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Ahmet Ziya Şahin[1], Özlem Usalan[1], Bahadır Demir[2], Şengül Kocamer Şahin[2], Mehmet Fatih Erdur[1], Celalettin Usalan[1]

Relationship between dialysis adequacy and cognitive function in hemodialysis patients

[1]Gaziantep University School of Medicine, Department of Nephrology, Gaziantep, Turkey
[2]Gaziantep University, Faculty of Medicine, Department of Psychiatry, Gaziantep, Turkey

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Abstract. *The prevalence of cognitive impairment is extremely high in dialysis patients, and it has been hypothesized that low urea clearance has an impact on cognitive impairment. However, several other studies conducted in the era of high-flux dialysis have not shown an association between lower Kt/V and poorer cognitive function. Therefore, studies that directly examine the relationship between dialysis adequacy and cognitive function in hemodialysis patients are essential. The present study aimed to investigate the cognitive functions of hemodialysis patients and their relationship with dialysis adequacy.*

Methods. This cross-sectional observational study included 100 patients and 100 healthy volunteers. Dialysis adequacy was assessed by the Kt/V ratio in the previous month. The Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment Test (MoCA), and the Clock Drawing Test (CDT) were used to assess cognitive function. Multiple regression analysis was used to determine the significant association between the cognitive assessments and the independent variables (Kt/V, age, education, hemoglobin, and albumin).

Results. There were no significant differences between patients and controls in age and sex. Patients had a mean Kt/V ratio of 1.52±0.29. MMSE, MoCA, and CDT were lower in patients than in controls. There were strong positive correlations between MMSE and Kt/V (r = 0.81), MoCA and Kt/V (r = 0.84), CDT and Kt/V (r = 0.79).

Conclusion. Cognitive functions in hemodialysis patients were significantly decreased compared with healthy controls and associated with dialysis adequacy. Dialysis adequacy should be questioned in patients with low cognitive function.

Keywords: *cognition, hemodialysis, dialysis adequacy.*

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Correspondence should be addressed to Ahmet Ziya Şahin: drahmetziya@hotmail.com

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Ахмет Зія Шахін[1], Озлем Усалан[1], Бахадир Демір[2], Шенгюл Кочамер Шахін[2], Мехмет Фатіх Ердур[1], Челалеттін Усалан[1]

Взаємозв'язок між адекватністю діалізу та когнітивною функцією у пацієнтів, які лікуються методом гемодіалізу

[1]Школа медицини університету Газіантеп, кафедра нефрології, Газіантеп, Туреччина

[2]Університет Газіантеп, медичний факультет, кафедра психіатрії, Газіантеп, Туреччина

Резюме. *Поширеність когнітивних порушень є надзвичайно високою серед пацієнтів, які лікуються методом гемодіалізу (ГД) і гіпотеза щодо взаємозв'язку між низьким кліренсом сечовини та когнітивними порушеннями була запропонована. Проте, кілька інших досліджень, проведених в епоху високопотокового діалізу, не показали зв'язку між низьким Kt/V і погіршенням когнітивних функцій. Саме тому дослідження, які безпосередньо вивчають зв'язок між адекватністю діалізу та когнітивними функціями у ГД пацієнтів є необхідними. Метою цього дослідження було оцінити когнітивні функції ГД пацієнтів та визначити їх взаємозв'язок з адекватністю діалізу.*

Методи. Це одномоментне щисльве дослідження включало 100 ГД пацієнтів і 100 здорових добровольців. Адекватність діалізу оцінювали за показником Kt/V. Для оцінки когнітивних функцій використовували Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment Test (MoCA) і Clock Drawing Test (CDT). Множинний регресійний аналіз використовувався для визначення взаємозв'язку між когнітивними функціями та незалежними змінними (Kt/V, вік, освіта, гемоглобін та альбумін).

Результати. ГД пацієнти та контрольна група не відрізнялись за віком та статтю. Середнє Kt/V ГД пацієнтів склало 1,52±0,29. MMSE, MoCA та CDT були статистично значущо нижчими у ГД пацієнтів у порівнянні з контролем. Визначено сильний прямий кореляційний зв'язок між MMSE та Kt/V (r = 0,81), MoCA та Kt/V (r = 0,84), CDT та Kt/V (r = 0,79).

Висновки. Когнітивні функції ГД пацієнтів значно знижені порівняно зі здоровими особами контрольної групи та достовірно асоціюються з адекватністю діалізу. На нашу думку, у ГД пацієнтів з низькою когнітивною функцією слід поставити під сумнів адекватність діалізу.

Ключові слова: *когнітивні функції, гемодіаліз, адекватність діалізу.*

Introduction. The kidneys are vital organs responsible for functions such as the elimination of toxins from the body, detoxification of drugs, hormone production, control of fluid osmolality, electrolyte, and acid-base balance, and the breakdown of insulin, parathyroid hormone, and growth hormones [1]. The condition in which the kidneys can no longer perform these functions due to various diseases is called renal failure. The definitive treatment for permanent, irreversible chronic renal failure is kidney transplantation [2]. However, as the kidneys of the patient waiting for transplantation do not function properly, harmful substances such as urea, creatinine, phosphorus, and potassium accumulate in his body. Of these substances, the increase in urea in particular is known to impair cognitive functions [3]. Certainly, urea has not been the only focus of studies on cognitive function. Factors such as cerebral hypoperfusion during hemodialysis (HD), serum albumin levels, and blood pressure may contribute to a decline in cognitive function [4-6].

Ahmet Ziya Şahin
drahmetziya@hotmail.com

Dialysis adequacy is defined as the dialysis dose and measured by solute removal. It aims to reduce morbidity and mortality associated with renal failure and dialysis and to improve patient's quality of life [7]. The proper HD dose for individuals is determined by the Kt/V ratio, urea reduction ratio (URR), time-averaged urea concentration TACurea, clinical status, and others. Kt/V means that the total blood volume excreted during the session is equal to the urea distribution volume [7, 8]. Although URR is easy to calculate, we did not prefer this formula because it does not account for urea removed by ultrafiltration or intradialytic urea production, which may lead to differences in urea kinetics [7]. TACurea has been shown not to reflect actual urea kinetics during and after dialysis treatment [8].

Memory, attention, information processing, language, and executive functions are just a few of the many areas covered by cognitive processes [9]. In recent years, several researchers have discovered a link between poor kidney function and cognitive impairment at the so-called kidney-brain axis [10, 11]. Even at younger ages, dialysis patients have a high incidence of generalized cognitive impairment [12]. According to a previous study, each 10 ml decrease in the estimated

glomerular filtration rate below 60 ml/min/1.73 m^2 increases the likelihood of cognitive impairment by 11% [13]. In addition, cognitive functions are important for the quality of life of HD patients and are associated with poor outcomes [14, 15]. However, the effect of HD on cognitive functions is still unclear [16, 17].

The present study aimed to investigate the cognitive functions of HD patients and their relationship with dialysis adequacy.

Materials and Methods. This was a cross-sectional observational study. The Kt/V ratio was recorded in the last month of patients who continued treatment with HD in our clinic between June 01, 2022, and October 01, 2022, and met the criteria for inclusion. HD patients who were over 18 years of age, had no mental retardation, dementia, or psychosis, were in a medically stable condition and had evidence of the last 6 months on the HD unit were included in the study. Patients with cardiovascular disease were excluded. Healthy subjects were those who presented to the nephrology outpatient clinic, in whom examinations revealed no pathological findings. They had no additional diseases (neuropsychiatric diseases such as dementia or psychosis), and the glomerular filtration rate was greater than 90 ml/min/1.73 m^2.

The study was approved by the Ethics Committee of the Clinical and Research Committee of Gaziantep University under reference number 2022/222 and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

The Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCa) Test, and the Clock Drawing Test (CDT) were performed to measure cognitive function. The cognitive tests were performed immediately before HD.

The MMSE is a rapid and reliable cognitive assessment tool for dementia screening. The Turkish validity and reliability study of the scale was conducted by Guengen et al [17]. According to the study, the threshold score of 23/24 was the most appropriate to discriminate between mild dementia and healthy controls. This value had a sensitivity of 0.91 and a specificity of 0.95. In addition, a validity and reliability study of the questionnaire was conducted for the educated and uneducated Turkish populations. In this study, we used these two validated instruments for educated and uneducated patients [18].

The MoCA test was developed by Nasreddine et al. for screening for mild cognitive impairment (MCI) [19]. It was adapted into Turkish by Selekler et al [20]. The Turkish version of MoCA (MoCA- TR) has been validated in Alzheimer's dementia and Parkinson's disease [21, 22]. MoCA-TR consists of seven cognitive domains: visual-spatial abilities, naming, abstract thinking/executive functions, attention, language, short-term memory/ recall, and orientation. MoCA total scores range from 0 to 30, with higher scores indicating better cognitive performance. The MoCA is a suitable cognitive screening tool for hemodialysis patients [23].

The CDT is used as a very sensitive cognitive screening tool [24]. It is a practical and easy-to-use test. When using the CDT, the patient is asked to draw a circle on a sheet. He is then asked to place the numbers and arrows on the "clock" to determine the time indicated in the instructions. This exercise requires a combination of cognitive skills such as visual-spatial skills, executive functions, semantic knowledge, and general cognitive skills. In the Turkish validity and reliability study, the measurements showed high test-retest and inter-rater reliability with high concurrent and critical validity [25].

Kt/V ratio was calculated using formulas developed from the kinetic model of urea using pre- and post-dialysis measurements of urea concentration.

The SPSS 22.0 Windows package program was used for the statistical analysis. The agreement of the numerical variables with the normal distribution was tested using the Shaphiro-Wilk test. The paired t-test was used for normally distributed data. The Spearman rank correlation coefficient was used to evaluate the relationship between MMSE, MoCA, CDT, and Kt/V. Relationships between categorical variables were tested using the chi-square test. A multiple linear regression model was applied to evaluate the independent influence of each variable on Kt/V and the possibility of obtaining the predicted Kt/V. It was considered that Hb, albumin, education, and age affect cognitive function. Therefore, the adjusted R2 values were calculated in the multiple linear regression model including hemoglobin, albumin, education, and age.

Results. The sociodemographic, laboratory and cognitive test results of HD patients and the control subjects are summarized in Table 1.

Table 1

The sociodemographic, laboratory and cognitive test results of HD patients and the control subjects

		Hemodyalisis Patients	Controls	P-value
Sex	Male	50 (50%)	50 (50%)	1
	Female	50 (50%)	50 (50%)	
Age, year		48.3±15.2	48.2±4.8	0.090

Continuation of Table 1

		Hemodyalisis Patients	Controls	P-value
Smoking	Yes	22 (22%)	25 (25%)	0.369
	No	78 (78%)	75 (75%)	
Education		7±3.5	7.4±3.5	0.367
MMSE, scores		22.4±4.3	26.1±3.3	0.001
MoCA, scores		18.8±5.3	24.6±4.4	0.001
CDT, scores		2.9±2.2	5.4±0.8	0.001
Hemoglobin, g/L		108±10.2	134±13	0.001
Albumin, g/L		37.6±4.08	39.9±2.7	0.001
Kt/V		1.52±0.29	-	

As presented in Table 1, MMSE, MoCA, CDT, hemoglobin, and albumin levels were significantly low in HD patients compared with controls.

There were positive correlations between the scores of all studied cognitive function tests and the Kt/V ratio of the patients (Table 2).

Table 2

Spearman's correlations between cognitive tests and Kt/V

	MoCA	CTV	Kt/V
MMSE	.886**	.758**	.814**
MoCA		.850**	.838**
CTV			.788**
** Correlation is significant at the 0.01 level.			

In the multiple linear regression analysis, MMSE levels explained 57% of the variation in the Kt/V ratio ($\beta = 11.1 \pm 0.9{,}30$, $p<0.001$). MoCA levels explained 67% of the variation in the Kt/V ratio ($\beta = 14.7 \pm 1.04$ $p < 0.001$). CTS levels explained 62% of the variation in the KT/V ratio ($\beta = 5.96 \pm 0.46$, $p < 0.001$).

Discussion. In this study, we investigated the relationship between dialysis adequacy and cognitive function in HD patients. We found a strong direct correlation between the Kt/V ratio and cognitive function. We also showed that deterioration of cognitive function in all cognitive instruments (MMSE, MoCA, CDT) explained about 60% of dialysis inadequacy.

Moderate to severe cognitive impairment is common in HD patients and is not diagnosed [15]. In our study, we demonstrated that cognitive function in the patient group was significantly worse than in the control group on all cognitive assessments. Similarly, a recent study found that the prevalence of mild cognitive impairment was significantly higher in hemodialysis patients than in the general population [25]. Lu et al. identified cognitive impairment as one of the most common complications in hemodialysis patients in the maintenance phase [17]. A supporting meta-analysis also found that hemodialysis patients were more likely to have cognitive impairment compared with the general population [26].

The highly significant association between the adequacy of dialysis treatment and cognitive function is the most important finding of this study. Similarly, Luo et al. examined the Kt/V ratio between patients with mild and severe cognitive impairment and found that the Kt/V ratio was higher in elderly hemodialysis patients with mild cognitive impairment than in patients with severe cognitive impairment [27]. Similar results were found for the adequacy of peritoneal dialysis. Peritoneal dialysis adequacy was found to be significantly associated with the occurrence of cognitive impairment [28]. In other words, regardless of the type of dialysis, its adequacy may affect cognitive function. In contrast, Giang et al. found no association between lower Kt/V and poorer cognitive performance [29]. They included only patients with Kt/V≥1 and had performed cognitive tests under hemodialysis. It may also affect the cognitive results when the test is performed. Because blood pressure fluctuations during hemodialysis may affect

cerebral perfusion, cognitive function may also be affected. In our literature search, we could not find any other study that examined the relationship between dialysis adequacy and cognitive function. Therefore, we believe the results will be informative.

The appropriateness of dialysis is significantly related to prognosis. Patients with chronic kidney disease are already at a much higher risk of developing cognitive impairment compared with the general population. Low glomerular filtration rate and the presence of albuminuria are associated with the development of cognitive impairment [30]. In addition, volume balance and uremic symptoms inform clinicians about the appropriateness of dialysis treatment. Assessment of dialysis adequacy based solely on these parameters using conventional methods may not be useful. The Kt/V ratio is more objective. Given the significant relationship between the Kt/V ratio and the cognitive tests, we used in the study, the low cognitive function should alert the clinician to inadequate dialysis performance, even if the Kt/V ratio cannot be monitored regularly. Even a simple cognitive assessment, which can be performed by drawing a clock "CDT," provides information about dialysis ability.

Sample size and cross-sectional design are one of the limitations of our study. Depression is also common in hemodialysis patients [31] and may impair cognitive function. Therefore, it is a limitation of this study that all other psychiatric diagnoses were not excluded by structured interviews. It has also been shown that in most people with chronic kidney disease, cognitive impairment is likely a primary vascular process. Although we excluded patients with diagnosed cardiovascular disease, another limitation of this study is that systemic microvascular disease, including cerebrovascular small vessel disease, is not a known-another limitation of the study.

Conclusions. The results of our study suggest that cognitive functions are associated with dialysis adequacy in HD patients. It is important to monitor the cognitive functions that affect the quality of life of HD patients.

Conflict of Interest. The authors declare no conflict of interest.

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Authors' contribution:

AZS, ÖU, and BD equally contributed to conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, and project administration. ŞKŞ, MFE, and CU equally contributed to resources, software, super-vision, validation, visualization, writing – original draft preparation, and writing. All authors equally contributed to the review and editing

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