

Relationship between Cognitive Impairment and Depression in Dialysis Patients

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Purpose: Patients with chronic kidney disease frequently show cognitive dysfunction. The association of depression and cognitive function is not well known in maintenance dialysis patients. We evaluated cognitive impairment and depression, as well as their relationship in regards to methods of dialysis, maintenance hemodialysis (MHD) and chronic peritoneal dialysis (CPD). **Materials and Methods:** Fifty-six maintenance dialysis patients were recruited and their clinical and laboratory data were collected. The Korean version of the mini-mental state exam (K-MMSE) was applied to screen the patient's cognitive function, while the Korean version of the Beck Depression Inventory (K-BDI) was used for depression screening. **Results:** The average age of the participants was 54.2±10.2 years; 29 (51.8%) were female. The average dialysis vintage was 4.2±3.8 years. The CPD group showed significantly higher K-MMSE score (27.8±2.9 vs. 26.1±3.1, $p=0.010$) and lower K-BDI score (12.0±8.4 vs. 20.2±10.4, $p=0.003$) compared with the MHD group. The percentage of patients with depression symptoms was higher in the MHD group (51.7% vs. 18.5%). There was a negative correlation between cognitive function and prevalence of depressive symptoms. Depression and education level were shown to be independent predictors for cognitive impairment in multivariate analysis. **Conclusion:** Cognitive impairment was closely correlated with depression. It is important to detect cognitive impairment and depression early in maintenance dialysis patients with simple bedside screening tools.

Key Words: Cognitive impairment, depression, hemodialysis, peritoneal dialysis

INTRODUCTION

Chronic kidney disease (CKD) is a debilitating illness, and is now a growing issue in worldwide health care. CKD patients frequently have cognitive problems in close relation with decreased renal functions.^{1,2} Many dialysis patients exhibit memory disturbance, slow motor performance and impaired attention.^{3,4} Moreover, the prevalence of cognitive impairment will continue to grow with increases in age and vascular risk factors.⁵ As many patients with cognitive impairment progress to dementia, it is very important to detect cognitive impairment in maintenance dialysis patients. The prevalence of cognitive impairment in maintenance

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hemodialysis (MHD) patients in recent studies was reported as 30 to 60%.⁶ This prevalence is more than double that of the U.S. general population.^{4,7}

The mortality rate for dialysis patients is still high, despite improvements in medicine and dialysis techniques. This may be due to the increasing number of elderly patients and concurrent systemic illnesses among the dialysis patient population. However, cognitive impairment and psychiatric factors also have been shown to affect mortality in maintenance dialysis patients.⁸ To screen for cognitive function, the mini-mental state exam (MMSE) is one of the most widely used in clinical practice.⁹ Since its introduction by Folstein in 1975, the MMSE has been a reliable test for screening cognitive function. It is a simple bedside test that takes 10-20 minutes to perform, and has been used in many observational and clinical studies. Most previous studies on cognitive dysfunction were conducted in older cohorts of MHD patients with dementia.^{3,4,10} They did not include chronic peritoneal dialysis (CPD) and milder cognitive impairment groups. Only a few studies have been performed on cognitive impairment in CPD patients.^{11,12}

Depression is another issue that can affect the overall mortality and quality of the life of these dialysis patients.¹³ An association between depression and mortality has been shown in many studies.^{14,15} The lack of energy and initiative, hopelessness and cognitive deficits associated with depression can lead to lower adherence to medication regimens and exercise programs, thus decreasing the quality of life in CKD patients.¹⁶ The association of depression and cognitive function is not well known in maintenance dialysis patients.

The object of this preliminary study was to evaluate the occurrence of cognitive impairment and its relationship to depression in Korean patients on maintenance dialysis including CPD. We also examined risk factors for decline of cognitive function in dialysis patients and elucidated the relation between cognitive function and dialysis modalities.

MATERIALS AND METHODS

Patient population

This study included end-stage renal disease (ESRD) patients who had been receiving either MHD or CPD between July and October 2009 from a single dialysis center at Hallym University Kangnam Sacred Heart Hospital, in Seoul, Korea. The inclusion criteria for this study were as follows:

age ranging from 20-80 years, on chronic dialysis for at least 3 months, no history of diagnosed dementia or depression prior to this study, no history of renal transplantation, no history of drugs that may affect cognitive function such as anti-depressants or neuroleptics, and female participants must be nonpregnant. All cognitive tests were performed during the off-dialysis time, with a minimum one hour interval from the last dialysis treatment. Clinical data including age, sex, body weight and height for Body Mass Index calculation, history of smoking, dialysis vintage, underlying cause of renal disease, comorbid diabetes and history of cardiovascular disease such as coronary artery disease or peripheral vascular disease were evaluated. Laboratory data such as hemoglobin, albumin, creatinine, parathyroid hormone, cholesterol, calcium, and phosphate were also collected. The protocol was approved by the institutional review board of Hallym University Kangnam Sacred Heart Hospital. Written informed consent for participation in the study was obtained from all patients.

Neuropsychological evaluations

The Korean version of the MMSE (K-MMSE) was applied to all subjects. Total score of the K-MMSE is 30 points, and consists of five domains of cognition: orientation, registration, attention/calculation, recall, and language. Scores of 24 or less suggest the presence of decline of cognition.¹⁷ We used the cutoff point of ≤ 24 as indicative of cognitive impairment. All tests were performed in a quiet room without external stimuli. The time within at least one hour after a meal was avoided and the entire test was performed after dialysis for MHD patients. Substances which can affect the central nervous system such as alcohol, smoking and coffee were restricted at the time of evaluation. The participants' level of education was also recorded in addition to their K-MMSE score. Depressive symptoms were determined using the Korean version of the Beck Depression Inventory II (K-BDI). The K-BDI, a 21-item scale, was previously validated for both the normal population and patients with medical illness. A K-BDI cutoff score of ≥ 21 was selected to identify patients with as being at risk for depression.

Statistical analysis

All values are expressed as means \pm standard deviations. Chi-square test for continuous variables, Mann-Whitney U test for categorical variables, Spearman's coefficient for correlation analysis, and logistic regression analysis test for multivariate analysis were used for the statistical analysis.

Statistical analyses were conducted using the SAS package (version 6.10, SAS institute, Cary, NC, USA). *p*-values less than 0.05 were considered statistically significant.

RESULTS

A total of 56 dialysis patients were eligible for this study. The average age of all participants was 54.2±10.2 years and 29 were female (51.8%). The average dialysis vintage was 4.2±3.8 years. The primary causes of ESRD were diabetes (37.5%, n=21), hypertension (33.9%, n=19), glomerulonephritis (17.9%, n=10), others (3.6%, n=2), and unknown (7.1%, n=4). Twenty-two patients (39.3%) had a history of cardiovascular disorders. The average score of the K-MMSE was 26.9±3.1 and cognitive impairment (scores ≤24) was detected in 10 (17.9%) of the participants. The participants scored an average of 16.3±10.3 on the K-BDI and 20 (35.7%) of them were regarded as being at risk for depression.

The numbers of patients in the MHD and the CPD groups were 29 (51.8%) and 27 (48.2%), respectively. Demographic factors including age, sex, education level, diabetes, and cardiovascular disease history were not significantly different between the two groups. The MHD patients showed significantly longer dialysis vintage, higher systolic blood pressure and lower serum total cholesterol level compared with the CPD patients. Neuropsychological evaluation demonstrated that the CPD group showed significantly higher K-MMSE scores (27.8±2.9 vs. 26.1±3.1, *p*=0.010) and lower K-BDI scores (12.0±8.4 vs. 20.2±10.4, *p*=0.003) compared with the MHD group. The percentage of the prevalence of depressive symptoms was higher in the MHD group than the CPD group (51.7% vs. 18.5%, *p*=0.013). The prevalence of cognitive impairment also seemed higher in the MHD group than the CPD group (24.1% vs. 11.1%), but this was not statistically significant. The demographic and the clinical characteristics of each group are summarized in Table 1.

Table 2 describes the number of dialysis patients with

Table 1. Clinical and Laboratory Characteristics of Hemodialysis and Peritoneal Dialysis Groups

	MHD (n=29)	CPD (n=27)	<i>p</i> value
Age (yrs)	55.8±8.7	52.4±11.6	0.137
Female	16 (55.2)	13 (48.1)	0.789
Diabetes mellitus	12 (41.4)	9 (33.3)	0.589
Previous CVD	13 (44.8)	9 (33.3)	0.423
Dialysis vintage (yrs)	5.6±4.7	2.6±1.6	0.014
Education (yrs)			0.999
0-11	14 (48.3)	13 (48.1)	
≥12	15 (51.7)	14 (51.9)	
Smoking	6 (20.7)	6 (22.2)	0.999
BMI (kg/m ²)	22.4±3.2	24.1±4.3	0.085
SBP (mm Hg)	147.2±11.3	130.0±15.2	<0.001
DBP (mm Hg)	83.8±9.8	85.4±10.6	0.700
Hemoglobin (g/dL)	10.1±1.1	10.6±1.1	0.168
Albumin (g/dL)	4.1±0.4	4.0±0.5	0.273
Calcium (mg/dL)	8.5±0.8	8.8±0.7	0.097
Phosphorus (mg/dL)	5.8±2.1	5.2±1.7	0.228
Creatinine (mg/dL)	8.4±2.4	9.4±3.9	0.321
Total cholesterol (mg/dL)	152.0±32.8	179.5±35.7	0.007
Triglyceride (mg/dL)	131.4±92.0	155.1±53.1	0.128
LDL-cholesterol (mg/dL)	84.2±23.0	104.4±29.7	0.080
Intact-PTH (pg/mL)	211.2±230.2	160.1±180.0	0.436
hs-CRP (mg/L)	3.07±6.85	2.26±1.75	0.568
MMSE	26.1±3.1	27.8±2.9	0.010
Cognitive impairment	7 (24.1)	3 (11.1)	0.299
BDI	20.2±10.4	12.0±8.4	0.003
Depressive symptoms	15 (51.7)	5 (18.5)	0.013

MHD, maintenance hemodialysis; CPD, chronic peritoneal dialysis; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; PTH, parathyroid hormone; hs-CRP, high sensitivity-C reactive protein; MMSE, mini-mental state exam; BDI, Beck Depression Inventory.

Female gender, diabetes mellitus, previous CVD, education and smoking are expressed as the number (percent).

Table 2. Prevalence of Cognitive Impairment in Dialysis Patients

	Normal cognition (n=46)	Cognitive impairment (n=10)	p value
Age (yrs)			0.308
<50	17 (89.5%)	2 (10.5%)	
50-59	17 (85.0%)	3 (15.0%)	
≥60	12 (70.6%)	5 (29.4%)	
Sex			0.731
Female	23 (79.3%)	6 (20.7%)	
Male	23 (85.2%)	4 (14.8%)	
Education (yrs)			0.038
0-11	19 (70.4%)	8 (29.6%)	
≥12	27 (93.1%)	2 (6.9%)	
Dialysis vintage (yrs)			0.254
0-1	17 (94.1%)	1 (5.6%)	
2-3	16 (76.2%)	5 (23.8%)	
≥4	13 (76.5%)	4 (23.5%)	
Diabetes mellitus			0.727
No	28 (80.0%)	7 (20.0%)	
Yes	18 (85.7%)	3 (14.3%)	

Table 3. Risk Factors of Cognitive Impairment in Dialysis Patients

Variables	OR (95% CI)	p value
Depressive symptoms	7.667 (1.104-53.228)	0.039
Education (≥12 yrs)	0.106 (0.102-0.957)	0.046
Age (per 1 yr)	1.079 (0.988-1.179)	0.092
Serum albumin level (g/dL)	0.199 (0.023-1.706)	0.141
Diabetes mellitus	0.286 (0.041-1.980)	0.205
Dialysis vintage (per 1 yr)	1.010 (0.846-1.206)	0.911

OR, odds ratio; CI, confidence interval.

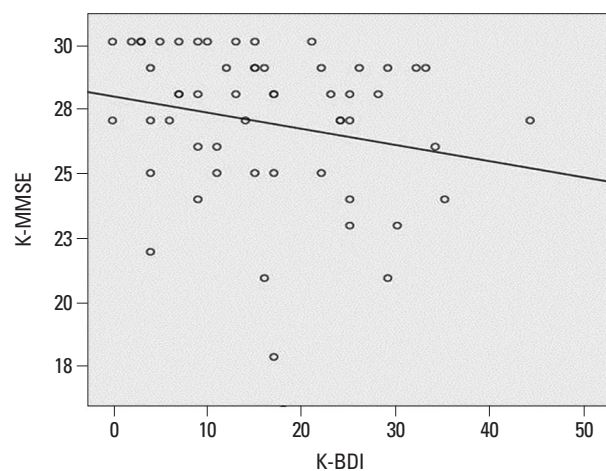


Fig. 1. Correlation analysis between K-MMSE and K-BDI in dialysis patients ($r=-0.296$, $p=0.026$). K-MMSE, Korean version of the mini-mental state exam; K-BDI, Korean version of the Beck Depression Inventory.

cognitive impairment according to age, sex, education, dialysis vintage, and diabetes mellitus. The patients with ≥12 years of education were less likely to have cognitive impairment than those with 0-11 years of education (6.9% vs.

29.6%, $p=0.038$). The percentage of cognitive impairment also seemed higher in the older patients and those with longer dialysis vintage, but this was not statistically significant. The correlation analysis showed a significant negative correlation between the K-MMSE and the K-BDI in dialysis patients ($r=-0.296$, $p=0.026$) (Fig. 1). Age ($r=-0.299$, $p=0.025$) and dialysis vintage ($r=-0.332$, $p=0.012$) were also negatively correlated with the K-MMSE.

All variables associated with cognitive impairment were included in the logistic regression analysis test. Depressive symptoms (odds ratio 7.667, 95% confidence interval 1.104-53.228, $p=0.039$) and education level (odds ratio 0.106, 95% confidence interval 0.102-0.957, $p=0.046$) were shown to be the independently predictive of cognitive impairment in multivariate analysis (Table 3).

DISCUSSION

For many years cognitive impairment in maintenance dialy-

sis patients has been neglected by clinicians and researchers. Studies have only recently begun to report a high frequency of cognitive impairment in dialysis patients. However, most studies have focused on MHD patients and their association with high mortality.^{18,19} Only few studies have been performed in CPD patients, focusing on their quality of life.^{16,20} In addition to mortality, health-related quality of life (QOL) issues are now recognized as an important outcome measure in many clinical research studies and trials for chronic debilitating disease including chronic dialysis patients.²¹ Patient QOL is affected by multifactorial components including physical, socioeconomic, cultural, cognitive, and psychological factors. These factors can affect QOL independently, but can also interact with each other. Among these factors, cognition is a major determinant in a patient's QOL, and is known to be associated with mortality in dialysis patients.

Several explanations may account for cognitive impairment in maintenance dialysis patients. Patients with cognitive impairment are apt to impede medication adherence, ignore dietary restrictions, and less likely to comply with dialysis schedules.²² Cognitive impairment may result in suboptimal care and increase in mortality. Moreover, the accumulation of toxic substances resulting from reduced metabolic rates can impair central nervous system functions.²¹ Dialysis patients have been demonstrated to develop uremic or dialysis-related encephalopathy.^{23,24} Direct effects of uremic toxin on neurons may also contribute declines in cognition. Additionally, development of cerebrovascular disease can also affect the cognition of dialysis patients, as well as anemia, secondary hyperparathyroidism, and serum albumin level.^{3,7,25,26} This study enrolled subjects with no history of dementia and depression. Therefore, the rate of cognitive impairment may have been relatively low (17.9%), compared to other studies.^{4,6,7}

Mild cognitive impairment cannot be easily detected by clinicians and health care providers. The early detection of cognitive impairment is very important, because cognitive impairment can progress to dementia and is associated with impaired QOL and increased mortality.²⁷ For early detection of cognitive impairment in dialysis patients at the clinic or dialysis center, fast and simple screening tools are required. Although the MMSE has some weaknesses such as easily being affected by education and age, and not being suitable for executive functions, the MMSE can estimate the overall cognitive status of a patient within 15 to 20 minutes.²⁸ The MMSE does not need to be applied by well-trained neuropsychologists but can be performed by clini-

cians and other health care providers. Whereas a detailed and systematic neuropsychological test is required to evaluate the cognitive status of the patients for further studies, simple and easy screening tools such as the MMSE are suitable for bedside examination. The K-MMSE is the Korean translated and validated version of the MMSE.²⁹ Although the original MMSE used ≤ 23 as a cutoff value for dementia, many studies including Korean studies use a cutoff point of ≤ 24 in terms of the total score to determine patients with cognitive impairment.^{17,30} To screen the mood of our participants we used the K-BDI, which is the Korean translated and validated version of the BDI.³¹ The K-BDI is a self-reporting questionnaire for depression and does not require psychiatric experts to perform the test. We used a cutoff point of 21 in terms of total score to detect depressive symptoms in CKD patients instead of a cutoff point of 13. With the cutoff point of 13, 56% of all subjects were shown to have depression in the Korean validation study.³¹

This study presents the possible impact of different dialysis modalities on cognitive function and depressive mood, which may affect QOL and mortality in dialysis patients. Results from previous studies comparing cognitive function in MHD and the CPD patients show conflicting results. Some data showed that the prevalence of cognitive impairment was high in MHD patients, whereas CPD patients had consistently better cognitive function than MHD patients.^{11,20} On the contrary, Kalirao, et al.²⁰ reported that cognitive impairment in CPD patients was almost as common as that in MHD patients. Some researchers suggested that the difference in the prevalence of cognitive impairment and the level of cognitive function between MHD and CPD patients might be caused by selection bias rather than the dialysis procedure itself.¹⁹ The difference could be due to mismatched important variables, including age or level of education, and due to differences in cognitive functions prior to start of dialysis. However, this study showed that cognitive function was higher and the prevalence of cognitive impairment was lower in the CPD group in spite of a well-matched selection of the patients. There was no difference in demographic factors including age, sex, education level, diabetes, and cardiovascular disease history between the two groups. We hypothesized that the superior effects for CPD over MHD on cognitive impairment may stem from continuous treatment and better removal of middle molecular weight uremic toxins.

Among all the factors affecting cognitive impairment, symptoms of depression and education level were detected

as significant risk factors in the multivariate logistic regression analysis of the present study. Cognitive decline was associated with depression in maintenance dialysis patients. Similar to our findings, Agganis, et al.³² noted that MHD patients with a greater burden of depressive symptoms performed worse on tests of cognition. They suggested that the increased vascular risk factors likely put MHD patients at an increased risk of white matter disease that potentially leads to both depression and cognitive impairment. Although the relationship between cognitive impairment and depression was not clear in CPD patients, they exhibit as many vascular risk factors as in MHD. Therefore, this explanation might be applicable in both patients. Their findings indicated that dialysis modality can affect cognitive function indirectly by means of lowering QOL and inducing depression. Less than 12 years of education (did not finish high school) was another factor associated with cognitive impairment. This observation is consistent with the results of a study by Murray, et al.⁴ who reported an association between cognitive impairment and education in MHD patients.

There are several limitations in this study. Compared with other studies, the sample size of each group was small. This might dampen the reliability of the results. A second limitation is the screening of the enrolled patients. Exclusion of patients with dementia was based on medical records or history taken from the patients or the care givers. Undetected mild dementia could bias the prevalence of cognitive impairment. However, the high average scores of the K-MMSE in both MHD and CPD patients suggest that our sample was dementia free at the time of the screening. Another potential limitation is that we did not examine the brain images of the study participants. To clarify the difference of cognition by modality of dialysis, brain images to detect lesions which influence cognition of both MHD and CPD patients should be taken. However, development of cerebrovascular disorders could also be a cause of cognitive impairment in dialysis patients.

In conclusion, this study showed that more MHD patients than CPD patients were affected by cognitive impairment and depression. Cognitive impairment was closely correlated with the presence of depressive symptoms. As cognitive impairment can affect the quality of life of maintenance dialysis patients without sufficient evidence of dementia, it is important to detect cognitive impairment and depression in dialysis patients in an early state of ESRD with simple bedside screening tools.

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