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Anatomic Brain Disease in Hemodialysis Patients: A Cross-sectional Study

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Abstract

Background—Although dialysis patients are at high risk for stroke and have a high burden of cognitive impairment, there are few reports on anatomic brain findings in the hemodialysis population. Using brain magnetic resonance imaging (MRI), we compared the prevalence of brain abnormalities in hemodialysis patients to a control population without known kidney disease.

Study Design—Cross-sectional cohort.

Setting & Participants—45 maintenance hemodialysis patients and 67 controls without reported kidney disease, both without prior history of known stroke.

Predictor—The primary predictor was dialysis status. Covariates included demographics (age, race, sex), vascular risk factors (diabetes and hypertension) and cardiovascular disease (coronary artery disease, congestive heart failure).

Outcomes—Brain MRI features including severity of white matter disease and cerebral atrophy (sulcal prominence and ventricular atrophy), hippocampal size, and small/large vessel infarcts.

Measurements—Semi-quantitative scale (0-9 for white matter disease and cerebral atrophy, 0-3 for hippocampal size) and infarct prevalence.

Results—The mean age of hemodialysis patients and controls was 55 ± 17 (SD) and 53 ± 13 years, respectively. In comparison with controls, hemodialysis patients had more severe white

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Supplementary Material Table S1: Comparison of hemodialysis patients with and without magnetic resonance imaging.
Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org
Descriptive Text for Online Delivery Hyperlink: Supplementary Table S1 (PDF)
About: Comparison of hemodialysis patients with and without magnetic resonance imaging.

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matter disease (1.6 v 0.7) and cerebral atrophy (sulcal prominence = 2.3 v 0.6; ventricular enlargement = 2.3 v 0.9; hippocampal size = 1.3 v 1.0) with all p-values <0.001. In multivariable analyses, hemodialysis status was independently associated with worse white matter disease and atrophy grades. Hemodialysis patients also had a higher prevalence of small (17.8%) and large (7.8%) vessel infarcts than controls (combined 22% vs 0%, p<0.001).

Limitations—The dialysis cohort is likely healthier than the overall US hemodialysis population, partly limiting generalizability.

Conclusions—Hemodialysis patients have more white matter disease and cerebral atrophy compared to controls without known kidney disease. Hemodialysis patients also have a high prevalence of unrecognized infarcts.

Keywords

Hemodialysis; brain abnormalities; cerebral atrophy; white matter disease; magnetic resonance imaging (MRI)

Hemodialysis patients have a 2-6 fold higher incidence of stroke than patients in the general population[1]. This increased risk for cerebrovascular disease may reflect longstanding exposure to traditional risk factors, such as hypertension, dyslipidemia, and hyperglycemia as well as non-traditional risk factors unique to dialysis patients, such as hemodynamic shifts associated with the hemodialysis procedure, oxidative stress, vascular calcification and anemia[2-4].

The clinical diagnosis of stroke, however, underestimates the true burden of cerebrovascular disease in individuals in the general population[5]. Brain magnetic resonance imaging (MRI) is sensitive for detecting both clinical and subclinical strokes while also identifying white matter disease (WMD). Characterized by hyperintense changes seen on T2-weighted MRIs, WMD is thought to result from ischemia, and therefore is highly correlated with both vascular disease and its risk factors[6,7]. Additionally, MRI can provide a detailed assessment of brain volume, allowing for evaluation of atrophy and hippocampal size[8,9]. In patients without kidney disease, the presence of infarcts and WMD on brain MRIs are associated with both cognitive impairment as well as elevated risk of future clinically-apparent strokes, while cerebral atrophy and smaller hippocampal volume have both been associated with dementia[10-15].

MRI data may be particularly important for categorizing future risk of stroke and helping to delineate the pathogenesis of the high prevalence of cognitive impairment in hemodialysis patients[16-20]. However, there are few data on detailed brain MRI findings in this population. Accordingly, we obtained brain MRIs in a cross-sectional hemodialysis cohort and compared the prevalence and severity of structural brain disease to controls without kidney disease. Specifically, we assessed for presence and severity of WMD, cerebral atrophy, hippocampal size, and cerebral infarcts and then evaluated whether these abnormalities were more common in hemodialysis patients.

METHODS

Study Population

All patients receiving hemodialysis at 5 Dialysis Clinic Inc units and one hospital-based dialysis unit in the greater Boston, MA area who enrolled at baseline in the Cognition and Dialysis Study (01/21/04 to 06/29/11), a prospective cohort of maintenance hemodialysis patients, were also approached to consent for brain MRI scans. Eligibility criteria for the Cognition and Dialysis Study is described elsewhere[20] but, briefly, required age 18 years or

older, English fluency, medically stable condition, and receipt of hemodialysis therapy for at least one month. The most common reasons for not undergoing an MRI were lack of interest and therefore not providing consent, and ineligibility for MRI due to metallic and electronic implants. Demographic information regarding history of diabetes, hypertension, coronary artery disease, stroke, and congestive heart failure was obtained through participant report, medical charts, and the Dialysis Clinic Inc and hospital databases. Patients with a history of stroke were eligible to undergo brain MRI but were excluded from this analysis. The Tufts Medical Center (Tufts MC) Institutional Review Board approved the study, and all dialysis participants signed informed consent.

Controls were recruited from Tufts MC and Beth Israel Deaconess Medical Center (BIDMC), both in the Boston metropolitan area. At Tufts, controls were approached if they were already scheduled for a brain MRI for another indication and were between 18-75 years of age. Among controls, the most common indications for undergoing an MRI were headache (56%), vertigo (8%), and facial pain (8%). At BIDMC, controls were recruited by advertisement to undergo brain MRI and were required to be greater than 50 years of age[21,22]. Exclusion criteria for both centers were kidney disease, a presentation with symptoms or signs of stroke or history of stroke, cerebral hemorrhage, psychiatric disease, dementia, other serious neurological disorder and brain malignancy. Self-reported demographic data on age, sex, race, and history of diabetes, hypertension, coronary artery disease, and congestive heart failure were collected. At Tufts, kidney disease was considered absent if there was documentation of estimated glomerular filtration rate (eGFR, CKD-EPI creatinine equation [2009][23]) of greater than 60 ml/min/1.73 m^2 within 1 year of MRI (80%) and through review of the medical record if an eGFR was not available (20%). At BIDMC, participants underwent a history and physical exam and were excluded if kidney disease was reported or suspected. All controls provided signed informed consent, which was approved by each institution's respective Institutional Review Board.

Outcomes

Magnetic resonance imaging was performed in 45 hemodialysis patients and 67 controls and were obtained on a 3-T Philips scanner and included 3D-T1-weighted coronal images; intermediate and T2-weighted conventional spin-echo axial images; and fluid attenuation inversion recovery (FLAIR) turbo spin echo axial images. White matter disease (WMD) was defined as hyperintense changes on FLAIR and T2-weighted images with no corresponding T1 abnormality. A board-certified neuroradiologist (RB), who was blinded to clinical characteristics, semi-quantitatively graded white matter hyperintensity, ventricular size, sulcal prominence, and hippocampal size using previously validated criteria[24,25]. Briefly, WMD severity was scored on a scale of 0-9, with grade 0 being no detectable change and grade 9 all white matter involved. Cerebral atrophy was assessed through two different measures: sulcal prominence (more prominence = more atrophy) and ventricular size (larger size = more atrophy). Sulcal prominence ranged from small sulci (grade 0) to very large sulci (grade 9), while ventricular size ranged from slit-like ventricles (grade 0) to markedly enlarged (grade 9). Hippocampal size was assessed on a scale from 0 to 3, with 0 being no atrophy and 3 being severe atrophy. Large vessel (LV) infarcts were defined as infarcts larger than 1.5 cm in size and in a major vascular territory[26]. Any infarct in a cortical location was considered to be a manifestation of LV disease. Small vessel (SV) infarcts were defined as a focal subcortical brain lesion between 3mm and 1.5-cm in size, hyperintense on T2-weighted and hypointense on T1-weighted images. For a subset of both the hemodialysis cohort and control groups, each outcome was re-scored by the same neuro-radiologist (RB) (in a blinded manner with regard to the initial reading) to confirm the reliability of the grading system.

Statistical analysis

Demographic characteristics for the hemodialysis group and control group were reported as means with standard deviations or percentages and were compared using χ^2 tests, Fisher exact test, *t* tests, and ANOVA as appropriate. Hemodialysis patient and control data were combined and linear regression performed to assess to the association between hemodialysis status and white matter disease and cerebral atrophy in univariate analyses and after multivariable adjustment for age, sex, race, vascular disease and vascular risk factors. For hippocampal size, the outcome was dichotomized (grades 0-1 vs grades 2-3) and logistic regression performed to assess the association between dialysis status and hippocampal size, with similar multivariable adjustment for covariates. Small vessel infarcts and large vessel infarcts were reported as either present or absent. All analyses were performed using SAS (9.2) and all hypothesis tests were two-sided, with a $p<0.05$ considered as significant.

RESULTS

Study Participants

There were 45 hemodialysis patients and 67 controls. Hemodialysis patients undergoing MRI were on average younger, more likely to be African American, and had higher rates of coronary artery disease compared to the overall Cognition and Dialysis Cohort, while the two were similar with respect to sex, education status, history of diabetes, hypertension, and primary cause of kidney disease (Table S1, provided as online supplementary material). The semi-quantitative scoring system used for white matter disease and three measures of cerebral atrophy was found to be reproducible (intra-class correlation coefficient for WMD scoring = 96%, ventricular atrophy scoring = 95%, sulcal atrophy scoring = 97%, and hippocampal atrophy scoring = 74%). The mean (SD) age of the hemodialysis group was 55 (17) years compared to 53 (13) for controls, and 51% of hemodialysis patients versus 43% of controls were men (Table 1). African Americans comprised 38% of the hemodialysis population versus 11% of controls. Hemodialysis patients were more likely than controls to have vascular risk factors including diabetes and hypertension as well as a history of coronary artery disease and heart failure.

White matter disease

The hemodialysis group had a mean global white matter grade of 1.6 compared to 0.7 for the controls ($p<0.001$) (Table 1), and a higher proportion of hemodialysis patients had WMD grades of 2-3 and 4+ versus controls (Figure 1). In multivariable analyses adjusting for age, sex, race, vascular disease and vascular disease risk factors, hemodialysis status was significantly associated with a higher global white matter grade [$\beta=0.69$; 95% CI, 0.04-1.33; $p=0.04$] (Table 2).

Cerebral atrophy

Hemodialysis patients had more prominent sulci, with a mean sulcal grade of 2.3 compared to 0.6 in controls, and larger ventricular size, with a mean grade of 2.3 compared to 0.9 in controls (Table 1, both p values <0.001). A higher proportion of hemodialysis patients had sulcal and ventricular size grades of 2-3 and 4+ versus controls (Figure 1). In multivariable analyses, hemodialysis status was associated with higher sulcal grade after adjustment for age, sex, race, vascular disease and vascular risk factors [$\beta=1.36$; 95% CI, 0.87-1.84; $p<0.001$] (Table 3). Similarly, in multivariable analyses, ventricles were significantly larger in hemodialysis patients [$\beta=1.06$; 95% CI, 0.39-1.74; $p=0.002$] (Table 4).

Hippocampal Size

Hippocampal grade was higher in hemodialysis patients compared to controls (mean score 1.3 vs 1.0, p =0 .002). Hemodialysis patients had a higher proportion of hippocampal grades 2 and 3, indicating smaller hippocampal size, indicating more atrophy (Figure 1). In multivariable logistic regression, hemodialysis status was associated with smaller hippocampal size after adjustment for age, sex, race, vascular disease and vascular risk factors [OR = 13.52 (95% CI, 1.09-168.19) for grade 2-3 versus grades 0-1, p = 0.04] (Table 5).

Stroke

As all participants had no clinical history of stroke, the finding of infarcts on brain imaging refers to silent strokes. Among hemodialysis patients, 10 had evidence of infarcts, with 7 participants having small vessel infarcts only, 2 having large vessel infarcts, and 1 having both small and large vessel infarcts. No control participants had MRI findings of infarcts ($p<0.001$) (Table 1).

DISCUSSION

In this study we demonstrate that hemodialysis patients have a higher prevalence and severity of WMD, cerebral atrophy, and hippocampal atrophy compared to controls without kidney disease, even after adjusting for demographic factors, vascular risk factors and prevalent vascular disease. Additionally, hemodialysis patients had a higher prevalence of unrecognized small and large vessel infarcts, indicating a high burden of “silent” disease.

Overall, our results suggest that multiple abnormal brain findings are pervasive within hemodialysis patients, and, importantly, each of these structural abnormalities has previously been associated with negative clinical outcomes in patients without kidney disease. Both undetected cerebral infarcts and WMD are associated with a higher future stroke risk[7,27], while cerebral atrophy and smaller hippocampal size each has been associated with memory deficits, cognitive impairment and dementia[10,11,15]. Additionally, although it is well known that cognitive impairment is common in patients receiving hemodialysis[18], the etiology remains incompletely defined. Given what is known in the general population, it may be reasonable to suspect that the high rates of anatomic brain abnormalities within hemodialysis patients play an important role in the development of cognitive impairment.

Our results are consistent with a few prior studies in hemodialysis patients which have either evaluated individual aspects of brain anatomy and/or focused on prevalence of various aspects of brain anatomy. Fazekas et al. demonstrated a higher prevalence of cerebral atrophy, defined by sulcal prominence and ventricular enlargement on brain MRI, in 30 hemodialysis patients compared with 30 controls. Confluent white matter hyperintensities were present in 10 of the 30 hemodialysis participants[14]. Similarly, Geissler et al noted that 56% of 26 dialysis patients had focal white matter lesions compared with 27% in controls of a similar age[28], while Kim et al. reported that 68% of 57 peritoneal dialysis patients had WMD versus 17.5% of age and sex matched hypertensive controls[29]. Strokes also appear common, with Fazekas et al. showing large vessel infarcts in 10% [12] while Nakatani et al. demonstrated silent cerebral infarction in 49% of hemodialysis (n=123) patients compared to 9.6% (n=52) of controls[30].

Similar brain pathology is also seen in patients with chronic kidney disease (CKD) not yet on hemodialysis. A study by Khatri et al found an increased prevalence of white matter disease as eGFR decreased, with highest rates in patients with an eGFR between 15-60 ml/min/1.73m2 compared to those with more modest reductions (61-90 ml/min/1.73m2) and

normal kidney function (>90 ml/min/1.73m2)[31]. Likewise, large observational studies show higher rates of both subclinical and clinical stroke in patients with CKD [32,33].

Our study significantly adds to the current literature by evaluating multiple measures of anatomic brain disease, including WMD, atrophy, hippocampal size and large and small vessel strokes. We utilize T3 MRI equipment, allowing better delineation of subtle findings. Importantly, we include a comparison without kidney disease, and evaluate as well as adjust for vascular disease and traditional vascular risk factors in our analyses. Furthermore, we utilize well validated scales for grading of the abnormalities[24], which also provide important information on disease severity and allow comparison with other well-described cohorts. In particular, we employ a standardized and validated method identical to that used by the Cardiovascular Health Study (CHS). When comparing our hemodialysis cohort (mean age of 55 years) to that of CHS (mean age of 72 years), for the most part we find a similar burden of WMD, cerebral atrophy, and infarcts[25,26]. Despite the inherent limitations of this historical comparison, these results suggest that hemodialysis patients may experience premature aging of the brain.

There are several potential reasons why hemodialysis patients have high rates of WMD, atrophy, and infarcts. First, hemodialysis patients have a higher prevalence of vascular risk factors than those without kidney disease as noted in Table 1. Although hemodialysis status was an independent risk factor for each of the MRI abnormalities, the need for kidney replacement therapy may serve as a proxy for increased severity and longer exposure to each of these risk factors during all stages of CKD. Second, it is possible that the hemodialysis procedure may contribute to anatomical abnormalities, perhaps through repeated hypotension and dialysis disequilibrium, heparin use and subclinical bleeding[2,3,34-36]. As alluded to above, the latter however is likely not the only explanation as incident dialysis patients and individuals during the earlier stages of CKD also have a higher prevalence of MRI abnormalities compared to controls without kidney disease[31,37]. Third, non-traditional risk factors unique to kidney disease such as vascular calcification, anemia and inflammation may contribute to brain abnormalities in dialysis patients but are not adjusted for in the analyses[33,38,39].

The implications of the results are as follows: WMD, cerebral atrophy (including hippocampal atrophy) and small vessel strokes are highly prevalent in hemodialysis patients and are present in patients without a clinical history of cerebrovascular disease. This suggests a high prevalence of subclinical cerebrovascular disease in hemodialysis patients. Future research should be directed in several directions. First, larger studies in older and perhaps less select populations should be conducted to confirm these results. Second, the specific risk factors for each particular type of MRI abnormality should be evaluated in larger studies. Third, the relationship between each MRI abnormality and measures of cognitive function should be evaluated. Finally, the prognostic associations of the various MRI abnormalities need to be ascertained in longitudinal studies.

Our study has several limitations. First, the study is cross-sectional and therefore is limited by survivor bias. Despite having a high prevalence of diabetes, coronary disease and heart failure, the hemodialysis patients who consented for MRI are younger than the overall US dialysis population, and likely healthier than the average US hemodialysis patient. The latter may have led to an underestimation of the prevalence of MRI abnormalities. Second, only the presence, rather than the severity of major vascular risk factors were ascertained in both hemodialysis patients and controls, leading to the potential for both unmeasured and residual confounding. Third, referral bias may have led to an increased prevalence of brain abnormalities in the Tufts controls and thereby an underestimate of the differences between dialysis patients and controls. That is, Tufts controls had neurological symptoms that led to

the MRI, and therefore may be more likely to have anatomical abnormalities. Finally, given the small and heterogeneous nature of the dialysis MRI cohort it is difficult to evaluate risk factors for MRI abnormalities in this group.

In conclusion, we demonstrate that multiple brain abnormalities are prevalent in dialysis patients compared to controls without kidney disease. These findings are overtly silent and undetected by clinical history alone. Future studies should confirm these results and evaluate the causes as well as the consequences of these abnormalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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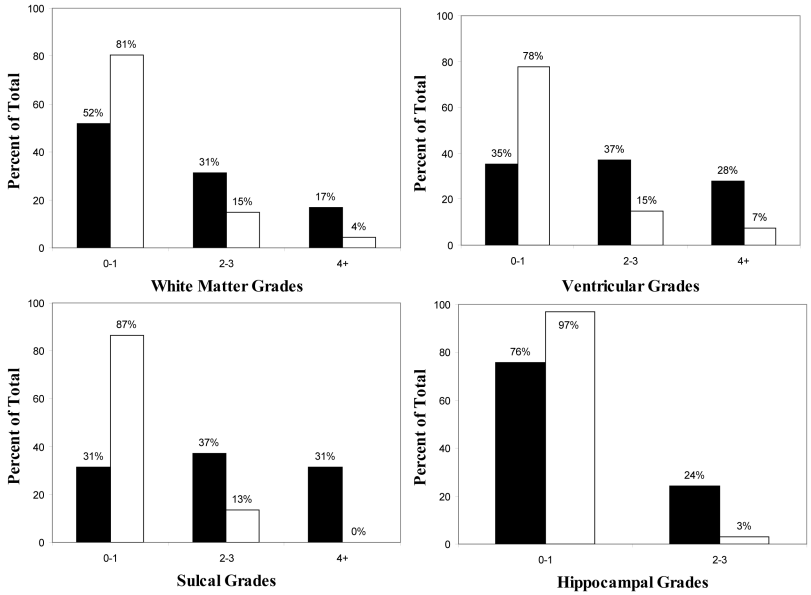

Figure 1. Distribution of White Matter Disease and Atrophy Grades

Black bars indicate hemodialysis group; white bars, control group without reported kidney disease

Table 1

Demographic and clinical characteristics of hemodialysis patients and controls

	Total (N = 112)	Hemodialysis (n = 45)	Controls (n = 67)	p-value
Age				0.5
Mean (y)	54 ± 15	55 ± 17	53 ± 13	
Median (y)	55 [45-65]	59 [43-67]	53 [45-65]	
Range (y)	18-89	19-89	18-74	
Male	46.4%	51.1%	43.3%	0.4
Race				0.002
White	68.8%	55.6%	77.6%	
African American	21.4%	37.8%	10.5%	
Other/unknown	9.8%	6.7%	11.9%	
Diabetes	19.6%	40.0%	6.0%	<0.001
Heart Failure	11.6%	22.2%	4.5%	0.004
Coronary Artery Disease	8.0%	20.0%	0%	<0.001
Hypertension	46.4%	88.4%	19.4%	<0.001
Medical Center				
BID	27.7%	0%	46.3%	NA
Tufts	72.3%	100%	53.7%	NA
White Matter Grade	1.1 ± 1.4	1.6 ± 1.5	0.7 ± 1.2	<0.001
Cerebral Atrophy				
Sulcal Grade	1.3 ± 1.5	2.3 ± 1.8	0.6 ± 0.7	<0.001
Ventricular Grade	1.5 ± 1.7	2.3 ± 2.0	0.9 ± 1.3	<0.001
Hippocampal Grade	1.2 ± 0.4	1.3 ± 0.6	1.0 ± 0.2	<0.001
SVI	7.1%	17.8%	0%	<0.001
LVI	2.7%	6.7%	0%	0.06
SVI or LVI	8.9%	22.2%	0%	<0.001

Note: Hemodialysis patients and controls both without self-reported stroke. Unless otherwise indicated, values for continuous variables presented as mean ± SD or median [IQR]; values for categorical variables given as percentage.

Abbreviations: BID, Beth Israel Deaconess; NA, not applicable;SVI small vessel infarct; LVI, large vessel infarct.

Table 2

Association of Hemodialysis Status with White Matter Grades Adjusted for Clinical Characteristics

	Unadjusted		Adjusted†	
	β Coefficient [95% CI]	p	β Coefficient [95% CI]	p
Age (per 15 y increase)	0.66 (0.43 to 0.89)	<0.001	0.64 (0.40 to 0.88)	<0.001
Female vs Male	−0.14 [−0.66,0.38]	0.6	0.02 [−0.44, 0.49]	0.9
White vs Non-White	0.06 [−0.50,0.62]	0.8	−0.001 [−0.54, 0.54]	0.9
Diabetes	0.56 [−0.09,1.21]	0.09	−0.36 [−1.02, 0.30]	0.3
CHF or CAD history	1.01 [0.32,1.69]	0.004	0.37 [−0.37, 1.11]	0.3
Hypertension	0.75 [0.23,1.26]	0.005	0.30 [−0.32, 0.92]	0.3
Hemodialysis	0.88 [0.37,1.38]	0.001	0.69 [0.04, 1.33]	0.04

Note: β coefficient equals the white matter absolute grade change per the corresponding change in the covariate.

Abbreviations: CI, confidence interval; CHF, congestive heart failure; CAD, coronary artery disease.

† adjusted for all other covariates

Table 3

Association of Hemodialysis Status with Sulcal Grades Adjusted for Clinical Characteristics

	Unadjusted		Adjusted†	
	β Coefficient [95% CI]	p	β Coefficient [95% CI]	p
Age (per 15 y increase)	0.87 [0.64,1.10]	<0.001	0.71 [0.53,0.89]	<0.001
Female vs Male	−0.85 [−1.40,−0.31]	0.003	−0.49 [−0.84,−0.15]	0.006
White vs Non-White	0.16 [−0.44,0.77]	0.6	0.07 [−0.34,0.47]	0.8
Diabetes	1.48 [0.82,2.13]	<0.001	0.41 [−0.08,0.91]	0.1
CHF or CAD history	2.14 [1.49,2.80]	<0.001	0.53 [−0.03,1.08]	0.06
Hypertension	1.04 [0.52,1.57]	<0.001	−0.14 [−0.61,0.32]	0.5
Hemodialysis	1.71 [1.23,2.19]	<0.001	1.36 [0.87,1.84]	<0.001

Note: β coefficient equals the sulcal absolute grade change per the corresponding change in the covariate.

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval.

† adjusted for all other covariates

Table 4

Association of Hemodialysis Status with Ventricular Grades Adjusted for Clinical Characteristics

	Unadjusted		Adjusted†	
	β Coefficient [95% CI]	p	β Coefficient [95% CI]	p
Age (per 15 y increase)	1.00 [0.74,1.26]	<0.001	0.88 [0.63,1.13]	<0.001
Female vs Male	−0.77 [−1.40,−0.14]	0.02	−0.44 [−0.92,0.05]	0.08
White vs Non-White	0.38 [−0.31, 1.07]	0.3	0.23 [−0.05,0.92]	0.4
Diabetes	1.31 [0.54,2.08]	0.001	0.41 [−0.28,1.10]	0.2
CHF or CAD history	1.80 [0.99,2.60]	<0.001	0.19 [−0.58,0.97]	0.6
Hypertension	0.87 [0.25,1.49]	0.006	−0.01 [−0.66,0.64]	0.9
Hemodialysis	1.37 [0.77,1.97]	<0.001	1.06 [0.39,1.74]	0.002

Note: β coefficient equals the ventricular absolute grade change per the corresponding change in the covariate.

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval.

† adjusted for all other covariates

Table 5

Association of Hemodialysis Status with Hippocampal Grades Adjusted for Clinical Characteristics

	Unadjusted		Adjusted†	
	OR* [95% CI]	p	OR* [95% CI]	p
Age (per 15 years increase)	5.52 [2.08, 14.67]	0.001	4.74 [1.46,15.35]	0.01
Female vs Male	0.30 [0.09, 1.02]	0.05	0.35 [0.07, 1.76]	0.2
White vs Non-White	0.26 [0.03, 2.13]	0.2	0.88 [0.14, 5.59]	0.9
Diabetes	2.65 [0.79, 8.89]	0.1	1.09 [0.16, 7.49]	0.9
CHF or CAD history	7.91 [2.33, 26.82]	0.001	0.93 [0.13, 6.68]	0.9
Hypertension	2.56 [0.72, 9.06]	0.2	0.48 [0.05, 4.76]	0.5
Hemodialysis	11.82 [2.50, 55.92]	0.002	13.52 [1.09, 168.19]	0.04

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; OR, odds ratio.

*Note that for Hippocampal grade ORs are presented instead of beta-coefficents

†adjusted for all other covariates