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Cognitive Function and Uremic Toxins after Kidney Transplantation: An Exploratory Study

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Abstract

Background Cognitive functions are altered in patients with CKD. However, it is suggested that cognitive functions improve after kidney transplantation, at least partially. A possible cause for this improvement could be the reduction of uremic retention solutes after transplantation. This study assessed the association between the changes in uremic toxin concentration with the changes in cognitive function in patients after kidney transplantation.

Methods Ten recipients of kidney transplants were compared with 18 controls (nine patients on hemodialysis, and nine patients with CKD stage 4 or 5 [eGFR <30 ml/min per 1.73 m^2] who were not on dialysis). An extensive neuropsychological assessment, covering the five major cognitive domains (*i.e.*, memory, attention and concentration, information processing speed, abstract reasoning, and executive function), was done before transplantation, at 1 week post-transplant, and 3 months after transplantation. Similarly, assessments of the 18 matched, control patients were performed longitudinally over a period of 3–5 months. Concentrations of 16 uremic retention solutes (indoxyl glucuronide, *p*-cresyl glucuronide, phenylglucuronide, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, indoxyl sulfate, *p*-cresyl sulfate, hippuric acid, phenyl sulfate, kynurenine, tryptophan, kynurenic acid, tyrosine, indole-3-acetic acid, phenylalanine, trimethylamine *N*-oxide, and phenylacetylglutamine) were measured in serum samples collected at the time of the neuropsychological assessments.

Results A significant improvement in cognitive function was only found in the processing-speed domain, and this was observed in both patients who received a transplant and patients with CKD. No significant differences between patients who received a transplant and the control groups were seen in the other cognitive domains. As expected, the serum concentration of most uremic toxins decreased significantly within 1 week after kidney transplantation.

Conclusions There was no significant improvement in cognitive function that could be specifically related to kidney transplantation in the first 3 months after the procedure. These data do not support the notion that uremic toxins exert an immediate effect on cognitive function.

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Introduction

A large proportion of patients with CKD experience cognitive impairment (1–5). This impairment predominantly develops at an eGFR of <30 ml/min per 1.73 m^2 and affects all cognitive domains (3,6). Cerebrovascular disease, related to the well-documented increased risk of atherosclerosis in CKD, is widely assumed to be the most significant risk factor. However, the association between cognitive impairment and CKD persists (7–9), even after adjusting for cerebrovascular diseases (1–3). Moreover, cognitive impairment has been observed in children with CKD, the large majority of whom do not have cerebrovascular disease (10). Most importantly, several studies showed that cognitive function improved and, sometimes, almost normalized after kidney transplantation (11–15). Therefore, other factors likely contribute to impaired cognition in patients with CKD.

In this respect, uremic toxins may be relevant. Uremic toxins are defined as retention solutes that accumulate in the serum of patients with renal failure and exert toxic biologic or biochemical functions in the body (16–18). To date, >150 uremic retention solutes have been described by the European Uremic Toxin Workgroup (18,19). Uremic retention solutes are found to be present in different brain regions and in the cerebrospinal fluid of patients with CKD, so at least some uremic retention solutes are able to pass through

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the blood brain barrier (BBB) and the blood–cerebrospinal fluid barrier (20–22). The transport through the BBB and blood–cerebrospinal fluid barrier seems to be mediated by drug transporters and is saturable and competing, which are typical characteristics of carrier-mediated transport. *In vitro*, efflux transport from brain to blood results in an interaction, at the transporter level, between uremic toxins and neurotoxins or drugs, and mutually between uremic toxins (23,24). Attenuation of brain-to-blood efflux transport may result in the accumulation of uremic toxins.

The short-term effects of kidney transplantation on cognitive function have not been studied extensively, and most assessments were done ≥6 months after transplantation. If uremic toxins play a direct role in cognitive function, we would expect a rapid improvement in cognitive function after kidney transplantation, because major changes in blood uremic toxin concentration occur within days after restoration of kidney function (25).

To the best of our knowledge, no well-controlled studies have examined the relationship between changes in cognitive function and changes in uremic toxin concentrations after kidney transplantation. In this exploratory, pilot study, we investigated the change in cognitive function within 3 months after kidney transplantation and the possible association with changes in uremic toxin concentrations.

Materials and Methods

Participants and Procedure

We performed an observational, controlled, cohort, pilot study. We included patients who were planned to undergo solitary living-kidney transplantation within 4–6 weeks (group 1) between December 2015 and April 2017. For the control group, we recruited patients treated with hemodialysis (group 2) and patients with CKD stage 4–5 (eGFR <30 ml/min per 1.73 m^2) who were not on dialysis (group 3). Eligibility criteria included age ≥18 years, fluent in written and spoken Dutch, and able to provide informed consent. Patients in the dialysis and CKD groups were matched with the recruited patients receiving a transplant with respect to age, sex, and education level. We defined the following strict exclusion criteria to increase comparability between the groups: disorders that may have affected cognitive function unrelated to CKD, such as frailty and evident cerebrovascular disease, as reflected by neurologic deficits; traumatic brain injury; presence of acute or chronic psychosis; evident depression; severe learning disabilities; or major visual or hearing impairment. The study was approved by the Medical Review Ethics Committee Region Arnhem-Nijmegen (CMO 2015-1898), and all participants gave written informed consent.

Neuropsychological Tests and Self-Report Questionnaires

All patients underwent three extensive neuropsychological assessments (NPAs) by a trained neuropsychologist (C.J.M.v.R.). Assessments took about 90 minutes and were performed either at the outpatient clinic, or at the patient's home. Patients from group 1 were first studied approximately 4 weeks before kidney transplantation (visit 1), and subsequently 4–6 days (visit 2) and approximately 12 weeks after kidney transplantation (visit 3). Patients in the control groups 2 and 3 were evaluated three times over a period of 3–5 months (visits 1–3). In group 2 patients, the NPA was not performed immediately after a dialysis session to exclude the interference from BP reductions that often occur postdialysis.

The assessment consisted of 12 validated Dutch versions of widely used, highly sensitive tests covering the major cognitive domains, *i.e.*, memory, attention and concentration, information processing speed, abstract reasoning, and executive function. Working memory was assessed using the Letter–Number Sequencing and Digit Span subtests of the Wechsler Adult Intelligence Scale, Fourth Edition; verbal memory was measured using the Rey Auditory Verbal Learning Test and the Story Recall subtest of the Rivermead Behavioral Memory Test, Third Edition. Attention and concentration were measured using the computerized Test of Attentional Performance Alertness reaction time test, the d2 Test of Attention, and the Stroop Color and Word Test, part 3. Information processing speed was assessed using the Stroop Color and Word Test, parts 1 and 2, and the Test of Attentional Performance, Flexibility and Alertness subtests. Abstract reasoning was assessed using the short form (Set I) of the Raven Advanced Progressive Matrices, and executive function was assessed by the Brixton Spatial Anticipation Test and the verbal fluency (letter and category) tests. Finally, premorbid intelligence was assessed with the Dutch version of the National Adult Reading Test, and performance validity was tested with the Dutch version of the Amsterdam Short-Term Memory Test. To control for possible material-specific practice effects, three parallel versions for all memory tests were used. All tests are described in detail in Lezak *et al.* (26).

In addition, several self-report questionnaires were administered to assess depressive symptoms and anxiety (Hospital Anxiety and Depression Scale), fatigue (20-Item Checklist Individual Strength), quality of life (RAND 36-Item Short Form Health Survey [RAND-36]), and subjective cognitive complaints (Cognitive Failure Questionnaire).

Uremic Toxins

Blood samples were obtained within 24 hours before or after NPA. In addition, blood samples were also obtained 1–2 days before and 2–3 days after kidney transplantation in patients from group 1 to detect rapid changes in blood uremic toxin concentration after kidney transplantation. Blood was analyzed for the following 16 uremic retention solutes: indoxyl glucuronide, *p*-cresyl glucuronide, phenylglucuronide, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), indoxyl sulfate, *p*-cresyl sulfate, hippuric acid, phenyl sulfate, kynurenine, tryptophan, kynurenic acid, tyrosine, indole-3-acetic acid, phenylalanine, trimethylamine *N*-oxide (TMAO), and phenylacetylglutamine. Except for TMAO and phenylacetylglutamine, the solutes are protein bound (27,28). The compounds were measured by ultra-performance liquid chromatography–mass spectrometry (Acquity Xevo TQS; Waters, Zellik, Belgium), as described previously (29). Briefly, 50 μl serum sample, 20 μl of internal standard mixture, and 150 μl acetonitrile were thoroughly mixed in 96-well Ostro plates (Waters). After separation by positive pressure manifold, the organic phase was removed by a gentle stream of nitrogen for 30 minutes at 40°C, and then dissolved with 1000 μl of Milli-Q water,

and 5 μl of the final solution was injected on the ultra-performance liquid chromatography–mass spectrometry system. Chromatographic separation was performed on an Acquity CSH Fluoro-Phenyl column (50×2.5 mm; 1.7 μm particle size; Waters). The mobile phase, delivered at a flow rate of 0.5 ml/min at 40°C, was a gradient of 0.1% formic acid in Mill-Q water and methanol. Ionization was achieved using alternating electrospray positive ionization mode and negative ionization mode. The multiple-reaction monitoring transitions, cone voltage, and collision energy were optimized for each individual compound.

The total, within-run, between-run, and between-day method imprecision, determined according to the National Committee for Clinical Laboratory Standards-Evaluation of Precision Performance of Quantitative Measurement Methods guidelines, were <15% for all compounds. Mean recoveries were between 83% and 104% for all of the compounds.

Statistical Analyses

Neuropsychological tests and self-reported questionnaires were administered and scored according to their manuals. Raw test scores were converted into standardized *z*-scores, using the mean and SD of raw scores of the whole study sample to enable crosstest comparisons. To reduce the amount of statistical comparisons, domain scores were calculated for each cognitive domain by calculating the mean of the *z*-scores for tests assigned to that domain (30). Higher scores indicate a better performance. If one test of a particular domain was missing, the domain score was based on the remaining tests of that domain.

Differences in domain scores between the three groups were compared at follow-up with General Linear Model repeated-measures analysis with time as the within-subject factor (three levels: baseline, 6-week follow-up, 3-month follow-up) and group as the between-subject factor (three levels: transplant group, dialysis group, and CKD group), using the different domains as measures and age as a covariate to adjust for slight differences in age.

Results

Participants

We included ten recipients of kidney transplants (group 1), nine patients on dialysis (group 2), and nine patients with CKD stage 4 and 5 (group 3). Table 1 shows all patient characteristics. There were slight differences in age and sex distribution between the groups, but no significant between-group differences in education level. In the transplant group, five patients did not fully complete the second assessment due to lack of energy postsurgery. In one patient, the NPA assessment was delayed until 10 days after the transplantation due to logistic reasons. In the immediate post-transplant period, there were no postsurgical complications and no delayed graft functions. One patient developed an acute rejection type 2b on day 3, for which he was treated with methylprednisolone. Duration of hospitalization was 7 days, except for the patient with rejection who was admitted for 12 days. The immunosuppressive regimen for all patients consisted of a calcineurin inhibitor, mycophenolate mofetil, and prednisone. At 3 months, all patients used prednisone at a dosage of 7.5–10 mg/d.

In the group of patients on dialysis, one patient underwent surgery during the study period to create a brachiocephalic arteriovenous fistula. The patients with CKD visited the outpatient clinic at regular intervals. During the study period, the following adverse events occurred: one patient was admitted to our hospital because of a urinary tract infection, one was admitted twice because of unstable angina pectoris, and one was diagnosed with severe obstructive sleep apnea syndrome.

Neuropsychological Test Results

Supplemental Table 1 shows the raw scores per test, and Table 2 shows the calculated domain scores. All participants displayed good performance validity on the Amsterdam Short-Term Memory Test. The cognitive results did not show significant between-group differences in any of the cognitive domains for the three assessments: executive function ($F[2, 23]=1.521$, $P=0.24$), memory ($F[2, 24]=0.804$,

Table 1. Characteristics of the study groups

Characteristics	Kidney Tx (n=10)	Dialysis (n=9)	CKD Stage 4/5 (n=9)
Age in years (range)	53.1 (22–65)	60.8 (43–72)	59.7 (42–69)
Male, *n* (%)	7 (70)	6 (67)	4 (44)
Pre-emptive, *n* (%)	6 (60)	—	—
Months on dialysis (SD)	6.8 (3.1)	33.3 (35.8)	
GFR (MDRD Equation), ml/min per 1.73 m^2 (SD)			
Baseline	<15	<15	18.6 (5.9)
First follow-up	54.6 (17.3)	<15	18.3 (5.6)
Second follow-up	57.3 (14.0)	<15	15.1 (4.6)
CNI post-transplantation, *n* (%)	10 (100)		
Mean education level (SD)[a]	5.2 (0.6)	5.2 (0.7)	5.0 (1.0)
NART IQ (range)	91.8 (76–113)	97.3 (79–111)	95.3 (77–115)
Time between visit 1–2, d (SD)	31.4 (2.8)	58.7 (8.4)	69.7 (43.1)
Time between visit 2–3, d (SD)	105.3 (25.0)	69.1 (17.9)	81.8 (62.7)

Values are given as number (%), means (SD). Tx, transplantation; MDRD, Modification of Diet in Renal Disease; CNI, calcineurin inhibitor; NART, National Adult Reading Test.
[a]Education levels as assessed using seven categories in accordance with the Dutch educational system (1= less than primary school; 7= academic degree).

Table 2. Cognitive subdomain scores

Subdomain	Visit	Kidney Tx	Dialysis	CKD Stage 4/5
Executive function	1	0.06 (0.30)	−0.16 (0.44)	0.12 (0.21)
	2	0.06 (0.60)	−0.3 (0.93)	0.13 (1.28)
	3	0.46 (0.33)	0.28 (0.77)	0.82 (0.55)
Memory	1	−0.07 (0.19)	−0.05 (0.30)	0.13 (0.20)
	2	0.50 (0.40)	0.29 (0.05)	0.52 (0.13)
	3	0.32 (0.25)	0.48 (0.16)	0.69 (0.22)
Abstract reasoning	1	0.32 (0.88)	−0.16 (1.14)	−0.16 (1.00)
	2	0.23 (0.62)	−0.16 (1.14)	−0.06 (1.11)
	3	0.04 (1.34)	−0.16 (0.66)	−0.50 (0.98)
Attention and concentration	1	−0.04 (0.21)	−0.18 (0.25)	0.23 (0.06)
	2	0.31 (0.31)	0.29 (0.09)	0.49 (0.13)
	3	0.56 (0.26)	0.27 (0.14)	0.62 (0.19)
Information processing speed	1	−0.03 (0.22)	0.05 (0.27)	−0.02 (0.06)
	2	0.18 (0.26)	0.16 (0.28)	0.35 (0.26)
	3	0.48 (0.30)	0.16 (0.08)	0.41 (0.24)
Symptom validity	1	0.04 (0.93)	0.20 (0.66)	−0.28 (1.40)
	2	0.27 (0.83)	0.28 (0.80)	−0.45 (1.02)
	3	−0.14 (1.15)	−0.06 (0.66)	−0.56 (1.42)

Values are presented as the average of mean *z*-scores (SD). Tx, transplant.

P=0.46), abstract reasoning (F[2, 22]=0.257, P=0.78), attention and concentration (F[2, 23]=0.519, P=0.60), and processing speed (F[2, 23]=0.107, P=0.90) (the F-statistic represents the ratio between the variation between the sample means and the variation within the samples [with the between- and within groups degrees of freedom reported in

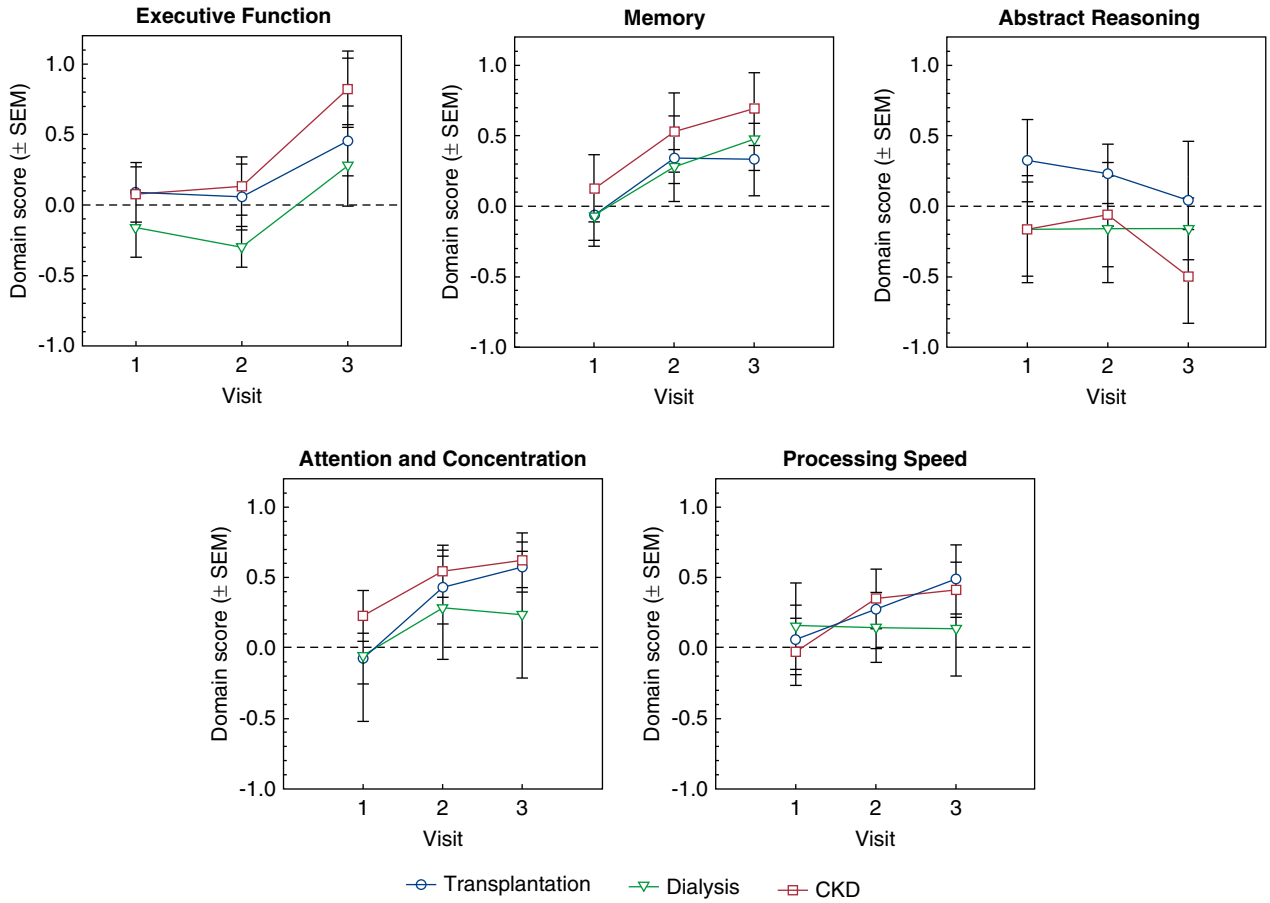

Figure 1. | No significant between group differences on executive function, memory, abstract reasoning, attention and concentration, and processing speed.

brackets], indicating whether different group means actually represent signifcantly different distributions).

However, a significant improvement in cognition was found across the three assessments in time in the cognitive domain executive function (F[2, 46]=5.932, P=0.005) and abstract reasoning (F[1.586, 34.898]=4.429, P=0.03). The other cognitive domains did not show any cognitive improvement over time: memory (F[2, 48]=2.430, P=0.10), attention and concentration (F[2, 46]=0.733, P=0.49), and information processing speed (F[2, 46]=2.093, P=0.14).

Furthermore, we found a significant group-by-time interaction for the domain processing speed (F[4, 46]=3.598, P=0.01). Further analysis shows that an increase in processing speed performance over the three time points was found in both the transplant group (time point 1 [T1], −0.15; 95% CI, −0.67 to 0.38; T2, 0.19; 95% CI, −0.32 to 0.69; T3, 0.33; 95% CI, −0.20 to 0.87) and the CKD group (T1, 0.01; 95% CI, −0.50 to 0.53; T2, 0.38; 95% CI, −0.12 to 0.87; T3, 0.46; 95% CI, −0.07 to 0.98), whereas the performance in the dialysis group remained stable over time (T1, 0.23; 95% CI, −0.29 to 0.75; T2, 0.20; 95% CI, −0.30 to 0.70; T3, 0.22; 95% CI, −0.31 to 0.74). In the other domains, no significant changes were observed: executive function (F[4, 46]=0.683, P=0.61), memory (F[4, 48]=0.779, P=0.55), abstract reasoning (F[3.173, 34.898]=0.265, P=0.86), and attention and concentration (F[4, 46]=1.041, P=0.40) (Figure 1).

All analyses were performed using age as a covariate, but the results did not differ from the analyses without this adjustment.

Self-Report Questionnaires

All patients managed to complete the questionnaires three times, with the exception of one patient in the transplant group who completed the questionnaires only at two time points. Patients who received a transplant showed a significant decrease in levels of fatigue over time (F[2, 18]=8.575, P=0.002) (Table 3). In addition, on the RAND-36 questionnaire, patients who received a transplant showed a significant decrease over time of complaints in the domains "physical functioning" (F[2, 16]=28.559, P≤0.001), "social functioning" (F[2, 16]=10.957, P=0.001), "role—physical" (F[2, 16]=5.529, P=0.02), "pain" (F[2, 16]=5.811, P=0.01), and "vitality" (F[2, 16]=6.074, P=0.01), predominantly between visit 2 and visit 3. None of the other domains of the RAND-36 were statistically significant. No significant

Table 3. Self-reported psychologic well-being, subjective cognitive complaints, depressive symptoms, and level of fatigue

Measure	Visit	Kidney Tx, Mean (SD)	Dialysis, Mean (SD)	CKD Stage 4/5, Mean (SD)
HADS[a] total score	1	11.40 (7.28)	7.11 (5.49)	10.22 (4.79)
	2	12.50 (10.65)	8.00 (4.56)	8.11 (4.26)
	3	7.30 (5.17)	8.33 (3.74)	10.33 (5.15)
CIS[a] total score	1	79.90 (19.77)	72.00 (31.65)	78.13 (21.82)
	2	82.70 (29.64)	74.78 (19.87)	73.56 (21.34)
	3	59.00[b] (27.34)	86.67 (24.44)	75.11 (25.63)
RAND-36 in %				
Physical functioning	1	73.50 (17.49)	59.38 (21.62)	61.11 (30.70)
	2	29.50 (27.33)	58.33 (16.01)	64.44 (28.77)
	3	79.44[b] (16.09)	47.22 (23.99)	57.22 (32.12)
Social functioning	1	65.00 (31.07)	71.88 (23.86)	69.44 (25.85)
	2	33.75 (18.68)	69.44 (18.87)	73.61 (24.56)
	3	69.44[b] (32.54)	59.72 (29.17)	65.28 (31.73)
Role—physical	1	50.00 (48.59)	34.38 (48.07)	38.89 (46.96)
	2	10.00 (21.08)	44.44 (41.04)	41.67 (45.07)
	3	47.22[b] (40.40)	36.11 (37.73)	38.89 (43.50)
Role—emotional	1	79.97 (32.18)	91.66 (23.57)	77.77 (28.86)
	2	56.66 (49.81)	92.58 (14.70)	70.36 (42.31)
	3	92.58 (22.22)	59.25 (49.37)	62.96 (42.31)
Mental health	1	78.40 (13.49)	81.50 (10.24)	74.67 (13.27)
	2	72.80 (23.84)	83.11 (9.55)	76.89 (14.39)
	3	78.67 (17.20)	79.11 (14.11)	74.67 (13.56)
Pain	1	86.74 (20.82)	74.74 (34.34)	70.74 (28.77)
	2	51.22 (26.89)	74.15 (22.80)	66.89 (30.56)
	3	78.23[b] (27.72)	78.00 (31.66)	70.97 (27.26)
Vitality	1	53.50 (20.55)	51.88 (14.87)	50.00 (28.17)
	2	39.00 (21.06)	55.56 (14.24)	58.33 (25.86)
	3	66.11[b] (27.70)	46.67 (17.68)	52.22 (22.38)
General health	1	52.50 (28.11)	41.88 (18.11)	35.56 (16.29)
	2	45.00 (20.82)	38.33 (15.81)	32.78 (16.22)
	3	61.67 (24.1)	35.56 (13.10)	32.78 (11.49)
CFQ[a] total score	1	35.80 (20.05)	24.89 (10.12)	26.11 (11.41)
	2	36.11 (15.84)	31.44 (12.11)	22.78 (9.00)
	3	32.80 (13.76)	27.00 (13.83)	23.89 (7.88)

HADS, Hospital Anxiety and Depression Scale; CIS, Checklist Individual Strength; RAND-36, RAND 36-Item Short Form Health Survey; CFQ, Cognitive Failure Questionnaire.
[a]Higher scores reflect worse performance.
[b]Significant decrease of complaints over time.

Table 4. Uremic toxin concentration

Uremic Toxin	Kidney Tx (μM)					Dialysis (μM)			CKD Stage 4/5 (μM)		
	V1	Pre	Post	V2	V3	V1	V2	V3	V1	V2	V3
p-Cresyl glucuronide	4.41	4.85	0.15	0.07	0.06	5.81	5.74	6.04	1.00	0.85	1.12
Phenylglucuronide	0.36	0.30	0.01	0.01	0.02	0.58	0.81	1.29	0.17	0.12	0.23
CMPF	10.78	10.56	8.07	6.36	3.93	5.44	6.53	7.53	4.85	5.89	5.37
Indoxyl sulfate	97.94	115.66	4.03	5.05	5.57	124.45	116.53	123.94	32.75	32.37	34.80
p-Cresyl sulfate	153.65	203.59	28.98	11.66	13.38	98.89	105.89	112.02	111.87	107.55	114.91
Hippuric acid	103.07	105.25	2.17	1.99	6.27	187.09	183.91	206.90	22.09	23.55	19.78
Phenyl sulfate	38.07	31.89	2.58	1.08	10.20	29.36	39.86	51.74	33.45	28.37	43.26
Kynurenine	3.86	3.63	1.77	2.26	1.96	5.08	4.99	4.54	3.64	3.61	3.97
Tryptophan	28.86	27.02	46.38	56.89	57.49	31.55	37.34	32.48	35.67	34.98	35.46
Kynurenic acid	0.99	1.10	0.07	0.07	0.06	1.28	1.27	1.37	0.26	0.28	0.35
Tyrosine	40.40	43.13	59.30	62.34	68.66	54.80	60.26	51.84	50.96	52.05	55.92
Indole-3-acetic acid	5.91	6.28	2.55	1.87	4.20	5.78	5.22	5.23	3.88	4.00	3.89
Phenylalanine	67.46	67.64	87.50	82.60	72.66	88.56	88.24	77.45	72.60	71.24	76.23
TMAO	86.16	57.48	6.85	3.50	11.72	72.76	191.30	99.78	20.06	21.94	24.13
Phenylacetylglutamine	69.25	76.97	3.99	2.28	2.84	105.55	95.93	101.58	19.43	18.18	20.78

For visits 1, 2, and 3, samples were collected at the time of the neuropsychological assessment (see Methods). Tx, transplant; V1, visit 1; Pre, pretransplant (sample taken immediately before transplantation); Post, post-transplant (sample taken 2–3 d after transplantation); V2, visit 2; V3, visit 3; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; TMAO, trimethylamine N-oxide.

differences were found between the three groups on subjective cognitive complaints and depressive symptoms.

Uremic Toxins

At baseline, the concentration of most uremic toxins was lower in the patients of group 3 (CKD), compared with patients of groups 1 (transplantation) and 2 (dialysis). We observed clear changes in the concentration of uremic toxins after kidney transplantation (Table 4). Most changes were already observed within 3 days after kidney transplantation (Figure 2). In the first 3 days, large reductions (more than ten-fold) were observed for *p*-cresyl glucuronide, phenylglucuronide, indoxyl sulfate, hippuric acid, phenyl sulfate, kynurenic acid, TMAO, and phenylacetylglutamine; moderate reductions were observed for CMPF, *p*-cresyl sulfate, kynurenine, and indole-3-acetic acid; and an increase of serum concentration was observed for tryptophan, tyrosine, and phenylalanine. No statistically significant changes were observed in uremic toxin concentration over time in the other two groups.

Discussion

NPA suggested an improvement in cognitive function within 3 months after successful kidney transplantation in almost all cognitive domains. However, similar improvements in cognitive function over time were observed in the two control groups. Therefore, the improvement of cognitive function over time was not the consequence of kidney transplantation but rather reflected nonspecific practice effects as a consequence of repeated testing. This observation clearly illustrates the need to include matched control groups in studies that evaluate changes in cognitive function over time (26). We observed that patients who received a transplant and those in the CKD group significantly outperformed patients on dialysis in the tests performed after 3 months, but only for the processing speed domain. However, this effect cannot be attributed to the kidney transplant procedure because a similar finding was also noted in patients with CKD. We do not have a clear explanation for this finding. One hypothesis is that patients on dialysis are less susceptible to learning effects over time.

The results of our study are in contrast with the conclusions of other studies that reported an improvement in cognitive function on several cognitive domains after renal transplantation (12–15,31–33). There are several explanations for this discrepancy. Most studies had important methodologic limitations, such as the absence of a control group (13–15,34). Other limitations included the lack of a comprehensive assessment of all cognitive domains (31,33) or cross-sectional comparisons (32,33). A recent meta-analysis concluded there was some evidence that cognition improved in some domains after successful kidney transplantation, but also emphasized the important limitations of the included studies, namely, length of follow-up, number of tested cognitive domains, lack of a control group, and small sample sizes (35). We identified one well-conducted study that had a prospective longitudinal design, included a matched control group, and used a comprehensive cognitive test battery (11). This study included 27 patients who had been transplanted, and showed an improvement in cognition 8 months after transplantation when compared with patients on dialysis and healthy controls. There are some important differences between this study and ours: a major difference is the timing of the cognitive function test after transplantation, 8 months in their study versus 3 months in ours. Also, duration of dialysis before transplantation differed, 34 months in their study versus 7 months in ours. To the best of our knowledge, there is only one study that tested patients at 3 months after transplantation (34). This study included 11 patients and found an improvement in memory and executive function. However, this study can be criticized for the lack of a matched and similarly tested control group.

We hypothesized that uremic toxins, which pass the BBB, might negatively affect cognition. Despite a notable decrease in the concentration of most uremic toxins in the

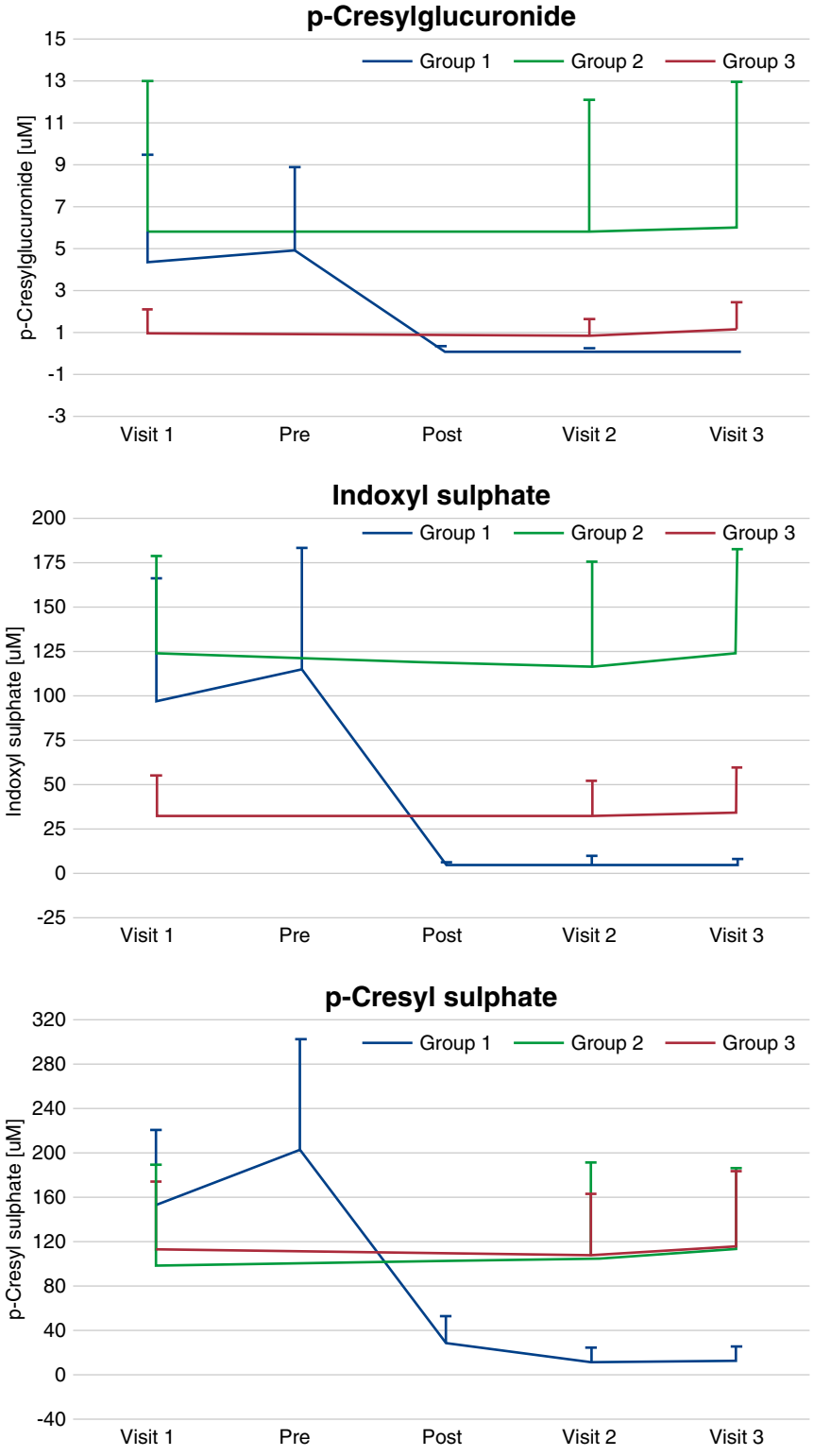

Figure 2. | Clear changes in concentration (with 1 SD) of *p*-cresyl sulfate, indoxyl sulfate, and *p*-cresyl glucuronide after kidney transplantation in comparison with the control groups.

patients who received a transplant, we did not observe a significant improvement in cognitive function.

As expected, there were no differences in the serum levels of uremic toxins at baseline between the patients who received a transplant and the patients on dialysis. In line with previous studies, the patients with CKD had lower uremic toxin concentrations (36,37). The uremic toxin concentrations remained stable over a follow-up of 4–5 months

in the patients who had not received a transplant, that is, the patients on dialysis and those with CKD. We observed heterogeneous changes in the concentration of uremic toxins after transplantation. Although the concentration of most uremic toxins decreased, we observed an increase in the concentration of the amino acids tryptophan, tyrosine, and phenylalanine. Few studies have examined changes in uremic toxin concentration after kidney transplantation. In agreement with our observations, a substantial decrease was reported in the concentration of *p*-cresyl sulfate, *p*-cresyl glucuronide, indoxyl sulfate, TMAO, and phenylacetylglutamine (25,38).

At first glance, the increase in the concentration of some blood constituents may seem remarkable. However, it has been shown that concentrations of some blood constituents paradoxically decrease in the uremic state. Indeed, de Vries *et al.* (39) demonstrated that tryptophan concentrations decreased in kidney transplant recipients with graft failure. The authors hypothesize that this phenomenon is a consequence of increased breakdown of tryptophan to kynurenine, *via* the tryptophan/kynurenine pathway, by the proinflammatory uremic environment. In addition to tryptophan, this is also seen for tyrosine and phenylalanine, and some uremic retention solutes (40,41).

Our study has several limitations. First, the groups are small, limiting the power to detect any statistically significant differences between the groups. However, it is important to note that our group sizes are similar to other longitudinal studies. Secondly, the groups were not perfectly matched in terms of age and sex distribution. Group 1 consisted of younger and predominantly male participants compared with the other groups. However, we adjusted for differences in age by using age as a covariate in the analysis, but the results did not differ. In addition, sex differences in cognition are typically very small, if present at all. Therefore, we consider the sex differences in these groups to be irrelevant.

Furthermore, the performance of the transplant patients at the second NPA is likely affected by postoperative influences, *i.e.*, stress, fatigue, pain, or use of higher doses of corticosteroids, which also corresponds with higher scores on the Hospital Anxiety and Depression Scale and 20-item Checklist Individual Strength self-report questionnaires. In addition, a test battery that takes 90 minutes is mentally demanding for patients a few days postsurgery. Any improvement in cognition in the first postoperative days could have been masked. Still, this seems highly unlikely because no improvement was noted even after 3 months. Finally, this study has a relatively short follow-up. Although this was done intentionally for reasons explained earlier, a longer follow-up might have unmasked differences, because recipients of transplants are only considered clinically stable after approximately 1 year post-transplant.

In summary, we did not find evidence for cognitive changes after kidney transplantation compared with control groups consisting of patients on hemodialysis or patients with CKD. However, we observed clear changes in the serum concentration of uremic toxins after transplantation, even within 3 days after kidney transplantation. As expected, no significant changes in uremic toxins were observed in the patients who did not receive a transplant.

Disclosures

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Author Contributions

H. De Loor, E. te Linde, and C. van Roij were responsible for formal analysis; R. Kessels, E. te Linde, and C. van Roij were responsible for methodology; B. Meijers, R. Kessels, and J. Wetzels provided supervision and reviewed and edited the manuscript; E. te Linde wrote the original draft, and was responsible for data curation and project administration; E. te Linde and C. van Roij were responsible for investigation; J. Wetzels conceptualized the study; and all authors contributed to the final approval of the article.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.K3602020000027/DCSupplemental.

Supplemental Table 1. Neuropsychological test scores.

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