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Cognitive Function and Dialysis Adequacy: No Clear Relationship

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Key Words
Cognitive function · Dialysis adequacy · Chronic kidney disease

Abstract
Background/Aims: Cognitive impairment is common in hemodialysis patients and may be impacted by multiple patient and treatment characteristics. The impact of dialysis dose on cognitive function remains uncertain, particularly in the current era of increased dialysis dose and flux. ***Methods:*** We explored the cross-sectional relationship between dialysis adequacy and cognitive function in a cohort of maintenance hemodialysis patients. Adequacy was defined as the average of the 3 most proximate single pool Kt/V assessments. A detailed neurocognitive battery was administered during the 1st hour of dialysis. Multivariable linear regression models were adjusted for age, sex, education, race and other clinical and demographic characteristics. ***Results:*** Among 273 patients who underwent cognitive testing, the mean (SD) age was 63 (17) years and the median dialysis duration was 13 months, 47% were woman, 22% were African American, and 48% had diabetes. The mean (SD) Kt/V was 1.51 (0.24). In univariate, parsimonious and multivariable models, there were no significant relationships between decreased cognitive function and lower Kt/V. ***Conclusion:*** In contrast to several older studies, there is no association between lower Kt/V and worse cognitive performance in the current era of increased dialysis dose. Future studies should address the longitudinal relationship between adequacy of dialysis and cognitive function to confirm these findings.

Introduction

Cognitive impairment is highly prevalent in hemodialysis patients [1–3]. There are several potential reasons for this, including a high prevalence of cerebrovascular disease, side effects of medications, anemia and depression [4–8]. Recent epidemiologic studies have shown that cognitive impairment may be common in earlier stages of CKD and appears to become increasingly prevalent as kidney function worsens [9–13]. It remains unknown, however, whether uremia per se is an important contributor to cognitive impairment and whether higher doses of dialysis, and therefore greater solute clearance, may be associated with better cognitive function.

Several older studies have suggested a that decreased dialysis dose may be associated with worse cognitive function in hemodialysis patients, with multiple cognitive domains affected, including attention, mental processing, memory, intelligence and perceptual-motor function [14, 15]. Conversely, other older studies and an-

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other more recent study failed to appreciate a link between dialysis adequacy and cognitive function [16–18]. Several of these studies have important limitations: the study of Kutlay et al. [16] and colleagues used only the Mini-Mental State Examination (MMSE) for cognitive assessment while Pliskin et al. [17] only studied 16 well-dialyzed individuals. Tamura et al. [18] performed the most current evaluation of this question, using baseline data from the Frequent Hemodialysis Network trials. In this study, where global cognitive impairment was defined as a score <80 on the Modified MMSE (3MS), and impaired executive function was defined as a score ≥300 s on the Trail Making Test (part B only), there was no association between dialysis adequacy and cognitive performance. The latter study, however, did not focus on dialysis adequacy. There are no studies of which we are aware that have evaluated the relationship between adequacy of dialysis and cognitive function using a detailed cognitive battery in the current era of increased dialysis dose.

Methods

Participants

All patients receiving hemodialysis at 5 Dialysis Clinic Inc. (DCI) units in the greater Boston area were considered for the Cognition and Dialysis Study. Eligibility criteria included English fluency, sufficient visual and hearing acuity to complete cognitive testing, absence of pre-existing advanced dementia or confusion (based on provider testimony or medical chart review), a medically stable condition without acute non-access-related hospitalization within the previous month, receipt of maintenance hemodialysis for at least 1 month, and single pool Kt/V (spKt/V) >1.0. Demographic information was obtained through participant report, medical charts and the DCI database. The Tufts Medical Center Human Investigation Review Board approved the study, and all participants signed informed consent and research authorization forms.

Outcomes: Cognitive Function

Subjects were administered a battery of cognitive tests by trained research assistants to assure quality and inter-rater reliability. Reassessment of research assistants by the study neuropsychologist (T.S.) with either mock training sessions or witnessed testing of study participants occurred at 3- to 6-month intervals. To limit subject fatigue, all testing was completed during the 1st hour of hemodialysis. The neuropsychological battery included well-validated and commonly used cognitive tests that possess high inter- and intrarater reliability and have established age, gender and education-matched normative scores. Tests included the MMSE [19], the North American Adult Reading Test [20], the Wechsler Memory Scale-III Word List Learning Subtest [21], the Wechsler Adult Intelligence Scale-III Block Design and Digit Symbol-Coding tasks [21], and Trail Making Tests A and B [22] (online suppl. table 1, www.karger.com/doi/10.1159/000322611). The overall battery assessed a broad range of functioning including global ability, verbal intelligence, supraspan learning, auditory retention, visual retention, attention/mental processing speed, visual construction/fluid reasoning and motor speed.

Exposure: Kt/V

Adequacy of dialysis was quantified by spKt/V. The value for spKt/V was obtained from the monthly charts of the DCI electronic database. In order to improve the appropriate classification of the exposure variable, an average of the 3 most proximate spKt/V values for each participant was used.

Statistical Analysis

Baseline characteristics of eligible dialysis patients who consented and did not consent to participate were compared using χ^2 tests, t tests and ANOVA as appropriate. Similarly, baseline characteristics of participants enrolled in the study were compared by sex-specific quartiles of spKt/V. Primary analyses used linear regression to explore the association of spKt/V with performance on individual cognitive tests, with the raw test scores serving as the dependent variables. Kt/V was modeled linearly with parameter estimates (β-coefficients) calculated per 1 SD increase and also using sex-specific quartiles to assess for nonlinear relationships. Analyses where performance on the Trails B test was the outcome used Tobit regression, censoring for failure to complete the task within 5 min [23]. Parsimonious models were adjusted a priori for age, sex, race (African American vs. non-African American) and education (did not graduate high school, high school graduate and/or 1 year of college, 2+ years of college). Fully adjusted models were further adjusted for cause of ESRD, dialysis vintage, BMI, history of smoking, history of cardiovascular disease, hematocrit and albumin. Secondary analyses explored this association using sex-specific quartiles of spKt/V, reflecting the findings from the HEMO Study, which suggested there may be a different effect of adequacy on mortality in men and women, and recognizing that there are frequently inherent differences in the ability to achieve Kt/V targets by sex [24–26]. Finally, in sensitivity analyses we examined the association between spKt/V and cognitive performance in separate models for men and women. All analyses were performed using SAS, version 9.2 (SAS Institute, Cary, N.C., USA); differences were considered statistically significant at $p < 0.05$.

Results

Among the 753 dialysis patients who were screened, 430 were eligible for the study. Of the eligible patients, 280 consented and 273 completed the testing. Eligible patients not enrolled were similar to those who were enrolled across all measured characteristics, including age, race, sex, dialysis vintage and primary cause of ESRD, with the exception of lower phosphate [mean (SD): 5.1 (1.5) mg/dl], serum albumin [3.7 (0.5) mg/dl] and intact parathyroid hormone [median: 196 pg/ml (interquartile range: 126–300)] in eligible patients who did not consent.

Table 1. Characteristics of participants by sex-specific quartiles of spKt/V

	Total (n = 273)	Kt/V, Q1 (n = 68)	Kt/V, Q2 (n = 68)	Kt/V, Q3 (n = 68)	Kt/V, Q4 (n = 69)	Trend p value
Age, years	63 ± 17	60 ± 17	63 ± 16	67 ± 15	64 ± 18	0.099
Female	47	47	47	48	47	0.932
African American	22	24	31	16	16	0.092
Education						0.045
<12th grade	10	16	4	4	13	
High school graduate	58	49	69	56	59	
2+ years college	32	35	26	40	28	
Medical history						
Peripheral vascular disease	22	25	15	29	19	0.862
Coronary artery disease	33	28	29	41	35	0.207
Hypertension	87	82	90	88	88	0.357
Stroke	20	22	18	21	19	0.755
Diabetes	48	56	54	46	35	0.008
Heart failure	34	34	37	35	30	0.647
Primary cause of ESRD						0.042
Diabetes	37	44	45	40	19	
Glomerulonephritis	18	21	11	12	28	
Hypertension	20	12	20	21	26	
Other	19	16	17	19	23	
Unknown	7	7	8	9	4	
Smoking history						0.034
Never	38	40	39	32	40	
Past	55	52	46	68	52	
Current	8	8	15	0	8	
spKt/V	1.51 ± 0.24	1.25 ± 0.10	1.42 ± 0.09	1.56 ± 0.09	1.79 ± 0.19	<0.001
Systolic BP, mm Hg	143 ± 21	142 ± 22	146 ± 20	141 ± 20	142 ± 21	0.713
Diastolic BP, mm Hg	73 ± 12	75 ± 14	74 ± 2	71 ± 11	73 ± 12	0.163
BMI (kg/m^2)	28 ± 7	31 ± 9	29 ± 6	27 ± 6	26 ± 6	<0.001
Hematocrit, %	36 ± 3	36 ± 4	36 ± 3	35 ± 3	35 ± 3	0.020
Serum albumin, g/dl	3.8 ± 0.3	3.8 ± 0.4	3.9 ± 0.3	3.9 ± 0.4	3.9 ± 0.3	0.061
Phosphate, mg/dl	5.5 ± 1.5	5.8 ± 1.9	5.3 ± 1.5	5.1 ± 1.2	5.5 ± 1.4	0.463
Dialysis vintage, months	13 (6–32)	9 (4–19)	12 (5–28)	17 (10–38)	19 (11–39)	<0.001
PTH, pg/ml	223 (143–390)	226 (129–414)	227 (141–332)	217 (152–343)	225 (145–403)	0.996

Continuous data shown are means ± SD, except dialysis vintage and PTH which are medians (interquartile range); categorical data are presented as percentages. p values for education, primary cause of ESRD and smoking are from a χ^2 test. p values for dialysis vintage and PTH are from the Kruskal-Wallis test. Conversion factors for units: albumin in g/dl to g/l, multiply by 10; phosphate in mg/dl to mmol/l, multiply by 0.3229. BP = Blood pressure; PTH = parathyroid hormone.

The mean (SD) age of enrolled participants was 63 (17) years; 47% were female, 22% African American, 48% had diabetes and the median (interquartile range) of dialysis vintage was 13 months (6–32). Mean (SD) Kt/V was 1.51 (0.24) (table 1).

We noted no consistent relationship between lower levels of Kt/V and worse cognitive function (table 2). In fact, participants with higher Kt/V performed significantly worse on the MMSE in univariate linear regression analyses and after parsimonious and multivariable adjustments. Participants with higher Kt/V also had worse performance in the recognition task after parsimonious and multivariable adjustments (table 2). Results were consistent using sex-specific quartiles with no association between lower levels of Kt/V and worse cognitive function. The sex-specific quartile analyses demonstrated worse performance on the MMSE with higher Kt/V, when evaluating the unadjusted means (table 3). Results were consistent in sex-specific quartiles examining the β-coefficients after multivariable adjustments (table 3).

Table 2. Cognitive testing by Kt/V

Cognitive test	Function tested	Univariate		Parsimonious		Multivariable	
		β-coefficient	p value	β-coefficient	p value	β-coefficient	p value
MMSE	screen	–0.45	0.010	–0.57	0.001	–0.48	0.012
NAART	intelligence	0.04	0.958	–0.57	0.413	–0.95	0.220
Percent retention	primary cortical (memory)	–1.12	0.519	–2.69	0.126	–1.32	0.510
Recognition		–0.29	0.116	–0.47	0.007	–0.46	0.024
Block design	primary subcortical (executive function and processing speed)	–0.56	0.396	–0.59	0.327	–0.13	0.843
Digit symbol coding		0.72	0.524	–0.68	0.462	–0.61	0.546
Trails A		0.37	0.876	1.68	0.472	0.60	0.820
Trails B		1.28	0.857	7.12	0.255	1.50	0.823

Results represent per 1 SD (0.24) increase in Kt/V. Trails B analyses were performed using Tobit regression to account for failure to complete the task within 5 min. Negative β-coefficients indicate worse performance associated with high Kt/V for all tests except Trials A and B where a positive score indicates worse performance. Parsimonious models adjust for age, sex, race and education while full multivariable models additionally adjust primary cause of ESRD, dialysis vintage, BMI, history of smoking, history of cardiovascular disease, hematocrit and albumin. NAART = North American Adult Reading Test.

Table 3. Univariate means and multivariable β-coefficients for cognitive testing by sex-specific quartiles of Kt/V

Cognitive test	Function tested	Univariate means by sex-specific Kt/V quartiles					Multivariable β-coefficients by sex-specific Kt/V quartiles			
		Kt/V Q1	Kt/V Q2	Kt/V Q3	Kt/V Q4	trend p value	Kt/V Q1	Kt/V Q2	Kt/V Q3	trend p value
MMSE	screen	27.1	26.6	26.9	25.8	0.007	1.03	1.00	1.07	0.056
NAART	intelligence	101.8	103.2	102.5	100.5	0.474	3.21	4.91	1.49	0.051
Percent retention	primary cortical (memory)	55.8	52.0	52.9	49.5	0.251	0.17	0.71	1.68	0.983
Recognition		21.0	21.1	21.0	20.0	0.062	0.74	1.43	1.15	0.144
Block design	primary subcortical (executive and processing speeds)	26.3	28.0	24.8	26.4	0.604	–1.37	1.84	–0.84	0.771
Digit-symbol coding		42.4	40.1	37.8	40.7	0.440	0.19	1.42	–0.11	0.810
Trails A		58.0	59.4	60.6	64.0	0.368	–2.92	–5.98	–6.16	0.692
Trails B		172.5	177.4	209.4	178.2	0.435	7.63	–9.83	16.42	0.986

Results represent the mean raw score by sex-specific Kt/V quartiles and β-coefficient by sex-specific quartiles. Trails B analyses were performed using Tobit regression to account for failure to complete the task within 5 min. β-Coefficients by sex-specific quartiles are in reference to Kt/V, Q4. Minimum and maximum spKt/V for each quartile by sex – men: Q1 (0.97–1.28), Q2 (1.29–1.41), Q3 (1.42–1.54), Q4 (1.55–1.96); women: Q1 (1.06–1.43), Q2 (1.43–1.58), Q3 (1.58–1.73), Q4 (1.73–2.56). NAART = North American Adult Reading Test.

In the sensitivity analyses stratified by sex, there was no association between lower levels of Kt/V and worse cognitive function in either men or women (data not shown). However, in men in both univariate and parsimonious models, those with higher Kt/V performed worse in the MMSE (β-coefficient = –0.57, p = 0.018; β-coefficient = –0.64, p value = 0.005, respectively). This finding was not seen in women.

Discussion

In maintenance hemodialysis patients, we saw no evidence that lower levels of dialysis adequacy are associated with worse function on memory or executive function. In fact, we noted that testing of global cognitive function, measured by the MMSE, and recognition were slightly worse in those with higher Kt/V levels, although this finding was inconsistent across cognitive domains.

These results suggest that, in the current era of increased dialysis dose, there is no association of higher Kt/V with better cognitive function. Our results are consistent with a recent study from the Frequent Hemodialysis Network (FHN) trials where cognitive function was evaluated in 383 relatively healthy dialysis participants. In that particular study, the 3MS and Trails B were used as indicators of global cognitive function and executive function, respectively. Results showed that higher, rather than lower, Kt/V was significantly associated with worse cognitive performance on Trails B, but there was no relationship of Kt/V with the 3MS. In combination, both studies are consistent with the absence of an association of higher levels of cognitive function with higher Kt/V. The current study, however, adds to the FHN study by evaluating a more comprehensive battery of cognitive tests, focusing exclusively on the relationship between cognitive function and Kt/V rather than on multiple risk factors for cognitive impairment, and in using a more generalizable population.

The paradoxical finding of better cognitive function in those with lower Kt/V in the FHN study and with recognition in our current study most likely reflects residual confounding. That is, patients who able to achieve high Kt/V are usually underweight and more malnourished [27]. Frequently, these patients are also more susceptible to toxicity caused by more intensive dialysis, have more comorbid conditions, are sicker and, therefore, are more likely to have worse cognitive function [28, 29].

Our study has several strengths. First, the extensive and detailed neurocognitive evaluation allowed us to examine the relationship between dialysis adequacy and several cognitive domains. Second, we had a relatively large sample with minimal exclusion criteria. This led to relatively generalizable population with participants having characteristics and distribution of causes of ESRD similar to those found in the prevalent US dialysis population [30].

Our study also has several limitations. First, as alluded to above, because of the observational nature of the study, residual confounding may be present. Second, our study only included patients with spKt/V$\geq$1; therefore, we cannot comment on whether levels below those are associated with worse cognitive function. Third, cognitive testing was performed on hemodialysis, which may lead to slightly worse performance on cognitive testing [31]. Testing during dialysis, however, should not alter the relationship between Kt/V and cognitive function, the primary outcome of this study. Furthermore, although there may be a downside to assessing patients during hemodialysis, it does have the advantage of testing patients in the same environment where they are likely to receive most of the medical counseling from physicians, nurses and nutritionist providers. Finally the study was cross-sectional and we cannot rule out an association of higher Kt/V with higher levels of cognitive function in prospective analyses.

In summary, in the current era of increased dialysis dose, we have not demonstrated any association between higher achieved dialysis dose and better performance on any measure of cognitive testing. Future research should confirm these results in longitudinal analyses.

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Disclosure Statement

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