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Original Article

The relationship between cognitive function and having diabetes in patients treated with hemodialysis

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ABSTRACT

Purpose: Patients undergoing maintenance hemodialysis (MHD) have a higher prevalence of cognitive impairment and inferior cognitive performance than the general population, and those with cognitive impairment are at higher risk of death than those without cognitive impairment. Having diabetes has been associated with an increased risk of cognitive decline in end-stage kidney disease patients treated with peritoneal dialysis or kidney transplant. However, these findings may not extend to the hemodialysis population. Thus, we aim to investigate the relationship between having diabetes and cognitive function in MHD patients.
Methods: This was a cross-sectional study. A total of 203 patients treated with MHD from two blood purification centers were enrolled as subjects. The Chinese version of the Montreal Cognitive Assessment (MoCA) was utilized to assess cognitive function.
Results: MHD patients with diabetes had a significantly higher prevalence of global cognitive impairment and inferior performance in global cognition, visuospatial/executive function, naming, language, abstraction and orientation tasks compared with those without diabetes. According to the multiple linear analyses, having diabetes was significantly associated with lower global cognitive function, naming, and language scores, with β coefficients and 95% CIs of −1.30 [−2.59, −0.01], −0.25 [−0.47, −0.02], and −0.32 [−0.58, −0.07], respectively (all $P < 0.05$). Having diabetes could not independently predict an increased risk of global cognitive impairment.
Conclusions: In MHD patients, having diabetes is significantly associated with lower cognitive function scores. Medical staff should evaluate early and focus on the decline of cognitive function in MHD patients with diabetes, in order to achieve early diagnosis and early intervention.

What is known?

- Cognitive impairment is frequently observed in patients undergoing maintenance hemodialysis.
- Diabetes is common among patients undergoing maintenance hemodialysis, yet it remains unknown whether diabetes will further impair cognitive function in these patients.

What is new?

- Maintenance hemodialysis patients with diabetes showed a higher prevalence of global cognitive impairment than those without.
- The performance of maintenance hemodialysis patients with diabetes was inferior to those without regarding the global cognitive function as well as the specific domains including visuospatial/executive function, naming, language, abstraction and orientation tasks.

1. Introduction

Cognitive impairment is prevalent in the population treated

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with maintenance hemodialysis (MHD): up to 87.3% of patients aged 55 years and older have cognitive dysfunction, with moderate to severe cognitive impairment accounting for 73.4% [1,2]. It is known that cognitive impairment reduces the ability to make informed decisions and comply with dialysis activities [3,4] and is an independent risk factor for mortality in individuals undergoing hemodialysis [5,6]. Consequently, identifying correlates of poor cognitive ability is critically important and is the first step to early prevention and delaying the decline of cognition in the MHD population.

The potential causes of cognitive decline among MHD patients are thought to be multifactorial. Previous analyses have reported several risk factors of cognitive impairment, such as age, gender, education level, body mass index (BMI), cardiovascular disease and so on [7–9]. However, these findings have been not consistent among published studies.

Diabetes was another common illness affecting up to 45% of patients with end-stage kidney disease (ESRD) [10]. Although several studies have shown that having diabetes is associated with an increased risk of general or specific cognitive impairment in ESRD patients treated with peritoneal dialysis or kidney transplant [11–13], these findings may not extend to the hemodialysis population. The data on the association between having diabetes and cognitive function in hemodialysis patients are still limited and controversial. One important report on this issue showed that vascular causes of ESRD, including diabetes, were associated with an increased likelihood of severe cognitive impairment in bivariate analyses of 374 subjects using a 45-minute battery of nine validated neuropsychological tests. However, this relationship disappeared after adjusting for age, sex, and race in logistic regression analyses [1]. The primary limitation of that study is that it examined the risk factors of severe cognitive impairment instead of all degrees of cognitive impairment. In another investigation, the presence of diabetes was associated with poor executive function performance but not memory dysfunction in hemodialysis patients, whether in unadjusted or adjusted analyses [14]. However, from a dialysis population perspective, the dialysis duration of this study was short; the mean duration was 14 months, and over 40% of subjects had 12 months or shorter dialysis duration. Therefore, the correlation between having diabetes and cognitive function in MHD population was still unclear.

In the proposed cross-sectional study, we aimed to explore the relationship between having diabetes and cognitive function in populations treated with MHD, which is conducive to attracting medical staff to pay more attention to the cognitive function decline of hemodialysis patients with diabetes, and investigating the risk factors associated with diabetes in cognitive decline in such specific populations.

2. Materials and methods

2.1. Study design and recruitment

Two blood purification centers from Jiangsu Province in China participated in this cross-sectional study. Both centers had board certified physicians and nurses and well-maintained databases recording baseline data for patients. The data from each center were gathered following a standard and strict quality control framework and further inspected to ensure the integrity and accuracy of the materials. All researchers and assistants completed a training and mentoring programme, which taught them the methods and processes of the current study.

This study used a convenience sample of hemodialysis patients during a period spanning August 2018 to January 2019. Eligibility criteria for participants were as follows: 18 years or older; received a elementary school or above education; undergoing clinically stable and regular dialysis (2–3 times per week and 3–4 hours each time) for 3 or more months. Patients were excluded if they had any known neurological disorders such as dementia, or Parkinson's disease; history of mental illness, such as depression or schizophrenia; any other severe health condition, such as a malignant tumour or serious infection; or impairments in vision, hearing, language, or comprehension skills.

2.2. Clinical characteristics

The sociodemographic characteristics and comorbidities of the subjects were recorded, including age, sex, educational level, BMI, dialysis duration, the presence of dyslipidaemia, and history of cardiovascular disease. Educational level was recorded as the highest level of education, including elementary school, middle school, high school, or above high school. BMI was calculated from dry weight and height. The presence of one of following conditions was considered to be dyslipidaemia: high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and high triglycerides. Patients who had at least one of following conditions were defined as having cardiovascular disease: class III or IV congestive heart failure (classified by the New York Heart Association), stenocardia, history of myocardial infarction or cerebrovascular accident, peripheral arterial disease, or transient ischaemic attack. Data on the sociodemographic characteristics and comorbidities were obtained using participants' self-reports. Additionally, electronic medical and paper records were inspected for the above information.

2.3. Laboratory parameters

Biochemical data including serum creatinine, blood urea nitrogen, and hemoglobin were obtained from venous blood, which was sampled within 5 minutes prior to dialysis.

2.4. Diabetes information

Diabetes Mellitus (DM) was defined as the presence of type 1 or type 2 diabetes. Access to this information was based on subjects' self-reports, and then we again carefully checked the data through electronic and paper medical records.

2.5. Cognitive assessments

All participants performed a cognitive function test using the Chinese version of the Montreal Cognitive Assessment (MoCA) which is considered a suitable cognitive screening instrument with good sensitivity and specificity for hemodialysis population [15]. The Cronbach's α was 0.88, suggesting good internal consistency. There was a high correlation between MoCA scores and those of the Mini Mental State Examination ($r = 0.83$), indicating high criterion-related validity [16]. The instrument assessed seven cognitive domains, namely, visuospatial/executive function, naming, attention, language, abstraction, delayed recall, and orientation [17]. The possible scores ranged from 0 to 30 with higher scores indicating better cognitive status. We defined cognitive impairment as an overall score of less than 26 for participants with a high school or below education and 27 for those with an above high school education because mean scores on the MoCA differed depending on education level [18].

The assessment of cognitive function was conducted in a quiet room with one medical researcher for per subject. To ensure quality and inter-rater reliability, the testing was observed by four members of the research team after completing a training programme that taught the research team the standard cognitive function testing and scoring methods. To minimize participant fatigue, testing was completed within 10 minutes before dialysis.

2.6. Standard protocol approval

The research was approved by the Medical Ethics Committee of the Lishui branch of Zhongda Hospital, which is affiliated with Southeast University. All participants signed informed consent prior to initiation of study activities.

2.7. Statistical analyses

Subjects were divided into two groups based on the presence of diabetes (that is, DM or non-DM group). Categorical variables were expressed as frequencies (proportions, %), and their differences were compared using the Fisher's exact test, chi-square test, or Wilcoxon rank test, when appropriate. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For normally distributed continuous variables, they were described as *Means* ± standard deviations (*SD*) and compared using unpaired *t*-test; otherwise, they were expressed as medians (P_{25}–P_{75}) and their differences were analysed using the Wilcoxon rank test.

The multiple linear regression analyses were utilized to explore the relationship between the scores of cognitive function and having diabetes, and the multiple logistic regression analyses were employed to examine whether having diabetes was associated with an increased risk of cognitive impairment. In both analyses, two models were introduced, with model 1 controlled for the sociodemographic factors including age, gender, education level, and BMI; and model 2 additionally controlled for cerebrovascular disease (having or not having). Two-sided *P* values less than 0.05 were considered statistically significant. All statistical analysis were performed using SPSS (version 25.0) for Windows software.

3. Results

3.1. Participant characteristics

A total of 203 MHD patients were enrolled in this study. These enrolled subjects had a mean age of 54.83 ± 13.61 years, BMI of 21.92 ± 3.20 kg/m^2, and serum creatinine of 669.18 ± 346.61 μmol/L; median dialysis duration of 33.00 (14.00–70.00) months, hemoglobin of 102.00 (86.00–117.00) g/L, and blood urea nitrogen of 16.92 (8.65–25.46) mmol/L. Of these participants, 61.1% were men, 90.6% had a high school or less than a high school education, 31.5% had diabetes, 29.1% had history of cardiovascular disease, and 17.7% had dyslipidaemia (Table 1).

3.2. Diabetes, clinical characteristics, and cognitive function

Subjects with diabetes tended to be older and to have higher BMI, shorter dialysis duration, lower serum creatinine level, and higher proportion of cardiovascular disease and dyslipidaemia compared to those without diabetes ($P < 0.05$). Sex, education level, hemoglobin, and blood urea nitrogen did not differ between these two groups ($P > 0.05$) (Table 1).

Patients with diabetes had a higher prevalence of cognitive impairment, lower MoCA scores and lower scores for visuospatial/executive function, naming, language, abstraction and orientation tasks compared with those without diabetes ($P < 0.05$). There were no differences in score for attention and delayed recall between the two groups ($P > 0.05$) (Table 2).

3.3. Relationship between having diabetes and cognitive function

When the data were analysed using multiple linear regression analyses, the results showed that having diabetes was associated with lower MoCA, naming, and language scores after adjusting for sociodemographic factors and cardiovascular disease ($P = 0.048$, 0.032, and 0.013 respectively) (Table 3). Logistic regression analyses found that having diabetes was associated with cognitive impairment (odds ratio, 4.46; 95% CI, 1.29 to 15.37; $P = 0.018$). However, after adjusting for sociodemographic characteristics and cardiovascular disease, having diabetes could not independently predict an increased risk of global cognitive impairment (Table 4).

4. Discussion

In this study, we found the prevalence of cognitive impairment among the hemodialysis population was 82.3%. The cognitive impairment incidence was relatively lower than the 87.5% incidence reported in the previous study [1]. This difference may result from the younger subjects, the diverse diagnostic criteria for cognitive impairment, and the exclusion of patients with dementia in the present study.

In the current study, we found that diabetes was significantly associated with not only global cognitive function but also several specific domains, including naming and language ability, after adjusting for demographic characteristics. Moreover, upon further adjusting for cardiovascular disease, this association still existed. Limited published materials have focused on this issue for the hemodialysis population. Our results are consistent with previously published studies on the relationship between diabetes and cognitive function in the general population [19,20]. The mechanism behind this association is unclear, but it may involve chronic cerebral ischaemia, amyloid deposition, and toxic advanced glycation end product accumulation [21–23].

It is noteworthy that we did not find that having DM could independently predict the risk of global cognitive impairment in MHD patients after adjusting for multivariate. The result is contradictory to studies targeting the general population [24,25]. There were some possible speculations regarding this result. First, multiple factors associated with end-stage renal disease, such as inflammation, endothelial dysfunction, atherosclerosis, vascular calcification and hyperhomocysteinemia, also play an important role in the development and progression of CI [26–28]. In these situations, the influence of having diabetes on cognitive impairment in MHD patients may be weaker. Second, patients with acute complications, weakness or diagnosed dementia may not be able to undergo neuropsychological tests, which may bias the results to some extent. Third, Liao J et al. observed a similar result in patients with peritoneal dialysis [29]; they found that having diabetes with retinopathy rather than diabetes alone was significantly associated with global cognitive impairment and with cognitive impairment in several specific domains, including visuospatial/executive function and memory ability. These correlations still persisted after controlling for sociodemographic characteristics, laboratory parameters, and cardiovascular diseases. Several cross-sectional and cohort studies have revealed that the presence of retinal microangiopathy was an independent predictor of cognitive impairment in patients with diabetes [30–32], and it was also related to evidence of brain atrophy detected through subclinical cerebral infarction and magnetic resonance imaging in adults without diabetes [33,34]. Given the intimate anatomical and physiological connections between the retinal and cerebrovascular networks [35], we could not eliminate the possibility that microvascular complications of diabetes, rather than diabetes itself, independently predicts cognitive dysfunction in MHD patients and that the

Table 1
Clinical characteristics in MHD patients with and without diabetes.

Variables	Total	Non-DM	DM	$t/\chi^2/Z$	*P*
No. of patients, *n* (%)	203 (100.0)	139 (68.5)	64 (31.5)	–	–
Age, years, *Mean* ± *SD*	54.83 ± 13.61	52.67 ± 14.19	59.53 ± 10.94	−3.43	0.001
Gender, *n* (%)				0.35	0.555
Male	124 (61.1)	83 (59.7)	41 (64.1)		
Female	79 (38.9)	56 (40.3)	23 (35.9)		
Level of education, *n* (%)				−0.28	0.778
Elementary school	64 (31.5)	44 (31.7)	20 (31.3)		
Middle school	74 (36.5)	48 (34.5)	26 (40.6)		
High school	46 (22.7)	35 (25.2)	11 (17.2)		
>High school	19 (9.4)	12 (8.6)	7 (10.9)		
BMI, kg/m^2, *Mean* ± *SD*	21.92 ± 3.20	21.50 ± 3.11	22.84 ± 3.22	−2.82	0.005
Dialysis duration, months, *Median* (P_{25}–P_{75})	33.00 (14.00–70.00)	45.00 (16.00–84.00)	20.00 (10.00–48.75)	−3.27	0.001
Hb, g/L, *Median* (P_{25}–P_{75})	102.00 (86.00–117.00)	103.00 (88.00–118.00)	100.50 (85.00–116.75)	−0.81	0.419
Scr, μmol/L, *Mean* ± *SD*	669.18 ± 346.61	720.68 ± 372.72	557.32 ± 249.68	3.68	<0.001
BUN, mmol/L, *Median* (P_{25}–P_{75})	16.92 (8.65–25.46)	17.35 (8.52–27.94)	15.21 (8.74–22.04)	−0.93	0.353
CVD, *n* (%)	59 (29.1)	34 (24.5)	25 (39.1)	4.53	0.033
Dyslipidaemia, *n* (%)	36 (17.7)	14 (10.1)	22 (34.4)	17.74	<0.001

Note: MHD, maintenance hemodialysis; DM, diabetes mellitus; BMI, body mass index; Hb, hemoglobin; Scr, serum creatinine; BUN, blood urea nitrogen; CVD, cardiovascular disease.

Table 2
Cognitive function parameters in MHD patients with and without diabetes [*Median* (P_{25}–P_{75})].

Variables	Full mark	Total (*n* = 203)	Non-DM(*n* = 139)	DM(*n* = 64)	$t/\chi^2/Z$	*P*
Cognitive impairment, *n* (%)	–	167 (82.3)	107 (77.0)	60 (93.8)	8.45	0.004
MoCA score, *Mean* ± *SD*	30	18.45 ± 5.76	19.32 ± 5.80	16.56 ± 5.27	3.25	0.001
Visuospatial/executive function score	5	2.00 (1.00–4.00)	3.00 (1.00–4.00)	2.00 (1.00–3.00)	−2.22	0.033
Naming score	3	2.00 (2.00–3.00)	3.00 (2.00–3.00)	2.00 (1.25–3.00)	−3.37	0.001
Attention score	6	3.00 (2.00–3.00)	3.00 (2.00–3.00)	2.00 (1.25–3.00)	−1.75	0.081
Language score	3	2.00 (1.00–2.00)	2.00 (1.00–3.00)	1.00 (1.00–2.00)	−3.59	<0.001
Abstraction score	2	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–0.00)	−2.01	0.044
Delayed recall score	5	1.00 (0.00–3.00)	1.00 (0.00–4.00)	0.00 (0.00–2.75)	−1.94	0.052
Orientation score	6	6.00 (5.00–6.00)	6.00 (5.00–6.00)	6.00 (5.00–6.00)	−2.35	0.019

Note: MHD, maintenance hemodialysis; DM, diabetes mellitus; MoCA, Montreal Cognitive Assessment.

Table 3
Association of having diabetes with cognitive function by multiple regression analyses.

Dependent variables	Model 1		Model 2	
	β (95% CI)	*P*	*β* (95% CI)	*P*
MoCA score	−1.39 (−2.67, −0.12)	0.034	−1.30 (−2.59, −0.01)	0.048
Visuospatial/executive function score	−0.29 (−0.67, 0.10)	0.146	−0.29 (−0.69, 0.04)	0.150
Naming score	−0.27 (−0.49, −0.04)	0.020	−0.25 (−0.47, −0.02)	0.032
Attention score	−0.08 (−0.34, 0.19)	0.561	−0.08 (−0.35, 0.18)	0.543
Language score	−0.34 (−0.59, −0.09)	0.009	−0.32 (−0.58, −0.07)	0.013
Abstraction score	−0.11 (−0.30, 0.08)	0.247	−0.11 (−0.29, 0.08)	0.275
Delayed recall score	−0.10 (−0.56, 0.35)	0.650	−0.08 (−0.53, 0.38)	0.737
Orientation score	−0.21 (−0.45, 0.04)	0.094	−0.21 (−0.46, 0.04)	0.093

Note: Model 1:Adjusted for age, sex, educational level, body mass index; Model 2: Adjusted for age, sex, educational level, body mass index, cerebrovascular disease. MoCA, Montreal Cognitive Assessment.

Table 4
Association of having diabetes with cognitive impairment by logistic regression analyses.

Dependent variables	Univariable		Model 1		Model 2	
	OR (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*
cognitive impairment	4.46 (1.29, 15.37)	0.018	2.62 (0.53, 13.16)	0.241	2.53 (0.49, 13.15)	0.269

Note: Model 1:Adjusted for age, sex, educational level, body mass index; Model 2: Adjusted for age, sex, educational level, body mass index, cerebrovascular disease.

microvascular complications may lead to cerebral dysfunction by means of reducing effective delivery of substrates to neurons [36]. To clarify the issue, further investigation of the effect of diabetic microvascular complications on cognitive impairment should be considered in MHD patients.

A major strength of this study is that the design targeted the effect of having diabetes on MHD, to which very little attention had been paid by researchers to date. Our neuropsychological testing assessed the cognitive function of global and multiple specific domains, including visuospatial/executive function, language, memory ability and so on.

The current study has some limitations. First, the diagnosis of cognitive impairment using only neuropsychological testing lacked imaging evidence. Second, we determined the presence of diabetes based solely on self-reported data from participants without further confirming with blood testing, which may have introduced bias. Third, since this a cross-sectional study, we could not determine whether controlling blood glucose levels would reduce the risk of cognitive dysfunction among the MHD population with diabetes.

5. Conclusion

In conclusion, this cross-sectional study examining the relationship between having diabetes and cognitive status in MHD patients found that having diabetes was associated with global cognitive function and that of several specific domains, including visuospatial/executive function, naming, and language. However, having diabetes could not independently predict an increased risk of global cognitive impairment in MHD patients after adjusting for multivariate. Further studies will be needed to investigate whether controlling blood glucose might delay cognitive impairment in MHD patients.

Author contributions

Lei Cui: Conceptualization, Investigation, Resources, Formal analysis, Writing - Original Draft, Writing - Review & Editing. Weixia Chen: Investigation, Resources. Xingxing Yu: Investigation, Resources. Changping Ju: Conceptualization, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that no conflict of interest exists, and the manuscript is approved by all authors for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijnss.2019.12.003.

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