well as pathological studies confirming vascular damage6,7 In addition, WMH may carry an increased risk of stroke,8 cognitive decline,9 and dementia.10

Given the enigmatic nature of WMH, it is important to find novel risk factors that may clarify their pathophysiology and serve as targets for risk reduction. Chronic kidney disease (CKD) has emerged as an independent risk factor for stroke and other cardiovascular events11–13 as well as cardiovascular and noncardiovascular mortality.12,14 In addition, CKD has also been linked to proinflammatory and procoagulant states15,16 that may contribute to WMH development.4,17,18
White matter hyperintensities are more prevalent in patients with end-stage renal disease, but the association between WMH and less severe kidney disease is uncertain. One case–control study found an increased prevalence of WMH in CKD subjects, but this study was small (n = 52) and also included subjects with end-stage renal disease (creatinine clearance ≤15 mL/min) who have a substantial burden of medical comorbidities and a greater risk of cardiovascular disease than those with less severe CKD. We hypothesized that milder forms of kidney impairment would also be associated with increased WMH. Few studies have examined this relationship, especially in blacks and Hispanics who have a greater risk of cerebrovascular disease and dementia.

Methods

Selection of Prospective Cohort
The Northern Manhattan Study (NOMAS) included a stroke-free cohort of 3298 subjects enrolled between 1993 and 2001. Subjects were recruited from the area of northern Manhattan by random digit dialing and were eligible if (1) at least 40 years of age, (2) did not have a history of stroke, and (3) had resided in northern Manhattan for at least 3 months in a household with telephone. The overall response rate was approximately 68%. This study was approved by the Columbia University Medical Center Institutional Review Board.

Baseline Measurements
Data regarding baseline status and risk factors were collected through interviews by trained research assistants, physical and neurological examination by study physicians, in-person measurements, and analysis of fasting blood specimens. Data were obtained from participants (99%) or proxies using standardized data collection instruments. Participants self-identified ethnicity as Hispanic or non-Hispanic and race as white, black, or other. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose. Hypertension was defined as systolic blood pressure 140 mm Hg or diastolic blood pressure 90 mm Hg, physician diagnosis, or self-report of history of hypertension or antihypertensive use. Diabetes mellitus was defined as fasting blood glucose 126 mg/dL or self-report of such a history or insulin or hypoglycemic use. Baseline fasting blood samples were drawn into serum tubes and spun within 1 hour at 3000g and 4°C for 20 minutes and immediately frozen at −70°C (shown to be stable for tHcy assays). We measured serum tHcy levels using methods licensed for commercial use. Serum creatinine was determined using the kinetic alkaline picrate assay (Jaffé reaction). Subjects were weighed using calibrated scales.

Selection of MRI Substudy and MRI Measurements
Stroke-free NOMAS subjects were recruited into the MRI substudy during annual telephone follow-up beginning in 2003 and were eligible if (1) at least age 55, (2) no contraindications to MRI, and (3) willing to sign informed consent. These participants were scheduled for a visit to the Hatch Imaging Center (New York, NY). All images were acquired using a 1.5-T MRI system (Philips Medical Systems, Best, The Netherlands). White matter hyperintensity volumes (WMHV) were determined using fluid-attenuated inversion recovery images.

Quantitative analysis of WMHV was performed at the University of California–Davis using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. All analyses were performed blinded to subject personal identification. Before WMH segmentation, nonbrain elements were manually removed by operator-guided tracing of the dura mater within the cranial vault. This process included the middle cranial fossa but omitted the posterior fossa as well as the cerebellum.

White matter hyperintensity segmentation was performed in 2 steps as described previously. Step one involved the identification of brain matter. Image intensity nonuniformities were removed from the image, and the corrected image was then modeled as a mixture of 2 Gaussian probability functions with the segmentation threshold determined at the minimum probability between these 2 distributions. After segmentation of brain matter, a single Gaussian distribution was fitted to image data. A segmentation threshold for WMHV was determined a priori to be 3.5 SDs above the mean of the fitted distribution of brain parenchyma. In addition, morphometric erosion of 2 exterior image pixels was applied to the brain matter image before modeling to remove any image artifact resulting from cerebrospinal fluid pixels on WMH calculation. WMHV was calculated as a proportion of total cranial volume to account for variation in head size among subjects and, for the continuous measure, was log-transformed (log-WMHV) to achieve a normal distribution.

Estimation of Kidney Function
Baseline kidney function was estimated using serum creatinine as well as creatinine clearance (CCl) using the Cockcroft-Gault formula and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula:

\[
\text{CCl} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{(\text{serum creatinine} 	imes 72)} \times (0.85 \text{ for women})
\]

\[
\text{eGFR} = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times (0.742 \text{ for women}) \times (1.21 \text{ for blacks})
\]

Serum creatinine was log-transformed (log-cr) to achieve a normal distribution. Subjects with a CCI or eGFR <15 mL/min (N = 1) were excluded to focus on mild and moderate CKD rather than end-stage renal disease.

Statistical Analysis
We examined CCI and eGFR by creating 3 categories: moderate–severe CKD (15 to 60 mL/min), mild CKD (60 to 90 mL/min), and normal (>90 mL/min). We tested for the following potential confounders of the relationship between log-WMHV and CKD using \( \chi^2 \) tests for categorical variables and analysis of variance tests for continuous variables: age, race–ethnicity, gender, education, hypertension, cardiac disease, tHcy level, and diabetes. Variations in log-WMHV by covariate were tested using 2-sample t tests or analysis of variance tests for statistical significance. Potential confounders were selected based on if (1) there was a well-established association from prior studies between the variable and WMH (to improve comparability between studies) or (2) the variable was associated with kidney function in this sample. We constructed linear regression models of the association between CKD and continuous log-WMHV adjusting for relevant confounders. We tested for effect modification by including interaction terms. All analyses were conducted using SAS software (v8.02; SAS Institute).

Results

Baseline Characteristics
There were 615 participants with brain MRI scans and kidney function measurements available (mean follow-up = 6.4 years, SD = 2.3). We excluded participants without WMHV measurements, those with CCl or eGFR <15 mL/min, and those without baseline kidney function or covariate data. The average age of the study group at the time of MRI was 70 years (SD = 7) and was similar to the overall cohort (60% women, 62% Hispanic, 21% black, 18% white). The MRI subgroup was younger and had significantly lower prevalences of diabetes (18% versus 25%), hypertension (68%...
versus 75%), and cardiac disease (13% versus 23%) than those who were not in the MRI study. The characteristics of the study sample are presented in Table 1 and shows the distribution of covariates across the tiers of kidney function.

Regardless of which estimation of kidney function was used, moderate–severe CKD was independently associated with greater WMHV adjusting for age, gender, race–ethnicity, and education (Table 2). These findings remained significant adjusting further for vascular risk factors, including hypertension, diabetes, cardiac disease, and tHcy levels. With CCl, there was also a relationship for mild CKD, although this was not significant when using eGFR as the marker of kidney function.

Of note, homocysteine concentrations are typically inversely related to kidney function,31 but were not significantly different across the 3 tiers of CCl (see Table 1). However, there did appear to be a significant negative relationship with eGFR. In a previous analysis of the NOMAS MRI cohort, tHcy was found to be associated with WMHV.4 In that study, tHcy was partitioned into 3 levels with cut points at the median and 1 SD above the median. We used the same cutoffs (median=8.4 μmol/L, 1 SD above median=12 μmol/L). For log-cr, there was a significant interaction with tHcy above 12 μmol/L (β 0.931; 95% CI, 0.048 to 1.815) and a borderline interaction with tHcy levels between 8.4 and 12 μmol/L (β 0.621; 95% CI, −0.017 to 1.258) suggesting that for higher levels of tHcy, each unit increase in serum creatinine is associated with greater WMHV. For eGFR, there was a significant interaction between tHcy 8.4 to 12 μmol/L and eGFR 15 to 60 mL/min (β 0.647; 95% CI, 0.103 to 1.192), suggesting an increase in WMHV for subjects with moderate levels of total homocysteine and moderate–severe kidney disease. There were no statistically significantly interactions between tHcy and CCI.

**Discussion**

We found that subjects with CKD had a greater burden of WMHV after adjusting for sociodemographic and vascular risk factors. To our knowledge, this is the first study to show an association between mild and moderate–severe CKD and

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**Table 1. Sample Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CCl</th>
<th>eGFR</th>
</tr>
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<tr>
<td></td>
<td>15–60 mL/min</td>
<td>60–90 mL/min</td>
</tr>
<tr>
<td>No.</td>
<td>85</td>
<td>318</td>
</tr>
<tr>
<td>Age at MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 years</td>
<td>69 (81)</td>
<td>185 (58)</td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>16 (19)</td>
<td>133 (42)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.079</td>
<td>0.478</td>
</tr>
<tr>
<td>Men</td>
<td>60 (71)</td>
<td>185 (58)</td>
</tr>
<tr>
<td>Women</td>
<td>25 (29)</td>
<td>133 (42)</td>
</tr>
<tr>
<td>Completed high school</td>
<td>0.061</td>
<td>0.024</td>
</tr>
<tr>
<td>Yes</td>
<td>53 (62)</td>
<td>153 (48)</td>
</tr>
<tr>
<td>No</td>
<td>32 (38)</td>
<td>165 (52)</td>
</tr>
<tr>
<td>Race</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>White</td>
<td>22 (26)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>Black</td>
<td>25 (29)</td>
<td>67 (21)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>38 (45)</td>
<td>194 (61)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>0.857</td>
<td>0.955</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (12)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>No</td>
<td>75 (88)</td>
<td>276 (87)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.306</td>
<td>0.003</td>
</tr>
<tr>
<td>Yes</td>
<td>54 (64)</td>
<td>212 (67)</td>
</tr>
<tr>
<td>No</td>
<td>31 (36)</td>
<td>106 (33)</td>
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<tr>
<td>Diabetes</td>
<td>0.435</td>
<td>0.224</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (16)</td>
<td>51 (16)</td>
</tr>
<tr>
<td>No</td>
<td>71 (84)</td>
<td>267 (84)</td>
</tr>
<tr>
<td>Total homocysteine</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>&lt;8.4 μmol/L</td>
<td>31 (36)</td>
<td>154 (9)</td>
</tr>
<tr>
<td>8.4–12 μmol/L</td>
<td>39 (46)</td>
<td>134 (42)</td>
</tr>
<tr>
<td>&gt;12 μmol/L</td>
<td>31 (18)</td>
<td>154 (48)</td>
</tr>
</tbody>
</table>

Results are presented as N (%) unless noted.
WMH using quantitative measures. A previous study also found an increased prevalence of WMH in subjects with CKD (including end-stage renal disease), but did not find a significant relationship between either CKD severity or duration and WMH.20 However, the authors did find a significant relationship between vascular nephropathy and WMH in multivariate analysis, suggesting that increased WMH in those with CKD was a marker of systemic vascular disease. That study was limited by a small sample size (n=52) and use of semiquantitative WMHV measurement.

CKD has been associated with subclinical vascular disease in the form of subclinical brain infarcts32 and carotid intima media thickness.33 Although subclinical brain infarcts, intima media thickness, and WMH have different risk factor profiles, they may all represent markers of systemic vascular disease and inflammation. Although the causal pathways are complex, there is increasing evidence that CKD may actually be a risk factor for these associated conditions and not just a result of them.

Potential mechanisms to explain the role, if any, that kidney insufficiency may have in WMH development include elevated levels of inflammatory and procoagulant mediators seen in subjects with CKD. Studies regarding the association between hypercoagulability and WMH have been mixed. The Cardiovascular Health Study found elevated levels of factor VII to be associated with worsening of white matter disease on serial MRI studies,17 whereas a cross-sectional analysis found that subjects with elevated creatinine also had significantly higher levels of factor VIIc.15 In addition, Hassan et al18 showed increased levels of prothrombotic markers, including thrombomodulin, in subjects with extensive WMH, but this was not verified in a prospective, although possibly underpowered,34 study.

Although WMH may be due to arteriosclerotic changes and lipohyalinosis,35 some researchers have postulated that edema and a faulty blood–brain barrier secondary to endothelial dysfunction may be partially responsible as well.18,36 CKD, through numerous mechanisms including increased oxidative load and through the endothelin family of peptides, is also associated with endothelial dysfunction and may contribute to WMH genesis by this hypothesis.

Moderate CKD is also associated with elevated levels of uremic toxins, including plasma asymmetric dimethylarginine, a powerful inhibitor of nitric oxide synthesis.39 Asymmetric dimethylarginine has been implicated as a possible mediator connecting CKD and increased cardiovascular disease risk.40 In turn, endothelium-derived nitric oxide plays a prominent role in cerebral blood flow regulation41 and functions as a vasodilator42 and inhibitor of smooth muscle cell proliferation.43 In addition, impaired cerebral blood flow autoregulation is thought to contribute to WMH.44 Thus, CKD may cause WMH due to a parallel increase in asymmetric dimethylarginine levels and subsequent decrease in nitric oxide within the cerebral vasculature. Preliminary studies have also found that endothelial nitric oxide synthase gene polymorphisms, which have been associated with decreased bioavailability of nitric oxide,45 are associated with increased WMH.46

It is also possible that WMHV seen in subjects with CKD is mediated by hyperhomocysteinemia. We found interactions between tHcy >12 μmol/L and log-cr and tHcy between 8 and 12 μmol/L and eGFR. Homocysteine has been associated with WMHV in previous studies, and although decreased kidney function may lead to increased levels of homocysteine, homocysteine itself may be damaging to the kidney. Prospective studies are needed to clarify the causal roles of CKD and tHcy in WMH development.

There was a significant association for mild CKD and WMHV using CCI, but not eGFR, between 60 and 90 mL/min as the criterion. Intrinsic differences between the 2 formulas may account for this discordance. eGFR is more precise in patients with compromised kidney function but has less precision when kidney function is normal.47 A glomerular filtration rate between 60 and 90 mL/min can be considered normal (for age) in the absence of proteinuria, which was not measured in this cohort. Therefore, the discrepant association between WMHV and mild kidney dysfunction (CCI/eGFR 60 to 90 mL/min) using Cockcroft-
Gault and Modification of Diet in Renal Disease formulas may be secondary to their lack of specificity. Also noteworthy, there is no consensus on the superior formula in Hispanic populations.

Furthermore, we analyzed the effect of certain medications that may have impacted serum creatinine measurement, including angiotensin-converting enzyme inhibitors, diuretics, and antibiotics. Our findings remained the same excluding subjects on antibiotics (n = 5). We also found that angiotensin-converting enzyme inhibitor and diuretic use were not related to our estimates of kidney function using any of the 3 measures nor did including these medications in the final multivariate analysis alter our results.

There are several limitations to this study. One is the cross-sectional design because our results cannot be used to demonstrate causality. Also, the MRI sample is somewhat healthier than the overall cohort due to a survivor effect and has slightly lower prevalences of comorbid risk factors. However, this would tend to minimize our findings. Kidney function was estimated using serum creatinine and serum creatinine-based formulas. More exact estimations such as 24-hour urine collections for iothalamate were not obtained because of the expense and impracticality of performing these collections in a large epidemiologic study. However, the use of either the Cockcroft-Gault or Modification of Diet in Renal Disease formula is accepted as a valid surrogate of kidney function instead of gold standard 24-hour measures in both epidemiologic studies and in clinical practice. 48 Another limitation is that urine was not sampled, thus potentially misclassifying subjects with high CCl/eGFR and proteinuria.

Summary

This study demonstrates that CKD is associated with a greater burden of WMH and adds to the growing body of evidence that kidney disease is an important, independent risk factor for cerebrovascular disease. Moreover, our data suggest that even mild levels of kidney dysfunction are associated with white matter abnormalities, and the association becomes even stronger with more severe degrees of kidney disease. Early recognition of CKD and prevention of its progression might have a beneficial impact on the development of white matter abnormalities, but more studies are needed to confirm the association between mild CKD and WMH. According to an analysis from the Third National Health and Nutrition Examination Survey, an estimated 8.3 million individuals have stage 3 to 5 chronic kidney disease in the United States. 49 Understanding the relationship between CKD and WMH may reveal targets for prevention of cerebrovascular disease with important public health implications.

Acknowledgments

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Disclosures

None.

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