Kidney Function and Cerebral Blood Flow: The Rotterdam Study

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ABSTRACT

CKD is linked with various brain disorders. Whereas brain integrity is dependent on cerebral perfusion, the association between kidney function and cerebral blood flow has yet to be determined. This study was performed in the framework of the population-based Rotterdam Study and included 2645 participants with mean age of 56.6 years (45% men). We used eGFR and albumin-to-creatinine ratio to assess kidney function and performed phase–contrast magnetic resonance imaging of basilar and carotid arteries to measure cerebral blood flow. Participants had an average (SD) eGFR of 86.3 (13.4) ml/min per 1.73 m² and a median (interquartile range) albumin-to-creatinine ratio of 3.4 (2.2–6.1) mg/g.

In age- and sex-adjusted models, a higher albumin-to-creatinine ratio was associated with lower cerebral blood flow level (difference in cerebral blood flow [milliliters per minute per 100 ml] per doubling of the albumin-to-creatinine ratio, −0.31; 95% confidence interval, −0.58 to −0.03). The association was not present after adjustment for cardiovascular risk factors (P=0.10). Each 1 SD lower eGFR was associated with 0.42 ml/min per 100 ml lower cerebral blood flow (95% confidence interval, 0.01 to 0.83) adjusted for cardiovascular risk factors. Thus, in this population-based study, we observed that lower eGFR is independently associated with lower cerebral blood flow.


Cerebrovascular diseases and dementia occur more often in patients with CKD.1 Incident rates of stroke are 1.9–7.6 times higher in patients with CKD compared with subjects without kidney disease depending on age and the population studied.2 Likewise, individuals at all stages of CKD have higher risk of developing dementia than the general population.3 An increasing body of evidence suggests that the link between impairment in kidney function and cognitive impairment is mediated through vascular mechanisms.4,5 In line with this notion, Seliger et al.5 showed that higher serum creatinine was related to vascular-type dementia rather than Alzheimer-type dementia. Intact kidney function is crucial for regulation of total blood volume and vascular tone.6 Therefore, impairments in kidney function can lead to disturbances in regulation of blood flow in organs that are critically dependent on constant and adequate blood flow, such as the brain.2 Cerebral hypoperfusion has been implicated in the development of vascular and neurodegenerative disorders of the brain.7,8 Although cerebral circulation is of great importance in control of adequate brain perfusion, previous literature suggests that systemic factors also play a role in regulation of cerebral blood flow.9 Different hemodynamic disturbances have been reported in patients with CKD.10,11 Nevertheless, it is not clear whether impaired kidney function is associated with lower cerebral blood flow in the general population. Therefore, we aimed to investigate the association between different measures of kidney function and cerebral blood flow in a population-based cohort of individuals 45 years old and older. In addition, we investigated the association between kidney function and cerebrovascular diseases (stroke or dementia) in subjects with different levels of cerebral blood flow. Table 1 presents characteristics of the study population in categories of eGFR on the basis of creatinine and cystatin C (eGFRcrcys). Participants’ characteristics on the basis of their albumin-to-creatinine values are presented in Supplemental Table 1.

Table 2 shows the association of measures of kidney function with cerebral blood flow. In age- and sex-adjusted models, a higher log–transformed albumin-to-creatinine ratio was associated with 0.31 ml/min per 100 ml lower cerebral blood flow (95% confidence interval [95% CI], −0.58 to −0.03). After adjusting for potential confounders in the second model, the association was not present (P=0.10). Each 1 SD higher eGFRcrcys was associated with 0.42 ml/min per 100 ml higher cerebral blood flow (95% CI, 0.01 to 0.83) after adjusting for cardiovascular risk factors. Each 1 SD higher eGFR on the basis of creatinine (eGFRcr) was...
associated with 0.48 ml/min per 100 ml higher cerebral blood flow (95% CI, 0.11 to 0.85). Additional adjustments did not change the association. We did not observe any association between eGFR on the basis of cystatin C (eGFRcys) and cerebral blood flow (P>0.05). Adjustments for eGFRcys in the analysis with the albumin-to-creatinine ratio as the determinant and albumin-to-creatinine ratio in the analyses with eGFR as determinant did not alter our findings (Table 2). The associations between kidney function markers and cerebral blood flow in different arteries were consistent (Supplemental Figure 1).

We observed a linear trend between different categories of kidney function and cerebral blood flow, indicating lower cerebral blood flow in persons with worse kidney function (Figure 1). In a series of sensitivity analyses, exclusion of individuals with CKD, stroke, or dementia did not change our findings (Supplemental Figure 2).

Comparing the effect estimates of age with albumin-to-creatinine ratio in relation to cerebral blood flow, we showed that doubling of the albumin-to-creatinine ratio corresponds to 1.7 years of increase in age. Likewise, each 1 SD lower eGFRcys was associated with higher prevalence of stroke or dementia (odds ratio, 1.62; 95% CI, 1.01 to 2.36), whereas there was not such an association in subjects with high cerebral blood flow (P for interaction =0.02). There was no difference between subjects with high or low cerebral blood flow in the association between albumin-to-creatinine ratio and higher prevalence of stroke or dementia (P for interaction =0.14) (Table 3). In addition, we observed that subjects with both low eGFRcys and low cerebral blood flow performed worse in cognitive tests compared with subjects with both high eGFRcys and cerebral blood flow (Supplemental Figure 3).

In this population–based cross-sectional study, we observed that lower eGFRcys and lower eGFRcr are independently associated with lower cerebral blood flow. The association between higher albumin-to-creatinine ratio and lower cerebral blood flow was not independent of cardiovascular factors.

Previous studies have reported a close link between kidney function and brain outcomes.3,12,13 Lee et al.14 in a meta-analysis, showed that individuals with eGFR<60 ml/min per 1.73 m² have a higher risk for stroke. Similarly, epidemiologic studies established a strong association between kidney function and dementia.3 Beyond clinically evident cerebrovascular disorders, prevalence of

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**Table 1. Population characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Population (n=2645)</th>
<th>eGFRcys (ml/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;60 (n=80)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56.6 (6.4)</td>
<td>66.8 (10.1)</td>
</tr>
<tr>
<td>Men</td>
<td>1186 (44.8)</td>
<td>31 (38.8)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>132.0 (18.5)</td>
<td>143.6 (23.3)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>82.3 (10.8)</td>
<td>84.2 (11.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5 (4.3)</td>
<td>29.3 (5.0)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>1593 (60.2)</td>
<td>46 (57.5)</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>783 (29.6)</td>
<td>17 (21.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>689 (26.0)</td>
<td>19 (23.8)</td>
</tr>
<tr>
<td>Former</td>
<td>1157 (43.7)</td>
<td>42 (52.5)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6 (1.0)</td>
<td>5.4 (1.1)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>206 (7.8)</td>
<td>18 (22.5)</td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td>92 (3.5)</td>
<td>8 (10.0)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>35 (1.3)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Dementia</td>
<td>9 (0.3)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>582 (22.0)</td>
<td>48 (60.0)</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>556 (21.0)</td>
<td>28 (35.0)</td>
</tr>
<tr>
<td>GFRcr, ml/min per 1.73 m²</td>
<td>86.1 (13.3)</td>
<td>53.5 (13.0)</td>
</tr>
<tr>
<td>GFRcys, ml/min per 1.73 m²</td>
<td>86.2 (15.8)</td>
<td>47.4 (10.2)</td>
</tr>
<tr>
<td>GFRcrys, ml/min per 1.73 m²</td>
<td>86.3 (13.4)</td>
<td>49.4 (10.0)</td>
</tr>
<tr>
<td>Albumin-to-creatinine ratio, mg/g</td>
<td>3.4 [2.2–6.1]</td>
<td>5.9 [2.8–19.0]</td>
</tr>
<tr>
<td>CBF, ml/min per 100 ml brain volume</td>
<td>58.5 (9.7)</td>
<td>54.7 (10.2)</td>
</tr>
</tbody>
</table>

Categorical variables are number (percentage), and continuous variables are mean (SD). Albumin-to-creatinine ratio is as presented as median [interquartile range]. The following variables had missing data: BP (n=9), smoking (n=5), alcohol (n=12), lipid-lowering medication (n=24), antihypertensive medication (n=24), HDL cholesterol (n=7), total cholesterol (n=5), history of cardiovascular disease (n=28), body mass index (n=2), hypertension (n=24), and dementia (n=3). CBF, cerebral blood flow.
magnetic resonance imaging (MRI) -defined microvascular damages, such as cerebral microbleeds, lacunar infarcts, and white matter lesions, is higher among individuals with impaired kidney function. Comparing five patients on hemodialysis with six healthy individuals, Pierro et al. showed that blood transit time in the cerebral microcirculation is significantly longer in patients on hemodialysis. Given the important role of cerebral hyperperfusion in occurrence of brain abnormalities, in this study, we studied the association of kidney function and cerebral blood flow. In agreement with the previous evidence, we showed that worse kidney function is associated with lower levels of cerebral blood flow. We also found a more prominent association between eGFR and prevalence of stroke or dementia in participants with lower cerebral blood flow. In addition, we observed that subjects with both impaired kidney function and low cerebral blood flow have the lowest cognitive function. These findings might suggest that cerebral blood flow levels might play a role in the association of kidney function with brain outcomes. However, given the cross-sectional setting of our study, future longitudinal studies are needed to examine the potential role of cerebral blood flow in the relation between kidney function and brain outcomes.

Intact cerebral autoregulation is dependent on preservation of endothelial function and vasoreactivity. In subjects at risk for accelerated vascular endothelial damage, such as patients with impaired kidney function, this regulatory mechanism might fail short and put the brain at the risk of hyperperfusion. In line with this notion, it is reported that impaired cerebral autoregulation is related to not only cerebrovascular disorders and dementia but also, higher risk of mortality. Association between kidney function and cerebral blood flow can be explained in different ways. Brain and kidney share common traditional cardiovascular risk factors, such as hypertension and diabetes, which can lead to vascular injuries in both organs. Impaired kidney vascular integrity, as reflected in albuminuria, might show vascular damage in not only the kidney but also, other organs with similar vascular bed, like the brain. Additionally, impaired kidney function with alterations in water and electrolytes balance, vascular resistance, and promotion of chronic inflammation and sympathetic nerve over reactivity can contribute to vascular injury and endothelial dysfunction in the brain. Another explanation could be that accumulation of vasoactive species, such as asymmetric dimethyl arginine, in kidney impairment results in vasoconstriction of cerebral vessels, which ultimately decreases perfusion to the brain. Future studies are required to address the mechanisms behind the association between kidney function and brain outcomes.

We observed an association between eGFRcr and cerebral blood flow but not between eGFRcys and cerebral blood flow. This finding is in contrast to previous studies evaluating the link between kidney function and brain outcomes. For instance, in the study by Darsie et al., eGFRcys shows larger effect size in relation to decline in cognitive function compared with eGFRcr. These discrepancies might suggest the role of factors independent of GFR in influencing the association between eGFRcr and cerebral blood flow. In addition, eGFRcys levels are reported to be more accurate in populations with lower creatinine production, such as the elderly, and people with comorbidities. Given the relatively young population in our study with high levels of eGFR and low prevalence of comorbidities, eGFRcr might be a better marker for evaluating kidney function. We also observed an association between the albumin-to-creatinine ratio as well as the combined eGFRcrcys equation and cerebral blood flow. eGFRcrcys measurements are reported to be more precise and perform better than either marker alone. However, given the high correlation between eGFRcrcys and either of the markers, it is also possible that measures of eGFRcrcys are influenced by eGFRcr levels.
Previous studies showed that the range of cerebral blood flow in healthy middle-aged and older subjects is between 56 and 60 ml/min per 100 ml. In this study, the average value of cerebral blood flow was 58.5 ± 9.7, which indicates that the majority of our study population had a normal cerebral blood flow. Despite our relatively young and healthy population-based sample, significant associations were observed between kidney function and cerebral blood flow. Therefore, we could expect that the magnitude of the association would be larger in patient populations.

Limitations of this study should be acknowledged. First, urinary albumin and creatinine were on the basis of a single spot urine sample, which is a common practice in the epidemiologic research setting. Second, although we adjusted the analyses for conventional cardiovascular risk factors, the potential roles of unmeasured cardiovascular risk factors cannot be excluded. Third, the cross-sectional design of this study limits our ability to infer directionality of the associations. Nevertheless, the population-based design of this study, large sample size, and availability of extensive data on various sociodemographic and cardiovascular factors, which enables us to control for several potential confounders, can be marked as the main strengths of this study.

Overall, we observed that lower eGFR, indicating worse kidney function, is independently associated with lower cerebral blood flow. Our findings extend previous literature by providing additional evidence for the vascular origin of the link between impaired kidney function and brain disorders. Understanding of these concomitant pathologies can be of importance for early detection of subjects who are at risk for developing structural and functional brain abnormalities.

**CONCISE METHODS**

**Population**

The study was performed in the third cohort of the Rotterdam Study (2005–2009) and included 3932 participants 45 years old and older living in Ommoord, a district of Rotterdam, The Netherlands. From 3932 individuals participating in the study, cerebral blood flow was 58.5 ± 9.7, which indicates that the majority of our study population had a normal cerebral blood flow. Despite our relatively young and healthy population-based sample, significant associations were observed between kidney function and cerebral blood flow. Therefore, we could expect that the magnitude of the association would be larger in patient populations.

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blood flow using brain MRI was measured in 2956 participants, of whom 5 participants with 3 SDs higher or lower values for cerebral blood flow were excluded (mainly because of cortical infarcts or vessel occlusions). This resulted in 2951 participants, of whom 2797 participants had data on albumin-to-creatinine ratio, 2840 participants had data on serum creatinine levels, 2724 participants had data on serum cystatin C levels, and 2645 participants had data on both creatinine and cystatin C measurements (Supplemental Figure 4). The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study executed by the Ministry of Health, Welfare and Sports of The Netherlands. A written informed consent was obtained from all participants.27

Kidney Function

Serum creatinine and cystatin C were measured with an enzymatic assay method and a particle-enhanced immunonephelometric assay, respectively. Creatinine values were standardized to isotope–dilution mass spectrometry–traceable measurements. eGFR on the basis of the Chronic Kidney Disease Epidemiology Collaboration formula was calculated for eGFRcr and eGFRcys separately and both measurements combined (eGFRcr,cys).25 Participants collected the first morning urine before arriving to the research center. Urine albumin and creatinine were determined by a turbidimetric method and measured by a Hitachi MODULAR P Analyzer (Roche/Hitachi Diagnostics, Mannheim, Germany).28 Albumin-to-creatinine ratio (milligrams per gram) was estimated by dividing albumin by creatinine. Because albumin-to-creatinine ratio was not normally distributed, we used log-transformed values to obtain values per doubling of the albumin-to-creatinine ratio. We added one to the untransformed values to account for those who did not have albuminuria. We defined three categories of kidney function using information from both eGFR and albumin-to-creatinine ratio. Kidney function was defined according to two criteria: eGFR on the basis of the Chronic Kidney Disease Epidemiology Collaboration formula was calculated for eGFRcr and eGFRcys with cerebral blood flow (in milliliters per minute) was calculated using an automated enzymatic method.

Cerebral Blood Flow

MRI of the brain was performed on a 1.5-T MRI scanner (Signa Excite II; General Electric Healthcare, Milwaukee, WI).29 An eight–channel head coil was used for reception of the signal. For flow measurement, two-dimensional phase-contrast imaging was performed.29 A sagittal two–dimensional phase-contrast MRI angiographic scout image was performed (repetition time=24 ms, echo time=9 ms, field of view=32 cm², matrix=256; 160, flip angle=101, number of excitations=1, bandwidth=8.06 kHz, velocity encoding=60 cm/s, and slice thickness=60 mm). Acquisition time was 12 seconds. On this scout image, a transverse imaging plane perpendicular to both the precavernous portion of the internal carotid arteries and the middle part of the basilar artery was chosen for a two–dimensional gradient–echo phase–contrast sequence (repetition time=20 ms, echo time=4 ms, field of view=19 cm², matrix=256; 160, flip angle=81, number of excitations=8, bandwidth=22.73 kHz, velocity encoding=120 cm/s, and slice thickness=5 mm). Acquisition time was 51 seconds, and no cardiac gating was performed.30 For the assessment of brain volumes, the structural MRI scans (T1–weighted, proton density–weighted, and fluid–attenuated inversion recovery) were used. Details, including preprocessing steps and the classification algorithm, have been described elsewhere.30

Flow (in milliliters per second) was calculated by multiplying the average velocity with the cross–sectional area of the vessel.31 To calculate global cerebral blood flow (in milliliters per minute), flow rates for the carotid arteries and the basilar artery were summed and multiplied by 60 s/min. To measure parenchymal cerebral blood flow in milliliters per minute per 100 ml brain tissue, values were divided by each individual’s brain volume (milliliters), and the obtained results were multiplied by 100 (Supplemental Figure 5). Retest reliability was performed by two independent experienced technicians in 533 scans for all manual drawing around both carotids and the basilar artery and subsequent flow measurements. This showed inter-rater correlations >0.94 for all vessels, indicating an excellent agreement.29

Covariates

Information related to smoking (past/current/never) and alcohol consumption was on the basis of interviews using questionnaires. Alcohol consumers were categorized into none, moderate (<15 g/d) and heavy (>15 g/d) drinkers. Information on lipid-lowering medication and antihypertensive medication use was on the basis of home interview. Serum total and HDL cholesterol levels were measured using an automated enzymatic method. BP was measured two times in a single visit, and the average of two measurements, separated by a count of the pulse rate, was used in the analyses. History of coronary heart disease was considered as experiencing myocardial infarction or coronary revascularization procedures. Diabetes mellitus were defined by use of blood glucose–lowering medication and/or a fasting serum glucose level ≥7.0 mmol/L. Information on stroke was acquired through digital record linkage with general practitioners and medical specialists in the research area.32 To define patients with dementia, individuals with the Mini Mental State Examination (MMSE) <26 or the Geriatric Mental Schedule organic level >0 underwent an examination and informant interview with the Cambridge Examination for Mental Disorders in the Elderly. Additional neurologic testing was applied for participants who were suspected of having dementia. Covariates were selected on the basis of the previous knowledge and literature. We checked the absence of colinearity between covariates in the model using the Variance Inflation Factor. We did not observe any colinearity between the covariates included in the models.

Statistical Analyses

Associations of measures of kidney function (albumin-to-creatinine ratio, eGFRcr, eGFRcys, and eGFRcr,cys) with cerebral blood flow were evaluated using multiple linear regression models. β-values and 95% CIs were estimated per 1 SD decrease for measures of kidney function. All analyses were adjusted for age and sex. Then, we further adjusted the analyses for systolic BP, diastolic BP, body mass index, alcohol consumption, smoking, total cholesterol, HDL cholesterol, MMSE, coronary heart disease, diabetes mellitus, lipid-lowering medication, and BP-lowering medications (diuretics, β-blockers, angiotensin converting enzyme inhibitors,
and calcium channel blockers). In the third model, analyses with eGFRs as determinants were further adjusted for albumin-to-creatinine ratio, and analysis with albumin-to-creatinine ratio as the determinant was further adjusted for eGFRcrCyS. There was no departure from linearity in the association between kidney function markers and cerebral blood flow. We performed the analysis of covariance, where adjusted mean values of cerebral blood flow were compared across three categories of kidney function. In addition, we performed a series of sensitivity analyses excluding subjects with CKD (eGFRcrCyS<60 ml/min per 1.73 m²), stroke, or dementia. To explore whether the association between kidney function and cerebral blood flow was consistent between right and left carotid internal and basilar arteries, we assessed the association between kidney function measures and cerebral blood flow in different arteries separately. Furthermore, to compare the magnitude of the association with age as an established risk factor for brain disorders, we calculated the effect estimates for the association of age with cerebral blood flow and reported the corresponding ratios. To investigate whether the link between kidney function and cerebrovascular diseases is mediated through lower cerebral blood flow, we evaluated the interaction between kidney function and cerebral blood flow in relation to presence of clinical stroke or clinical dementia. In addition, in the stratified analysis, we investigated the association of eGFRcrCyS and albumin-to-creatinine ratio with stroke or dementia in two groups of participants with low and high cerebral blood flow. To evaluate whether subjects with both low eGFRcrCyS and cerebral blood flow have worse performance in cognitive test, we calculated mean scores of different cognitive domains (memory, executive function, processing speed, and motor speed) across different categories of eGFRcrCyS and cerebral blood flow in individuals without dementia. Cognitive function was assessed with the following neuropsychological test battery: the MMSE, a 15–word verbal recall learning test, the Stroop tests, the Letter–Digit Substitution Task (LDST), the Purdue Pegboard Test, and a word fluency test. The compound score for memory was the average of the z scores for the immediate and delayed recall of the 15–word verbal learning test. Executive function was constructed by averaging the z scores for the Stroop tests, the LDST, and the word fluency test. Information processing speed was the average of the z scores for the Stroop reading and Stroop color naming tests and the LDST. Details of the cognitive assessments are provided elsewhere.33 All analyses were carried out using SPSS 20.0.2 for windows or R version 2.15.0.

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Nestlé Nutrition (Nestec Ltd.), Metagenics Inc., and AXA had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

DISCLOSURES

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