Investigating the Relationship between Cerebral Blood Flow and Cognitive Function in Hemodialysis Patients

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ABSTRACT

Background The immediate and longer-term effects of hemodialysis on cerebral circulation, cerebral structure, and cognitive function are poorly understood.

Methods In a prospective observational cohort study of 97 adults (median age 59 years) receiving chronic hemodialysis, we used transcranial Doppler ultrasound to measure cerebral arterial mean flow velocity (MFV) throughout dialysis. Using a well validated neuropsychological protocol, we assessed cognitive function during and off dialysis and after 12 months of treatment. We also used brain magnetic resonance imaging (MRI) to assess atrophy, white matter hyperintensities (WMHs), and diffusion parameters, and tested correlations between MFV, cognitive scores, and changes on MRI.

Results MFV declined significantly during dialysis, correlating with ultrafiltrate volumes. Percentage of decline in MFV correlated with intradialytic decline in cognitive function, including global function, executive function, and verbal fluency. At follow-up, 73 patients were available for repeat testing, 34 of whom underwent repeat MRI. In a subgroup of patients followed for 12 months of continued dialysis, percentage of decline in MFV correlated significantly with lower global and executive function and with progression of WMH burden (a marker of small vessel disease). Twelve of 15 patients who received renal transplants during follow-up had both early and follow-up off-dialysis assessments. After transplant, patients' memory (on a delayed recall test) improved significantly; increased fractional anisotropy of white matter (a measure of cerebral diffusion) in these patients correlated with improving executive function.

Conclusions Patients undergoing hemodialysis experience transient decline in cerebral blood flow, correlating with intradialytic cognitive dysfunction. Progressive cerebrovascular disease occurred in those continuing dialysis, but not in transplanted patients. Cognitive function and cerebral diffusion improved after transplant.

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Cognitive impairment is highly prevalent in those on hemodialysis (HD); up to 70% in an unselected cohort demonstrated cognitive impairment.[1] The etiology of cognitive impairment in HD is multifactorial: dialysis is associated with profound metabolic abnormalities, chronic inflammation, and oxidative and hemodynamic stressors. However, two important findings support the theory that cerebrovascular disease is the primary driving force. Specifically, dialysis preferentially induces deficits in executive function,[2–4] a pattern traditionally observed early in vascular cognitive impairment but only a later complication of other dementias such as Alzheimer disease,[5] and that more regular frequent dialysis does not improve cognitive function,[6] whereas renal transplantation can.[7]

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The frequency of cerebrovascular disease in people with ESRD is up to ten-fold greater[8] compared with the general population and mortality rates approximately three-fold greater.[9] Although conventional stroke risk factors such as hypertension are ubiquitous in ESRD and partly responsible, it is likely renal-specific factors contribute to this inordinate difference. For example, there is increasing evidence that both initiation[10] of, and exposure[11,12] to HD for ESRD is associated with stroke, although the mechanism is not fully explained. Interestingly, this risk appears to be reduced by receiving a renal transplant.[13]

The concept that HD can induce cerebral injury is supported by previous studies. Two recent prospective European studies have demonstrated evidence of decreased intradialytic cerebral perfusion,[14,15] relating this to dialysis-related factors such as intradialytic hypotension or ultrafiltration volume. Alterations in cerebral structure are also described. For example, white matter hyperintensities (WMHs), a marker of small vessel disease, are present incidentally in 11%–21% of the general population aged around 64 years,[16] whereas this rises to 52% in those on HD.[17] Increasing WMH burden is associated not only with stroke,[18] but also cognitive impairment.[1]

Real-time, noninvasive measurement of cerebral blood flow is possible using transcranial Doppler (TCD) ultrasound, a noninvasive, inexpensive tool that is well tolerated and capable of performing repeated measurement throughout a dialysis session. Our primary hypothesis is that cerebral blood flow, measured by TCD, is reduced by HD and correlates with a decline in intradialytic cognitive function. Second, we hypothesize that a reduction in cerebral blood flow is capable of reducing longer term cognitive function, inducing ischemic damage as measured by WMH burden and that progressive ischemia on brain magnetic resonance imaging (MRI) at 12 months will correlate with progressive cognitive decline.

Therefore, we present a prospective investigation of real-time dialysis related cerebral blood flow, cognitive function on and off dialysis and brain MRI findings over a 12-month follow-up of continuous treatment for ESRD.

The primary aim of this study was to explore whether HD was associated with changes in cerebral blood flow and determine whether these changes relate to intradialytic cognitive dysfunction. Our secondary aims focus on (*1*) assessment of longitudinal changes in cerebral structure and function using brain MRI and cognitive assessment at baseline and after 12 months, correlating this to alterations in cerebral blood flow; and (*2*) to compare cognitive outcomes at follow-up in those who remain on HD and those who receive a renal transplant.

METHODS

Recruitment began in April 2015 and the first visit took place on June 3, 2015. All visits were completed by July 7, 2017.

Significance Statement

Recent data suggest that hemodialysis can reduce cerebral blood flow, and many assume—given the reported propensity of dialysis-related cognitive impairment to present as executive dysfunction—that alterations in cerebral circulation are implicated in cognitive decline. In this prospective observational study, using real-time vascular imaging (to measure cerebral blood flow) and neurocognitive assessments during a single dialysis session and after 12 months of ongoing treatment, the authors demonstrate a correlation between dialysis-related decrease in cerebral blood flow and measures of executive function. Brain imaging showed an increase in markers of small vessel disease in those remaining on dialysis. In transplanted patients, cerebral diffusion (and cognitive function) improved after transplant. These findings point to reduced cerebral blood flow as a mechanism of cerebral injury in hemodialysis.

Participants were asked to attend three visits over a 12-month follow-up period. Two visits took place within the first month: one during their routine dialysis treatment (intradialytic assessment), and a second on a nondialysis day (interdialytic assessment). A repeat nondialysis assessment was performed at 12 months.

Study Participants

All adult patients aged 18–85 years inclusive, receiving hospital HD for ESRD at the Glasgow Renal and Transplant unit were considered. We approached all adults who were expected to remain on hospital HD for ≥6 months. Exclusion criteria were inability to consent, poor comprehension of English language, a prior diagnosis or neuroimaging evidence of cerebrovascular disease, and prior diagnoses of cognitive impairment. Neuroimaging evidence of cerebrovascular disease included all those with prior ischemic or hemorrhagic stroke, in addition to those with evidence of small vessel disease. Written informed consent was completed for each participant. This study was approved after ethical review by the West of Scotland Research Ethics Committee 5 (reference REC 15/WS/0024), and registered on Clinicaltrials.gov under identifier NCT02393222.

Clinical Variables

Patient demographics were acquired from the electronic patient record. Duration of ESRD was calculated in years from date of first RRT commencement until date of first visit. Pre- and post-BP and ultrafiltration volumes were recorded and presented as an average of the last six readings. Laboratory values utilized the three latest results preceding their first visit. During the intradialytic assessment visit, BP and weight were recorded before and after dialysis, and ultrafiltration rate was calculated as volume of fluid removed divided by duration of session.

Dialysis Schedule

This observational study was designed to assess the effect of dialysis in a "real-world" cohort, without intervention or

interference with each participant's routine treatment schedule. All participants underwent their routine prescribed dialysis treatment. The median duration of dialysis was 4 (interquartile range [IQR], 4–4.5) hours, with median blood flow rates of 300 (IQR, 287.5–305.0) ml/min. Dialysate temperature throughout all units was set at 36.5°C. The first dialysis session after the "long gap" was completely avoided. All Doppler readings were performed with patients sitting upright. It was essential that patients remained comfortable during their cognitive assessments, therefore food and rest periods were permitted.

Cognitive Assessments

Assessments were carried out by medical and nursing staff after training in appropriate use of the assessments by an experienced psychologist. At the midpoint of our study, retraining was performed to ensure consistency of assessment. Intradialytic testing was performed within the first 2 hours of dialysis, omitting the first 15 minutes for initial physiologic monitoring and routine nursing checks. All physical assessment as part of routine dialysis was performed manually, by usual dialysis nursing staff. The dialysis unit staff were aware to keep interruption to a minimum and cognitive testing was halted during scheduled BP checks. Where practically possible, to account for environmental effects on cognitive function, participants returned to the dialysis unit for their interdialytic assessment.

A modified 30-minute National Institute of Neurologic Disorders and Stroke-Canadian Stroke Network neuropsychological battery was used to assess cognitive function.[19] This well validated protocol was chosen because of its feasibility, acceptability and increased sensitivity at detecting vascular cognitive impairment. It consists of verbal and written assessments of multiple cognitive domains. Specifically, we included the Montreal Cognitive Assessment (MOCA), using the accepted cut-off of <26 to define cognitive impairment. Verbal fluency was assessed using phonemic and semantic fluency, executive function using Trail-Making tests A and B (TMTA, TMTB) and the letter-digit substitution test (LDST) and auditory–verbal memory *via* the Hopkins Verbal Learning Test (HVLT). Finally, an assessment of mood was performed using the Center for Epidemiologic Studies Depression Scale. Further information on each assessment is described in Supplemental Table 1. The MOCA was used to quantify "cognitive impairment," therefore presented as an education adjusted score (addition of one for those with 12 years or less of education). All other scores are presented as raw, unadjusted data.

In an attempt to blunt possible learning effects, all visits were held a minimal 14 days apart. Further, we used versions 7.1, 7.2, and 7.3 of the MOCA and HVLT 1, 2, 5, and 6 at differing visits throughout the study.

In cases where writing was not possible (for example, a participant's inability or unwillingness to move their dominant arm during dialysis; $n=9$), the MOCA-blind method was used, adjusting the cut-off for cognitive impairment <18, and the verbal LDST was performed.

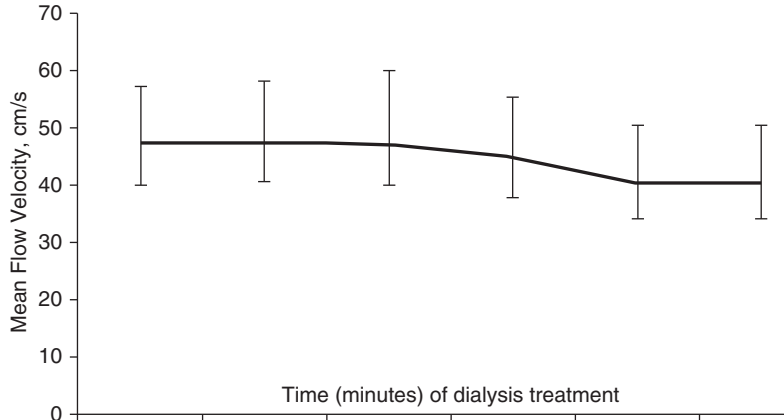
Imaging

After training from a research neuro-sonographer, all TCD ultrasound was performed by one operator (M.D.F.). Bilateral insonation of the middle cerebral arteries *via* trans-temporal windows was attempted in all patients during their intradialytic visits using the ST3 Transcranial Doppler Spencer Technologies TCD (Redmond, WA) with Power M-Mode 150. Measurements were performed with a sample of 6–9 mm and 2-MHz probes held *in situ* using a Marc600 head frame. Participants were asked to wear this throughout their dialysis session. Power began at 100 mW/cm^2 power and was reduced to the lowest possible setting for patient comfort. TCD recordings started at 50 mm of depth and adjusted to achieve the clearest possible signal. In participants with bilateral temporal windows, a median value was calculated for analyses. Recording were taken approximately 15 minutes before commencing dialysis, at set time intervals throughout dialysis and within 30 minutes of completion (Figure 1). Change in mean flow velocity (MFV) was calculated as the reading at 30 minutes after completion minus the reading 15 minutes before commencing dialysis.

Brain MRI was performed in a subset of patients using 3-T MRI Siemens research scanners (MAGNETOM Verio or PRISMA; Siemens Healthcare, Erlangen, Germany), allocated randomly as the first 40 participants that consented to the study willing and with no contraindications to MRI. All follow-up imaging was performed on their original scanner to allow direct comparison. T1, T2, fluid attenuated inversion recovery, and diffusion tensor imaging sequences were used to determine markers of atrophy (determined by change in volume of cortical gray matter, normal-appearing white matter, and supratentorial cerebrospinal fluid volumes), WMH burden, and cerebral diffusion, calculated as mean diffusivity (MD) and fractional anisotropy (FA).

Image Analyses

MRI results were analyzed using volumetric analyses software. The first step in automated extraction of WMH volumes was to estimate the white matter area in each participant using atlas-based segmentation. A probability map of white matter was previously created from 313 volunteers aged 18–96 years,[20] and registered to each participant using nonlinear (diffeomorphic) registration to provide an initial estimate of white matter in each individual.[21] Hyperintense outliers were identified on T2 fluid-attenuated inversion recovery by transforming each voxel to a standard (z) score.[22] Voxels with $z \geq 1.5$ and within the estimated white matter area were initially defined as WMH. Final WMH estimates were defined by three-dimensional Gaussian smoothing to reduce noise and account for partial volumes around WMH edges. Automatic WMH estimates were visually checked and stroke infarcts masked by a trained image analyst following STRIVE guidelines.[23] Normal-appearing tissues, including cortical gray matter, subcortical gray matter, cerebral normal-appearing white matter, and supratentorial cerebrospinal fluid, were segmented using



	–15	15	30	90	180	+30
Median MFV, cm/s	47.38	47.38	47.00	45.00	40.25	40.75

Figure 1. Haemodialysis related decline in cerebral mean flow velocity The change in MFV during dialysis session (n=82), is presented as a median value and IQR (error bars). TCD recordings were taken prior, during, and after completion of dialysis, demonstrating a significant decline in MFV after dialysis; weighted GEE $P<0.001$.

population-specific tissue probability maps, within-patient T1 intensity data, and adjoining voxel data. Normal-appearing tissue segmentations were checked and edited in the same manner as WMH.

Measures of cerebral diffusion included FA and MD that were calculated from the eigenvalues (magnitude of water movement in each diffusion direction) obtained with diffusion MRI. The BrainSuite Diffusion Pipeline[24,25] corrected geometric distortions in diffusion images and coregistered diffusion and structural images. FA and MD were calculated in regions of WMH and normal-appearing white matter.

Change in Modality of RRT

The primary aim of our study is to observe the effect of HD treatment on cerebral function and structure. However, we acknowledge that many patients suitable for recruitment may be listed for renal transplantation. Therefore, patients who remained on HD and those who received a renal transplant remained under follow-up. Death, patient request, or use of peritoneal dialysis resulted in withdrawal from the study. A flow chart outlining recruitment, follow-up, and testing is available in Supplemental Figure 1.

Statistical Analyses

Baseline demographic variables are presented as medians and compared using Mann–Whitney U or chi-squared tests, as appropriate.

Primary Analyses

Our primary aim was to describe alterations in cerebral blood flow and correlate this with intradialytic cognitive variation. Thus, MFV is presented as a median of MFV of all patients, demonstrating the change of MFV throughout the dialysis session. We applied a weighted generalized estimating equation (GEE) to model change in MFV, which had small amounts of missing data missing at random (Supplemental Table 2). Cognitive scores are paired data, comparing either on or off dialysis or again at 12 months follow-up, thus the Wilcoxon signed-rank test was used. Correlation between percentage of decline in MFV, dialysis-related variables, and change in cognitive score were performed using Spearman rank correlation. Multiple cognitive tests were correlated against change in MFV. To account for multiple comparison errors, we have provided both the Bonferroni and false discovery rate correction, highlighting significant values within each table. Further details are provided in Supplemental Tables 3 and 4.

Secondary Analyses

At follow-up the cohort was divided into those remaining on HD and those with a renal transplant for comparison. Cognitive assessments off dialysis were compared at 0 and 12 months using Wilcoxon signed-rank test, and correlation with baseline percentage of decline in MFV was assessed using Spearman rank correlation. Changes in MRI findings at 0 and 12 months are also paired and were compared using Wilcoxon signed-rank test and correlated with changes in cognitive assessment as above. Selected correlation plots are available in Supplemental Figures 2–5.

Statistical analyses were performed on SPSS version 24 (IBM, Armonk, NY) and the GEE was implemented using the "PROC GEE" statement in SAS version 9.4 (2002–2012; SAS Institute Inc.).

Power Calculations

To assess cognitive function, we calculated 73 patients would be required to show that a decline in HD, on the basis of published baseline ranges of a mean rescaled executive function of 8.7 (SD 2.8)[3] and assuming a decline of 1 during follow up, with an SD of 3. To allow for a 25% dropout rate, we aimed to recruit 97 patients.

Table 1. Demographics of the study cohort, split by presence or absence of mild cognitive impairment using MOCA score <26 on baseline nondialysis day assessment (*n*=88)

Characteristic	No Cognitive Impairment	Cognitive Impairment	All	*P* Value
Median age, yr [IQR]	58 [49–66]	58 [51–67]	58 [50.5–66.5]	0.61
Women, *n* [%]	20 [44.4]	15 [34.9]	35 [39.8]	0.36
Active on transplant waiting list, *n* [%]	20 [44.4]	17 [39.5]	37 [38.6]	0.64
Ethnicity, *n* [%]				0.96
European	43 [95.6]	41 [95.3]	84 [95.5]	
Asian	2 [4.4]	2 [4.7]	4 [4.5]	
Primary renal diagnosis, *n* [%]				0.36
Diabetes	8 [17.8]	10 [23.3]	18 [20.5]	
GN	8 [17.8]	11 [25.6]	19 [21.6]	
Interstitial	11 [24.4]	5 [11.6]	16 [18.2]	
Multisystem	7 [15.6]	10 [23.3]	17 [19.3]	
Other	11 [24.4]	7 [16.3]	18 [20.5]	
Past medical history, *n* [%]				
Hypertension	37 [82.2]	41 [95.2]	78 [88.6]	0.05
Diabetes mellitus	14 [31.1]	15 [34.9]	29 [33.0]	0.71
Ischemic heart disease	11 [24.4]	8 [18.6]	19 [21.6]	0.51
Congestive cardiac failure	3 [6.7]	6 [14.0]	9 [10.2]	0.26
Peripheral vascular disease	3 [6.7]	3 [7.0]	6 [6.8]	0.95
Atrial fibrillation	5 [11.1]	4 [9.3]	9 [10.2]	0.78
Depression	8 [17.8]	10 [23.3]	18 [20.5]	0.52
Duration of ESRD, yr [IQR]	1.39 [0.61–3.34]	1.92 [0.52–4.39]	1.62 [0.57–4.02]	0.84
Dialysis-related variables, median [IQR]				
Pre-SBP, mm Hg	133.5 [120.8–153.3]	148.8 [129.3–168.0]	143.5 [121.4–158.5]	0.02
Pre-DBP, mm Hg	70.8 [65.2–81.7]	74.8 [65.0–79.8]	73.1 [65.1–80.7]	0.61
Post-SBP, mm Hg	122.7 [112.4–143.8]	135.7 [118.2–158.0]	130.7 [113.4–148.5]	0.03
Post-DBP, mm Hg	68.0 [59.5–80.2]	71.2 [61.0–77.7]	69.3 [60.1–78.2]	0.59
UF volume, L	2.0 [1.3–2.4]	2.1 [1.4–2.9]	2.1 [1.4–2.6]	0.13
UF rate, ml/h	−442.1 [−240.0 to −575.0]	−500.0 [−350 to −622.2]	−484.4 [−261.9 to −484.4]	0.32
Dialysis access, *n* [%]				0.28
AV access	34 [75.6]	28 [65.1]	62 [70.5]	
Central venous catheter	11 [24.4]	15 [34.9]	26 [29.5]	
Median laboratory values [IQR]				
Serum-adjusted calcium, mmol/L	2.39 [2.29–2.46]	2.37 [2.27–2.45]	2.38 [2.28–2.46]	0.59
Serum phosphate, mmol/L	1.76 [1.42–2.03]	1.74 [1.49–2.04]	1.75 [1.47–2.04]	0.90
Hemoglobin, g/L	117.7 [106.7–122.7]	110.7 [101.0–120.33]	113 [102.2–122.0]	0.13
Serum albumin, mmol/L	33.0 [31.7–35.3]	33.3 [29.7–34.3]	33.2 [30.8–35.0]	0.94
PTH, nmol/L	68.6 [42.6–98.2]	53.3 [32.3–103.5]	61.6 [37.4–99.0]	0.31
Urea reduction ratio	71.5 [69–77]	73.5 [70.0–76.0]	72.8 [69.5–77.0]	0.58
Median years of education [IQR]	12 [11.0–13.5]	12 [11.0–14.0]	12 [11–14]	0.71

SBP, systolic BP; DBP, diastolic BP; UF, ultrafiltration; AV, arteriovenous; PTH, parathyroid hormone.

The primary analysis for the MRI study was to detect correlation between TCD and MRI findings for WMH lesion burden. To detect correlation (r=0.5), using a two-sided test at 5% significance with 80% power, the required sample size was 29. To allow for 25% dropout (death and renal transplant), a minimum of 40 patients were required.

RESULTS

Ninety seven patients were recruited, with a median age of 59 (IQR, 51–67) years; 40 (41.2%) were women and 32 (33%) were diabetic. Median duration of dialysis at first visit was 1.76 (IQR, 0.6–4.0) years. Eighty eight patients completed both baseline intra- and interdialytic visits. Median duration between baseline visits was 27 (IQR, 22–34) days.

Cognitive Impairment at Baseline Off Dialysis

Cognitive impairment was present in 43 (48.9%) participants who were not known to have cognitive impairment, on the basis of MOCA score <26. Those with cognitive impairment were more likely to have evidence of systolic hypertension; predialysis systolic BP 148.8 versus 133.5 mm Hg (P=0.02). There were no differences in age or duration of ESRD Demographics are demonstrated in Table 1.

Table 2. Clinical variables and their correlation to percentage of decline in middle cerebral artery MFV (*n*=82)

Variable	Spearman Rho	*P* Value
Ultrafiltration volume, ml	0.512	<0.001
Ultrafiltration rate, ml/h	0.493	<0.001
ΔSBP, mm Hg (pre−post)	0.196	0.08
ΔDBP, mm Hg (pre−post)	0.163	0.14
ΔWeight, kg (pre−post)	0.463	<0.001
ΔMAP, mm Hg (pre−post)	0.219	0.05
Diabetes mellitus	−0.304	0.005

Δ Values are calculated as pre minus post values, therefore the greater the fall after dialysis the higher the value. A positive correlation denotes that as percentage of decline becomes more positive (*i.e.*, a greater decline in MFV), the associated variable becomes more positive. SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure.

HD and Cerebral Blood Flow

Insonation of one or both middle cerebral arteries was possible in 82 participants, but was not visible or was deemed unreliable in the remainder. Eighteen out of 82 participants were unable to continuously wear the headset throughout dialysis: in eight participants the headset was ill-fitting or uncomfortable, and a further ten participants requested removal within the first 2 hours, with six complaining of a headache that relieved immediately on removal. MFV declined after dialysis, remaining lower up to 30 minutes after completion of dialysis (median MFV reading 47.38–40.75 cm/s; $P<0.001$; Figure 1). The median percentage of decline was −10% (IQR, −21.9% to 0.0%). The percentage of decline in MFV correlated with ultrafiltration volume and rate and change in weight (rho 0.512, 0.493, and 0.463, respectively; $P<0.001$), but not change in absolute BP values. Change in mean arterial pressure and presence of diabetes weakly correlated with percentage of decline in MFV (Table 2). Changes in MFV per participant, split by presence of cognitive impairment are presented in Supplemental Figures 6–8.

Cognitive Function: On- and Off-Dialysis Assessments

Compared with their assessments during an off-dialysis period, participants scored lower in assessments of executive function during dialysis (processing speed [LDST], 22 versus 24.5; $P<0.001$ and attention/task-switching [TMTB] time taken 88.5 versus 75 seconds; $P<0.001$; Table 3).

Significant correlations between the percentage of decline in MFV during dialysis and a decline in TMTA (rho −0.454; $P<0.001$), TMTB (rho −0.323; $P=0.01$), and phonemic fluency (rho 0.302; $P=0.01$) during dialysis were detected. Further, worsening scores on global cognitive assessment (MOCA) during dialysis correlated with percentage of decline in MFV (rho 0.270; $P=0.02$; Table 3).

Follow-Up

Median follow-up was 1.05 (IQR, 1.0–1.1) years. At follow-up, 15 participants had been transplanted, four withdrew, and six died (Supplemental Figure 1). Those who were transplanted were younger (median, 51 [IQR, 40–63] versus 60 [IQR, 52–67] years)

Table 3. Differences in cognitive scores during and off dialysis (*n*=88), and correlation between percentage of decline in MFV and cognitive scores

Assessment, *n*=88	Intradialytic Assessment	Interdialytic Assessment	*P* Value	Correlation with Percentage of Decline in MFV, Rho	*P* Value
Global cognitive function					
MOCA	25.0 [22.0, 27.0]	25.0 [21.5, 27.0]	0.44	0.270	0.02[a]
Verbal fluency					
Semantic	18.0 [14.5, 21.5]	18.0 [15.0, 22.0]	0.28	0.172	0.14
Phonemic	33 [26.0, 41.5]	34.0 [25.0, 43.5]	0.49	0.302	0.01[a]
Executive function					
TMTA	38.0 [26.5, 51.0]	35.5 [26.9, 50.0]	0.63	−0.454	<0.001[a,b]
TMTB	88.5 [62.0, 136.0]	75.0 [54.0, 112.0]	<0.001	−0.323	0.01[a]
LDST	22.0 [18.0, 27.0]	24.5 [20.0, 30.0]	<0.001	−0.170	0.15
Auditory–verbal memory					
HVLT					
Total recall	22.0 [19.5, 25.5]	20.0 [17.0, 23.0]	<0.001	0.089	0.45
Delayed recall	7.0 [5.0, 9.0]	6.0 [4.0, 9.0]	0.13	0.098	0.41
Retention	80.0 [60.0, 90.0]	80.0 [60.0, 100.0]	0.60	−0.046	0.70
Discrimination	10.0 [9.0, 11.0]	10.0 [9.0, 11.0]	0.90	0.057	0.63
Mood					
CES-D	8.0 [4.0, 17.0]	9.0 [4.0, 17.5]	0.80	0.097	0.41

Difference in cognitive score is calculated as nondialysis score minus dialysis score. Positive rho indicates that as percentage of decline increases (*i.e.*, a greater fall in MFV), the difference in cognitive scores becomes more positive. In the above tests a positive difference in cognitive score describes a lower cognitive score during dialysis, with the exception of TMTA, TMTB, and CES-D, where the inverse is true. CES-D, Center for Epidemiologic Studies Depression Scale; FDR, false detection rate.

[a]Correlations that remain significant after FDR.

[b]Correlations that remain significant after Bonferroni correction.

Table 4. Differences in cognitive scores at baseline and follow-up (using interdialytic assessments), and correlation between percentage of decline in MFV and cognitive scores in those remaining on hemodialysis and those receiving a kidney transplant

Assessment	Baseline Assessment	Follow-Up Assessment	*P* Value	Correlation with Percentage of Decline in MFV, Rho	*P* Value
Continued hemodialysis, *n*=61					
MOCA	24.0 [21.0, 27.0]	26.0 [23.0, 28.0]	<0.01	0.276	0.04
Semantic	19.0 [15.0, 21.0]	18.0 [15.0, 21.0]	0.45	0.201	0.15
Phonemic	35.0 [28.0, 44.0]	37.0 [27.0, 46.0]	0.06	0.150	0.28
LDST	24.0 [20.0, 31.0]	26.0 [20.0, 31.0]	0.87	−0.085	0.55
TMTA	34.0 [26.0, 47.0]	31.0 [26.0, 45.0]	0.09	−0.209	0.15
TMTB	71.0 [49.0, 99.0]	66.0 [49.0, 99.0]	0.90	−0.403	0.005[a]
HVLT					
Total recall	20.0 [17.0, 23.0]	21.0 [17.0, 26.0]	0.28	0.098	0.48
Delayed recall	7.0 [4.0, 10.0]	7.0 [4.0, 9.0]	0.97	0.243	0.08
Retention	80.0 [62.5, 100.0]	80.0 [55.6, 90.9]	0.45	0.219	0.15
Discrimination	11.0 [9.0, 12.0]	11.0 [9.0, 12.0]	0.92	0.149	0.30
CES-D	10.0 [5.0, 18.0]	10.0 [4.0, 18.0]	0.59	0.139	0.32
Transplanted at follow-up, *n*=12					
MOCA	26.0 [24.5, 27.0]	26.0 [25.0, 28.5]	0.23	0.086	0.81
Semantic	18.0 [15.5, 26.0]	21.0 [20.5, 23.5]	0.42	0.609	0.06
Phonemic	33.5 [28.5, 46.0]	36.0 [28.5, 42.0]	0.96	0.758	0.01
LDST	31.0 [26.0, 35.0]	33.0 [26.0, 35.0]	0.43	0.383	0.28
TMTA	35.0 [26.0, 37.0]	34.5 [20.5, 41.0]	0.63	−0.500	0.17
TMTB	63.0 [51.0, 108.0]	58.0 [45.0, 82.0]	0.33	−0.317	0.41
HVLT					
Total recall	21.0 [17.5, 24.0]	22.5 [19.5, 27.5]	0.35	0.329	0.35
Delayed recall	6.5 [4.5, 8.0]	9.5 [7.0, 10.0]	0.02	−0.123	0.74
Retention	68.3 [59.8, 94.4]	100.0 [79.8, 105.0]	0.03	−0.358	0.31
Discrimination	10.0 [10.0, 11.0]	11.0 [10.5, 12.0]	0.03	0.273	0.45
CES-D	6.5 [1.0, 13.0]	2.5 [1.0, 8.0]	0.31	−0.334	0.35

Difference in cognitive score is calculated as baseline minus follow-up score. Therefore, a positive rho value indicates that as percentage of decline increases (*i.e.*, a greater fall in MFV), the difference in cognitive change becomes more positive. In the above tests a positive difference in cognitive score denotes deterioration at follow-up, with the exception of TMTA, TMTB, and CES-D, where the inverse is true. CES-D, Center for Epidemiologic Studies Depression Scale; FDR, false detection rate.
[a]Correlations that remain significant after FDR.

and had a shorter duration of ESRD (median, 0.6 [IQR, 0.2–1.6] versus 2.1 [IQR, 0.7–4.5] years; Supplemental Table 5). Paired 0 and 12 month interdialytic assessments were possible in 61 participants who remained on HD and 12 who received a kidney transplant. Baseline and follow-up MRI data were available in 24 participants who continued HD and ten who were transplanted.

Cognitive Function at Follow-Up: Continued HD versus Transplanted

At the 12-month follow-up, those who remained on dialysis had an improvement in MOCA score (26 versus 24; $P<0.01$). No other assessment revealed significant differences. In contrast, those who underwent transplant had no change in their MOCA score (26 versus 26; $P=0.23$), but demonstrated an improvement in verbal memory (delayed recall, 9.5 versus 6.5; $P=0.02$; retention, 100% versus 68.3%; $P=0.03$; and discrimination, 11 versus 10; $P=0.03$; Table 4).

In those who remain on dialysis, percentage of decline in MFV was significantly correlated with worsening score in global cognitive function (MOCA) and executive function (TMTB) on follow-up (rho 0.276; $P=0.04$ and rho −0.403; $P=0.005$, respectively; Table 4).

In those who received a transplant, an observed percentage of decline in MFV correlated with worsening phonemic fluency at follow-up (rho 0.758; $P=0.01$; Table 4).

MRI-Derived Structural Changes

In those who continued on dialysis, progressive lobar atrophy was evident in frontal, parietal, and temporal lobes ($P<0.05$; Table 5), and WMH burden increased (from 2.96 to 3.36 ml; $P=0.02$; Figure 2). There were no changes in diffusion tensor imaging measures, FA, and MD (Table 5).

After kidney transplant, a similar pattern of lobar atrophy was noted. However, there was no progression in WMH burden and FA in white matter increased (from 0.28 to 0.29; $P=0.02$; Table 5).

Correlating Structural Changes with Cognitive Function

There was no correlation between percentage of decline in MFV assessed at baseline and MRI findings.

In those who continue dialysis, greater frontal atrophy correlates with worsening score in global cognitive and executive

Table 5. Differences in neuroimaging parameters at baseline and follow-up in those who remained on dialysis and those who received a kidney transplant

Assessment	Baseline Assessment	Follow-Up Assessment	*P* Value
Continued hemodialysis, *n*=24			
Median lobar volume, ml			
Frontal GM	160.3 [150.8 to 166.3]	155.2 [147.4 to 162.3]	0.02
Parietal GM	93.9 [89.1 to 102.6]	92.9 [85.4 to 99.2]	0.03
Temporal GM	116.8 [110.5 to 122.8]	111.3 [105.6 to 121.6]	0.009
Occipital GM	60.4 [55.2 to 65.9]	58.3 [54.8 to 63.6]	0.08
WMH volume, ml	2.96 [0.87 to 6.07]	3.36 [0.82 to 7.35]	0.02
DTI			
FA_WM	0.27 [0.02]	0.26 [0.02]	0.41
FA_WMH	0.26 [0.04]	0.26 [0.03]	0.64
MD_WM 10^3 m^2/s	0.9 [0.1]	0.9 [0.1]	0.19
MD_WMH 10^3 m^2/s	1.2 [0.01]	1.2 [0.1]	0.05
Transplanted at follow-up, *n*=10			
Median lobar volume, ml			
Frontal GM	166.9 [159.9 to 185.0]	162.2 [157.4 to 186.4]	0.03
Parietal GM	102.6 [98.1 to 114.8]	101.6 [97.8 to 112.2]	0.05
Temporal GM	115.0 [111.6 to 136.6]	113.8 [108 to 134.5]	0.009
Occipital GM	64.2 [60.1 to 75.6]	64.8 [59.7 to 73.9]	0.33
WMH volume, ml	1.02 [0.79 to 2.01]	1.17 [0.64 to 1.25]	0.24
DTI			
FA_WM	0.28 [0.01]	0.29 [0.01]	0.02
FA_WMH	0.25 [0.03]	0.26 [0.03]	0.07
MD_WM 10^3 m^2/s	0.8 [0.01]	0.8 [0.02]	0.62
MD_WMH 10^3 m^2/s	1.1 [0.1]	1.1 [0.1]	0.72

DTI data in Table 5 is mean [SD]. GM, gray matter; DTI, diffusion tensor imaging; FA_WM, fractional anisotropy in white matter; FA_WMH, fractional anisotropy in white matter hyperintensities; MD_WM, mean diffusivity in white matter; MD_WMH, mean diffusivity in white matter hyperintensities.

function (MOCA, rho 0.454; *P*=0.04; TMTB, rho 0.620; *P*=0.01; and auditory–verbal memory, rho 0.805; *P*=0.01). An increase in WMH burden correlates with verbal fluency and mood (rho 0.585; *P*=0.01 and rho −0.485; *P*=0.03, respectively; Table 6).

In who received a kidney transplant, an increase in WMH burden correlates with worsening executive function (TMTB, rho −0.81; *P*=0.02). In contrast, an increase in FA correlates with an improvement in executive function (LDST, rho −0.886; *P*=0.02). Surprisingly, worsening frontal atrophy correlates with improvement in executive function.

DISCUSSION

This prospective study of people with ESRD encompassing blood flow and functional and structural assessments of the brain has several important findings. First, we demonstrated that cerebral blood flow declines during dialysis, correlating with ultrafiltration volumes and with a measurable decline in executive function. At follow-up, a correlation was detected between reduced cerebral blood flow and executive function in those who remained on dialysis but not those who were transplanted. After transplant, verbal learning and memory improved. Finally, brain MRI revealed progressive WMH burden in those who remain on dialysis, but not those who were transplanted. In contrast, after transplantation increased FA of the white matter correlated with improved executive function.

We believe this study supports the hypothesis that HD may be associated with short-term "cerebral stunning," and demonstrates progressive injury in those who remain on dialysis, whereas there is a demonstrable improvement in memory and white matter integrity in those who are transplanted. Early recognition of those at risk may limit this cerebral injury, which appears potentially reversible by transplantation.

Cognitive Function in ESRD: Incidence and Consequences

We have demonstrated in a "low-risk" HD population, without recorded cerebrovascular disease or cognitive impairment, that mild cognitive impairment is present in 48.9% of the population. Once ESRD is established, it is estimated that up to 70% of those on HD have cognitive impairment.[1] Surprisingly, in that particular study only approximately 3% had documentation of cognitive impairment. We demonstrated intradialytic cerebral blood flow declines with increasing ultrafiltration volumes Therefore, in ESRD, failure to recognize cognitive impairment could perpetuate future cognitive decline: in those with existing cognitive impairment, patient concordance with fluid restriction is poor, the corresponding increase in ultrafiltration volumes compromises cerebral circulation, cognition worsens, and concordance worsens further. Morbidity aside, cognitive dysfunction is also associated with all-cause mortality[25,26] and dialysis withdrawal.[28]

Dialysis and Cognitive Dysfunction

Multiple factors are reported to influence cognitive function in CKD. Conventional risk factors such as age, diabetes, hypertension, and dyslipidemia are abundant; however, unconventional "renal" factors, including treatments for CKD (*e.g.*, the historical effect of aluminum toxicity,[29] or more recently, the effect of dialysis itself), are implicated.[2,30–32] In contrast to neurodegenerative cognitive disorders where memory is predominantly affected, the pattern of cognitive impairment most commonly described in those with CKD is loss of executive function,[2–4] a phenotype associated with vascular cognitive impairment. Further, more intensive dialysis does not improve function.[6,7] This has led to the conclusion that cognitive impairment is driven by cerebrovascular disease.

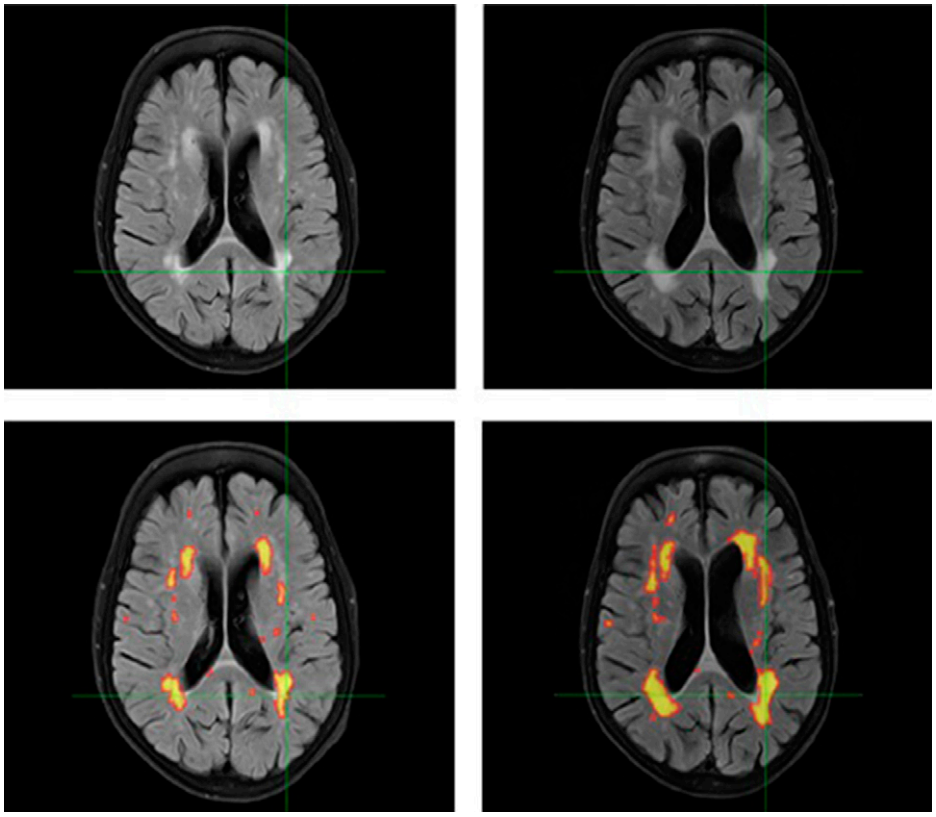


Figure 2. White matter hyperintensities progress in those on continued haemodialysis. The images on the left represent baseline MR images and on the right MR imaged at follow-up following 12 months of treatment. Additionally, a loss of cerebral volume can be appreciated as enlargement of lateral ventricles. This figure demonstrates visible progression of WMH on standard T2 fluid-attenuated inversion recovery sequences (top row) and after application of volumetric analyses software (bottom row).

Previous data on cognitive variation around the dialysis session are conflicting. Authors have described both improvements[32,33] and worsening[31] of postdialysis cognition. To our knowledge, this is the first study to correlate an acute change in cerebral blood flow with real-time alterations in cognitive function. This has several important implications. Immediately, clinicians should be aware that detailed clinical discussions should not be undertaken during HD as comprehension and recall maybe affected. Further, this must prompt additional research designed to limit the damage observed on MRI. One clinical trial has demonstrated that dialysate cooling can provide stability in white matter integrity at 1 year of treatment.[34] The beneficial cognitive effects of renal transplantation require further attention and the benefit of expediting transplantation as a treatment for early cognitive dysfunction should not be overlooked.

Transplantation and Cognitive Dysfunction

Renal transplantation remains the gold-standard treatment for ESRD.[35] Transplantation reduces the risk of cardiovascular disease,[36] increasing life expectancy, and improves quality of life.[37] In our study, we observed an improvement in cognitive function after transplantation, specifically memory, in agreement with previous studies,[38–40] albeit in a small cohort of our patients. FA is a marker of white matter integrity and deficits in diffusion are recognized to precede WMH formation and are associated with worsening executive function.[41] In those who received a renal transplant, FA improved and correlated with improved executive function, whereas there was no demonstrable improvement in anisotropic diffusion in those remaining on HD. Previous authors have demonstrated improvement in executive function after transplantation,[39] a finding that does not appear to be achievable by more frequent dialysis. In an analysis of participants in the Frequent Hemodialysis Network, an improvement in auditory–verbal memory and processing speed was observed after transplantation, but not after 12 months of frequent HD (6 days a week).[7] This is supportive of a side effect produced by HD, ameliorated by transplantation.

Limitations

This prospective, observational cohort study has demonstrated important findings in a real-world ESRD cohort. However, we recognize the following limitations. As an observational study we cannot prove causation because of inability to account for

Table 6. Correlations of changes in neuroimaging with change in cognitive testing over 12 months, in those who remain on hemodialysis and those receiving a kidney transplant

Assessment	Correlation with ΔWMH	*P* Value	Correlation with ΔFA_WM	*P* Value
Continued hemodialysis, *n*=21				
MOCA	0.172	0.46	0.225	0.48
Semantic	−0.028	0.90	−0.175	0.59
Phonemic	0.585	0.01	−0.365	0.24
LDST	0.129	0.58	0.116	0.72
TMTA	0.328	0.16	−0.278	0.41
TMTB	−0.384	0.12	−0.103	0.78
HVLT				
Total recall	0.271	0.23	0.327	0.30
Delayed recall	0.268	0.24	0.160	0.62
Retention	0.172	0.46	0.056	0.86
Discrimination	0.296	0.19	−0.381	0.22
CES-D	−0.485	0.03	0.140	0.66
Transplanted at follow-up, *n*=9				
MOCA	−0.092	0.81	0.319	0.54
Semantic	−0.301	0.43	−0.600	0.21
Phonemic	0.460	0.21	−0.667	0.15
LDST	−0.101	0.80	−0.886	0.02
TMTA	0.071	0.87	0.200	0.75
TMTB	−0.810	0.02	−0.600	0.29
HVLT				
Total recall	0.025	0.95	−0.232	0.66
Delayed recall	0.522	0.15	0.353	0.49
Retention	0.483	0.19	−0.143	0.79
Discrimination	−0.173	0.65	0.152	0.77
CES-D	0.460	0.21	−0.143	0.79

For all neuroimaging results, values show follow-up minus baseline, hence a reduction in value with time will produce a negative result. Difference in cognitive score is calculated as baseline minus follow-up score. Therefore, a positive rho indicates that a positive neuroimaging change relates to a positive cognitive score at follow-up. In the above tests, a positive follow-up cognitive score denotes deterioration, with the exception of TMTA, TMTB, and CES-D, where the inverse is true. FA_WM, Fractional anisotropy in white matter; CES-D, Center for Epidemiologic Studies Depression Scale.

unmeasured variables. For example, we do not have data on bicarbonate or blood viscosity levels, which may be of greater significance than ultrafiltration volume on MFV. We excluded those with any known evidence of cerebrovascular disease, which resulted in a younger cohort. This reduces generalizability and makes it likely we have underestimated the prevalence of cognitive impairment and the effect of ongoing treatments on more "fragile" brains. Although we acknowledge this as a limitation, we also believe it makes our findings all the more striking. No attempts were made to standardize dialysis regimes. Although this could mask findings acutely, we believe this provides a more realistic view of dialysis. Use of TCD ultrasound to measure cerebral blood flow has limitations, namely operator variability and absence of acoustic windows. All TCD readings were performed by one trained operator to reduce variation and we acknowledge TCD was not possible in 15 (15%) of our recruited cohort. Our findings are correlated to MFV changes over a single dialysis session, with follow-up spanning an entire year. Generalizing one session to an entire year may affect correlations at follow-up. As TCD measurements were taken at fixed time points, it not possible to comment on unrecorded episodes of acute decline in MFV. Finally, throughout this article we refer to cerebral blood flow. It is important to clarify that TCD measures cerebral blood flow velocity, an indirect measure of cerebral blood flow, provided the diameter of the insonated vessel does not change during measurements. It is not known whether HD alters cerebral vessel diameter.

Attempts were made to limit a learning effect. Namely, multiple versions of MOCA and HVLT were used, a minimum of 14 days between assessments was allowed, and visit order was reversed in a randomly selected 20% of the cohort. Despite our attempts we cannot completely exclude this learning effect. Frontal atrophy correlated with improved executive function in transplanted patients. Although frontal atrophy is a marker of aging and executive function can improve after transplantation,[39] it is important to acknowledge our low number of transplant patients at follow-up, which could introduce both type 1 and 2 errors. In particular, this small number may lead to chance association between MRI findings and change in cognitive function. We did not detect correlation between MFV and MRI changes. Only 24 patients completed follow-up scans while on continued dialysis. Therefore, correlating percentage of MFV decline with MRI findings is underpowered and may account for the lack of effect. Finally, and with particular reference to the young age of our cohort, we did not detect progressive cognitive dysfunction, but rather, improvement in MOCA score at 12 months in those on continued dialysis. It is likely that the follow-up time was too short to detect a measurable difference in cognitive function in this recruited cohort. In conclusion, our study highlights the high frequency of occult cognitive impairment, affecting 50% of our prevalent dialysis cohort without known cerebrovascular disease. HD is capable of inducing a transient decline in cerebral blood flow, correlating with intradialytic cognitive dysfunction. Evidence of progressive cerebrovascular disease is demonstrated in those who remain on dialysis, whereas after transplantation, improvement in cognitive function and cerebral anisotropic diffusion is suggestive of reversibility. Urgent interventions are required to limit cerebral stunning and prevent progressive cognitive decline.

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DISCLOSURES

None.

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2018050462/-/DCSupplemental.

SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Flow chart demonstrating recruitment, follow-up and participant attendance to study visits and MRI. CeVD, cerebrovascular disease.

Supplemental Figure 2. Correlation plot of ultrafiltration and percentage of decline in MFV (Spearman rho −0.512; $P<0.001$). More positive ultrafiltration volumes correlate with more negative percentage of decline in MFV.

Supplemental Figure 3. Correlation plot of ΔTMTB (early visits) and percentage of decline in MFV (Spearman rho −0.323; $P=0.01$). Δ Score is calculated as score during dialysis minus score off dialysis. Thus, for TMTB, if time taken to complete on dialysis is longer then the Δ score is positive. A more positive ΔTMTB denotes worsening of executive function during dialysis.

Supplemental Figure 4. Correlation plot of ΔTMTB (long-term) and percentage of decline in MFV in those on continued HD (Spearman rho −403; $P=0.005$). Δ Score is calculated as score at follow-up minus score at baseline. Thus, for TMTB, if time taken to complete is longer at follow-up, Δ score is more positive. A more positive ΔTMTB denotes a worsening executive function at follow-up.

Supplemental Figure 5. Correlation plot of ΔCES-D (long-term) and ΔWMH volume in those on continued HD (Spearman rho 485; $P=0.03$). Δ Score is calculated as score at follow-up minus score at baseline. Thus, for CES-D, if depression scoring is greater at follow-up, Δ score is more positive. A more positive ΔCES-D denotes a worsening in depressive symptoms at follow-up. CES-D, Center for Epidemiologic Studies Depression Scale.

Supplemental Figure 6. Trajectory of MFV during dialysis, in those without cognitive impairment.

Supplemental Figure 7. Trajectory of MFV during dialysis, in those with cognitive impairment.

Supplemental Figure 8. Trajectory of MFV during dialysis, in those with and without cognitive impairment, grouped.

Supplemental Table 1. Modified Hachinski protocol of cognitive assessments used both on and off dialysis. All assessments could be competed in <1 hour. For assessments completed during dialysis, all tests were completed within the first 2 hours of dialysis.

Supplemental Table 2. Missing at random (MAR)- and missing completely at random (MCAR)-based results for weighted GEE, with time as an ordinal variable.

Supplemental Table 3. Correlation of change in cognitive assessment and MFV as demonstrated in Table 3, with false detection rate and Bonferroni corrections. For comparison, FDR is calculated using an α of 0.1, where each P-value=rank/number of test multiplied by 0.1.

Supplemental Table 4. Correlation of change in cognitive assessment and MFV as demonstrated in Table 4, with false detection rate and Bonferroni corrections. For comparison, FDR is calculated using an α of 0.1, where each P-value=rank/number of test multiplied by 0.1.

Supplemental Table 5. Demographic of study cohort, split by those who remained on dialysis, or were transplanted. AV, arteriovenous; DBP, diastolic BP; PTH, parathyroid hormone; SBP, systolic BP; UF, ultrafiltration.

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