Nephrol Dial Transplant (2015) 30: 1322–1329
doi: 10.1093/ndt/gfv030
Advance Access publication 26 February 2015

Structural and functional assessment of the brain in European Americans with mild-to-moderate kidney disease: Diabetes Heart Study-MIND

Mariana Murea[1], Fang-Chi Hsu[2], Amanda J. Cox[3,4], Christina E. Hugenschmidt[5], Jianzhao Xu[3,4], Jeremy N. Adams[6], Laura M. Raffield[3], Christopher T. Whitlow[7], Joseph A. Maldjian[7], Donald W. Bowden[3,4] and Barry I. Freedman[1,3]

[1]Internal Medicine-Nephrology, Wake Forest School of Medicine, Winston-Salem, NC, USA, [2]Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA, [3]Center for Diabetes Research, Wake Forest School of Medicine, Winston-Salem, NC, USA, [4]Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC, USA, [5]Internal Medicine-Geriatrics and Gerontology, Wake Forest School of Medicine, Winston-Salem, NC, USA, [6]Molecular Genetics and Genomics, Wake Forest School of Medicine, Winston-Salem, NC, USA and [7]Radiologic Sciences and Advanced NeuroScience Imaging (ANSIR) Laboratory, Wake Forest School of Medicine, Winston-Salem, NC, USA

Correspondence and offprint requests to: Mariana Murea; E-mail: mmurea@wakehealth.edu

ORIGINAL ARTICLE

ABSTRACT

Background. Advanced chronic kidney disease (CKD) is associated with altered cerebral structure and function. Relationships between mild-to-moderate CKD and brain morphology and cognitive performance were evaluated in European Americans (EAs).

Methods. A total of 478 EAs with estimated glomerular filtration rate (eGFR) $\geq$ 45 mL/min/1.73 m^2 and urine albumin:creatinine ratio (UACR) < 300 mg/g, most with type 2 diabetes (T2D), were included. Measures of total intracranial volume (TICV), cerebrospinal fluid volume, total white matter volume (TWMV), total gray matter volume (TGMV), total white matter lesion volume (TWMLV), hippocampal white matter volume (HWMV) and hippocampal gray matter volume (HGMV) were obtained with magnetic resonance imaging. Cognitive testing included memory (Rey Auditory Visual Learning Test), global cognition (Modified Mini-Mental State Examination) and executive function (Stroop Task, Semantic Fluency, Digit Symbol Substitution Test). Associations with CKD were assessed using log-transformed eGFR and UACR, adjusted for age, sex, body mass index, smoking, hemoglobin A1c, blood pressure, diabetes duration, cardiovascular disease and education.

Results. Participants were 55.2% female, 78.2% had T2D; mean ± SD age 67.6 ± 9.0 years, T2D duration 16.4 ± 6.5 years, eGFR 92.0 ± 22.3 mL/min/1.73 m^2 and UACR 23.8 ± 39.6 mg/g. In adjusted models, eGFR was negatively associated with TICV only in participants with T2D [parameter estimate (β): −72.2, P = 0.002]. In non-diabetic participants, inverse relationships were observed between eGFR and HGMV (β: −1.0, P = 0.03) and UACR and normalized TWMLV (β: −0.2, P = 0.03). Kidney function and albuminuria did not correlate with cognitive testing.

Conclusions. In EAs with mild CKD enriched for T2D, brain structure and cognitive performance were generally not impacted. Longitudinal studies are necessary to determine when cerebral structural changes and cognitive dysfunction develop with progressive CKD in EAs.

Keywords: albuminuria, brain, cognitive function, kidney disease, magnetic resonance imaging

INTRODUCTION

Independent of conventional cardiovascular disease (CVD) risk factors, advanced chronic kidney disease (CKD) is associated with cognitive impairment and intracranial small vessel disease on cerebral magnetic resonance imaging (MRI) across all ethnicities [1]. The prevalence of cerebral white matter (WM) lesions and cognitive impairment rises with declining estimated glomerular filtration rate (eGFR) and increasing urine albumin:creatinine ratio (UACR). The kidney–cerebral axis has been studied mainly in patients on dialysis and those with advanced CKD (eGFR < 45 mL/min/1.73 m^2 and UACR > 300 mg/g) through semi-quantitative neuroimaging scales and limited batteries of cognitive function tests [2–11]. In addition,

differences in brain structures and cognitive function exist in general populations across different race–ethnic groups [12, 13].

Relatively few studies have evaluated the relationship between early-stage CKD and quantitative measures of cerebral anatomy and cognitive performance in specific ethnic groups. For example, two recent studies involving African Americans (AAs) with type 2 diabetes (T2D) and mild CKD demonstrated significant associations between eGFR and UACR with brain structural changes and cognitive performance [14, 15]. To examine these relationships in non-AAs, a cross-sectional assessment of kidney function was performed in European Americans (EAs) enriched for type 2 diabetes mellitus (T2D) from the Diabetes Heart Study (DHS)-MIND, who were followed longitudinally to evaluate cerebral morphopathology using brain MRI and cognitive performance using neurocognitive tests. Participants were limited to those with an eGFR of $\geq$ 45 mL/min/1.73 m^2 and low-level albuminuria (UACR $\leq$ 300 mg/g).

MATERIALS AND METHODS

Study population

The study sample included self-identified EA DHS-MIND participants. Criteria for recruitment in DHS-MIND study included the presence of $\geq$2 siblings with T2D per family. When this criterion was met, an additional non-diabetic sibling from each family was recruited when possible. This cohort has been described in a previous report [16]. Analyses excluded non-EA individuals and those with UACR > 300 mg/g and/or eGFR < 45 mL/min/1.73 m^2. Participants with CVD (prior myocardial infarction, angina, percutaneous or surgical revascularization of coronary or carotid arteries, stroke, transient ischemic attack or carotid artery stenosis) were included. When incident diagnoses of CVD occurred during the study period, they were included in the demographics table and employed in statistical analyses. The Institutional Review Board at Wake Forest School of Medicine (WFSM) approved the protocol, and written informed consent was obtained from all participants.

Data collection

Questionnaires were administered by a trained interviewer and included information on age, sex, level of education, past medical history, current medications and smoking. Systolic blood pressure (SBP), diastolic blood pressure (DBP), height and weight were recorded; body mass index (BMI) was computed. Venipuncture was performed after >12 h of overnight fasting. T2D was ascertained based on physician diagnosis, fasting plasma glucose > 126 mg/dL or use of diabetes medications (insulin and/or oral hypoglycemic drugs). Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography at the MRI visit.

Serum creatinine concentrations were determined by the modified Jaffe kinetic method (Beckman AU System) calibrated to isotope dilution mass spectrometry and used to compute eGFR based on the CKD-Epidemiology Collaboration (CKD-EPI) equation [17]. UACR was measured on a morning spot urine sample using the Beckman Coulter AU System colorimetric method. The lower limit of detection of the assay was 5.0 mg/dL; values <5.0 mg/dL were assigned a value of 5.0 mg/dL. The inter-assay coefficient of variance was 4.8%. Albuminuria was assessed at a baseline DHS visit on an average of 6.7 ± 1.6 years (mean ± SD) prior to MRI/cognitive testing. Creatinine and electrolyte concentrations were measured on serum samples collected at the MRI visit and continuously stored at −80°C, except for a single prior thaw. Normalization for serum sodium concentration was performed to adjust for potential effects of the thaw.

Cerebral magnetic resonance imaging (MRI)

MRI acquisition. Scans were performed on a 1.5-Tesla (1.5 T) General Electric EXCITE HD scanner with twin-speed gradients using a neurovascular head coil (GE Healthcare, Milwaukee, WI). High-resolution T1 anatomic images were obtained using a 3D volumetric Inversion Recovery SPGR sequence [time to repeat (TR) = 7.36 ms; time to echo (TE) = 2.02 ms; inversion time (TI) = 600 ms; flip angle (FA) = 20 degrees; 124 slices, field of view (FOV) = 24 cm, matrix size = 256 × 256, 1.5-mm slice thickness]. Fluid-attenuated inversion recovery (FLAIR) images were acquired in the axial plane (TR = 8002 ms; TE = 101.29 ms; TI = 2000 ms; FA = 90 degrees; FOV = 24 cm; matrix size = 256 × 256; 3-mm slice thickness).

Image segmentation. Structural T1 images were segmented into gray matter (GM), WM and cerebrospinal fluid (CSF), normalized to Montreal Neurologic Imaging (MNI) space and modulated with the Jacobian determinants (non-linear components only) of the warping procedure to generate volumetric tissue maps using the Dartel high-dimensional warping and the SPM8 new segment procedure as implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). Total GM, WM and CSF volumes and intracranial volume (ICV, calculated as GM + WM + CSF) were determined from the VBM8 automated segmentation procedure, which outputs a text file with values for native space total GM, WM and CSF volumes. Additional region of interest (ROI)-based measures were generated for the right and left hippocampus using the automated anatomical labeling (AAL) atlas [18] as implemented in the WFU Pickatlas tool [19]. The AAL atlas hippocampal ROI is not specific to the GM; it encompasses GM, WM and CSF tissue types. The hippocampal ROIs (right and left) were applied to the modulated GM and WM volumetric tissue maps to generate hippocampal GM volume (HGMV) and hippocampal WM volume (HWMV). All volumes were reported in milliliters.

WM lesion segmentation was performed using the Lesion Segmentation Toolbox (LST) [20] for SPM8 at a threshold (k) of 0.25. We previously validated the LST against expert manual segmentation in a sample with T2D, as well identified the optimum threshold in this population [21]. Normalization to MNI space was accomplished by co-registration with the structural T1 and applying the normalization parameters computed in the VBM8 segmentation procedure. The WM lesion volume was determined by summing the binary lesion maps and multiplying by voxel volume.

Cognitive testing

Testing was performed in a quiet room after a light snack. The cognitive battery took ~45 min to complete. Global cognition was evaluated using the Modified Mini-Mental State Examination (3MSE, score range 0–100) [22]. Verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT), assessing the ability to memorize and retrieve a list of 15 words [23]. Two scores were derived from the RAVLT, the sum of the number of words recalled over the initial five trials (RAVLT Sum) and the number of words recalled after the reading of an interference word list and a 20-min delay (RAVLT Delay). For both measures, higher scores indicate better performance. Executive function was evaluated using the Stroop test, Semantic Fluency and Digit Symbol Substitution Test (DSST). The Stroop test evaluates the ability to view complex visual stimuli and respond to one stimulus dimension while suppressing response to another dimension, an 'executive' skill largely attributed to frontal-lobe function. Higher scores indicate greater degrees of impairment [24]. Semantic Fluency is a verbal fluency test that requires generation of words corresponding to a specific semantic category, such as animals. The number of correct words produced in 1 min is counted [25]. The DSST assesses processing speed, and the measure used was the number of correct responses within 2 min [26].

Statistical analysis

The mean and standard deviation (SD) for MRI and cognitive test results based on the categories of renal parameters, including CKD-EPI eGFR and UACR, were presented and compared with the use of marginal models incorporating generalized estimating equations (GEE). CKD-EPI eGFR was categorized as eGFR ≥ 90, 60–89 and 45–59 mL/min/1.73 m^2, and UACR as <10, 10–29 and 30–300 mg/g. Marginal models were also fitted to test for associations between renal disease parameters (independent variables) and quantitative measures of brain volume and cognitive performance (dependent variables). Renal parameters included CKD-EPI eGFR and UACR as continuous variables. Variables derived from brain MRI were total ICV volume (TICV), CSF volume (CSFV), total WM volume (TWMV), total GM volume (TGMV), total WM lesion volume (TWMLV), HWMV and HGMV. CSFV, TWMV, TGMV and TWMLV were adjusted for TICV. Cognitive function variables included 3MSE, RAVLT, Stroop, Semantic Fluency and DSST. If necessary, the appropriate transformation was applied to best approximate the distributional assumptions of conditional normality and homogeneity of variance of the residuals. The natural logarithm transformation was applied to the TWMLV, Stroop measure, eGFR and UACR. Model 1 adjusted for UACR for the eGFR analysis, and eGFR for the UACR analysis. Model 2 added adjustment for age, sex, BMI, smoking, HbA1c, duration of diabetes, SBP and DBP for imaging outcomes, and level of education for cognitive outcomes. To correct for the lapsed time between measurements of kidney function and brain MRI and cognitive testing, the study adjusted for the presence of vascular risk factors including CVD at baseline and at the time of neurologic assessments. Analyses were performed using SAS 9.3 (SAS Inc., Cary, NC). Statistical significance was accepted at $P < 0.05$.

RESULTS

Demographic and clinical characteristics of the 478 study participants from 235 nuclear families are described in Table 1. The sample was 55.2% female with mean ± SD age 67.6 ± 9.0 years, BMI 31.5 ± 6.6 kg/m^2 and 78.2% had T2D, with diabetes duration 16.4 ± 6.5 years and HbA1c 7.1 ± 1.4%. Smoking (past or current) was reported by 55% of participants, and 28% attended college. Stratified by kidney function, 287 (60.0%) had an eGFR of ≥ 90 mL/min/1.73 m^2, 145 (39.3%) eGFR 60–89 mL/min/1.73 m^2 and 46 (9.6%) eGFR 45–59 mL/min/1.73 m^2. Based on albuminuria, 246 (51.5%) had UACR < 10 mg/g, 140 (29.3%) UACR 10–29 mg/g and 92 (19.2%) UACR 30–300 mg/g. The distribution of UACR based on eGFR is shown in Table 1.

Table 1. Demographic and clinical characteristics of the study population (*N* = 478)

Variable	Mean	SD	Median
Age (years)	67.6	9.0	68.2
BMI (kg/m^2)	31.5	6.6	30.2
Age at diabetes (years)	51.7	9.1	51.9
Diabetes duration (years)	16.4	6.5	14.6
SBP (mmHg)	131.2	17.8	130.0
DBP (mmHg)	70.6	10.5	70.0
HbA1c (%)	7.1	1.4	6.8
CKD-EPI eGFR (mL/min/1.73 m^2)	92.0	22.3	96.5
≥90 mL/min/1.73 m^2	107.0	10.5	106.4
60–89 mLl/min/1.73 m^2	76.5	8.0	77.1
45–59mL/min/1.73 m^2	47.1	9.5	49.6
UACR (mg albumin/g creatinine)	23.8	39.6	9.5
<10 (*n* = 285; 53%)	5.3	2.5	5.3
10–29 (*n* = 158; 29%)	16.2	5.2	14.4
30–300 (*n* = 98; 18%)	84.8	58.0	62.4
Variable	***N***	**%**	
Sex (female)	264	55.2	
T2D	374	78.2	
HTN	412	86.2	
CVD	152	33.0	
Smoking			
Never	215	45.1	
Past	203	42.6	
Current	59	12.4	
Education			
Less than a high school diploma	83	17.4	
High school diploma	261	54.6	
Greater than high school diploma	134	28.0	
CKD-EPI eGFR ≥ 90 mL/min/1.73 m^2	287	60.0	
UACR <10 mg/g	157	54.7	
UACR 10–29 mg/g	83	28.9	
UACR 30–300 mg/g	47	16.4	
CKD-EPI eGFR 60–89 mL/min/1.73 m^2	145	30.3	
UACR <10 mg/g	70	48.3	
UACR 10–29 mg/g	46	31.7	
UACR 30–300 mg/g	29	20.0	
CKD-EPI eGFR < 60 mL/min/1.73 m^2	46	9.6	
UACR <10 mg/g	19	41.3	
UACR 10–29 mg/g	11	23.9	
UACR 30–300 mg/g	16	34.8	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HTN, hypertension; CVD, cardiovascular disease; CKD-EPI eGFR, Chronic Kidney Disease-Epidemiology Collaboration estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio; T2D, type 2 diabetes.

Brain volumes and cognitive test results in the full sample and based on eGFR and UACR are shown in Table 2, without covariate adjustment. Participants with lower eGFR had significantly higher CSFV ($P = 1.5 \times 10^{-7}$) and TWMLV ($P = 0.0004$), lower TGMV ($P = 1.5 \times 10^{-7}$) and HGMV ($P = 0.0001$), and poorer performance on all cognitive performance tests ($P = 3.6 \times 10^{-6}$ to 0.0008). Stratified by UACR (<10, 10–29, >30 mg/g), significant differences were not observed in measures of brain volumes on MRI or cognitive performance.

Correlations between brain volumes and cognitive performance as well as demographic and disease characteristics across the cohort are depicted in supplementary materials (Supplementary Table S1 for MRI volumes and Supplementary Table S2 for cognitive testing). Age was significantly associated with higher CSFV (a marker of cerebral atrophy) and TWMLV, lower TGMV and HGMV, and diminished proficiency on all cognitive tests. Female gender was associated with lower TICV and CSFV; higher TGMV, HWMV and HGMV; and better performance on most cognitive tests with lack of association with Semantic Fluency. As in other studies, significant associations between cerebral WM and GM volumes and blood pressure were not observed [27]. Only DBP showed a negative association with CSFV ($P = 0.04$), and SBP showed a positive association with TWMLV ($P = 0.003$). There was a negative association between BMI and HWMV ($P = 0.05$). A direct association was seen between HbA1c and TICV, CSFV, TGMV and TWMLV. Level of education was significantly correlated with performance on all cognitive tests, and active smoking was associated with poorer performance on 3MSE ($P = 0.0008$) and DSST ($P = 0.02$).

Table 3 contains results of the analysis for brain volume and cognitive testing associations with log-transformed eGFR and log-transformed UACR after adjustment for renal parameters (eGFR analyses adjusted for UACR, and UACR analyses adjusted for eGFR) (Model 1), followed by adjustment for age, sex, BMI, smoking, HbA1c, T2D duration, CVD, SBP and DBP for imaging outcomes, and level of education for cognitive tests (Model 2). Although kidney disease parameters were associated with other brain structural changes, memory and executive function in the unadjusted analysis, 'age' inclusion as a covariate led to loss of significant association; age was the most influential of all covariates in the full model. After full adjustment, associations between eGFR and brain morphologic findings (CSFV, TICV, TGMV, TWMLV, HGMV) and cognition were no longer significant. In the full cohort, albuminuria also did not correlate with brain structure or cognitive performance after full covariate adjustment. As such, age is an important contributor to declining cognitive performance and cerebral anatomy in EA individuals with T2D and eGFR > 45 mL/min/1.73 m^2.

We further analyzed whether there was a differential association between kidney function and brain MRI and neurocognitive testing based on diabetes status (Table 4). Participants with T2D ($n = 374$) had no significant correlations between eGFR and brain volumes on MRI, similar to the results in the full cohort. Interestingly, participants without diabetes ($n = 104$) had negative associations between both eGFR and UACR with normalized TWMLV (eGFR β: −1.0, SE: 0.04, $P = 0.01$; UACR β: −0.2, SE: 0.07, $P = 0.01$). Similar to the results in the full sample, cognitive performance did not correlate with renal parameters in diabetes-stratified analyses, except for the positive association between eGFR and 3MSE among non-diabetic participants (β: 5.5, SE: 2.4, $P = 0.02$).

Table 2. Brain volumes and cognitive test results in the full sample and stratified by eGFR and UACR

Parameter	All		eGFR ≥ 90 mL/min/1.73 m^2 ($n = 287$)		eGFR 60–89 mL/min/1.73 m^2 ($n = 145$)		eGFR 45–59 mL/min/1.73 m^2 ($n = 46$)		P-value	UACR <10 mg/g ($n = 246$)		UACR 10–29 mg/g ($n = 140$)		UACR 30–300 mg/g ($n = 92$)		P-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	
MRI volume[a]																
TICV	1339.9	142.5	1334.5	142.6	1357.3	139.0	1318.4	151.3	0.06	1338.1	141.6	1348.4	152.0	1330.8	129.1	0.87
CSFV[b]	254.2	44.8	245.7	40.4	267.5	46.3	268.3	54.3	1.5×10^{-7}	252.9	42.9	254.8	48.5	257.0	43.9	0.12
TWMV[b]	575.2	72.6	573.7	74.0	582.0	70.1	562.7	71.3	0.78	574.6	72.2	580.5	77.7	568.1	64.8	0.58
TGMV[b]	510.2	52.0	514.9	51.1	507.8	51.6	485.6	52.9	1.5×10^{-7}	510.3	54.1	512.5	51.4	505.7	46.6	0.27
TWMLV[b,c]	4.3	6.7	3.2	5.2	5.4	8.4	7.2	8.0	0.0004	4.2	7.1	4.0	6.3	4.8	6.5	0.12
HWMV	3.4	0.3	3.4	0.3	3.4	0.3	3.3	0.4	0.16	3.4	0.3	3.4	0.3	3.3	0.3	0.68
HGMV	8.6	1.1	8.8	1.1	8.4	1.0	8.1	1.0	0.0001	8.6	1.1	8.7	1.1	8.6	1.1	0.51
Cognitive test																
RAVLT	41.6	10.2	43.3	10.0	39.5	10.1	38.1	10.0	0.00008	42.0	10.4	41.9	9.7	40.2	10.5	0.19
Rey total_long	7.4	3.6	7.9	3.5	6.6	3.5	6.2	3.5	0.0001	7.5	3.6	7.3	3.6	7.0	3.5	0.47
3MSE	90.6	7.1	91.7	6.8	89.6	6.7	86.9	8.5	0.0002	90.8	7.2	90.5	8.1	90.2	7.1	0.75
Stroop[c]	35.5	19.9	31.8	15.8	39.4	20.1	46.2	32.8	0.0008	34.0	18.1	35.1	18.3	39.9	25.5	0.12
Semantic Fluency	15.9	4.4	16.4	4.5	15.3	4.1	14.1	4.5	0.0005	16.1	4.9	15.7	4.0	15.5	3.8	0.26
DSST	47.8	15.3	50.5	16.1	44.8	13.4	40.6	12.0	3.6×10^{-6}	48.8	15.1	46.7	14.8	46.8	16.5	0.16

eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio; SD, standard deviation; TICV, total intracranial volume; CSFV, cerebrospinal fluid volume; TWMV, total white matter volume; TGMV, total gray matter volume; TWMLV, total white matter lesion volume; HGMV, hippocampus gray matter volume; HWMV, hippocampus white matter volume; RAVLT, Rey Auditory Verbal Learning Test; 3MSE, Modified Mini-Mental State Examination; DSST, Digit Symbol Substitution Test.

[a]MRI volumes expressed in milliliters.

[b]Adjusted for TICV when calculating P-value using GEE model.

[c]Log transformed for calculating P-value.

Table 3. Relationships between kidney function with MRI brain volumes and cognitive performance

Domain	eGFR[b]				UACR[b]			
	Model 1		Model 2		Model 1		Model 2	
	Estimate ± SE	P-value	Estimate ± SE	P-value	Estimate ± SE	P-value	Estimate ± SE	P-value
MRI								
TICV	−3.3 ± 24.5	0.89	−2.1 ± 19.5	0.92	−1.5 ± 7.0	0.84	−4.4 ± 5.3	0.41
CSFV[a]	−33.5 ± 5.2	3.8×10^{-10}	−3.5 ± 3.8	0.37	1.7 ± 1.2	0.17	−0.02 ± 1.1	0.98
TWMV[a]	5.6 ± 4.4	0.20	−0.7 ± 4.8	0.89	−0.6 ± 1.1	0.58	−0.5 ± 1.1	0.63
TGMV[a]	29.6 ± 4.8	1.8×10^{-8}	3.7 ± 4.8	0.45	−1.0 ± 1.2	0.40	0.5 ± 1.2	0. 68
TWMLV[ab]	−0.77 ± 0.18	0.00002	0.03 ± 0.2	0.84	0.07 ± 0.04	0.10	0.02 ± 0.04	0.58
HWMV	0.14 ± 0.06	0.01	−0.003 ± 0.06	0.96	−0.01 ± 0.01	0.59	−0.002 ± 0.02	0.88
HGMV	0.8 ± 0.2	4.8×10^{-6}	−0.01 ± 0.2	0.95	−0.02 ± 0.05	0.72	0.04 ± 0.05	0.42
Memory								
RAVLT	7.9 ± 1.6	4.8×10^{-6}	0.5 ± 1.5	0.75	−0.5 ± 0.4	0.23	−0.1 ± 0.4	0.79
Rey total_long	2.5 ± 0.6	0.00007	−0.08 ± 0.5	0.88	−0.1 ± 0.2	0.55	0.01 ± 0.1	0.95
Cognition								
3MSE	6.0 ± 1.2	3.9×10^{-6}	1.9 ± 1.2	0.11	−0.1 ± 0.3	0.73	0.2 ± 0.3	0.61
Executive function								
Stroop[b]	−0.3 ± 0.08	0.0004	0.04 ± 0.09	0.67	0.03 ± 0.02	0.13	0.03 ± 0.02	0.22
Semantic Fluency	3.2 ± 0.7	8.0×10^{-6}	0.6 ± 0.7	0.35	−0.1 ± 0.2	0.45	0.1 ± 0.2	0.50
DSST	11.9 ± 2.1	4.4×10^{-8}	1.1 ± 2.1	0.61	−1.0 ± 0.6	0.09	−0.2 ± 0.5	0.74

Model 1 adjustment reflects UACR for eGFR analysis, and eGFR for UACR analysis.
Model 2 adjustment reflects, in addition to Model 1, adjustment for age, sex, BMI, smoking, HbA1c, duration of diabetes, CVD, SBP and DBP for imaging outcomes, and level of education for cognitive outcomes.
eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio; SD, standard deviation; TICV, total intracranial volume; CSFV, cerebrospinal fluid volume; TWMV, total white matter volume; TGMV, total gray matter volume; TWMLV, total white matter lesion volume; HGMV, hippocampus gray matter volume; HWMV, hippocampus white matter volume; RAVLT, Rey Auditory Verbal Learning Test; 3MSE, Modified Mini-Mental State Examination; DSST, Digit Symbol Substitution Test.
[a]Additionally adjusts for TICV in both Models 1 and 2.
[b]Log transformed.

ORIGINAL ARTICLE

Table 4. Kidney function associations with MRI brain volumes and cognitive performance based on diabetes status

Domain	eGFR[b]				UACR[b]			
	Diabetes		No diabetes		Diabetes		No diabetes	
	Estimate ± SE	P-value	Estimate ± SE	P-value	Estimate ± SE	P-value	Estimate ± SE	P-value
MRI								
TICV	−10.4 ± 23.1	0.65	49.2 ± 44.6	0.27	−4.6 ± 6.0	0.44	14.9 ± 11.4	0.19
CSFV[a]	3.0 ± 4.7	0.52	−21.6 ± 19.9	0.28	−0.3 ± 1.3	0.81	2.4 ± 3.4	0.49
TWMV[a]	−0.4 ± 5.3	0.94	−22.5 ± 14.1	0.11	−0.2 ± 1.3	0.90	3.3 ± 3.3	0.33
TGMV[a]	−0.1 ± 5.4	0.98	12.6 ± 14.4	0.38	0.8 ± 1.2	0.54	−0.7 ± 3.4	0.83
TWMLV[ab]	0.2 ± 0.2	0.29	−1.0 ± 0.4	0.01	0.07 ± 0.05	0.12	−0.2 ± 0.07	0.01
HWMV	−0.04 ± 0.06	0.47	0.1 ± 0.2	0.63	−0.01 ± 0.02	0.74	0.01 ± 0.03	0.74
HGMV	−0.10 ± 0.2	0.62	0.09 ± 0.5	0.85	0.09 ± 0.05	0.10	−0.1 ± 0.1	0.15
Memory								
RAVLT	0.4 ± 1.6	0.81	−2.8 ± 4.3	0.52	−0.06 ± 0.4	0.87	−0.9 ± 0.9	0.36
Rey total_long	−0.1 ± 0.6	0.81	−1.2 ± 1.5	0.43	0.0001 ± 0.1	0.99	−0.4 ± 0.4	0.36
Cognition								
3MSE	1.0 ± 1.3	0.43	5.5 ± 2.4	0.02	−0.01 ± 0.3	0.96	0.3 ± 0.6	0.60
Executive function								
Stroop[b]	0.1 ± 0.1	0.23	−0.3 ± 0.3	0.26	0.04 ± 0.02	0.07	−0.1 ± 0.1	0.26
Semantic Fluency	0.1 ± 0.7	0.85	−2.0 ± 1.6	0.21	0.1 ± 0.2	0.49	−0.2 ± 0.5	0.69
DSST	0.6 ± 2.3	0.78	−1.7 ± 4.0	0.67	−0.4 ± 0.6	0.56	−1.1 ± 1.1	0.31

Adjustment reflects UACR for eGFR analysis and eGFR for UACR analysis, plus adjustment for age, sex, BMI, smoking, HbA1c, duration of diabetes, CVD, SBP and DBP for imaging outcomes, and level of education for cognitive outcomes.
eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio; SD, standard deviation; TICV, total intracranial volume; CSFV, cerebrospinal fluid volume; TWMV, total white matter volume; TGMV, total gray matter volume; TWMLV, total white matter lesion volume; HGMV, hippocampus gray matter volume; HWMV, hippocampus white matter volume; RAVLT, Rey Auditory Verbal Learning Test; 3MSE, Modified Mini-Mental State Examination; Digit Symbol Substitution Test.
[a]Additionally adjusts for TICV.
[b]Log transformed.

DISCUSSION

In EAs with mild-to-moderate CKD in the DHS-MIND, kidney function parameters revealed different correlations with brain structure based on diabetes status, limited correlations were seen with cognitive performance. The presence of mild-to-moderate loss of eGFR in EAs with T2D correlated with higher TICV, independent of age, smoking, HbA1c, diabetes duration, CVD and blood pressure. In non-diabetic subjects, eGFR decline was associated with lower normalized HGMV, and microalbuminuria correlated with WM lesion volume. In contrast, memory, cognition and executive function were not significantly impacted by mild-to-moderate CKD in diabetic or non-diabetic EAs.

This study encompassed a relatively large cohort of EAs with T2D, as well as some non-diabetic individuals; all had early-stage CKD. The results were striking for the lack of significant impact of reduced eGFR (down to 45 mL/min/1.73 m^2) and microalbuminuria on cognitive performance or cerebral structure in EAs. In fact, cognitive performance did not significantly correlate with mild CKD based on either eGFR or UACR. These results stand in stark contrast to the strong associations seen between mild CKD and brain structural changes and cognitive performance in AAs; they are also markedly different than results in EAs with advanced-stage CKD. In a cohort comprised solely of AAs with T2D, mean(SD) age 60.2(9.7) years, CKD-EPI eGFR 86.0(23.2) mL/min/1.73 m^2 and UACR 155.8 (542.1) mg/g, eGFR and UACR strongly associated with smaller GM and higher WM lesion volumes, and lower performance on tests of cognition and executive function, with P values between 1.1×10^{-2} and 1.1×10^{-5} [14, 15].

Previous studies described associations between microalbuminuria and executive function. However, there are several differences between the previous reports and the present study. In the Nutrition, Aging and Memory in Elders (NAME) Study, although microalbuminuria was associated with poorer executive performance, the study included older subjects (mean age 73 years) and of multiple racial backgrounds (32% AAs) [5]. In the Rancho Bernardo Study, baseline microalbuminuria, but not eGFR, was significantly associated with cognitive functional decline after 6-year follow-up [28]. In the ACCORD-MIND study limited to subjects with diabetes, microalbuminuria was significantly associated with poor performance on RAVLT memory and DSST executive function testing, while eGFR > 60 mL/min/1.73 m^2 was not associated with measures of cognitive performance [29]. Importantly, both studies involved participants of diverse ethnic backgrounds.

Results from Knopman *et al.* further emphasize the significance of race-specific effects when examining relationships between kidney function and cerebral structure. The study included 1253 individuals from hypertensive sibships, mean age 64 years, 49% AA, eGFR >60 mL/min/1.73 m^2, and a small percentage with microalbuminuria, and showed that UACR was associated with increased WM hyperintensities in AAs and EAs, and with increased risk of brain atrophy only in AAs [30].

In the present study, eGFR > 45 mL/min/1.73 m^2 was negatively associated with TICV in participants with T2D. In prior studies, eGFR correlated with TWMV and TWMLV and with cognitive impairment. Of note, the present study contrasts with previous reports that included predominantly elderly and non-diabetic populations with more advanced CKD (eGFR < 60 mL/min/1.73 m^2) and binary outcomes of brain atrophy and WM lesions, as opposed to quantitative measures of brain volume [2–11]. The DHS-MIND population was enriched for participants with 16-year mean T2D durations; diabetes increases the risk for cognitive decline and alterations in cerebral WM [31, 32]. It, therefore, remains possible that DHS-MIND participants had cerebral structural and functional changes relating to T2D and that incipient kidney disease did not increase the risk for brain morphological changes.

Japanese subjects with fewer CVD risk factors (lower BMI, shorter T2D duration, fewer hypertensives and fewer smokers) with preserved kidney function (eGFR > 60 mL/min/1.73 m^2) had significant correlations between microalbuminuria and cerebral WM lesions [33]. In our study in EAs, microalbuminuria was negatively associated with TWMLV only in the small sample lacking diabetes; as such, paradoxical results likely relate to the small sample. In contrast, microalbuminuria has strong correlations with several brain morphologic changes in AAs: CSFV (P = 0.02), TGMV (P = 0.03), TWMLV ($P = 5.0 \times 10^{-4}$) and HWMV ($P = 1.6 \times 10^{-4}$) [14]. Differences in brain morphology and function are also observed in general populations based on race/ethnicity, with AAs reportedly having smaller brain volume and higher TWMLV burden [12, 34], higher incidence of ischemic strokes, [35] and more cognitive decline [36, 37] after controlling for vascular risk factors (age, smoking, diabetes, hypercholesterolemia, hypertension) and education. Moreover, vascular risk factors were found to be associated with poorer cognitive function in AAs, but not in EAs [13]. Mechanisms underlying the relationship between kidney disease and brain structural and functional changes are complex [38]. Cerebral microvascular diseases may contribute to vascular cognitive impairment with a continuum of disorders ranging from mild impairment to dementia [39, 40]. Albuminuria, even at levels within the 'normal' range, is a biomarker of vascular endothelial dysfunction with adverse CVD outcomes [41]. In the HOORN study, microalbuminuria was associated with maladaptive arterial remodeling and impaired arterial flow-mediated vasodilatation due to endothelial dysfunction [42]. Damage to the endothelial glycocalyx may lead to increased capillary wall permeability, albuminuria [43] and impaired cerebral and coronary microcirculations [44]. Research has emerged showing a biologic relationship between regional brain size in the hippocampus [36] and WM hyperintensities [45] with cognitive performance. Based on our results, it is conceivable that cerebral structural changes might precede changes in cognitive function in EAs with early-stage CKD.

This study has several strengths. To our knowledge, this is the first study to concomitantly delineate brain structural and cognitive measurements in mild-to-moderate CKD. We exclusively evaluated EAs, reducing the confounding factor of race/ethnicity. Prior reports often lacked detailed brain imaging and cognitive testing in individuals with mild degrees of nephropathy. Rather than using subjective rating scales, brain imaging in the present study utilized quantitative techniques to determine

volumes and WM lesion burden. This study also has limitations. Our analyses cannot determine causality between renal variables and brain volume or cognitive performance given the cross-sectional design. In addition, measurement of albuminuria was based on a single spot urine sample, although this method correlates well with 24-h urine albumin excretion and is widely utilized [46]. Given enrollment of EAs and enrichment for T2D, results may not be fully generalizable to non-diabetic subjects and other racial/ethnic groups. In addition, serum creatinine concentrations were measured using the Jaffe method, whereas enzymatic methods are preferred for the CKD-EPI eGFR equation.

In conclusion, in EAs with T2D and mild-to-moderate CKD (eGFR > 45 mL/min/1.73 m^2 and UACR <300 mg/g), kidney function parameters were not significantly associated with striking changes in brain structure or cognitive performance. These results contrast markedly with those reported in non-European populations and support the need for studies linking kidney disease with changes in cerebral structure and cognitive performance in different racial groups.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

The authors thank Diabetes Heart Study-MIND participants and study staff for their valuable contributions. This project was supported in part by the National Institutes of Health: RO1 NS058700 (D.W.B.), RO1 HL092301 (D.W.B.) and RO1 NS075107 (B.I.F.) and the General Clinical Research Center of the Wake Forest School of Medicine (MO1 RR07122, F32 HL085989).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Moodalbail DG, Reiser KA, Detre JA *et al.* Systematic review of structural and functional neuroimaging findings in children and adults with CKD. Clin J Am Soc Nephrol 2013; 8: 1429–1448
2. Kurella M, Chertow GM, Fried LF *et al.* Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. J Am Soc Nephrol 2005; 16: 2127–2133
3. Khatri M, Wright CB, Nickolas TL *et al.* Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). Stroke 2007; 38: 3121–3126
4. Kurella TM, Wadley V, Yaffe K *et al.* Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis 2008; 52: 227–234
5. Weiner DE, Bartolomei K, Scott T *et al.* Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. Am J Kidney Dis 2009; 53: 438–447
6. Barzilay JI, Gao P, O'Donnell M *et al.* Albuminuria and decline in cognitive function: The ONTARGET/TRANSCEND studies. Arch Intern Med 2011; 171: 142–150
7. Kurella TM, Muntner P, Wadley V *et al.* Albuminuria, kidney function, and the incidence of cognitive impairment among adults in the United States. Am J Kidney Dis 2011; 58: 756–763
8. Helmer C, Stengel B, Metzger M *et al.* Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. Neurology 2011; 77: 2043–2051
9. Takahashi W, Tsukamoto Y, Takizawa S *et al.* Relationship between chronic kidney disease and white matter hyperintensities on magnetic resonance imaging. J Stroke Cerebrovasc Dis 2012; 21: 18–23
10. Naganuma T, Takemoto Y, Shoji T *et al.* Factors associated with cerebral white matter hyperintensities in haemodialysis patients. Nephrology (Carlton) 2012; 17: 561–568
11. Umemura T, Kawamura T, Umegaki H *et al.* Association of chronic kidney disease and cerebral small vessel disease with cognitive impairment in elderly patients with type 2 diabetes. Dement Geriatr Cogn Dis Extra 2013; 3: 212–222
12. Nyquist PA, Bilgel MS, Gottesman R *et al.* Extreme deep white matter hyperintensity volumes are associated with African American race. Cerebrovasc Dis 2014; 37: 244–250
13. Schneider BC, Gross AL, Bangen KJ *et al.* Association of vascular risk factors with cognition in a multiethnic sample. J Gerontol B Psychol Sci Soc Sci 2014; 10: 1–13
14. Sink KM, Divers J, Whitlow CT *et al.* Cerebral structural changes in diabetic kidney disease: African American-Diabetes Heart Study MIND. Diabetes Care 2015; 38: 206–212
15. Palmer N, Sink K, Smith C *et al.* Kidney disease and cognitive function: African American-Diabetes Heart Study MIND. Am J Nephrol 2014; 40: 200–207
16. Bowden DW, Cox AJ, Freedman BI *et al.* Review of the Diabetes Heart Study (DHS) family of studies: a comprehensively examined sample for genetic and epidemiological studies of type 2 diabetes and its complications. Rev Diabet Stud 2010; 7: 188–201
17. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612
18. Tzourio-Mazoyer N, Landeau B, Papathanassiou D *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002; 15: 273–289
19. Maldjian JA, Laurienti PJ, Kraft RA *et al.* An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 2003; 19: 1233–1239
20. Schmidt P, Gaser C, Arsic M *et al.* An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. Neuroimage 2012; 59: 3774–3783
21. Maldjian JA, Whitlow CT, Saha BN *et al.* Automated white matter total lesion volume segmentation in diabetes. AJNR Am J Neuroradiol 2013; 34: 2265–2270
22. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987; 48: 314–318
23. Lezak M, Howleson D, Loring D. Neuropsychological Assessment. 2004. New York: Oxford University Press
24. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. Exp Aging Res 1993; 19: 209–224
25. Strauss E, Sherman EMS. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, 2006
26. Wechsler D. Manual for the Wechiser Adult Intelligence Scale-Revised. New York: Psychological Corporation, 2014
27. Jongen C, van der GJ, Kappelle LJ *et al.* Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. Diabetologia 2007; 50: 1509–1516
28. Jassal SK, Kritz-Silverstein D, Barrett-Connor E. A prospective study of albuminuria and cognitive function in older adults: the Rancho Bernardo study. Am J Epidemiol 2010; 171: 277–286
29. Murray AM, Barzilay JI, Lovato JF *et al.* Biomarkers of renal function and cognitive impairment in patients with diabetes. Diabetes Care 2011; 34: 1827–1832
30. Knopman DS, Mosley TH, Jr, Bailey KR *et al.* Associations of microalbuminuria with brain atrophy and white matter hyperintensities in hypertensive sibships. J Neurol Sci 2008; 271: 53–60

31. van Elderen SG, de RA, de Craen AJ *et al.* Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up. Neurology 2010; 75: 997–1002
32. Verdelho A, Madureira S, Moleiro C *et al.* White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. Neurology 2010; 75: 160–167
33. Anan F, Masaki T, Iwao T *et al.* The role of microalbuminuria and insulin resistance as significant risk factors for white matter lesions in Japanese type 2 diabetic patients. Curr Med Res Opin 2008; 24: 1561–1567
34. Brickman AM, Schupf N, Manly JJ *et al.* Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. Arch Neurol 2008; 65: 1053–1061
35. White H, Boden-Albala B, Wang C *et al.* Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. Circulation 2005; 111: 1327–1331
36. DeCarli C, Reed BR, Jagust W *et al.* Brain behavior relationships among African Americans, whites, and Hispanics. Alzheimer Dis Assoc Disord 2008; 22: 382–391
37. Manly JJ, Tang MX, Schupf N *et al.* Frequency and course of mild cognitive impairment in a multiethnic community. Ann Neurol 2008; 63: 494–506
38. Bugnicourt JM, Godefroy O, Chillon JM *et al.* Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol 2013; 24: 353–363
39. Gorelick PB, Scuteri A, Black SE *et al.* Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42: 2672–2713
40. Rincon F, Wright CB. Vascular cognitive impairment. Curr Opin Neurol 2013; 26: 29–36
41. Solomon SD, Lin J, Solomon CG *et al.* Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. Circulation 2007; 116: 2687–2693
42. Hermans MM, Henry RM, Dekker JM *et al.* Albuminuria, but not estimated glomerular filtration rate, is associated with maladaptive arterial remodeling: the Hoorn Study. J Hypertens 2008; 26: 791–797
43. Friden V, Oveland E, Tenstad O *et al.* The glomerular endothelial cell coat is essential for glomerular filtration. Kidney Int 2011; 79: 1322–1330
44. Becker BF, Chappell D, Jacob M. Endothelial glycocalyx and coronary vascular permeability: the fringe benefit. Basic Res Cardiol 2010; 105: 687–701
45. Birdsill AC, Koscik RL, Jonaitis EM *et al.* Regional white matter hyperintensities: aging, Alzheimer's disease risk, and cognitive function. Neurobiol Aging 2014; 35: 769–776
46. Dyer AR, Greenland P, Elliott P *et al.* Evaluation of measures of urinary albumin excretion in epidemiologic studies. Am J Epidemiol 2004; 160: 1122–1131

Received for publication: 19.5.2014; Accepted in revised form: 18.1.2015

Nephrol Dial Transplant (2015) 30: 1329–1335
doi: 10.1093/ndt/gfv037
Advance Access publication 27 March 2015

ORIGINAL ARTICLE

Longitudinal changes in hematocrit in hypertensive chronic kidney disease: results from the African-American Study of Kidney Disease and Hypertension (AASK)

Teresa K. Chen[1], Michelle M. Estrella[1,2], Brad C. Astor[3], Tom Greene[4], Xuelei Wang[5], Morgan E. Grams[1,2] and Lawrence J. Appel[2]

[1]Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, MD, USA, [3]Division of Nephrology, University of Wisconsin School of Medicine, Madison, WI, USA, [4]Division of Epidemiology, University of Utah School of Medicine, Salt Lake City, UT, USA and [5]Center for Clinical Investigation, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Correspondence and offprint requests to: Teresa K. Chen; E-mail: tchen39@jhmi.edu

ABSTRACT

Background. Anemia is common in chronic kidney disease (CKD) and associated with poor outcomes. In cross-sectional studies, lower estimated glomerular filtration rate (eGFR) has been associated with increased risk for anemia. The aim of this study was to determine how hematocrit changes as eGFR declines and what factors impact this longitudinal association. **Methods.** We followed 1094 African-Americans with hypertensive nephropathy who participated in the African-American Study of Kidney Disease and Hypertension. Mixed