MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2023; 29: e940409
DOI: 10.12659/MSM.940409

Received: 2023.03.18
Accepted: 2023.04.17
Available online: 2023.05.30
Published: 2023.06.19

A Case-Control Study of Cognitive Function in Patients with End-Stage Renal Disease Before and After Hemodialysis in Southern Spain

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Financial support: This research was supported by grant [PI-0674-2012] from the Council of Equality, Health, and Social Policy, Junta de Andalucía
Conflict of interest: None declared

Background: Cognitive problems are frequent in patients with end-stage renal disease (ESRD) treated with hemodialysis. However, previous studies used only a single cognitive screening test or a small number of cognitive indices, which is inadequate for an exhaustive evaluation of cognitive deficits. This case-control study aimed to evaluate cognitive function in patients with ESRD before and after hemodialysis at centers in southern Spain, and included analysis of associations between cognitive function and duration of hemodialysis, biochemistry, body composition, and treatment variables.

Material/Methods: Cognitive performance was evaluated in 42 healthy participants (HPs) and in 43 ESRD patients, before and after hemodialysis. The tests measured verbal and visual memory, sustained/selective attention, and processing speed. The diagnostic criterion for ESRD was a glomerular filtration rate <15 mL/min/1.73 m^2. Correlation and multiple regression analyses were used to explore the relationships between cognitive and clinical variables, controlling for age, schooling, mood, and blood pressure.

Results: Scores for verbal memory, sustained/selective attention, and processing speed were lower in patients with ESRD treated with hemodialysis than in HPs, with no between-group differences in visual memory. No acute hemodialysis-specific effect on performance was observed. Several biochemistry variables were associated with performance, both negatively (eg total cholesterol, calcium, and total protein) and positively (eg sodium, phosphorus, and creatinine).

Conclusions: Patients with ESRD treated with hemodialysis showed cognitive deficits in verbal memory, sustained/selective attention, and processing speed. Performance was not significantly different between tests administered before and after hemodialysis. An adequate diet as well as physical exercise could be useful to improve cognitive performance in this population.

Keywords: **Neuropsychological Tests • Cognitive Dysfunction • Renal Dialysis • Renal Insufficiency, Chronic**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/940409

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Background

Cognitive problems are frequently observed in patients with end-stage renal disease (ESRD) treated with hemodialysis [1-3], including disorders in processing speed, attention, visual and verbal memory, language, logical memory, cognitive change, and planning [4-7]. Disorders in components of executive functions were also recently observed in ESRD patients treated with hemodialysis, including working memory, fluency, cognitive flexibility, inhibitory control, and decision-making [8]. However, many of these studies used only a single cognitive screening test [9-11] or only a small number of cognitive performance indices [12-14], which is inadequate for a complete evaluation of associated deficits [15]. Cognitive disorders in these patients have been associated with a higher mortality risk [16-19]. For this, it is of great interest to exhaustively study these cognitive deficits in this population.

Discrepant findings have been observed in studies examining the acute effect of hemodialysis on cognitive domains, which are likely attributable to differences in the timing of evaluations. Costa et al [6] observed slower reaction times in alertness and interference tasks and worse verbal memory scores immediately after hemodialysis in comparison with those recorded the day before, contrasting with the improvement shown by healthy controls between a first and second evaluation. Researchers conducting evaluations after longer post-hemodialysis intervals observed improvements in: attention, concentration, visual/verbal memory, and psychomotor speed at 24 h post-hemodialysis [20]; visual and logical memory, psychomotor speed, planning, and concentration at 19 h post-hemodialysis [4]; and inhibition of working memory at 20 h post-hemodialysis [8]. In this last case, no post-hemodialysis improvement was observed in planning, decision-making, figurative and verbal fluency, or cognitive flexibility and reasoning. Hence, the timing of evaluations may be a crucial factor to consider in assessing cognitive disorders and the acute effects of hemodialysis in these patients.

Previous findings about the associations between cognitive performance and clinical variables in ESRD patients treated with hemodialysis have been, in some cases, contradictory and inconclusive. Regarding the renal replacement therapy received, recent findings using screening measures (Brief Cognitive State Examination) have shown worse cognitive performance in ESRD patients treated with hemodialysis compared with transplantation patients [21], but previous research did not observe cognitive improvements after transplantation in attention, visual planning, mental processing speed, or motor abilities [22]. Worse attention and executive function [23] and increased risk of developing dementia have been observed in ESRD patients treated with hemodialysis compared with ESRD patients treated with peritoneal dialysis [24]. However, other investigations did not find systematic differences in cognitive performance when comparing both modalities of dialysis, in a wide variety of cognitive domains [25]. In terms of dialysis efficacy, low dialysis clearance time per body water volume (Kt/V) has been frequently associated with severe cognitive impairment [26,27]. In other cases, however, the relationship has been the opposite (with greater Kt/V associated with worse cognitive performance) [28,29]. With respect to body composition parameters, better post-hemodialysis cognitive-psychomotor performance has been observed in ESRD patients with high body mass index (BMI) [30], whereas the medical literature usually associates a higher BMI with cognitive impairment in normal populations [31], and neurological [32] and neuropsychological consequences of obesity and overweight are well known [33,34]. As to biochemical values, increased urea levels have been related to both the impairment [12] and improvement [8,20] of cognitive performance, while reports on the relationship of calcium, phosphorus, and sodium levels with neuropsychological performance have been inconsistent [6,20].

In general, studies on cognitive performance in ESRD patients treated with hemodialysis have small sample sizes, do not adequately control for sociodemographic variables related to cognitive performance (eg, age and years of education), and take little consideration into the timing of neuropsychological evaluations with respect to the hemodialysis [26,35]. The few investigations on the acute effect of hemodialysis share the same limitations [4,6]. In addition, due to the high prevalence of emotional disturbances such as anxiety and depression in ESRD patients treated with hemodialysis [36], and the relationship of these variables with cognitive performance [37,38], it is important to control for the influence of these variables on cognition.

With the above background, this case-control study aimed to evaluate cognitive function in 43 patients with ESRD before and after hemodialysis in centers located in southern Spain, including analysis of duration of hemodialysis, biochemistry findings, patient body composition, and treatment variables. Thus, the aims of this research were: (1) to compare cognitive performance, using memory, attention, and processing speed indices, between ESRD patients treated with hemodialysis and healthy participants (HPs, as a control group) matched for major sociodemographic characteristics; (2) to compare cognitive performance before and after hemodialysis; and (3) to analyze associations of cognitive performance with biochemical, treatment, and body composition variables. Our hypotheses were that: (1) cognitive performance would be lower in ESRD patients treated with hemodialysis than in HPs, when controlled for sociodemographic and emotional variables; (2) the performance would be superior after vs before hemodialysis; and (3) there would be associations between biochemical,

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treatment, and body composition variables and the cognitive performance indices studied.

Material and Methods

The study was approved by the Ethics Committee of the Jaén Hospital Complex (Spain) (March 28, 2012). All participants were informed of the study objectives and methods and previously signed a written informed consent, also approved by the Ethics Committee.

Participants

The study included 43 patients (8 female, 35 male) with ESRD treated with hemodialysis, and 42 HPs (13 female, 29 male). Seven of the ESRD patients had been previously under peritoneal dialysis, and 17 were previously transplanted. ESRD was diagnosed on the basis of a glomerular filtration rate <15 mL/min/1.73 m^2. The method used for hemodialysis was conventional high permeability hemodialysis. Inclusion criteria for the ESRD patients treated with hemodialysis group were: (1) hemodialysis treatment for ≥3 months before the study; (2) receipt of 3 weekly 4-hour hemodialysis sessions; (3) absence of neurological, infectious, or systemic disorders or traumatic brain injury; (4) absence of previous psychiatric diagnosis including drug abuse; and (5) absence of severe auditory and/or visual impairment. The same inclusion criteria were applied for the HP group, except for points 1 and 2. The 2 groups were similar in age, sex, and years of education (**Table 1**). The causes of ESRD were: glomerulonephritis (39.5%), hereditary (23.3%), vascular (11.6%), systemic (4.7%), interstitial (4.7%), diabetic (2.3%), miscellaneous (2.3%), or undefined (11.6%). All participants were native Spanish speakers.

Cognitive Assessment

The instruments used to evaluate cognitive processes were:

- *Visual memory* [39]. The Rey-Osterrieth Complex Figure (ROCF) test was used as follows. Participants were asked to make a free-hand copy of a complicated line drawing and then, after an interval of 15 minutes, draw it from memory. The accuracy of the copy (copy execution) and of the reproduction from memory (memory execution) were used as dependent variables.
- *Verbal memory*, using the Spanish version [40] of the *California Verbal Learning Test* [41]. The experimenter read aloud a list of nouns (shopping list A) that participants were directed to recall immediately, conducted in 5 trials. An interference list was then read aloud (shopping list B), and the short-term and long-term recall of list A was then tested by asking participants to identify words from this list within a list of 44 words. Dependent variables were: free short-term recall (TAVEC RLCP), free long-term recall (TAVEC RLLP), total words recalled in the set of 5 trials (TAVEC RIAT), and the discriminability index (TAVEC Discrim), calculated with the formula: (1- {false positives + omissions / 44} ×100).
- *Sustained and selective attention*, using the following indices of the d2 test [42]: total correct answers (d2 TCA); total attention capacity (d2 TOT), calculated as total number of processed elements (TR) minus the total number of omission (O) errors and commission (C) errors; and the concentration index (d2 CON), calculated as the number of total correct answers (d2 TCA) minus the number of C errors.
- *Processing speed*, using the following indices: execution times (s) under conditions 2 and 3 in Trail Making Test A, in which participants must arrange, as quickly and accurately as possible, numbers in ascending order (TMT-A C2) and letters in alphabetical order (TMT-A C3) [43]; execution times (s) of conditions 1 and 2 in the Stroop test, rapidly and accurately naming the color of different colored squares (Stroop C1) or written words in colored font (Stroop C2) [43]; execution times (s) of conditions 1 and 2 in the Five Digit Test [44], in which participants must name the number written in each box (5DT C1) or count the number of elements in each box (5DT C2) as quickly and accurately as possible; and (d2 TR) of the d2 attention test, measuring the total number of elements processed in a given time, in which the execution time is inversely related to the processing speed and directly related to the total number of processed elements [42].

Detailed information about these instruments and methods can be obtained elsewhere [8].

Clinical and Treatment Variables

Medical data for the ESRD patients treated with hemodialysis group were gathered from hospital records. The records included: disease etiology, current and total time (in months) under hemodialysis, number of transplants, total time (in months) since transplantation, total time (in months) under peritoneal dialysis or hemodialysis, dialysis effectiveness (Kt/V), and hours since the last hemodialysis. Furthermore, information was gathered before the hemodialysis (or first evaluation of controls) on the most recent biochemical analysis results (hemoglobin, hematocrit, total proteins, total cholesterol, ferritin, calcium, phosphorus, sodium, urea, and creatinine in blood tests), body composition (using a Bodystat® 1500 monitoring unit), and 7 blood pressure measurements (by a 3M Tensocare B100 arm blood pressure monitor). Anxiety and depression were measured using the Spanish version [45] of the Hospital Anxiety and Depression Scale (HADS) [46], avoiding the influence of somatic symptoms. Scores in the 2 subscales were added together to obtain a global mood score.

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Table 1. Sociodemographic, biochemical, blood pressure, body composition, and treatment characteristics data in end-stage renal disease patients treated with hemodialysis and heathy participants.

Variables		ESRD-HD (n=43)		HP (n=42)	
		Mean	SD	Mean	SD
Age		51.72	9.310	51.83	6.525
Years of education		10.98	4.405	11.14	3.653
Sex (%)	Male	81.4		69.0	
	Female	18.6		31.0	
Current months HD		42.00	61.53	–	–
Previous TX, n (%)		17 (39.53)		–	–
Nº TX		0.44	0.59	–	–
Total months TX		42.53	81.04	–	–
Total months HD		58.88	70.25	–	–
Total months PD		4.00	10.46	–	–
Total months D		62.88	68.32	–	–
Total months RRT		105.42	114.56	–	–
Total Kt/v		1.69	0.41	–	–
Pre-HD hours		56.56	5.34	–	–
Post-HD hours		20.84	2.83	–	–
Hours pre-post evaluation		47.67	36.47	35.31	6.61
Hypertensive patients, n (%)		38 (88.37)		–	–
Systolic blood pressure*		140.08	20.14	128.78	13.15
Diabetic patients, n (%)		3 (6.98)		–	–
Water%**		58.42	5.52	52.67	5.13
BMI*		25.71	3.55	27.64	3.45
Dry weight kg*		70.45	14.27	80.04	13.52
Hemoglobin g/dL**		11.74	1.46	15.18	1.12
Hematocrit%**		35.17	4.55	45.26	3.14
Total proteins g/dL		6.65	1.04	7.1	0.34
Total cholesterol mg/dL**		153.51	28.74	218.38	32.38
Ferritin ng/mL**		399.49	156.45	123.56	57.98
Calcium mg/dL		9.44	1.26	9.57	0.27
Phosphorus mg/dL*		4.75	1.61	3.36	0.63
Sodium mEq/L		139.52	2.56	139.96	2.34
Urea mg/dL**		124.33	33.49	35.40	11.04
Creatinine mg/dL**		9.56	2.46	0.92	0.14

* p<.05, ** p<.001. ESRD HD – end-stage renal disease treated with hemodialysis; HP – healthy participants; Current months HD – number of months under current hemodialysis treatment; Previous TX, n (%) – total number (and percentage) of patients previously transplanted; Nº TX – total number of previous transplants received; Total months TX – total number of months in transplantation; Total months HD – total number of months treated with hemodialysis; Total months PD – total number of months treated with peritoneal dialysis; Total months D – total number of months treated with dialysis (hemodialysis and/or peritoneal dialysis); Total months RRT – total number of months treated with renal replacement therapy (hemodialysis, peritoneal dialysis, transplantation); Total Kt/V – clearance time per body water volume, calculated with the second-generation Daugirdas formula; Pre-HD hours – hours that had elapsed since the last hemodialysis in evaluation 2; Post-HD hours – hours between the most recent hemodialysis session and the post-hemodialysis evaluation; Hours pre-post evaluation – hours elapsed between pre- and post-evaluations; Water% – percentage of body water; BMI – body mass index; Dry weight – ideal weight of individual with no excess fluid in blood.

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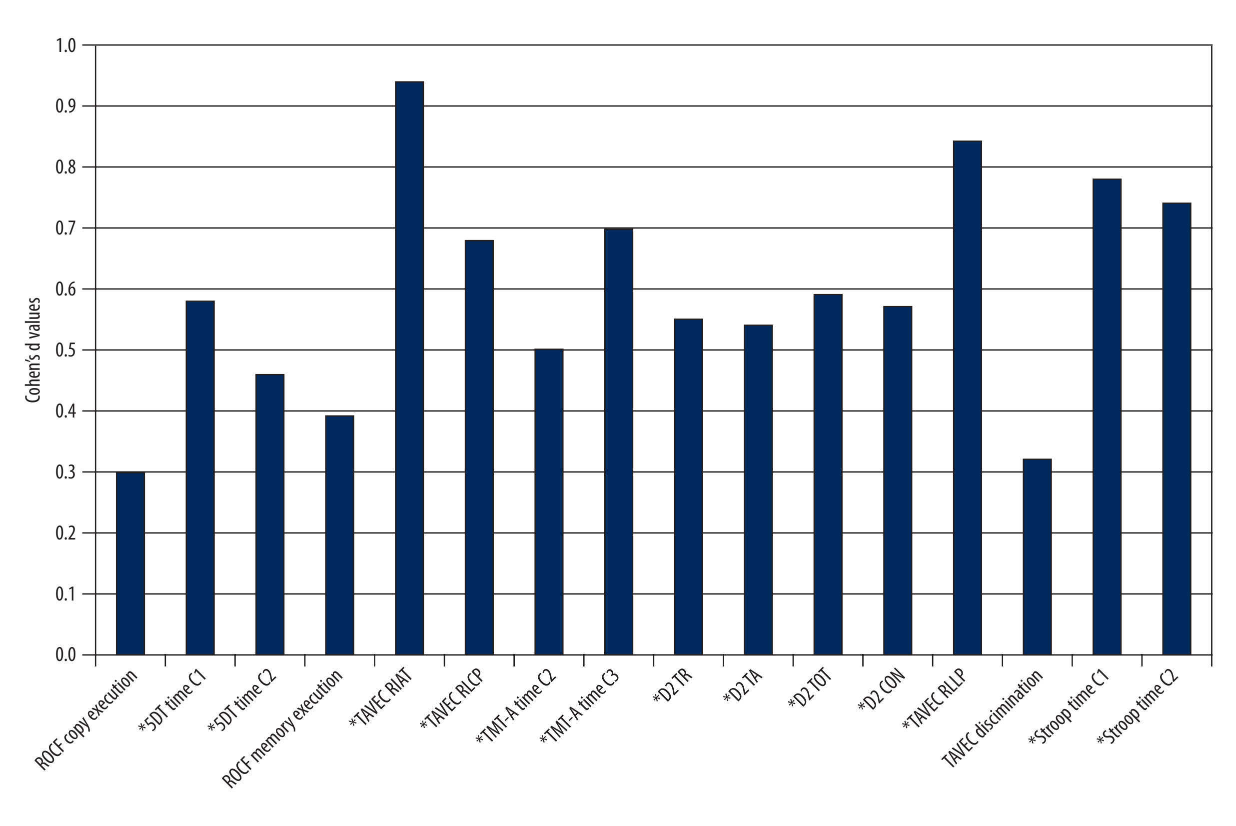

Figure 1. Cohen's d values for group comparisons of the dependent variables studied. The order of tests in the figure follows the sequence of their administration.

Procedure

The patients were selected from 5 hemodialysis centers in Granada and Jaén provinces (southern Spain). The patients were individually evaluated around 56 h after their previous hemodialysis (first evaluation; a few hours before receiving the second hemodialysis session). Then, they were evaluated again at approximately 20 h after the second hemodialysis session (around 48 hours after the pre-hemodialysis evaluation for the second hemodialysis session) (**Table 1**). HPs were also evaluated on 2 occasions with an equal period of time between evaluations as the hemodialysis patients. Participants did not consume tobacco, food, alcohol, or caffeine during the evaluations, which were conducted in the participants' homes after verifying that conditions were adequate for this purpose. Tests were performed in the same order by all participants, exchanging more/less difficult and verbal/non-verbal tests to avoid possible cognitive fatigue, which was also countered by allowing short 5-10 min rests between tasks. **Figure 1** depicts the test administration sequence.

Statistical Analysis

Group differences in cognitive performance were analyzed by multivariate analysis of variance (MANOVA), entering data from the pre-hemodialysis session (first evaluation of HPs) that included years of education, age, systolic blood pressure, and mood as covariates. A 2x(2) repeated-measures ANOVA was used to evaluate changes between the first and second evaluations (pre-post hemodialysis), with group as the between-subjects factor and the 2 assessments as repeated measures. A significant group x pre-post interaction effect associated with a greater increase from the pre- to the post- evaluations in the ESRD patients treated with hemodialysis group would indicate a hemodialysis-related improvement effect. Cohen's d and adjusted squared theta (η_p^2) served as effect size indicators for the group comparisons in the cognitive variables. Values of η_p^2 ≥01, ≥.06, and ≥.14 can be considered small, medium, and large effect sizes. Values of Cohen's d ≥0.10, ≥0.30, and ≥0.50 were considered small, medium, and large effect sizes, respectively. In the ESRD patients treated with hemodialysis group, Pearson correlations were first computed between cognitive performance and medical factors (body mass composition, biochemistry, and clinical parameters). Then, hierarchical multiple regression analyses were carried out, entering

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2 data blocks: (1) sociodemographic (years of schooling and age) and emotional (mood from HADS) variables that might influence performance, entered simultaneously; and (2) clinical factors, entered by the stepwise method. The adjusted R^2 of the prediction change associated with each block was calculated.

Results

Group Differences in Neuropsychological Performance

The MANOVA showed a main significant effect of group (F(16,64)=3.15, *P*=0.001, η_p^2=0.44) and significant effects of the covariates age (F(16,64)=2.63, *P*=0.003, η_p^2=0.40) and education level (F(16,64)=3.59, *P*≤0.001, η_p^2=0.47). **Table 2** lists the mean (and standard deviation) of each of the study variables and the comparison between groups. Before the hemodialysis (the first evaluation), the performance on 3 of the 4 verbal memory indices (TAVEC RLCP, TAVEC RLLP, TAVEC RIAT), all 3 sustained and selective attention indices (d2 TCA, d2 TOT, d2 CON), and 7 of the 9 processing speed indices (TMT-A C2, TMT-A C3, Stroop C1, Stroop C2, 5DT C1, 5DT C2, d2 TR) was lower in the ESRD patients treated with hemodialysis group than in the HP group. No between-group differences were observed in visual memory (ROCF copy and ROCF memory execution). Effect sizes (Cohen's d) ranged between 0.30 (ROCF copy execution) and 0.94 (verbal memory in TAVEC RIAT) (see **Figure 1**).

Pre-Post Dialysis Effect

The analysis revealed that the group factor (for global cognitive performance during both assessments) was significant for visual memory indices (ROCF copy execution: *P*=0.023, η_p^2=0.06), verbal memory (TAVEC RLCP: *P*=0.002, η_p^2=0.11; TAVEC RLLP: *P*<0.001, η_p^2=0.14; TAVEC RIAT: *P*<0.001, η_p^2=0.16); sustained and selective attention (d2 TCA: *P*=0.006, η_p^2=0.09; d2 TOT: *P*=0.014, η_p^2=0.07; d2 CON: *P*=0.011, η_p^2=0.07), and processing speed (TMT-A C2: *P*=0.003, η_p^2=0.10; TMT-A C3: *P*<0.001, η_p^2=0.14; Stroop C1: *P*=0.001, η_p^2=0.13; Stroop C2: *P*=0.001, η_p^2=0.13; 5DT C1: *P*=0.002, η_p^2=0.11; 5DT C2: *P*=0.034, η_p^2=0.05; d2 TR: *P*=0.034, η_p^2=0.05). There were marginally significant group differences for other visual (ROCF memory execution: *P*=0.057, η_p^2=0.04) and verbal (TAVEC Discrim: *P*=0.068, η_p^2=0.04) memory indices. Performance was poorer in the ESRD treated with hemodialysis group than in the HP group in all cases.

Performance levels in visual memory (ROCF memory execution), verbal memory (TAVEC RLCP, TAVEC RLLP, TAVEC RIAT, TAVEC Discrim), sustained and selective attention (d2 TCA, d2 TOT, d2 CON), and processing speed (ROCF copy time, TMT-A C2, TMT-A C3, Stroop C1, Stroop C2, 5DT C2, d2 TR) were superior before vs after the hemodialysis (**Table 3**). However, the group x pre-post interaction was not significant for any study variable.

Associations Between Neuropsychological Performance and Clinical Parameters in ESRD Patients Treated with Hemodialysis

Exploratory correlational analysis: The *total number of transplants* was positively associated with the total number of elements processed (ie, processing speed) (d2 TR: r=0.31, *P*=0.045)*;* the *total number of months under hemodialysis* was negatively associated with verbal memory (TAVEC Discrim: r=-0.32, *P*=0.037); *percentage of body water* was negatively associated with verbal memory (TAVEC Discrim: r=-0.39, *P*=0.009); *BMI* was negatively associated with execution time (ie, higher processing speed) (TMT-A C2: r=-0.32, *P*=0.035); *dry weight* was negatively associated with execution time (TMT-A C2: r=-0.35, *P*=0.020) but positively associated with sustained and selective attention (d2 CON: r=0.315, *P*=0.039); *total proteins* were negatively associated with verbal memory (TAVEC RLCP: r=-0.305, *P*=0.046; TAVEC RIAT: r=-0.39, *P*=0.011) and sustained and selective attention (d2 TCA: r=-0.33, *P*=0.030; d2 CON: r=-0.31, *P*=0.042); *total cholesterol* was negatively associated with verbal memory (TAVEC RLCP: r=-0.35, *P*=0.045; TAVEC RLLP: r=-0.37, *P*=0.037); *calcium* was positively associated with execution time (ie, lower processing speed) (TMT-A C2: r=0.34, *P*=0.025); *phosphorus* was positively associated with verbal memory (TAVEC Discrim: r=0.36, *P*=0.017), sustained and selective attention (d2 TCA: r=0.36, *P*=0.017; d2 TOT: r=0.37, *P*=0.015; d2 CON: r=0.39, *P*=0.010), and number of elements processed (d2 TR: r=0.31, *P*=0.042); *sodium* was positively associated with visual memory (ROCF copy execution: r=0.32, *P*=0.034); and *creatinine* was negatively associated with execution time (TMT-A C2: -0.37, *P*=0.016) and positively associated with sustained and selective attention (d2 TCA: r=0.31, *P*=0.045; d2 TOT: r=0.40, *P*=0.009; d2 CON: r=0.34, *P*=0.025) and the number of elements processed (d2 TR: r=0.40, *P*=0.009).

Multiple regression analysis for the prediction of neuropsychological functioning: After controlling for the effects of sociodemographic and mood variables, the following significant regression models were obtained: negative association of *total number of months under hemodialysis* with verbal memory (TAVEC Discrim: β=-0.40, r^2=0.15, t=-3.14, *P*=0.003); negative association of *total cholesterol* with verbal memory (TAVEC RLCP: β=-0.37, r^2=0.13, t=-2.25, *P*=0.032; TAVEC RLLP: β=-0.42, r^2=0.17, t=-2.58, *P*=0.015); positive association of *calcium* with execution time (ie, lower processing speed in TMT-A C2: β=0.29, r^2=0.08, t=2.39, *P*=0.022); positive association of *sodium* with visual memory (ROCF copy execution: β=0.37, r^2=0.13, t=2.58, *P*=0.014); and positive association of *creatinine* with sustained and selective attention (d2 TOT: β=0.31, r^2=0.09, t=2.71, *P*=0.010; d2 CON: β=0.25, r^2=0.06, t=2.10, *P*=0.042) and with number of elements processed (ie processing speed, d2 TR: β=*0*.34, r^2=0.11, t=2.67, *P*=0.011).

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Table 2. Mean (±SD) of cognitive variables for the 2 groups during the pre-hemodialysis evaluation.

Domain	Test	Dep. Var.	Group	Mean±SD	F (1,79)	p	η_p^2
Visual memory	Rey-Osterrieth complex figure (ROCF)	Copy execution	ESRD-HD	33.05±3.38	1.17	0.283	0.015
			Hp	33.90±2.16			
		Memory execution	ESRD-HD	16.85±6.14	2.46	0.121	0.030
			HP	19.01±4.71			
Verbal memory	Verbal learning test Spain-Complutense (TAVEC)	RLCP	ESRD-HD	9.12±3.16	9.29	0.003	0.105
			HP	11.12±2.71			
		RLLP	ESRD-HD	9.47±2.98	13.76	<0.001	0.148
			HP	11.86±2.67			
		RIAT	ESRD-HD	46.65±8.45	16.26	<0.001	0.171
			HP	54.43±8.17			
		Discriminability	ESRD-HD	91.61±5.57	1.68	0.198	0.021
			HP	93.57±6.51			
Sustained and selective attention	D2	TCA	ESRD-HD	125.12±34.73	5.36	0.023	0.063
			HP	144.17±36.09			
		TOT	ESRD-HD	318.14±79.57	7.65	0.007	0.088
			HP	365.74±82.47			
		CON	ESRD-HD	122.14±36.65	5.87	0.018	0.069
			HP	142.88±36.61			
Processing speed	Trail Making Test A (TMT-A)	C2	ESRD-HD	46.77±18.94	8.24	0.005	0.094
			HP	38.48±13.37			
		C3	ESRD-HD	58.74±29.66	8.42	0.005	0.096
			HP	41.86±16.49			
	Stroop	C1	ESRD-HD	33.95±6.73	14.70	<0.001	0.157
			HP	29.36±4.77			
		C2	ESRD-HD	23.60±5.54	14.63	<0.001	0.156
			HP	20.31±2.97			
	Five Digit Test (5DT)	C1	ESRD-HD	20.93±3.92	7.79	0.007	0.090
			HP	18.71±3.72			
		C2	ESRD-HD	23.00±4.24	6.49	0.013	0.076
			HP	21.17±3.72			
	D2	TR	ESRD-HD	339.95±80.75	7.09	0.009	0.082
			HP	384.29±80.59			

Results of group comparisons are also included. SD – standard deviation; ESRD HD – end-stage renal disease patients treated with hemodialysis; HP – healthy participants.

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Table 3. Means (±SD) of cognitive variables during the first and second evaluations (pre- and post-hemodialysis evaluations in end-stage renal disease patients treated with hemodialysis) for which significant changes were observed. Results of within-subject analysis are also included.

Domain	Test	Dep. Var.	Group	Mean±SD Pre	Mean±SD Post	F (1,83)	p	η_p^2
Visual memory	Rey-Osterrieth Complex Figure (ROCF)	Memory execution	ESRD-HD	16.85±6.14	22.53±6.21	166.35	<0.0001	0.667
			HP	19.01±4.71	24.89±5.90			
Verbal memory	Verbal Learning Test Spain-Complutense (TAVEC)	RLCP	ESRD-HD	9.12±3.16	11.67±2.79	109.34	<0.0001	0.568
			HP	11.12±2.71	13.38±2.87			
		RLLP	ESRD-HD	9.47±2.98	11.88±2.87	107.66	<0.0001	0.565
			HP	11.86±2.67	13.64±2.54			
		RIAT	ESRD-HD	46.65±8.45	57.60±11.37	182.67	<0.0001	0.688
			HP	54.43±8.17	65.60±10.63			
		Discriminability	ESRD-HD	91.61±5.57	94.05±3.90	25.92	<0.0001	0.238
			HP	93.57±6.51	95.92±4.68			
Sustained and selective attention	D2	TCA	ESRD-HD	125.12±34.73	144.91±41.08	128.23	<0.0001	0.607
			HP	144.17±36.09	169.74±37.27			
		TOT	ESRD-HD	318.14±79.57	365.81±88.21	145.81	<0.0001	0.637
			HP	365.74±82.47	408.10±87.68			
		CON	ESRD-HD	122.14±36.65	141.37±44.85	116.89	<0.0001	0.585
			HP	142.88±36.61	163.81±38.06			
Processing speed	Trail Making Test A (TMT-A)	C2	ESRD-HD	46.77±18.94	41.77±17.61	13.33	<0.0001	0.138
			HP	38.48±13.37	31.69±12.73			
		C3	ESRD-HD	58.74±29.66	51.12±26.83	17.49	<0.0001	0.174
			HP	41.86±16.49	34.31±14.18			
	Stroop	C1	ESRD-HD	33.95±6.73	31.81±6.18	20.83	<0.0001	0.203
			HP	29.36±4.77	28.21±4.80			
		C2	ESRD-HD	23.60±5.54	22.31±3.63	8.20	0.005	0.091
			HP	20.31±2.97	19.88±3.16			
	Five Digit Test (5DT)	C2	ESRD-HD	23.00±4.24	21.88±3.80	17.92	<0.0001	0.178
			HP	21.17±3.72	20.26±3.64			
	D2	TR	ESRD-HD	339.95±80.75	388.79±87.60	111.74	<0.0001	0.574
			HP	384.29±80.59	421.33±87.16			

SD – standard deviation; ESRD hemodialysis – end-stage renal disease patients treated with hemodialysis; HP – healthy participants.

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Discussion

Scores for verbal memory, sustained/selective attention, and processing speed were lower in ESRD patients treated with hemodialysis than in HPs, with no between-group differences in visual memory. No acute hemodialysis-specific effect on performance was observed. Several biochemistry variables were associated with performance, both negatively and positively. The finding of cognitive impairment in these functions is consistent with previous reports of disorders in attention [5,7], verbal and visual memory [26], and processing speed [5,7,26] in these patients.

In the second evaluation (ESRD patients, post-hemodialysis), superior results were obtained in visual and verbal memory, selective and sustained attention, and processing speed for both groups. However, as the interaction group x pre-post was not significant, this improvement can be explained by learning effects in the 2 groups. Thus, no acute hemodialysis-specific effect on performance was clearly observed, and our hypothesis that hemodialysis would improve neuropsychological performance was therefore rejected. In contrast, Griva et al [20] described significant improvements in attention and visual/verbal memory scores in ESRD patients treated with hemodialysis at 24 h post-hemodialysis in comparison with 2 h pre-hemodialysis, while no difference was observed in patients treated with peritoneal dialysis before and after dialysis. Schneider et al [4] observed significant improvements in processing speed and visual memory, but not in attention, at 19 h post-hemodialysis in comparison with 1 h pre-hemodialysis, while no differences in these domains were observed in HPs between a first and second evaluation. Discrepant results in the present study may have various explanations: the utilization of different evaluation tests (showing agreement only with those using TMT-A); the distinct groups used for comparison (eg, HPs in the present study vs peritoneal dialysis patients in Griva et al [20], differences in education level between cases and controls in some studies [4], or the inadequate control of learning processes between the 2 evaluations). Another possible explanation could be the duration of the kidney disease in the patients in the different studies. Compared with the patients who participated in the Griva et al [20] and Schneider et al [4] studies, our patients had a longer total duration of hemodialysis treatment (around a year longer on average). Maybe this suggests that in patients with a long history of kidney disease, constant exposure to a state of high uremia, and exposure to the invasive treatment for the vascular system that hemodialysis is, could be producing permanent changes in certain cognitive processes. Therefore, at a certain point in the diseases, hemodialysis treatment might not be able to remove excess urea at a rate sufficient to produce improvements in cognitive processes. Furthermore, maybe hemodialysis only produces improvements in cognitive performance if it is used for a short period of time. More studies should be carried out, with samples composed of patients who differ in the duration of their renal disease and hemodialysis treatment, to check this hypothesis.

Related to this last hypothesis, our results showed that a longer time period under hemodialysis was associated with reduced verbal memory (TAVEC Discrim). This is in agreement with previous reports of greater deterioration in memory [47], higher cognitive impairment [21], and dementia [24] rates, and more severe structural brain anomalies [48] in ESRD patients treated with hemodialysis vs ESRD patients treated with peritoneal dialysis. This increased impairment with longer-term hemodialysis may be attributable to a direct effect of the renal disease duration or may be related to this treatment modality. A larger number of transplants were associated with an increase in processing speed (d2 TR), consistent with previous findings of improved cognitive performance in transplanted patients vs ESRD patients treated with hemodialysis, in attention [5], processing speed [5,49,50], verbal memory [49-51], and visual memory [50,51], and a greater integrity of the white matter in brain areas associated with executive functions and memory [52]. According to the above data, brain and cognitive alterations may depend on the substitutive renal therapy modality and may be partially reversible.

With respect to body composition parameters, a higher percentage of body water was associated with a reduction in verbal memory (TAVEC Discrim), while a higher BMI and dry weight were related to increased processing speed (TMT-A C2). Dry weight was also positively associated with an improved performance in sustained and selective attention (d2 CON). These findings confirm previous observations on the relationship between nutrition [53,54] and hydration [55] status and cognitive performance. Worse processing speed scores (TMT-A) have been observed in patients with lower intradialytic weight [6]. Conversely, better performance in visual orientation, convergent thinking, and memory have been recorded in patients with higher BMI (≥23 vs <23) [30], and BMI and dry weight have been positively associated with working memory [8]. According to Giang et al [56], low-weight ESRD patients treated with hemodialysis are likely to have more comorbidities and are often malnourished, increasing the susceptibility to hemodialysis-related toxicity and the risk of cognitive impairment.

Our analysis of biochemical variables showed that total protein was negatively associated with verbal memory (TAVEC RLCP, TAVEC RIAT) and sustained and selective attention (d2 TCA, d2 CON). Increased total proteins may reflect a rise in acute-phase reactant proteins (eg, C-Reactive protein), which could be a marker of inflammation rather than protein nutrition [57]. Several studies have shown a relationship between high levels of inflammatory markers and cognitive

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impairment, both in the general population [58,59], and in hemodialysis [53,60] and chronic kidney disease [61] patients. Our results also showed that total cholesterol was negatively associated with verbal memory indices (TAVEC, RLCP, RLLP). Regression analysis confirmed a negative association of total cholesterol with these verbal memory variables. High total cholesterol levels have previously been associated with cognitive impairment and Alzheimer's disease [62], and low levels were found to predict improved cognitive functions in the cognitively impaired elderly [63]. In addition, a poorer performance in memory tasks [64] and executive functions [64,65] has been observed in patients with familial hypercholesterolemia, and attention and executive function deficits have been reported in patients with type-2 diabetes mellitus and poor cholesterol control [66].

In our results, phosphorus was positively associated with verbal memory (TAVEC Discrim), sustained/selective attention (d2 TCA, d2 TOT, d2 CON), and processing speed (d2 TR), whereas a previous study found an association between cognitive impairment and high phosphorus levels in ESRD patients treated with hemodialysis [67]. It is possible that the elevated phosphorus levels in the present patients reflected their superior nutritional status and were therefore only secondarily related to improved cognitive performance. Sodium was positively associated with visual memory (ROCF copy execution); regression analysis confirmed this association, in line with previous reports of an association between hyponatremia and cognitive impairment in patients with ESRD treated with hemodialysis [67,68] or peritoneal dialysis [69] and in those with chronic hyponatremia [70] or heart disease [71]. Conversely, the correction of sodium levels has been associated with an improvement in cognitive performance in older patient groups [72].

Creatinine levels were positively associated with sustained and selective attention (d2 TCA, d2 TOT, d2 CON) and with processing speed (TMT-A C2, d2 TR), and were found to predict improved performance in sustained and selective attention (d2 TOT, d2 CON) and processing speed (d2 TR) in the regression analysis. A positive relationship was also recently observed between creatinine levels and working memory in ESRD patients treated with hemodialysis [8]. In contrast, higher creatinine levels have previously been associated with a worse cognitive performance overall and in attention [73,74] and visual [73,74] and verbal [74] memory in chronic kidney disease, including patients treated with hemodialysis [73,74]. The higher creatinine levels may again reflect the good nutritional status of the present patients, with a consequent increase in muscle mass that may be linked to a superior cognitive performance. The contribution of creatinine to performance is also likely to be mediated by other clinical and biochemical variables.

No associations were found with other biochemical variables frequently associated with cognitive performance in patients with renal disease, such as urea [8,20], protein uremic toxins [75], hemoglobin [5,8,27,76], and hematocrit [77]. In the cases of hemoglobin and hematocrit, this may be because associations are observed at levels below those observed in the present patients (>10 g/dL and 35.17%, respectively). Likewise, no association was observed with Kt/V, which has frequently been associated with cognitive performance in ESRD patients treated with hemodialysis [26,27], although other studies found no such association [56].

A major strength of the present study is the extensive battery of cognitive performance tests applied and the large number of indices evaluated. Furthermore, we also examined the acute effect of hemodialysis on cognitive execution and the effects of clinical and biochemical parameters related to ESRD and hemodialysis. In comparisons between ESRD patients treated with hemodialysis and HPs, age, educational level, and mood were controlled for and the sample size was greater than in previous studies in this area [4]. The main limitation of our study is the small sample size. However, the majority of ESRD patients treated with hemodialysis at the Nephrology Services of the Provinces of Jaén and Granada that met the inclusion criteria did participate in the study.

Conclusions

In conclusion, measures of cognitive performance, including verbal memory, sustained and selective attention, and processing speed were worse in ESRD patients treated with hemodialysis than in healthy participants, but there was no difference in visual memory. Comparison of evaluations before and after hemodialysis revealed no acute hemodialysis-specific improvement in cognitive performance. The cognitive deficits may be an indicator of permanent cognitive damage associated with the duration of kidney disease. In addition, the total time under hemodialysis showed a negative association with cognitive performance, and a history of transplantation showed a positive association. More studies with groups of patients with different duration of renal disease and different types of treatment could clarify our results. Finally, our results suggest the importance of good nutritional status and hydration in these patients, information that may be useful for patients and for the medical professionals who work with them.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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