Cerebral Structural Changes in Diabetic Kidney Disease: African American–Diabetes Heart Study MIND

Kaycee M. Sink,[1] Jasmin Divers,[2] Christopher T. Whitlow,[3] Nicholette D. Palmer,[4,5] S. Carrie Smith,[4] Jianzhao Xu,[4] Christina E. Hugenschmidt,[1] Benjamin C. Wagner,[3] Jeff D. Williamson,[1] Donald W. Bowden,[4,5] Joseph A. Maldjian,[3] and Barry I. Freedman[5,6]

OBJECTIVE

Albuminuria and reduced kidney function are associated with cognitive impairment. Relationships between nephropathy and cerebral structural changes remain poorly defined, particularly in African Americans (AAs), a population at higher risk for both cognitive impairment and diabetes than European Americans. We examined the relationship between urine albumin:creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and cerebral MRI volumes in 263 AAs with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Cross-sectional associations between renal parameters and white matter (WM), gray matter (GM), hippocampal, and WM lesion (WML) volumes were assessed using generalized linear models adjusted for age, education, sex, BMI, hemoglobin A_{1c} (HbA_{1c}) level, and hypertension.

RESULTS

Participants had a mean (SD) age of 60.2 years (9.7 years), and 62.7% were female. Mean diabetes duration was 14.3 years (8.9 years), HbA_{1c} level was 8.2% (2.2%; 66 mmol/mol), eGFR was 86.0 mL/min/1.73 m^2 (23.2 mL/min/1.73 m^2), and UACR was 155.8 mg/g (542.1 mg/g; median 8.1 mg/g). Those with chronic kidney disease (CKD) (eGFR <60 mL/min/1.73 m^2 or UACR >30 mg/g) had smaller GM and higher WML volumes. Higher UACR was significantly associated with higher WML volume and greater atrophy (larger cerebrospinal fluid volumes), and smaller GM and hippocampal WM volumes. A higher eGFR was associated with larger hippocampal WM volumes. Consistent with higher WML volumes, participants with CKD had significantly poorer processing speed and working memory. These findings were independent of glycemic control.

CONCLUSIONS

We found albuminuria to be a better marker of cerebral structural changes than eGFR in AAs with type 2 diabetes. Relationships between albuminuria and brain pathology may contribute to poorer cognitive performance in patients with mild CKD.

[1]Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC
[2]Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC
[3]Department of Radiologic Sciences, Advanced Neuroscience Imaging Research Laboratory, Wake Forest School of Medicine, Winston-Salem, NC
[4]Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC
[5]Center for Diabetes Research, Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC
[6]Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC

Corresponding author: Barry I. Freedman, bfreedma@wakehealth.edu.

Incidence rates of type 2 diabetes and cognitive dysfunction/dementia are increasing at alarming rates in the U.S. and worldwide (1,2). Type 2 diabetes is a recognized risk factor for dementia and cognitive dysfunction (3). Markers of chronic kidney disease (CKD), particularly albuminuria and, to a lesser extent, reductions in estimated glomerular filtration rate (eGFR), potentiate cognitive decline in individuals with and without diabetes (4–8). Vascular injury, endothelial dysfunction, and direct neuronal toxicity are potential mechanisms for cognitive dysfunction as well as brain structural changes (9). African Americans (AAs) bear a disproportionate burden of type 2 diabetes and its complications, as well as a higher risk of Alzheimer's disease and other dementias.

Both type 2 diabetes and CKD have been associated with structural brain changes, particularly white matter (WM) lesions (WMLs) (10–12), and MRI studies of persons with type 2 diabetes have reported diabetes-associated decreases in total gray matter (GM) and WM volume, as well as more focal regional patterns of cerebral volume loss, including involvement of the hippocampus (13–17). However, less is known about the relationships between CKD and the effects of kidney disease parameters (especially with mild degrees of kidney dysfunction) on brain atrophy, including hippocampal atrophy, particularly in AAs. We were especially interested in the hippocampus since there is mounting evidence of a direct relationship between type 2 diabetes and Alzheimer's disease pathology, including a similarity in the patterns of regional cerebral volume loss and hippocampal dysfunction (18–20). In addition, the hippocampus is thought to be particularly vulnerable to the effects of neurotoxic stimuli that could be associated with type 2 diabetes and CKD, including chronic hypoperfusion and hypoglycemia, among others (21).

This analysis was performed to assess cerebral structural changes based on MRI findings in a sample of comprehensively phenotyped AA-Genetics of Cerebrovascular Disease and Cognitive Impairment in the Diabetes Heart Study (AA-DHS MIND) participants to detect relationships with measures of CKD in individuals lacking advanced nephropathy. We hypothesized that CKD, lower eGFR, and higher urine albumin:creatinine ratio (UACR) would be associated with greater brain pathology seen on MRI, specifically higher WML volumes and smaller GM volumes.

RESEARCH DESIGN AND METHODS

Participants

The analysis included 263 unrelated AAs with type 2 diabetes obtained by selecting all current Wake Forest School of Medicine (WFSM) AA-DHS MIND participants (n = 261) and 1 AA subject from each of 2 DHS MIND sibling pairs (22). The DHS MIND is a cross-sectional study of European American and AA families with siblings concordant for type 2 diabetes; the AA-DHS MIND enrolls unrelated AAs with type 2 diabetes. The combined study samples are herein referred to as AA-DHS MIND with study objectives to improve understanding of risk factors for cognitive impairment and to assess cerebral architecture using MRI in the AA population with type 2 diabetes. Individuals with prior serum creatinine concentrations >2 mg/dL or end-stage kidney disease were not recruited.

Participants were eligible if they had received a diagnosis of type 2 diabetes after age 30 years in the absence of diabetic ketoacidosis and in the setting of the following: 1) active medical treatment (insulin and/or oral hypoglycemic agents); 2) fasting blood glucose levels ≥126 mg/dL or nonfasting blood glucose levels ≥200 mg/dL; or 3) hemoglobin A_{1c} levels ≥6.5%. Hypertension was present if diagnosed by a physician, antihypertensive medications were prescribed, or blood pressures measured in the clinic were >140/90 mmHg. All studies were approved by the WFSM Institutional Review Board, and participants provided written informed consent.

Examinations were performed in the WFSM Clinical Research Unit. In addition to recording medical and education histories, vital signs, and current medications, subjects underwent fasting measurements of serum creatinine, blood urea nitrogen, thyroid-stimulating hormone, and vitamin B12 levels, and UACR (LabCorp, Burlington, NC). After a morning snack, cognitive testing and cerebral MRI were performed. Global cognitive function was assessed with the Modified Mini-Mental State Examination (3MSE) (23). Speed of processing and working memory were assessed with the digit symbol coding (DSC) test (24). Verbal memory was tested with the Rey Auditory Verbal Learning Test (RAVLT) (25), in particular delayed recall at 30 min.

Cerebral MRI

MRI Acquisition

The initial 73 scans were performed on a 1.5-T 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 three-dimensional (3D) volumetric inversion recovery spoiled grass gradient recalled sequence (repetition time [TR] 7.36 ms; echo time [TE] 2.02 ms; inversion time [TI] 600 ms; flip angle [FA] 20°; 124 slices: field of view 24 cm, matrix size 256 × 256, 1.5-mm slice thickness). Fluid-attenuated inversion recovery images were acquired in the axial plane (TR 8,002 ms; TE 101.29 ms; TI 2,000 ms; FA 90°; field of view 24 cm; matrix size 256 × 256; 3-mm slice thickness). Because of a change in scanners at the WFSM Center for Biomolecular Imaging, the subsequent 190 scans were performed on a 3.0-T) Skyra MRI scanner (Siemens Healthcare, Erlangen, Germany) using a high-resolution 20-channel head/neck coil. T1-weighted anatomic images were obtained using a 3D volumetric magnetization-prepared rapid acquisition gradient echo sequence (TR 2,300 ms; TE 2.99 ms; TI 900 ms; FA 9°; 192 slices; voxel dimension 0.97 × 0.97 × 1 mm). Fluid-attenuated inversion recovery images were acquired using a 3D SPACE inversion recovery sequence (TR 6,000 ms; TE 283 ms; TI 2,200 ms; FA 120°; 160 slices; voxel dimensions 1.1 × 1.1 × 1 mm).

Image Segmentation

Structural T1 images were segmented into GM, WM, and cerebrospinal fluid (CSF), normalized to Montreal Neurological Institute space, and modulated with the Jacobian determinants (nonlinear components only) of the warping procedure to generate volumetric tissue maps using the Dartel high-dimensional warping and the SPM8 (26) new segment procedure as implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). The modulation

step did not include the affine component of the normalization parameters, thereby correcting the volumetric tissue maps for total intracranial volume (ICV). Total GM, WM, and CSF volumes, and ICV (GM + WM + CSF volumes) 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 AAL (Automated Anatomical Labeling) atlas (27), as implemented in the wfu_pickatlas (28). 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, WM, and CSF volumetric tissue maps to generate hippocampal GM, hippocampal WM, and hippocampal CSF volumes, adjusted for ICV. All volumes were reported in cubic centimeters by summing the voxel values, multiplying by the voxel volume (in cubic millimeters) and dividing by 1,000, adjusted for ICV. Results were similar between the left and right hippocampus; therefore, we present only the total hippocampal volumes.

WML Segmentation
WML segmentation was performed using the lesion segmentation toolbox (29) for SPM8 at a threshold (k) of 0.25. We previously validated the lesion segmentation toolbox in the AA-DHS MIND cohort against expert manual segmentation, as well as identifying the optimum threshold in this population (30). Normalization to Montreal Neurological Institute space was accomplished by coregistration with the structural T1 and applying the normalization parameters computed in the VBM8 segmentation procedure. WML volume was determined by summing the binary lesion maps and multiplying by the voxel volume, and values are reported in cubic centimeters.

Interscanner Variability
To account for between-scanner variation, 15 study participants underwent both 1.5-T and 3.0-T MRI scans. The imaging data underwent identical processing for both data sets in each participant. Adjustments were made based on any systematic differences in volumetric measures between scanners (31,32).

Statistical Analyses
Calibration equations between the 1.5-T and 3.0-T measurements were estimated using linear regression. These equations were used to determine the corresponding 3.0-T MRI value from an MRI scan performed on a 1.5-T scanner. R^2 values obtained from the calibration equations also provide an estimate of the reliability of 1.5-T measurements as predictors of the 3.0-T MRI values. Since the MRI measurements serve as the dependent variables in the models, additional variation in the calibrated 1.5-T measurements do not bias the parameter estimates; they only reduce the power of the association test.

Generalized linear models were fitted to test for associations between parameters of kidney disease (independent variables) and brain MRI measures (dependent variables). The renal parameters were the binary trait of CKD (yes/no; CKD defined as an eGFR <60 mL/min/1.73 m^2 and/or a UACR >30 mg/g), UACR as a continuous variable, and eGFR as a continuous variable using the CKD Epidemiology Collaboration equation (33). Variables derived from

the brain MRI were WML, GM, WM, and CSF volumes. Hippocampal GM, hippocampal WM, and hippocampal CSF volumes were also assessed. All reported volumes were adjusted for ICV. The Box-Cox method was applied to identify the appropriate transformation best approximating the distributional assumptions of conditional normality and homogeneity of variance of the residuals (34). This method suggested taking the natural logarithm of CSF, WML, and hippocampal CSF volumes, and taking the squared value of the WM, GM, hippocampal WM, and hippocampal GM volumes. Models were run unadjusted, and successively adjusted for age and sex, BMI, severity of type 2 diabetes (hemoglobin A_{1c} [HbA_{1c}] level), hypertension (yes/no), and level of education (1 less than high school; 2–5 number of years in high school [5 graduate]; 6–9 number of years in college [9 graduate]; 10 postgraduate degree). Parameter estimates in Tables 3 and 4 are reported for the transformed variables corresponding to the change in each MRI outcome per 100 mg/g increase in UACR, 10 mL/min/1.73 m^2 increase in eGFR, and the presence of CKD

Table 1—Demographic, clinical, and cognitive characteristics of the study sample

Variable	Full sample (N = 263)	CKD absent* (N = 172)	CKD present* (N = 91)	P value†
Age (years)	60.4 (9.6)	60.3 (9.5)	60.5 (9.8)	0.94
Male sex	98 (37.3%)	61 (34.5%)	37 (40.7%)	0.26
Education				0.33
Less than a high school diploma	27 (10.3%)	15 (55.6%)	12 (44.4%)	
High school diploma	76 (28.9%)	48 (63.2%)	28 (36.8%)	
Some college or a college diploma	115 (43.7%)	75 (65.2%)	40 (34.8%)	
Graduate education	45 (17.1%)	34 (77.8%)	11 (22.2%)	
BMI (kg/m^2)	34.1 (7.9)	34.0 (8.2)	34.1 (7.7)	0.61
Age of diabetes diagnosis (years)	46.0 (11.0)	46.2 (11.2)	45.5 (10.8)	0.51
Duration of diabetes (years)	14.3 (8.9)	14.1 (9.2)	15.0 (8.3)	0.29
SBP (mmHg)	131.2 (18.6)	128.7 (17.0)	136.0 (20.5)	0.01
DBP (mmHg)	75.4 (10.8)	73.9 (9.4)	78.2 (12.6)	0.03
Smoking				0.88
Never	117 (44.7%)	76 (44.4%)	41 (45.1%)	
Past	91 (34.7%)	61 (35.7%)	30 (33.0%)	
Current	54 (20.6%)	34 (19.9%)	20 (22.0%)	
Hypertension	87 (33.1%)	47 (27.9%)	40 (43.0%)	0.006
Insulin use	108 (41.1%)	59 (34.0%)	49 (53.9%)	0.002
Lipid medications	93 (54.7%)	56 (51.4%)	37 (60.6%)	0.25
3MSE score (0–100)	84.6 (9.0)	85.1 (8.8)	83.8 (9.3)	0.30
DSC score (0–133)	48.1 (15.9)	50.2 (15.6)	44.2 (15.9)	0.004
RAVLT delayed recall (0–15)	5.4 (3.2)	5.4 (3.2)	5.4 (3.0)	0.64

Data are reported as mean (SD) or number (%). DBP, diastolic blood pressure; SBP, systolic blood pressure. *CKD present if eGFR <60 mL/min/1.73 m^2 and/or UACR >30 mg/g. †P value reflects comparison of CKD present vs. CKD absent.

(compared with the absence of CKD). Adjusted results in these tables refer to the model testing for association between renal and MRI variables after adjustment for all six covariates. We also included columns allowing the direct comparison of the effect of renal parameters on MRI variables to the effect of aging by 1 year on each outcome. To account for the multiple comparisons in Tables 3 and 4, we determined the corrected Bonferroni P value that accounts for the correlation between these measures (assuming that inference is based only on the adjusted models). This corrected Bonferroni threshold is $\alpha = 0.005$.

RESULTS

The reliability coefficient (or R^2) between MRI measures obtained on the 1.5-T and 3.0-T scanners ranged between 98% for the ICV and 92% for the GM volume. Hippocampal WM, GM, and CSF volumes had reliability estimates of 79%, 96%, and 79%, respectively. Table 1 contains demographic, clinical, and cognitive characteristics, and Table 2 contains laboratory and imaging characteristics of the AA-DHS MIND sample. In brief, 62.7% of study participants were

female, and the mean (SD) age was 60.4 years (9.6 years). Participants had type 2 diabetes for an average of 14.4 years (8.9 years); with mean fasting blood sugar level of 147.7 mg/dL (60.2 mg/dL) and HbA$_{1c}$ level of 8.2% (2.2%; 66 mmol/mol). They had a mean BMI of 34.1 kg/m^2 (7.9 kg/m^2), an eGFR of 86.0 mL/min/1.73 m^2 (23.2 mL/min/1.73 m^2), and a UACR of 154.9 mg/g (543.6 mg/g; median 8.1 mg/g). Among the 263 subjects, 54.7% were taking prescription lipid-lowering medications, and the overall mean LDL cholesterol, HDL cholesterol, and triglyceride concentrations were 109.1, 47.2, and 115.7 mg/dL, respectively; 33.1% of subjects had received a diagnosis of hypertension with overall mean systolic and diastolic blood pressures of 131.2 and 75.4 mmHg, respectively (100% of subjects diagnosed with hypertension were prescribed antihypertensive medications). Participants had mean (SD) 3MSE scores of 84.6 (9.0), DSC test scores of 48.1 (15.9) and RAVLT delayed recall scores of 5.4 words (3.2 words).

Table 2 also contains results of the cerebral MRI scans in the full sample, and in the subsets of participants with

and without CKD. In binary analyses (CKD present vs. absent), the percentage of ICV that was occupied by GM was significantly lower ($P = 0.006$) and the percentage occupied by CSF was significantly higher ($P = 0.02$) in the 91 participants with CKD, relative to the 172 without CKD, consistent with global atrophy. The percentage of ICV occupied by WM was not significantly different in the presence or absence of CKD ($P = 0.86$); however, significantly higher WML volumes were seen in those participants with CKD ($P = 0.002$). Further, hippocampal WM volume was significantly lower ($P = 0.05$) and hippocampal CSF volume significantly higher ($P = 0.001$) in participants with CKD, compared with those without. A trend toward lower hippocampal GM volume was seen with CKD ($P = 0.06$).

Unadjusted and adjusted analyses were performed to determine the relationships between continuous measures of kidney function (eGFR), albuminuria, and CKD status with cerebral anatomy (Table 3). Results of the fully adjusted models, controlling for the effects of age, sex, BMI, HbA$_{1c}$ level, hypertension, and level of education, follow. No

Table 2—Laboratory and MRI lesion volumes based on binary kidney disease trait (eGFR <60 mL/min/1.73 m^2 and/or UACR >30 mg/g)

Variable	Full sample (N = 263)	CKD absent (N = 172)	CKD present (N = 91)	P value*
Laboratory measures				
eGFR (mL/min/1.73 m^2)	86.0 (23.2)	91.7 (17.9)	75.3 (28.0)	5.9×10^{-5}
C-reactive protein (mg/dL)	1.1 (1.6)	0.9 (1.2)	1.4 (2.2)	0.24
Glucose (mg/dL)	147.5 (60.3)	142.7 (54.6)	156.8 (69.2)	0.17
UACR (mg/g)	154.9 (543.6)	7.5 (6.9)	433.5 (860.3)	7.1×10^{-28}
HbA$_{1c}$ (%)	8.2 (2.1)	7.7 (1.7)	9.0 (2.6)	7.1×10^{-4}
HDL cholesterol (mg/dL)	47.2 (11.9)	48.2 (11.4)	46.1 (12.6)	0.09
LDL cholesterol (mg/dL)	109.1 (37.7)	102.3 (33.5)	121.6 (41.8)	0.004
Serum creatinine (mg/dL)	1.0 (0.3)	0.9 (0.2)	1.2 (0.4)	4.8×10^{-7}
Triglycerides (mg/dL)	115.7 (72.3)	102.6 (54.2)	139.1 (92.4)	5.8×10^{-4}
Thyroid-stimulating hormone (μIU/mL)	2.0 (1.6)	1.8 (1.2)	2.3 (2.1)	0.19
Vitamin B12 (pg/mL)	686.4 (418.3)	713.2 (442.0)	635.6 (366.2)	0.40
MRI results (adjusted reflects adjustment for ICV)				
CSF volume (cm^3)	328.2 (51.2)	324.1 (50.5)	337.8 (50.7)	0.08
ICV occupied by CSF (%)	19.3	19.0	20.0	0.02
GM volume (cm^3)	732.2 (57.7)	738.0 (58.1)	720.3 (57.2)	0.009
ICV occupied by GM (%)	43.3	43.6	42.7	0.006
WM volume (cm^3)	629.6 (46.7)	631.1 (49.0)	627.6 (43.4)	0.62
ICV occupied by WM (%)	37.4	37.4	37.4	0.86
WML volume (cm^3)	7.9 (14.7)	7.3 (15.9)	9.5 (12.4)	0.002
Total hippocampal volume, adjusted (cm^3)	14.1 (1.1)	14.0 (1.1)	14.3 (1.2)	0.12
Hippocampal CSF volume, adjusted (cm^3)	2.1 (1.3)	1.9 (1.0)	2.5 (1.5)	0.001
Hippocampal GM volume, adjusted (cm^3)	9.2 (1.0)	9.3 (0.9)	9.1 (1.0)	0.06
Hippocampal WM volume, adjusted (cm^3)	2.8 (0.3)	2.8 (0.3)	2.7 (0.4)	0.05

Data are presented as mean (SD) unless otherwise indicated. *P value reflects comparison of CKD present vs. CKD absent.

Table 3—Unadjusted and adjusted continuous relationships between MRI ICVs and kidney disease phenotypes

MRI volume, adjusted for ICV	Kidney disease phenotype, analysis model	Estimate*	SE	P value	Predictor effect size	Age effect size
CSF volume	eGFR, unadjusted	−0.33	0.06	2.1×10^{-8}		
	eGFR, adjusted	−0.10	0.06	0.11	−0.05	0.06
	UACR, unadjusted	0.14	0.06	0.02		
	UACR, adjusted	0.13	0.06	0.02	0.03	0.06
	CKD, unadjusted	0.21	0.10	0.04		
	CKD, adjusted	0.34	0.12	0.006	0.37	0.06
GM volume	eGFR, unadjusted	0.19	0.06	0.001		
	eGFR, adjusted	−0.02	0.07	0.76	−0.01	−0.05
	UACR, unadjusted	−0.12	0.06	0.04		
	UACR, adjusted	−0.14	0.06	0.03	−0.03	−0.05
	CKD, unadjusted	−0.22	0.10	0.03		
	CKD, adjusted	−0.33	0.14	0.02	−0.34	−0.05
WM volume	eGFR, unadjusted	0.14	0.06	0.02		
	eGFR, adjusted	0.13	0.08	0.13	0.06	−0.01
	UACR, unadjusted	−0.04	0.06	0.52		
	UACR, adjusted	−0.02	0.08	0.78	−0.004	−0.01
	CKD, unadjusted	0.01	0.11	0.95		
	CKD, adjusted	−0.02	0.17	0.92	−0.02	−0.01
WML volume	eGFR, unadjusted	−0.29	0.06	2.2×10^{-6}		
	eGFR, adjusted	−0.09	0.07	0.23	−0.02	0.03
	UACR, unadjusted	0.17	0.06	0.007		
	UACR, adjusted	0.22	0.06	5.0×10^{-4}	0.03	0.04
	CKD, unadjusted	0.28	0.11	0.009		
	CKD, adjusted	0.45	0.14	0.002	0.28	0.04

Adjustment reflects age, education, sex, BMI, HbA_{1c} level, and hypertension. *Estimate of the change in each MRI outcome corresponding to increases of 100 mg/g in UACR and 10 mL/min/1.73 m^2 in eGFR, and the presence of CKD (vs. no CKD).

significant relationships were detected between glycemic control assessed by HbA_{1c} level and WML volume, GM volume, WM volume, or CSF volume ($P = 0.51$, $P = 0.36$, $P = 0.35$, and $P = 0.07$, respectively; data not shown). Higher UACR was associated with higher WML volume ($P = 5.0 \times 10^{-4}$), but not total WM volume ($P = 0.78$). Higher UACR was associated with smaller GM volume ($P = 0.03$) and with larger CSF volume ($P = 0.02$), consistent with atrophy. eGFR was not significantly associated with GM, WM, CSF, or WML volumes. Having CKD was associated with larger CSF volumes and smaller GM volumes ($P = 0.006$ and $P = 0.02$, respectively), as well as larger WML volumes ($P = 0.002$). The effect of having CKD on these MRI variables was similar to 6–7 years of aging (Table 3).

Relationships between hippocampal volume and CKD were considered next (Table 4). Higher UACR was associated with smaller hippocampal WM volume ($P = 1.6 \times 10^{-4}$) and larger hippocampal CSF volume ($P = 8.2 \times 10^{-4}$), but not with hippocampal GM volume. Higher eGFR was associated with larger hippocampal WM volume ($P = 0.016$). There

was no association between eGFR and hippocampal CSF or GM volumes. Having CKD was associated with larger hippocampal CSF volume and smaller hippocampal WM volume ($P = 0.003$ and $P = 0.01$, respectively). The effect of having CKD was similar to the effect of 7 years of aging on hippocampal CSF volume and 9–10 years of aging on hippocampal WM volume.

CONCLUSIONS

This report assessed relationships between MRI-based cerebral structural changes with albuminuria and eGFR in AAs with type 2 diabetes. Albuminuria was associated with statistically significant higher WML volumes, lower GM volumes, and higher CSF volumes, the latter being suggestive of cerebral atrophy. The presence of CKD was associated with significantly smaller GM volume, larger CSF volume, and higher WML volume with a magnitude of effect similar to about 6–7 years of aging. Perhaps surprisingly, HbA_{1c} level was not significantly associated with any of the MRI volumes, which is in contrast with findings from the ACCORD trial where intensive glycemic control was

associated with larger total brain volume. The inverse relationship between UACR and GM volume, but not between UACR and WM volume (or between eGFR and either WM or GM volume), suggests that cerebral atrophy in AAs with albuminuria results primarily from reductions in GM volume. Our finding that higher UACR is associated with cerebral atrophy is consistent with the findings by Knopman et al. (35) in 610 hypertensive AAs. However, that study did not detect a significant association between UACR and WML volumes in AAs in adjusted models, although it was significant in European Americans.

Because the hippocampus is critical to memory function and is particularly sensitive to neurotoxic stimuli that are associated with CKD and type 2 diabetes, hippocampal volume relationships were assessed with renal disease phenotypes, a novel contribution of the current study. Here, higher levels of eGFR (better kidney function) were associated with larger hippocampal WM volume. Similarly, higher UACR (worsening proteinuria) was significantly associated with smaller hippocampal WM volume and larger

Table 4—Unadjusted and adjusted continuous relationships between hippocampal volumes and kidney disease phenotypes

MRI hippocampal volume, adjusted for ICV	Kidney disease phenotype, analysis model	Estimate*	SE	P value	Predictor effect size	Age effect size
Hippocampal CSF volume	eGFR, unadjusted	−0.27	0.06	1.1×10^{-5}		
	eGFR, adjusted	−0.10	0.06	0.12	−0.06	0.05
	UACR, unadjusted	0.22	0.06	3.6×10^{-4}		
	UACR, adjusted	0.19	0.06	8.2×10^{-4}	0.04	0.06
	CKD, unadjusted	0.31	0.11	0.004		
	CKD, adjusted	0.40	0.13	0.003	0.44	0.06
Hippocampal GM volume	eGFR, unadjusted	0.20	0.06	0.001		
	eGFR, adjusted	0.11	0.08	0.16	0.05	−0.03
	UACR, unadjusted	0.00	0.06	0.94		
	UACR, adjusted	0.04	0.07	0.61	0.003	−0.04
	CKD, unadjusted	−0.12	0.11	0.26		
	CKD, adjusted	−0.23	0.16	0.15	−0.23	−0.04
Hippocampal WM volume	eGFR, unadjusted	0.24	0.06	1.2×10^{-4}		
	eGFR, adjusted	0.19	0.08	0.016	0.08	−0.03
	UACR, unadjusted	−0.24	0.06	1.1×10^{-4}		
	UACR, adjusted	−0.27	0.07	1.6×10^{-4}	−0.05	−0.04
	CKD, unadjusted	−0.20	0.11	0.07		
	CKD, adjusted	−0.40	0.16	0.01	−0.39	−0.04

Adjustment reflects age, education, sex, BMI, HbA$_{1c}$ level, and hypertension. *Estimate of the change in each MRI outcome corresponding to increases of 100 mg/g in UACR and 10 mL/min/1.73 m^2 in eGFR, and the presence of CKD (vs. no CKD).

hippocampal CSF volume. No significant association was seen with either UACR or eGFR and hippocampal GM volume.

Several studies (4–6,8) have shown that albuminuria negatively impacts cognitive function. GM, WM, and hippocampal volume loss, as well as WMLs are thought to underlie type 2 diabetes–associated cognitive dysfunction (16–18). It is hypothesized that the endothelial dysfunction resulting in albuminuria also occurs in the brain, resulting in extravasation of serum proteins into brain extracellular spaces and ultimately causing brain injury (36,37). Several studies (8,35,38) have supported this hypothesis and the role of albuminuria in cerebral microvascular disease. In the AA-DHS MIND sample, CKD status, and UACR in particular, was negatively associated with total GM volume. The smaller GM volumes may be reflected in the slightly lower, albeit not statistically significant, 3MSE scores (global cognitive function) seen in participants with CKD. Our lack of association between CKD measures and hippocampal GM volume (critical for memory) is consistent with the lack of an association between CKD status and delayed memory scores on the RAVLT. WML burden has been associated with poorer executive function (39). The significant differences in DSC performance (speed of processing and working memory) that were seen in CKD participants is consistent with

the increased WML volumes associated with CKD status and higher UACR, making these MRI findings clinically relevant. Thus, we feel that the relationships between markers of renal function and MRI anatomy in this study are consistent with cognitive performance and may be clinically relevant.

This study evaluated a relatively large sample of AAs with good healthcare access based on the prescription of lipid-lowering and antihypertensive medications, and on achieved blood pressures. This is an important strength of the study since a prior analysis by our group demonstrated that AAs and European Americans with type 2 diabetes having equivalent access to healthcare had similar MRI-based burdens of WM disease (40). Thus, an important benefit of studying the carefully phenotyped AA-DHS MIND cohort is that their systemic blood pressures, glycemic control, and risk factor profiles appear similar to those of other populations in the general type 2 diabetes–affected community. While the AA-DHS MIND study was initiated specifically to address the risk of cognitive decline and dementia in the high-risk AA population affected with type 2 diabetes, the fact that all of our participants have type 2 diabetes is a limitation in that results may not be generalizable to AAs without diabetes. In addition, this is a cross-sectional study, so the relationships between

markers of kidney disease and cerebral structural changes cannot be assumed to be causal. Further work is needed to examine the relationship between cognitive performance and specific MRI regions as well as to compare results from AAs with those of other race/ethnicity groups affected by type 2 diabetes.

We conclude that in AAs with type 2 diabetes, albuminuria is a better marker of cerebral structural changes seen on MRI than eGFR. Albuminuria and reduced kidney function often have different impacts on cognitive performance. In this report, we show that albuminuria and reduced kidney function also had differing effects on cerebral anatomy. Albuminuria is associated with lower GM volume and higher CSF volume suggestive of cerebral atrophy, as well as higher WM disease burden consistent with small vessel vascular disease. Although eGFR was positively associated with hippocampal WM volume, significant relationships between eGFR and total WM volume or GM volume were not observed. The effects of albuminuria on WML volume and GM volume loss may be mediated by systemic endothelial dysfunction and have been seen in early-stage CKD (9,36,37). It is imperative that methods to reduce WM disease burden and GM volume loss be identified in AAs with albuminuria and type 2 diabetes. These methods are likely to favorably impact the cognitive decline that is often

observed in the high-risk AA population with type 2 diabetes.

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