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Original Investigation

Associations of Early Kidney Disease With Brain Magnetic Resonance Imaging and Cognitive Function in African Americans With Type 2 Diabetes Mellitus

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Background: Relationships between early kidney disease, neurocognitive function, and brain anatomy are poorly defined in African Americans with type 2 diabetes mellitus (T2DM).

Study Design: Cross-sectional associations were assessed between cerebral anatomy and cognitive performance with estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (UACR) in African Americans with T2DM.

Setting & Participants: African Americans with cognitive testing and cerebral magnetic resonance imaging (MRI) in the African American–Diabetes Heart Study Memory in Diabetes (AA-DHS MIND; n = 512; 480 with MRI) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) MIND (n = 484; 104 with MRI) studies.

Predictors: eGFR (CKD-EPI creatinine equation), spot UACR.

Measurements: MRI-based cerebral white matter volume (WMV), gray matter volume (GMV), and white matter lesion volume; cognitive performance (Mini-Mental State Examination, Digit Symbol Coding, Stroop Test, and Rey Auditory Verbal Learning Test). Multivariable models adjusted for age, sex, body mass index, scanner, intracranial volume, education, diabetes duration, hemoglobin A_{1c} concentration, low-density lipoprotein cholesterol concentration, smoking, hypertension, and cardiovascular disease were used to test for associations between kidney phenotypes and the brain in each study; a meta-analysis was performed.

Results: Mean participant age was 60.1 ± 7.9 (SD) years; diabetes duration, 12.1 ± 7.7 years; hemoglobin A_{1c} concentration, 8.3%±1.7%; eGFR, 88.7 ± 21.6 mL/min/1.73 m^2; and UACR, 119.2 ± 336.4 mg/g. In the fully adjusted meta-analysis, higher GMV associated with lower UACR ($P < 0.05$), with a trend toward association with higher eGFR. Higher white matter lesion volume was associated with higher UACR ($P < 0.05$) and lower eGFR ($P < 0.001$). WMV was not associated with either kidney parameter. Higher UACR was associated with lower Digit Symbol Coding performance ($P < 0.001$) and a trend toward association with higher Stroop interference; eGFR was not associated with cognitive tests.

Limitations: Cross-sectional; single UACR measurement.

Conclusions: In African Americans with T2DM, mildly high UACR and mildly low eGFR were associated with smaller GMV and increased white matter lesion volume. UACR was associated with poorer processing speed and working memory.

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The AA-DHS MIND and ACCORD MIND Investigators are listed at http://fmri.wfubmc.edu/research/AADHSMind and in Murray et al[11], respectively.

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Compared with the general population, people with type 2 diabetes mellitus (T2DM) and advanced chronic kidney disease (CKD) have higher rates of cognitive dysfunction, more cerebral atrophy, and increased severity of white matter lesions on brain magnetic resonance imaging (MRI).[1-7] The associations of mildly reduced estimated glomerular filtration rate (eGFR) and albuminuria (typically assessed as spot urine albumin-creatinine ratio [UACR]) on brain anatomy and function have been assessed less often, although these disorders make up a much larger percentage of the population with CKD. Several studies from predominantly European-derived cohorts have associated subtle declines in executive function and possible MRI findings with mild kidney disease in people with diabetes.[8,9] The relationship between mild reductions in eGFR and low-level albuminuria with brain structure and function are not well studied in African Americans with T2DM. Although it is logical to assume that these relationships would be the same as in European Americans, differences in susceptibility to T2DM, subclinical cardiovascular disease, kidney disease, and risk for cognitive decline exist between people of African and European descent.[10] Brain findings may therefore differ between European Americans and African Americans, and variable access to medical care may further confound relationships between brain and kidney disease in the context of diabetes.

The objective of this study was to examine whether early markers of kidney disease are associated with cognitive impairment and brain MRI changes in African Americans with T2DM. Two African American cohorts with access to medical care were analyzed. Participants underwent extensive cognitive function testing and brain MRI. In contrast to existing reports, these well-characterized participants had generally preserved kidney function with low levels of albuminuria, as well as frequent receipt of medications to control blood pressure, blood glucose, and serum lipid concentrations.

METHODS

Setting

The African American−Diabetes Heart Study Memory in Diabetes (AA-DHS MIND) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) MIND studies evaluated cognitive performance and brain volumes with cerebral MRI in African Americans with T2DM.[11-15] AA-DHS MIND is an observational genetic and epidemiologic study that assesses relationships between T2DM, cardiovascular disease, brain anatomy, and neurocognitive function. ACCORD was designed to determine whether intensive lowering of blood glucose concentrations, intensive lowering of blood pressure, or treatment of blood lipid concentrations with a fibrate drug plus a statin drug can reduce the risk for major cardiovascular disease events in patients with T2DM who are at especially high risk for cardiovascular disease.

Study Size and Participants

The sample consisted of all self-reported African Americans with T2DM enrolled in the Wake Forest School of Medicine AA-DHS MIND and all African Americans with T2DM who were recruited in the ACCORD MIND substudy. Detailed AA-DHS MIND methods have been reported.[13,14] AA-DHS consists of 717 participants with T2DM actively treated with insulin and/or oral agents; those with known serum creatinine concentrations $>$ 2 mg/dL were not recruited. A total of 292 AA-DHS participants were re-examined in the AA-DHS MIND with cerebral MRI and cognitive testing, and another 220 individuals meeting identical inclusion criteria were later recruited. ACCORD was a randomized, multicenter, 2×2 factorial design trial that assessed 2 levels of hemoglobin A_{1c} (HbA_{1c}) control (standard vs intensive) on adjudicated major cardiovascular disease events; lipid lowering (with a statin with or without a fibrate), and blood pressure control arms (standard vs intensive) were also included. ACCORD MIND was an ancillary study that assessed the effects of blood glucose concentration, blood pressure, and lipid lowering on cognitive function.[11,12] Detailed recruitment strategies have been reported for both studies.[11-14] Medication, medical, and education histories were collected and body mass index (BMI) and blood pressure were recorded for all participants. These studies were approved by their respective institutional review boards and adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data Sources and Measurement

Biochemical Measures

Measurements of HbA_{1c}, fasting glucose, and lipids were performed. Albuminuria was quantitated with a spot UACR, and eGFR was computed using the CKD-EPI (CKD Epidemiology Collaboration) equation based on isotope-dilution mass spectrometry−validated serum creatinine concentrations in each study.[16]

Cognitive Testing

Partially overlapping cognitive batteries were administered to AA-DHS MIND and ACCORD MIND participants. Analyses included the 4 cognitive tests performed in both studies. The Digit Symbol Coding test (subtest of Wechsler Adult Intelligence Scale) primarily reflects processing speed and, to a lesser extent, working memory.[17] Digit Symbol Coding score was defined as the number of correct responses within 2 minutes; higher score indicates better performance. Response inhibition, a component of executive function, was assessed with a 40-item version of the Stroop task.[18] The interference score is reported, computed as [time to completion Stroop 3 + errors Stroop 3] − [time to completion Stroop 2 + errors Stroop 2], for which higher scores reflect poorer executive function. The Rey Auditory Verbal Learning Test (RAVLT) is a 15-item word list recall task that tests verbal memory and learning. The RAVLT measures delayed recall, which reflects the number of