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Longitudinal Changes in Diffusion Tensor Imaging in Hemodialysis Patients

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Abstract

Introduction: Hemodialysis patients have increased white matter and gray matter pathology in the brain relative to controls based on MRI. Diffusion tensor imaging is useful in detecting differences between hemodialysis and controls but has not identified the expected longitudinal decline in hemodialysis patients. In this study we implemented specialized post processing techniques to reduce noise to detect longitudinal changes in diffusion tensor imaging parameters and evaluated for any association with changes in cognition.

Methods: We collected anatomical and diffusion MRIs as well as cognitive testing from in-center hemodialysis patients at baseline and one year later. Gray matter thickness, white matter volume, and white matter diffusion tensor imaging parameters were measured to identify longitudinal changes. We analyzed the diffusion tensor imaging parameters by averaging the whole white matter and using a pothole analysis. 18 hemodialysis patients were included in the longitudinal analysis and 15 controls were used for the pothole analysis. We used the NIH Toolbox Cognition Battery to assess cognitive performance over the same time frame.

Findings: Over the course of a year on hemodialysis, we found a decrease in white matter fractional anisotropy across the entire white matter ($p < 0.01$), and an increase in the number of white matter fractional anisotropy voxels below pothole threshold ($p = 0.03$). We did not find any relationship between changes in whole brain structural parameters and cognitive performance.

Discussion: By employing noise reducing techniques, we were able to detect longitudinal changes in diffusion tensor imaging parameters in hemodialysis patients. The fractional anisotropy declines over the year indicate significant decreases in white matter health. However, we did not find that declines in fractional anisotropy was associated with declines in cognitive performance.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Approval Statement

All subjects gave their informed consent for inclusion before they participated in the study. The protocol was approved by the Medical College of Wisconsin Institutional Review Board.

Keywords

Hemodialysis; Kidney Disease; White Matter Integrity; Diffusion Tensor Imaging

Introduction

Patients with end-stage kidney disease treated with hemodialysis have significant cerebral atrophy noted on brain imaging. One hypothesis for these structural brain changes is due to the high prevalence of cerebrovascular disease in end-stage kidney disease patients that may result in ischemic injury that is exacerbated by the hemodialysis treatments. During the hemodialysis treatment, patients are noted to have increased circulatory stress resulting in drops in systems blood pressure which have been related to declines in cerebral blood flow.[1,2] This exposure to repetitive cerebral ischemia during the chronic, thrice weekly hemodialysis treatment may produce brain injury over time leading to cognitive decline.[2,3]

Measuring changes in brain structure may help us better understand pathophysiology of cerebral injury and degeneration in patients undergoing hemodialysis. One method for measuring structural changes in the brain is diffusion tensor imaging, which uses MRI to measure the diffusion in the brain and estimates parameters associated with cerebral integrity. These parameters are sensitive to changes in brain structure and correlate with histological changes.[4,5] Prior diffusion tensor imaging studies have shown decreased cerebral integrity in hemodialysis patients relative to controls, which has also been associated with cognitive deficits, particularly in executive function.[6,7] However, longitudinal studies have either failed to find changes in diffusion tensor imaging paramaters[8,9] or found changes in diffusion tensor imaging parameters not consistent with progression of injury.[10] In contrast to the current diffusion tensor imaging parameter understanding, Eldehni et al. found that in hemodialysis patient who had more stable hemodynamics due to use of cooled dialysate the fractional anisotropy did not change overtime in comparison to an increase in fractional anisotropy, that was seen in those with more hemodynamic fluctuation undergoing standard temperature hemodialysis, which is usually suggestive of better cerebral integrity.[10] These previous studies used standard clinical scan sequences and post processing algorithms, which might not account for diffusion tensor imaging complications that are more complex in hemodialysis patients, such as changes in cerebral water content or edema.[11–13]

In this study we use comprehensive processing techniques and novel analysis methods to test if diffusion tensor imaging is sensitive to longitudinal cerebral changes over the course of a year on hemodialysis. We also separately evaluated areas that may be more susceptible to ischemia, the cerebral watershed regions, compared to non-watershed regions to see if deficits were localized to those areas. We hypothesized that additional post-processing steps that would account for changes in cerebral water content we found find evidence of worsening cerebral integrity in the two main diffusion tensor imaging parameters (decreased fractional anisotropy, increased mean diffusivity) over a one-year period in the hemodialysis cohort. We also hypothesized that the changes in cerebral integrity would be associated with changes in cognitive test performance.

Materials and Methods

Participants

In this longitudinal study, we recruited participants with end-stage kidney disease treated with hemodialysis from Milwaukee, WI area dialysis units. Each end-stage kidney disease participant provided informed written consent to the protocol, which was approved by the Institutional Review Board at our institution. Inclusion criteria were age ≥50 years and ongoing thrice weekly conventional in-center HD. Participants also had to be on dialysis over 1 month but <2 years at enrollment. Exclusion criteria included a history of stroke, traumatic brain injury, brain tumor or surgery within the past year, non-English speaking, or diagnosis of dementia. Healthy control image data were used from a previous study;[14] diabetes and hypertension rates were not matched to the hemodialysis group. The healthy control group had the same imaging protocol as the hemodialysis cohort from a prior study, but did not have one year follow up data available.[14] The controls were used as normative data in a longitudinal pothole analysis, explained below. Image data from both the hemodialysis group and controls were processed and analyzed using the same processing pipeline, described below.

Cognitive testing

Each hemodialysis participant completed the NIH Toolbox cognition battery, which includes seven assessments that evaluate the following domains: language, attention, processing speed, executive function, working memory, and episodic memory, and three composite scores.[15] Testing was done the day after the participant's 2nd dialysis session of the week. This was to avoid the immediate changes in cognition during and immediately after a dialysis session.[16] All testing was done in a quiet room with a test administrator and completed on an iPad. The same procedure was repeated at 12 months. Only summary fluid, crystallized and total standard scores were used to correlate with brain structural measurements.

MRI

MRI was performed at baseline and a year follow-up in hemodialysis participants with the same acquisition; MRIs were only performed once in healthy controls. Every participant completed an MRI safety screen prior to the scan. T1-weighted anatomical images were acquired using an axial fast spoiled gradient recall 3D sequence (echo time = 3.2 ms, repetition time = 8.16 ms, flip angle = 12°, prep time = 450, bandwidth = 22.73, field of view = 240 mm, 156 1-mm slices, and matrix = 256 × 240). The diffusion-weighted volumes were acquired using an axial q-ball high angular resolution diffusion imaging sequence using single-shot echo-planar imaging (echo time = 72.3 ms, repetition time = 5,700 ms, b-value = 1,500 s/mm^2, 5 b0 images, 150 directions, FOV = 256 mm, 59 slices (2.5 mm), and matrix = 128 × 128).

Anatomical Image Processing

Anatomical image processing, including bias correction, skull stripping, spatial normalization, and segmentation, was completed using fMRIB software library (FSL), cat12

(http://www.neuro.uni-jena.de/cat/) and advanced normalization tools (ANTs).[17–19] Total volumes of gray matter, white matter, and cerebral spinal fluid and total intracranial volume were calculated with segmented anatomical volumes and used in further statistical analyses. Linear and non-linear registration of T1 anatomical space into Montreal Neurological Institute (MNI) 152 T1 standard space (2mm resolution) was done using ANTs.[20,21]

Diffusion Image Processing

Diffusion volumes were skull stripped and corrected for susceptibility, interslice motion, intraslice motion, volume motion, signal dropout and b-vector correction for volume motion.[22,23] Motion was calculated and saved as both absolute and relative motion between each volume. A threshold of >2 times the interquartile range of the relative motion across the group was considered an outlier and removed from the diffusion tensor imaging analyses. Linear registration from diffusion space into subject anatomical space was done using ANTs to register the mean of the b0 images to each individual T1 anatomical image.[21]

After registration was complete, the tensor model was fit in Diffusion Imaging in Python (https://dipy.org/) using the RESTORE algorithm which uses an iterative refitting of weights for nonlinear least squares to improve goodness of fit across the image and decrease the effects of motion on tensor estimation.[24,25] Fractional anisotropy and mean diffusivity were then calculated from the tensor fits to create individual volumes for each measure.

Whole White Matter Analysis

Partial volume voxels were removed from white matter masks to improve estimates of white matter diffusion parameters. Cerebral spinal fluid and gray matter segmentations from the anatomical pre-processing were each increased by one voxel. Each of the dilated masks were subtracted from the white matter masks to reduce partial volume effects from each tissue type, producing the final white matter mask for all further diffusion tensor imaging analysis. Fractional anisotropy and mean diffusivity were averaged within the final white matter masks as primary outcome variables for statistical testing. Example fractional anisotropy white matter images overlayed on standard MNI space in controls, hemodialysis baseline and hemodialysis follow-up participants are depicted in Figure 1.

Vascular Territory Border Zone Analysis

To explore the changes in watershed regions of the white matter, we used a vascular territories atlas from Schirmer et al. 2019 (http://www.resilientbrain.org/data.html), to get the bilateral anterior, middle, and posterior cerebral artery vascular territories.[26] Each of the six vascular territory masks were dilated by three voxels, the overlapping regions between the dilated masks were considered the vascular territory border zone watershed mask in MNI space. The standard watershed mask was transformed into subject T1 anatomical space and masked by individual subject white matter masks obtained during the whole white matter analysis as outlined above. A non-watershed white matter mask was made by subtracting the resulting watershed white matter mask from the whole white matter mask. Fractional anisotropy and mean diffusivity were then averaged within the resulting watershed and non-watershed white matter masks.

Pothole Analysis

We conducted a pothole analysis to detect non-spatially overlapping deficits (as opposed to assuming similar regions of deficits between participants, as is done in region of interest analysis) to compare the hemodialysis patients to controls at baseline and at one year follow up.[27] First, we transformed all fractional anisotropy and mean diffusivity maps into standard MNI space and took the mean and standard deviation of the healthy control group at every individual voxel. We then calculated the z-score for each voxel in each subject in both groups relative to the reference group mean and standard deviation. To identify abnormal voxels, we used a threshold of $z < -2.26$ for fractional anisotropy voxels and $z > 2.26$ for mean diffusivity voxels in the hemodialysis group and a threshold of $z < -1.89$ for fractional anisotropy and $z > 1.89$ for mean diffusivity voxels in the healthy controls group. Additionally, sign flipped thresholds were used to identify fractional anisotropy voxels $z > 2.26$ and mean diffusivity voxels $z < -2.26$ in the hemodialysis group. Note that separate thresholds were used for each group in accordance with the Disco-Z testing paradigm that corrects for the size of each group in estimating z threshold for abnormality.[27] White matter masks were additionally transformed into standard space, summed and threshold so that only voxels that were identified as white matter in every participant were considered. Abnormal voxels were then counted within those masks and used as dependent variables for additional statistical testing. Example pothole images in controls, hemodialysis baseline and hemodialysis follow-up participants are depicted in Figure 2.

Statistical Analysis

All longitudinal testing between baseline and one year follow-up was done using the paired Wilcoxon signed rank test. $p < 0.05$ was considered significant for all statistical testing and no multiple comparisons correction was used due to small sample size. Pearson correlation was used to evaluate the relationship between change in brain imaging parameters and change in summary cognitive test scores.

Results

Participants

We recruited 50 hemodialysis participants in total; of those, 37 completed a baseline MRI scan and 24 completed both a baseline and year follow-up MRI. One participant was removed for prior stroke, and one was removed due to prior brain surgery to remove an abscess with resulting distortion. Furthermore, three hemodialysis participants were removed from both the baseline and longitudinal analyses due to excessive motion during MRI data collection and one was identified as an outlier in diffusion tensor imaging measure changes post-hoc leaving 18 hemodialysis participants for the longitudinal analysis. Data from 15 healthy age-matched controls who had undergone MRI with the same parameters for a prior study were used to identify abnormal hemodialysis patient fractional anisotropy and mean diffusivity voxels.[14] The age of the age-matched controls was 62.3 ± 7.5 years, compared to the hemodialysis participants with mean age of 65.4 ± 6.5 years ($p = 0.22$) and 53.3% of controls were male compared to 72.2% of hemodialysis participants ($p = 0.26$). For the 18 hemodialysis participants included in the final longitudinal analysis, median follow-up was 371 days. hemodialysis patient information is summarized in Table 1.

Gray and White Matter Volumes

Our hemodialysis cohort had a non-significant longitudinal decrease gray matter (-0.05 ± 0.1 mm, p = 0.053, Figure 3). There was no significant group change in white matter relative volume (-0.08 ± 1.2%, p = 0.81).

Whole White Matter Analysis

Hemodialysis participants demonstrated longitudinal changes in the diffusion tensor imaging parameter of fractional anisotropy. Longitudinally, whole brain white matter fractional anisotropy significantly declined in hemodialysis participants (-0.0066 ± 0.0078, p = 0.03, average percent change = −1.5%) as shown in Figure 4. No significant changes in whole white matter mean diffusivity was noted (p=0.83). We also examined diffusion tensor imaging changes in watershed white matter areas, regions that may be more vulnerable to ischemic injury as they are at the end blood supply of the distal branches of two arteries vs non-watershed regions. hemodialysis participants showed evidence of white matter changes in both the watershed and non-watershed white matter regions. Supplementary Figure 1 shows the watershed analysis with fractional anisotropy significantly decreased ($p < 0.01$, median change = −0.0058) while mean diffusivity did not significantly change (p = 0.96). Supplementary Figure 2 shows the results of the non-watershed analysis; fractional anisotropy was significantly decreased ($p < 0.01$, median change = −0.0086) while mean diffusivity did not significantly change (p = 0.81). The difference in effects between watershed and non-watershed regions for longitudinal fractional anisotropy decline was small, but the watershed changes were greater than non-watershed changes ($Z_{watershed} = -2.68$, $Z_{non\text{-}watershed} = -2.59$).

Pothole Analysis

Longitudinally, there was a significantly greater number of decreased fractional anisotropy voxels (1.1 ± 2.2%, p = 0.03) and a trend in the number of increased mean diffusivity voxels (1.0 ± 2.7%, p = 0.09); no changes in the number of increased fractional anisotropy voxels (0.2 ± 2.7%, p = 0.78) or number of decreased mean diffusivity voxels (0.1 ± 0.6%, p = 0.59) were detected as shown in Figure 5.

Cognitive Score Changes and Correlation

The change in cognitive test scores was calculated as 12-month score minus baseline score, with a negative change indicating decline in cognitive performance. There was no significant decline in the cognitive test score over the 12 months. No changes in cognitive scores significantly correlated with changes in diffusion tensor imaging parameters.

Discussion

In this study using comprehensive processing techniques, we found a decrease in parameters of white matter integrity over the course of one year in patients on HD. Specifically, we used methodology targeted to improve accuracy of diffusion tensor imaging measures and detected a decrease in whole brain averaged fractional anisotropy and a higher number of decreased fractional anisotropy voxels from baseline to 12 months indicative of longitudinal deterioration of white matter integrity in the hemodialysis cohort. However, we did not find

that the changes we detected in white matter integrity were related to changes in cognitive performance. We also evaluated vascular watershed based cerebral regions and demonstrated that deficits do not localize to specific cerebral regions within the hemodialysis cohort but are likely unique to each individual.

Longitudinal Changes in Hemodialysis cohort

We found significant changes in diffusion tensor imaging parameters after one year on hemodialysis. Non-significant decrease in gray matter thickness indicates potential cortical atrophy in hemodialysis patients, the decrease of 0.05 mm in a year is 0.046 mm greater than previous published normal age declines, indicating cortical atrophy is accelerated in hemodialysis patients.[28] These changes included significant declines in whole white matter fractional anisotropy, watershed white matter fractional anisotropy, non-watershed white matter fractional anisotropy, and an increase in the number of decreased fractional anisotropy voxels. These changes are consistent with a decrease in cerebral integrity over the one-year period. We did not observe a change in overall white matter mean diffusivity, watershed white matter mean diffusivity, or non-watershed white matter mean diffusivity. However, there was an increasing trend of the number of mean diffusivity voxels above the threshold. While we did not collect longitudinal control data to compare normal aging with hemodialysis patients, two previous studies found about a −0.3% annual change in global fractional anisotropy for normal aging, much less than our −1.5% change in global fractional anisotropy, indicating an accelerated decline in hemodialysis patients.[29,30] We did not find any significant change in the cognitive test scores from baseline to 12 months for the cohort but there was significant variation with some participant showing decline and some stable or even improving. It is also unclear if 12 months is long enough to detect changes in cognition that may occur over the long term. Nor did we find a correlation between changes in cognitive tests scores and changes in brain white matter integrity. These findings demonstrate complex etiology of cognitive decline and its relationship to brain structure.

Watershed and Non-Watershed White Matter Deficits and Changes

Fractional anisotropy in watershed areas declined over the course of a year. The watershed areas may be more sensitive to vascular dysfunction and prone to incurring white matter lesions.[31,32] However, we found non-watershed areas also had declining fractional anisotropy in hemodialysis patients longitudinally. The effect of longitudinal decline was greater in watershed areas, however not by much ($Z_{watershed} = -2.68$, $Z_{non\text{-}watershed} = -2.59$). These declines could indicate new injury due to hemodialysis. New brain injury in regions susceptible to vascular injury supports a vascular hypothesis of hemodialysis -related neurodegeneration. However, this interpretation is complicated by non-watershed areas also declining longitudinally, suggesting that areas or damage may vary among hemodialysis patients. Further study is required to better understand the decline in microstructural integrity in watershed areas of the white matter in hemodialysis patients.

Key Methodological Considerations

We believe that some key methodological approaches were critical to detecting longitudinal changes in white matter integrity in hemodialysis patients. diffusion tensor imaging is known to be affected by motion and partial volume effects when estimating outcome

variables.[25,33,34] Our first motion mitigating step was to estimate mean relative motion from co-registration of diffusion MRI direction volumes, then applying the motion corrections to our b-vectors file.[23] Second, we used the RESTORE diffusion tensor imaging fitting method which reduces motion effects by algorithmically identifying outlier diffusion directions and reducing their effect on tensor estimation by reweighting nonlinear least squares fitting.[25] Finally, we used the motion estimate to determine outliers in each group and eliminate them from statistical testing. Additionally, partial volume correction was achieved by dilating gray matter and cerebral spinal fluid masks to restrict white matter masks when estimating whole white matter and in the pothole analysis estimates of deficits. While the steps taken in this study are not the only way to mitigate these errors in estimating diffusion tensor imaging parameters, we believe consideration and correction of these factors is required to correctly identify white matter degeneration with diffusion tensor imaging. In addition, we think it is important to utilize the pothole analysis method as an additional method to both confirm findings and evaluate changes in individual voxels that may occur but could be averaged out when looking at whole brain or specific regions in a group analysis. We did not find conclusive evidence that certain regions are more affected than others across participants but that each participant's localized changes may be unique, indicating that the pothole analysis, which is regionally non-specific, could be more illustrative of brain structural decline than a region of interest analysis.

Limitations

Our small sample size may have reduced our ability to identify statistically significant differences and changes in individual white matter tracts and our multiple comparisons may have yielded false positive results. Further, the heterogeneity of comorbidities in our group was unable to be controlled for by multi-factorial analyses due to our small sample size. Since diffusion tensor imaging only models a single fiber population, the tensor model is limited to describe microstructural changes in regions with crossing tracts, where a decrease in number of fibers can result in an increase in fractional anisotropy.[35] Further a single shell acquisition is relatively insensitive to differences in diffusion in intra- and extracellular compartments which may be important due to the greater variation in intra and extra-cellular water content that could be more significant in hemodialysis patients to quantify microstructural integrity than those with normal kidney function. Multi-shell acquisition paired with better tissue modeling could potentially correct for any artificial increases in fractional anisotropy due to crossing fibers and model contributions of different compartments to diffusion better. One such model, the mean apparent propagator can estimate parameters that are sensitive to axonal dispersion and compartment size, effectively accounting for changes due to differences in the number of fiber populations and intra- and extracellular compartment diffusion differences.[36,37] Additionally, we did not collect age-matched control longitudinal data, which means that the declines fractional anisotropy in hemodialysis participants may not be distinct from declines that would occur in an age-matched group over the course of a year. However, the decline in fractional anisotropy that we noted was much larger than previously noted age-related annual decline.[29,30] The lack of longitudinal data in controls limited our pothole analysis, since the idealized analysis would include longitudinal changes in the control group as well.[27] Finally, due to difficulties

with recruitment and dropout our sample was mostly male (72.2%), further study is required to see if there is a sex effect in brain structural decline in hemodialysis patients.

Conclusion

We found differences in diffusion tensor imaging parameters between controls and hemodialysis participants and longitudinal changes over the course of one year in hemodialysis participants. Longitudinally, fractional anisotropy decreased in the whole white matter indicating possible decreased axonal density in addition to the baseline cellular atrophy. This is the first known study to document longitudinal neuroimaging decline in hemodialysis patients using diffusion tensor imaging. Using these sensitive diffusion tensor imaging parameters to monitor cerebral changes can help determine the underlying pathophysiology of cerebral injury in hemodialysis patients. We did not find that the change in diffusion tensor imaging parameters was associated with cognitive changes but that may be due to multiple factors at play in this medically complex patient population. In the future diffusion tensor imaging may be used to identify risk factors for cerebral injury and help inform effectiveness of therapies aimed at reducing cerebral injury in this susceptible population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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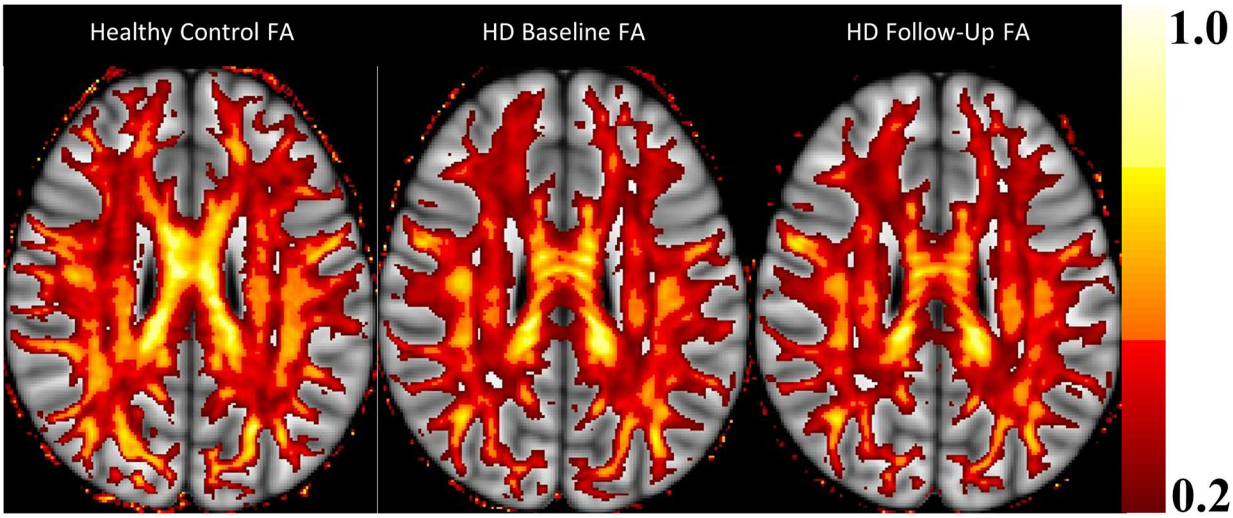

Figure 1.

Example of representative fractional anisotropy maps threshold from 0.2–1.0. From left to right, Age-matched control, baseline hemodialysis patient and follow-up hemodialysis patient.

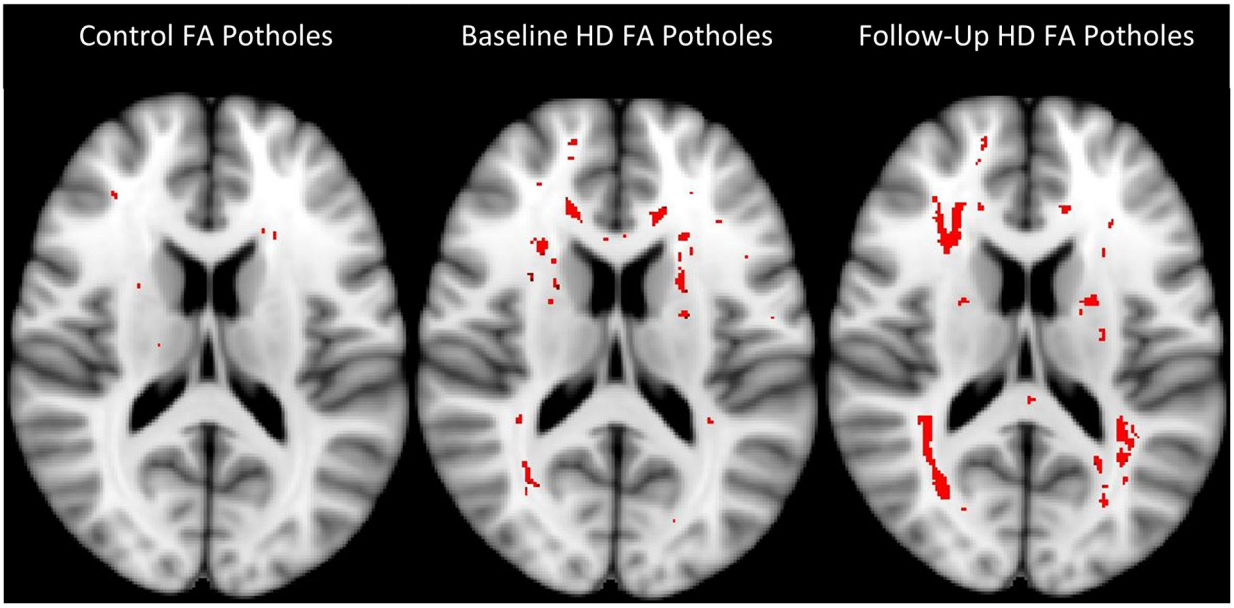

Figure 2.

Example of representative fractional anisotropy pothole maps below threshold ($Z_{control}$<-1.8, $Z_{Hemodialysis}$<-2.1). From left to right, Age-matched control, baseline hemodialysis patient and follow-up hemodialysis patient.

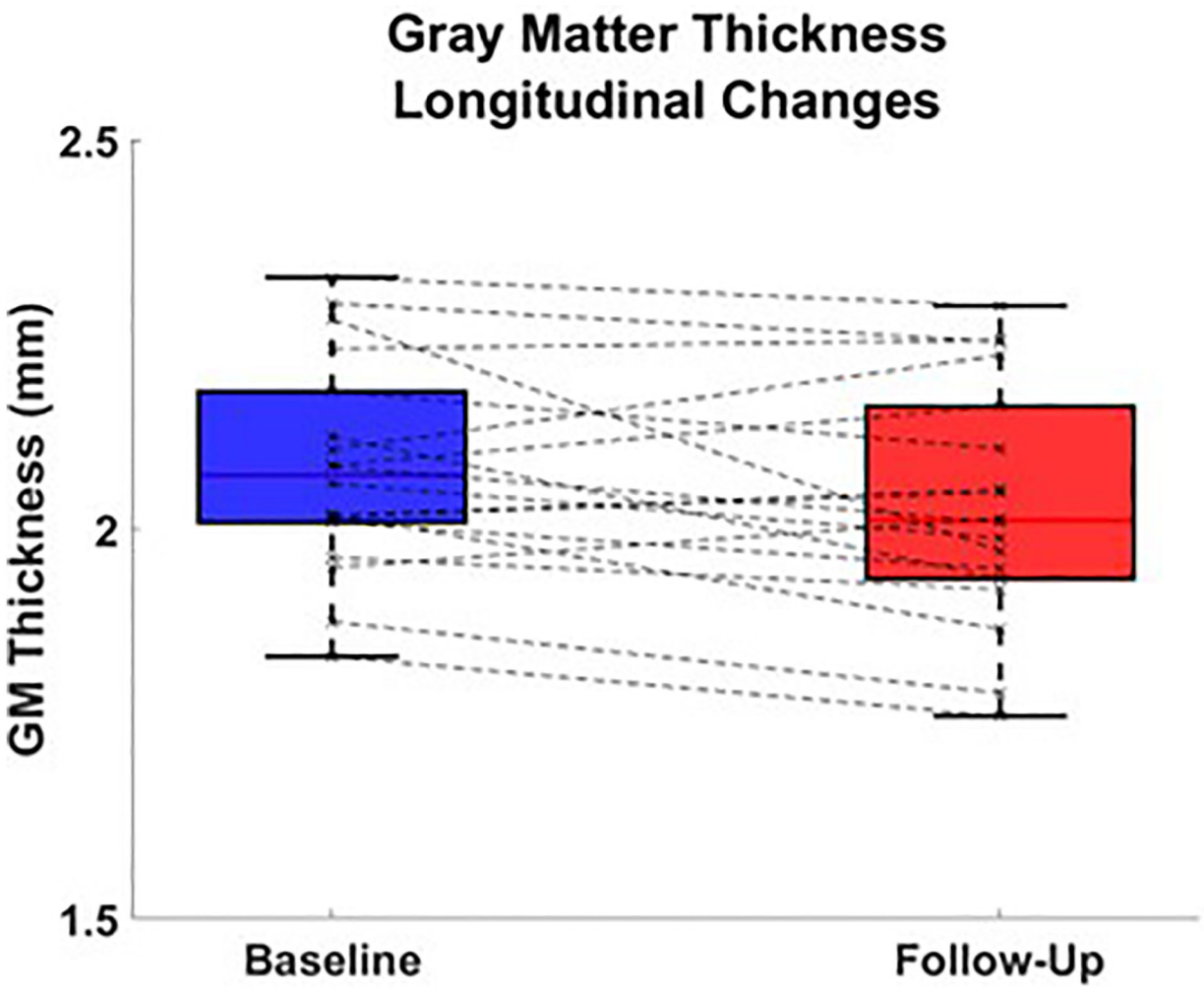

Figure 3.
Gray matter thickness longitudinal changes over the course of a year on hemodialysis (p=0.053).

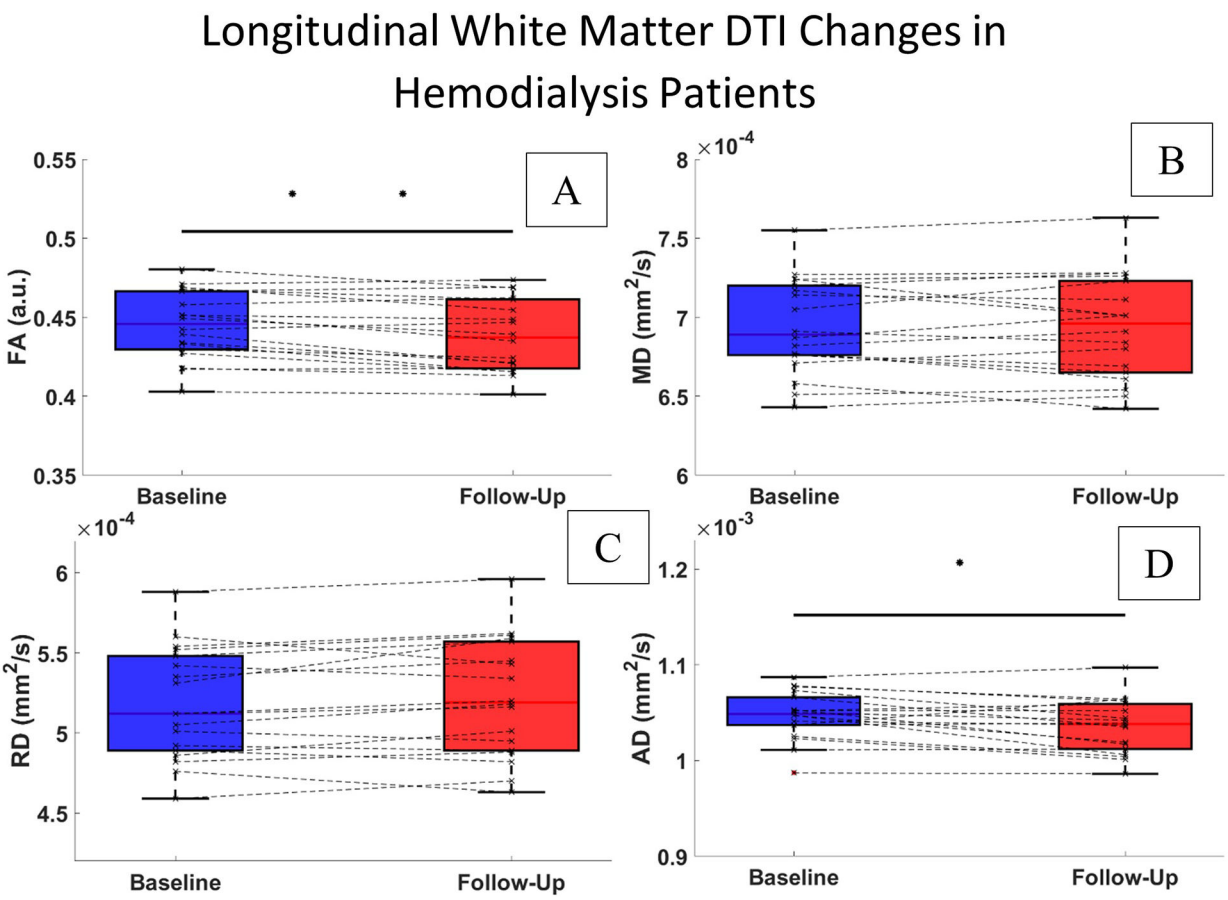

Figure 4.

Diffusion tensor imaging longitudinal changes in hemodialysis participants over the course of the year on hemodialysis fractional anisotropy (A, p=0.006), mean diffusivity (B, p=0.83), radial diffusivity (C, p=0.11) and axial diffusivity (D, p=0.02).

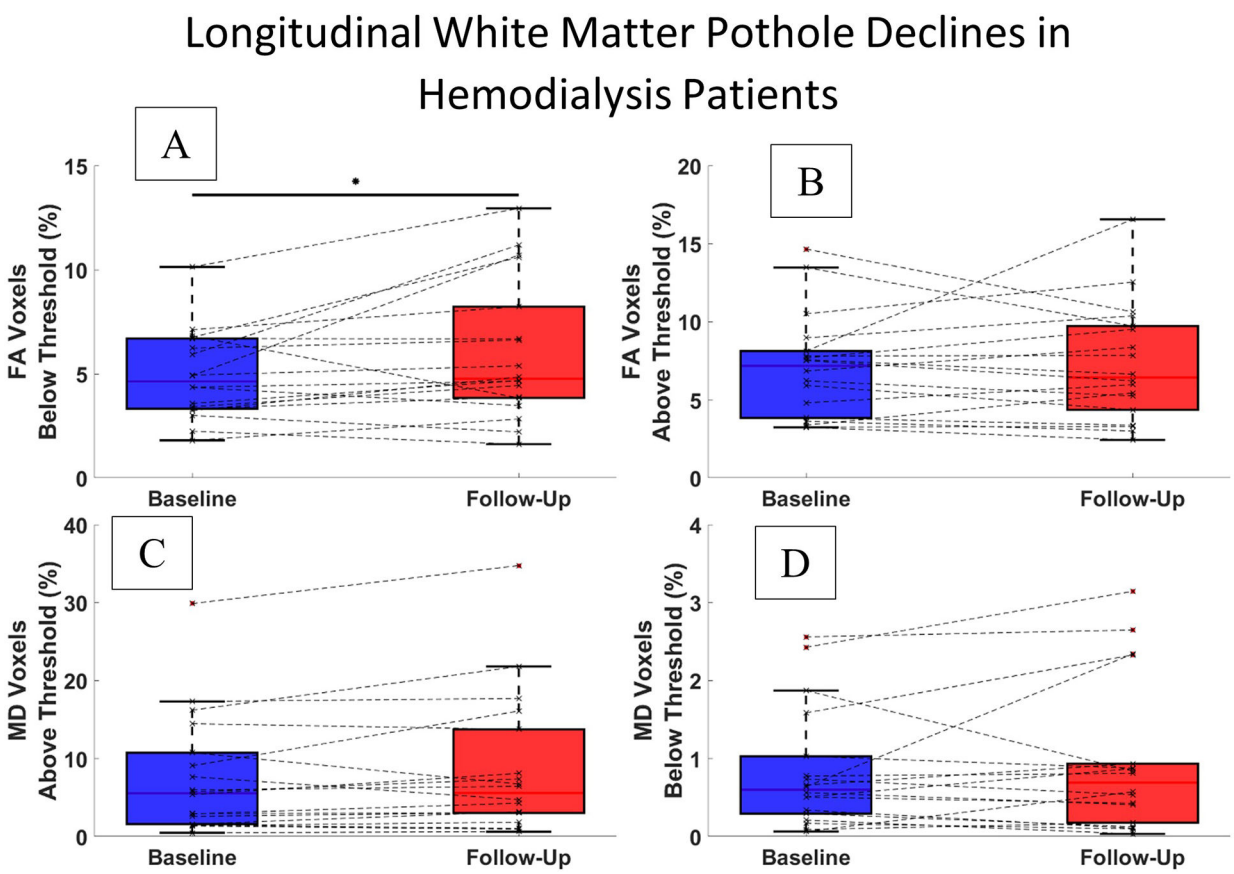

Figure 5.

Pothole analysis changes in hemodialysis participants over the course of one year on hemodialysis fractional anisotropy voxels below threshold (top left, p=0.03), fractional anisotropy voxels above threshold (top right, p=0.78). More fractional anisotropy voxels below threshold at follow up indicates worsening cerebral integrity. Mean diffusivity voxels above threshold (bottom left, p=0.09), and mean diffusivity voxels below threshold (bottom right, p=0.59). More mean diffusivity voxels above the threshold at follow up indicates worsening cerebral integrity.

Table 1.

Subject information table.

	Hemodialysis Participants (n=18)	***Healthy Controls (n=15)***	***p value***
Age (SD)	65.4 (6.5)	62.3 (7.5)	0.22
Male (%)	72.2%	53.3%	0.26
Hemodialysis Duration (Months at baseline)	7.9 ± 6.4	N/A	--
Comorbidities		N/A	--
Hypertension N (%)	14 (77.8)		--
Diabetes N (%)	12 (66.7)		--
CAD N (%)	6 (33.3)		--
PVD N (%)	2 (11.1)		--
CHF N (%)	6 (33.3)		
Race			
Caucasian	7 (38.9)		
African American	8 (44.4)		
Other	3 (16.7)		
Cause of ESRD		N/A	--
Diabetes	10 (55.6)		
Hypertension	6 (33.3)		
Other	2 (11.1)		
Educational level			
High school or less	8 (44.4)		
Some college/Bachelor's degree	6 (33.3)		
Advanced degree	4 (22.2)		

Abbreviations: CAD (coronary artery disease), PVD (peripheral vascular disease), CHF (congestive heart failure), and ESRD (end-stage renal disease).