Cerebral white matter changes in chronic kidney disease patients using DTI

J. Zhuo[1], J. Wang[1,2], S. Seliger[3], D. Lefkowitz[1], J. Betz[1,4], S. Waldstein[4], L. Katzel[5,6], S. Roys[1], and R. Gullapalli[1]

[1]Radiology, University of Maryland School of Medicine, Baltimore, MD, United States, [2]Computer Science and Electrical Engineering, University of Maryland Baltimore County, Baltimore, MD, United States, [3]Nephrology, University of Maryland School of Medicine, Baltimore, MD, United States, [4]Psychology, University of Maryland Baltimore County, Baltimore, MD, United States, [5]Gerontology, University of Maryland School of Medicine, Baltimore, MD, [6]Baltimore Geriatric Research, Education, and Clinical Center, Baltimore Veterans Affairs Medical Center, Baltimore, MD, United States

INTRODUCTION: Chronic kidney disease (CKD) affects nearly 10 million adults in the US, and these individuals suffer from diminished functional capacity, worse cognitive function[1], and a greater risk of dementia[2] relative to individuals without renal disease. A greater prevalence of cerebral atherosclerosis and both overt and covert brain infarcts have been described in CKD patients, and may explain in part this increased risk of functional impairment. However, there have been few investigations examining changes in brain white matter in CKD patients. Such changes have been associated with cerebrovascular risk factors and with neurcognitive impairment in the general population. Here we examine cerebral changes in chronic kidney disease patients using whole brain and regional analysis as well as voxel-based morphometry of diffusion tensor imaging (DTI) data in comparison to normal control subjects.

METHODS: **Imaging:** Twenty seven stroke-free CKD patient (glomerular filtration rate [GFR] ranging from 15 to 53, mean 34.7±9.9 cc/min/1.73m^2) and 12 normal adult volunteers were imaged with conventional MRI and DTI. Diffusion tensor images were obtained in 12 directions at an effective b-value of 1000 s/mm^2. All imaging was performed on a 1.5T Siemens Avanto scanner using a 12 channel head-neck coil. Other imaging parameters were: FOV 23cm^2; matrix 128x128; slice thickness 2mm with no gap; 3 averages; and a TE/TR of 95/11200ms, parallel imaging (GRAPPA) with a reduction factor of 2 was used. A total of 68 axial images were acquired to cover from top of the brain to the skull base. A volumetric T1-weighted scan was obtained covering the same slices as the DTI for anatomic reference.

Data Analysis: *Whole brain white matter (WM) histogram:* For whole brain analysis, the FA maps of all patients and controls were segmented into gray matter, white matter, and CSF categories using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The segmented white matter masks were then used to generate whole brain white matter ADC and FA histograms. *Voxel Based Morphometry:* FA and ADC maps and diffusion weighted images (DWIs), with background noise suppressed, were generated using DTI task card provided by MGH (courtesy Drs. Sorensen and Benner, Massachusetts General Hospital, Boston, MA). The DWIs were used as reference for brain extraction using BET(Brain Extraction Tool), part of FSL(FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Voxel-wise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics), part of FSL. TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics. *ROI measures:* FA and ADC values were also measured in ROIs within the following regions: frontal white matter at frontal horn level, later ventricle body level and centrum semiovale level and corpus callosum (CC) at genu, splenium and body.

RESULTS: Figure 1 shows the whole brain white matter FA and ADC histograms for CKD patients and normal control subjects. Both mean and peak ADC were significantly increased ($p<0.0001$) in the CKD patients (Mean ADC = 0.77±0.06, Peak ADC =0.73±0.05) compared to normal subjects (mean ADC=0.67±0.02, peak ADC =0.66±0.02). Mean FA decreased significantly ($p = 0.015$) and such a trend was seen in peak FA ($p = 0.077$) for CKD patients (mean FA 0.43±0.04, peak FA 0.37±0.04) compared to the normal subjects (mean FA 0.45±0.01, peak FA 0.4±0.02). Figure 2 shows the FA and ADC contrast maps ($p<0.05$) between the normal subjects and the CKD patients. ADC increases were seen in multiple areas including the frontal lobe, temporal lobe, parietal lobe and corpus callosum. Although not to the same extent, these regions also showed significant reductions in FA. When the patients were further subdivided in the diabetic (n=17) and non-diabetic (n=10) groups, the diabetic group exhibited significantly reduced whole brain WM peak FA value ($p = 0.05$) compared to the non-diabetics with a similar trend seen in mean FA value.

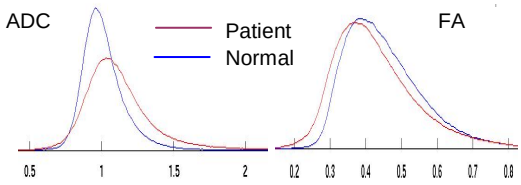

Figure 1 Whole brain white matter FA and ADC histograms.

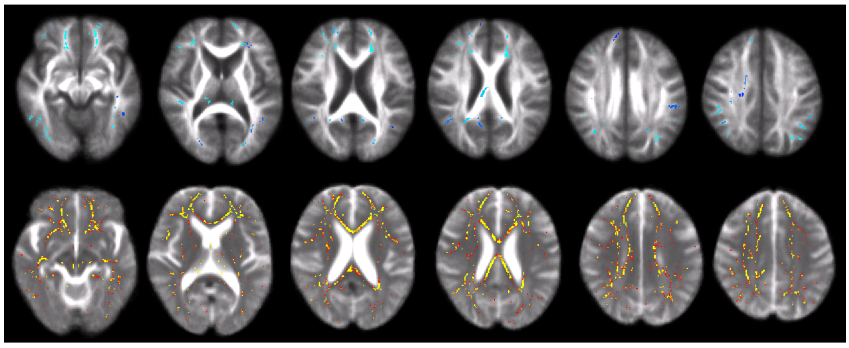

Figure 2. P-value ($p<0.05$) maps for significantly decreased FA values (upper) and significantly increased ADC values (lower) for CKD patients compare to normal controls.

However, no significant differences in the whole brain ADC measures between these two groups were observed. Regional measures showed a significant positive correlation of FA values ($p = 0.04$) with patient GFR scores in CC-Genu. Such a trend was also seen in FA in CC-splenium ($p = 0.1$). Diabetes patients also showed a significantly decreased FA value in frontal white matter at frontal horn level ($p = 0.02$) and lateral ventricle body level ($p = 0.03$) than non diabetic patients. ADC values in CC-body displayed a negative trend of correlation ($p = 0.09$) with GFR score.

CONCLUSION: To our knowledge this is the first study to utilize DTI to examine white matter changes in patients with chronic kidney disease, a population with a high cerebrovascular disease burden. In this pilot-level study, both ADC and FA values were altered globally and in various regions in CKD patients compared to normals, reflecting a disruption of white matter microstructure in CKD patients. Among CKD patients, higher GFR (indicating more preserved renal function) was correlated with lower ADC and higher FA within the corpus callosum (indicating more preserved white matter microstructure). Regional microstructural changes were also more pronounced among diabetic compared to non-diabetic CKD patients. Further research is needed to identify the underlying mechanisms which explain these white matter changes in CKD.

Reference: [1] Seliger SL et al. *J Am Soc Nephrol* 2004; 15:1904-11. [2] Kurella M et al. *J Am Geriatr Soc,* 2004; 52:1863-9.