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Cerebral oxygenation and body mass index association with cognitive function in chronic kidney disease patients without dialysis: a longitudinal study

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In chronic kidney disease (CKD) patients, the prevalence of cognitive impairment increases with CKD progression; however, longitudinal changes in cognitive performance remain controversial. Few reports have examined the association of cerebral oxygenation with cognitive function in longitudinal studies. In this study, 68 CKD patients were included. Cerebral regional oxygen saturation (rSO₂) was monitored. Cognitive function was evaluated using mini-mental state examination (MMSE) score. Clinical assessments were performed at study initiation and 1 year later. MMSE score was higher at second measurement than at study initiation ($p = 0.022$). Multivariable linear regression analysis showed that changes in MMSE were independently associated with changes in body mass index (BMI, standardized coefficient: 0.260) and cerebral rSO₂ (standardized coefficient: 0.345). This was based on clinical factors with $p < 0.05$ (changes in BMI, cerebral rSO₂, and serum albumin level) and the following confounding factors: changes in estimated glomerular filtration rate, hemoglobin level, proteinuria, salt and energy intake, age, presence of diabetes mellitus, history of comorbid cerebrovascular disease, and use of renin–angiotensin system blocker. Further studies with a larger sample size and longer observational period are needed to clarify whether maintaining BMI and cerebral oxygenation improve or prevent the deterioration of cognitive function.

In chronic kidney disease (CKD) patients, discussion and decisions about healthcare management, including the choice of renal replacement therapy, is important with patients' appropriate judgements throughout an accurate comprehension and cognitive function¹. Furthermore, cognitive impairment was reported to affect the decision-making capacity in patients with advanced CKD²; and therefore, efforts to maintain cognitive function are essential in the clinical settings of CKD therapy. In previous studies, cognitive impairment was reportedly associated with various clinical factors, such as ageing, classical vascular factors, nephrogenic factors, and a decrease in the estimated glomerular filtration rate (eGFR)^{3–7}. In particular, the prevalence of cognitive impairment reportedly increased with a reduction in eGFR⁷. However, it was recently reported that CKD progression and the degree of eGFR reduction are not associated with an increased risk of cognitive impairment⁸. Further, longitudinal studies have shown that cognitive performance was well-maintained in patients with CKD, which

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Variables	Study initiation	Second measurement	p
MMSE score (30 points)	27.0 (26.0–29.8)	28.0 (26.0–30.0)	0.022*
Orientation to time (5 points)	5 (5–5)	5 (5–5)	0.030*
Orientation to place (5 points)	5 (5–5)	5 (5–5)	0.020*
Registration (3 points)	3 (3–3)	3 (3–3)	1.000
Calculation (5 points)	3 (1–5)	3 (3–5)	0.046*
Memory recall (3 points)	3 (2–3)	3 (2–3)	0.071
Language (2 points)	2 (2–2)	2 (2–2)	0.317
Repetition (1 point)	1 (1–1)	1 (1–1)	0.257
Complex commands (6 points)	6 (6–6)	6 (6–6)	0.093
MMSE score \leq 23	5 (7.4)	2 (2.9)	0.438
Body mass index (kg/m ²)	23.0 (21.3–26.5)	23.0 (21.7–25.7)	0.452
Mean blood pressure (mmHg)	97.2 \pm 14.0	95.5 \pm 14.0	0.299
Sat O ₂ (%)	98.0 (98.0–98.0)	98.0 (98.0–98.0)	0.438
Cerebral rSO ₂ (%)	58.8 \pm 6.4	57.9 \pm 6.1	0.300
Laboratory findings			
eGFR (mL/min/1.73 m ²)	27.6 \pm 10.7	25.6 \pm 11.5	< 0.001*
Hb (g/dL)	12.3 \pm 1.6	12.3 \pm 1.8	0.926
Serum albumin (g/dL)	4.0 \pm 0.3	4.0 \pm 0.4	0.132
Serum Ca (mg/dL)	9.1 (8.8–9.4)	9.0 (8.8–9.3)	0.367
Serum P (mg/dL)	3.6 (3.1–4.0)	3.6 (3.1–4.1)	0.165
Proteinuria (mg/day)	355 (112–840)	436 (105–1253)	0.006*
Nutritional markers			
Salt intake (g/day)	5.6 (4.5–7.9)	5.9 (4.8–7.6)	0.680
Energy intake (kcal/kg ideal BW/day)	28.7 \pm 3.2	28.7 \pm 4.2	0.940
Protein intake (g/kg ideal BW/day)	0.8 \pm 0.2	0.8 \pm 0.2	0.870

Table 1. Comparison of clinical parameters between the study initiation and second measurements in this study. Categorical data are presented as number (%), continuous data are presented as mean \pm standard deviation or median and interquartile range. *Statistically significant. *BW* body weight, *eGFR* estimated glomerular filtration rate, *Hb* haemoglobin, *MMSE* Mini-Mental State Examination, *rSO₂* regional oxygen saturation.

could potentially be attributed to specific CKD therapies^{2,9,10}. Therefore, the association between changes in cognitive function and clinical factors such as eGFR, and longitudinal changes in cognitive impairment in patients with CKD, remain controversial.

Cerebral regional oxygen saturation (rSO₂), a real-time marker of cerebral oxygenation, has been evaluated using near-infrared spectroscopy (NIRS) in the clinical setting^{11–14}. In particular, CKD patients without dialysis therapy presented with relatively low cerebral rSO₂ values when compared with normal controls^{15–17}, and were reportedly affected by dietary intake and nutritional status, including energy and salt intake¹⁸. Furthermore, a cross-sectional study demonstrated that there were significant associations between cerebral rSO₂ and cognitive function¹⁷, in addition to the association between nutritional status and cognitive function¹⁹. However, to date, few reports have examined the association of clinical factors, including cerebral oxygenation and nutritional status, with cognitive function in longitudinal studies of CKD patients. Therefore, in this study, we aimed to longitudinally investigate the association between cognitive assessment scores and clinical factors, including cerebral rSO₂ and nutritional status, in CKD patients without dialysis therapy.

Results

The differences between clinical parameters measured at the study initiation and second measurement are summarized in Table 1. The median follow-up period was 364 days (interquartile range 352–385 days). MMSE score was significantly higher at the time of second measurement than at the study initiation ($p = 0.022$). The prevalence of cognitive impairment based on the MMSE score decreased at second measurement although the difference was not significant. The scores for the domains of orientation of place and calculation significantly increased at second measurement compared with those at study initiation ($p = 0.020$ and 0.046 , respectively), while slight and significant decrease in orientation of time was observed ($p = 0.030$). eGFR significantly decreased ($p < 0.001$) and proteinuria significantly increased ($p = 0.006$) at second measurement compared with that at the study initiation. However, no other clinical factors evaluated in this study showed significant differences. Furthermore, factors that correlated with the changes in MMSE were investigated using changes in clinical parameters between study initiation and second measurements (Table 2). Changes in body mass index (BMI) ($r = 0.266$, $p = 0.028$, Fig. 1), cerebral rSO₂ ($r = 0.349$, $p = 0.003$, Fig. 2), and serum albumin level ($r = 0.268$, $p = 0.027$) were significantly correlated with changes in MMSE. Multivariable linear regression analysis was performed for identifying independent factors

Δ MMSE	r	P
Δ Body mass index	0.266	0.028*
Δ Mean blood pressure	0.098	0.428
Δ Sat O ₂	-0.171 [#]	0.164
Δ Cerebral rSO ₂	0.349	0.003*
Δ eGFR	-0.047	0.703
Δ Hb	0.216	0.077
Δ Serum albumin	0.268	0.027*
Δ Serum Ca	0.007 [#]	0.957
Δ Serum P	0.109 [#]	0.376
Δ Proteinuria	0.173 [#]	0.158
Δ Salt intake	-0.116	0.345
Δ Energy intake	0.158 [#]	0.197
Δ Protein intake	0.233 [#]	0.056

Table 2. Correlation between changes in MMSE and those in clinical parameters during this study. *eGFR* estimated glomerular filtration rate, *Hb* haemoglobin, *MMSE* Mini-Mental State Examination, *rSO₂* regional oxygen saturation. *Statistically significant. #Indicates spearman's rank correlation for skewed distribution of data.

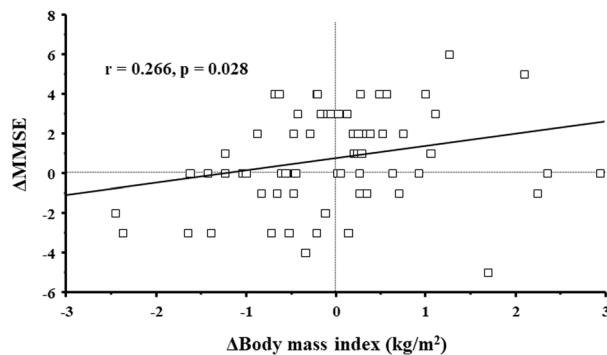


Figure 1. Correlation between changes in MMSE score and changes in body mass index from the study initiation to the second measurement. Δ MMSE MMSE score at the second measurement – MMSE score at the study initiation, Δ Body mass index body mass index at the second measurement – Body mass index at the study initiation, *MMSE* Mini-Mental State Examination.

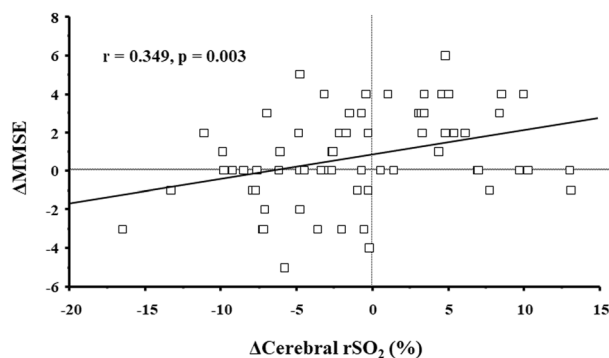


Figure 2. Correlation between changes in MMSE score and changes in cerebral rSO₂ from the study initiation to the second measurement. Δ MMSE MMSE score at the second measurement – MMSE score at the study initiation, Δ Cerebral rSO₂ cerebral rSO₂ at the second measurement – cerebral rSO₂ at the study initiation, *MMSE* Mini-Mental State Examination, *rSO₂* regional oxygen saturation.

Variables	Standardized coefficient	95% CI	P
ΔMMSE			
ΔBody mass index	0.260	0.023–0.088	0.023
ΔCerebral rSO ₂	0.345	0.045–0.208	0.003

Table 3. Multivariable linear regression analysis: independently associated factors of changes in MMSE. *CI* confidential interval, *MMSE* Mini-Mental State Examination, *rSO₂* regional oxygen saturation.

associated with changes in MMSE using parameters with $p < 0.05$ (changes in BMI, cerebral rSO₂, and serum albumin level), and the following confounding factors: changes in eGFR, hemoglobin, proteinuria, salt intake, and energy intake, age, presence of DM, history of comorbid cerebrovascular disease, and use of renin–angiotensin system blocker. As shown in Table 3, changes in MMSE were independently and significantly associated with changes in BMI (standardized coefficient: 0.260) and cerebral rSO₂ (standardized coefficient: 0.345).

Discussion

This longitudinal observational study focuses on the association between changes in cognitive function and clinical factors, including cerebral rSO₂ and nutritional status, in CKD patients without dialysis therapy. MMSE scores showed slight, but significant increase at second measurement compared with those at study initiation, and changes in MMSE score were independently associated with changes in BMI and cerebral rSO₂.

Among the several types of cognitive screening tests utilized in the clinical setting, MMSE was reportedly most commonly utilized²⁰. In patients with CKD and those undergoing hemodialysis, MMSE was found to be less superior to the Montreal Cognitive Assessment (MoCA) to detect the cognitive impairment^{21,22}. In contrast, the evaluation of cognitive function using MMSE confirmed decreased eGFR to be associated with an increased risk of cognitive impairment, similar to the results using MoCA²³. Both MMSE and MoCA were also reported to be moderately sensitive for evaluating cognitive impairment in poststroke patients²⁴. In addition, in CKD patients, there were no significant differences in area under the receiver operating curve for detecting cognitive impairment between MMSE and the Mini-Addenbrooke's Cognitive Examination²⁵. Based on these reports^{23–25}, MMSE would be effective as a screen for cognitive impairment in CKD patients; therefore, MMSE was used in this study. At study initiation, MMSE score was 27.0 (26.0–29.8) and the prevalence of cognitive impairment (defined as MMSE score ≤ 23) was 7.4% with eGFR of 27.6 ± 10.7 mL/min/1.73 m². Previous study has reported that MMSE, impaired MMSE (defined as MMSE score ≤ 23), and eGFR value were 25.3 ± 3.7 , 22%, and 24 ± 10 mL/min/1.73 m² in CKD patients with frailty, and were 27.3 ± 2.4 , 6%, and 25 ± 11 mL/min/1.73 m² in those without frailty²⁶. Thus, cognitive function in CKD patients included in this study might correspond to that in CKD patients without frailty²⁶.

The prevalence of cognitive impairment increases according to the progression of CKD stages. Risk factors for cognitive decline in CKD patients are proposed as follows: demographic factors (race, older age), vascular factors (hypertension, diabetes mellitus, a history of cardiovascular disease), and nephrogenic factors (uremic toxins, oxidative stress, anemia, albuminuria, inflammation)^[3,4,27,28]. In addition, a meta-analysis based on six longitudinal studies reported 1.4 times higher likelihood of poor cognition in patients with CKD compared to those without CKD²⁹. In contrast, recent reports have noted the preservation or improvement of cognitive function during the observational period in CKD patients without dialysis therapy^{2,9,10}. Additionally, renin–angiotensin system blocker was reported to be effective for preventing the progression of cognitive impairment in patients with CKD²⁸. In the present study, cognitive function evaluated by MMSE showed slight, but significant improvement during the study period, and this result is consistent with previous reports^{2,9,10}.

Regarding the association between cognitive function and clinical factors in CKD patients without dialysis therapy, a positive and independent association was observed between changes in BMI and cognitive function. To date, the association between BMI and cognitive function remains controversial. Initially, obesity was reportedly a higher risk for cognitive impairment, which was explained by hyperinsulinemia, adipokines and cytokines, and traditional vascular risk factors such as hypertension and dyslipidemia³⁰. However, an inverse association between BMI and the risk of dementia was recently reported³¹ and BMI was positively and independently associated with the MMSE score³². Furthermore, BMI > 25 kg/m² was associated with a lower risk of cognitive impairment both in patients with and without CKD^{8,33}, and this relationship became evident in the elderly aged 65 years or older³³. The age of CKD patients included in this study was 68.8 ± 11.6 years, which was considered to be relatively high. Therefore, the positive association between changes in cognitive function and those in BMI was consistent with that in previous reports^{31–33} and was similar to the relationship of BMI and the decrease in mortality, known as reverse epidemiology, in patients undergoing hemodialysis (HD)³⁴.

Cerebral rSO₂ values in CKD patients without dialysis therapy (approximately 55–60%) and those undergoing HD (approximately 40–50%) were reportedly lower than those in healthy controls (approximately 70%)^{15–18,35}. Furthermore, these values were reportedly associated with eGFR, serum albumin concentration, serum sodium concentration, hemoglobin level, energy intake, and energy intake/salt intake in CKD patients without dialysis therapy^{17,18}. In the evaluation of cognitive performance using the MMSE score in patients undergoing HD, cerebral rSO₂ values in patients with cognitive impairment (MMSE score ≤ 23) were reported to be significantly lower than those with normal cognition (MMSE score ≥ 24), and cerebral rSO₂ represented a positive and independent association with the MMSE score³⁶. Regarding the association of changes in the cerebral blood flow with CKD stages, lower eGFR, which indicates the deterioration of renal function, was independently associated with lower

cerebral blood flow³⁷. This association was explained by the commonality of vascular injuries and endothelial dysfunction in brain and kidney^{38,39}, and vasoconstriction of cerebral vessels induced by the accumulation of vasoactive agents in CKD status⁴⁰. Therefore, decreases in cerebral blood flow could impair microcirculation, leading to deterioration of cerebral oxygenation in CKD patients. In addition, cerebral rSO₂ showed a positive and significant correlation with MMSE score in a simple linear regression analysis¹⁷. In this study, changes in MMSE were independently and significantly associated with changes in cerebral rSO₂. Therefore, based on this result, cerebral oxygenation status could play an important role in maintaining cognitive function in CKD patients without dialysis therapy.

During the study period, eGFR significantly decreased from 27.6 ± 10.7 mL/min/1.73 m² to 25.6 ± 11.5 mL/min/1.73 m². However, there was no significant association between changes in MMSE score and those in eGFR. In the clinical setting of CKD therapy, cognitive impairment was reported to appear early in the course of CKD and was more global and severe in advanced disease stages^{5–7}. In contrast, no association between cognitive impairment and an increased risk of CKD progression was confirmed after accounting for traditional risk factors. The lack of association between them could be partially attributed to the difference in severity of CKD stages; that is, studies in patients with preserved kidney function would likely find positive correlations between both kidney function and cognitive decline⁴¹. Furthermore, a rapid decline in eGFR (> 4 mL/min/1.73 m²) had an increased relative risk of cognitive decline and dementia⁴². In CKD patients included in this study, the lack of association between changes in cognitive function and those in renal function could be due to the relatively advanced CKD status and mild eGFR decline (2.0 ± 3.9 mL/min/1.73 m²) exhibited by these patients. Regarding the association of dietary intake and nutritional status on cognitive function, it was found that subjects with insufficient energy intake and increased salt consumption presented with a significantly impaired cognitive status as compared to other subjects^{19,43}. However, in this study, there was no association between changes in the MMSE score and those in dietary intake, including energy, salt, and protein. This may be attributed to the fact that 46 of 68 patients in this study received nutritional education for CKD therapy at study initiation. Therefore, intake of salt (median 5.6 g/day), energy [28.7 ± 3.2 kcal/kg ideal body weight (BW)/day], and protein (0.8 ± 0.2 g/kg ideal BW/day) were within the recommended diet therapy levels for CKD patients, even at study initiation. Consequently, variation in the levels of each dietary component was found to be small and might not have been responsible for the changes in cognitive function seen in this study. However, adequate dietary intake for CKD management is essential to maintain the nutritional status, including BMI, as it was found to be associated with changes in cognitive function. Therefore, daily dietary intake of certain nutritional components could play an important role in preventing the deterioration of cognitive function in CKD patients.

The present study had several limitations that should be noted. First, the sample size was relatively small. Second, cognitive testing was performed during outpatient care in our hospital. The result of this being that there was limited time available for examining each patient, and only the MMSE could be used to assess cognitive function so as to avoid a delay in outpatient care. Third, albuminuria was reportedly associated with the progression of cognitive impairment as one of nephrogenic factors in patients with CKD^{3,27,28}. However, in this study, albuminuria was not measured; therefore, changes in proteinuria, instead of albuminuria, were used as a confounding factor with changes in MMSE and no association was found between them. Therefore, further evaluation, including the assessment of albuminuria as a confounding factor, would be required. Fourth, the observational period in which changes in cognitive function were monitored was around 1 year after study initiation. This was considered to be a relatively short timeframe and it would be preferable to observe these changes for a longer period. Finally, plausible confounding factors, such as low socioeconomic status, low education levels, inflammation, oxidative stress, and vascular calcification, were not considered in this study. Therefore, further studies over a longer observational period are required to investigate the association between cognitive ability, including evaluation of specific aspects of cognition, and various clinical factors that were not considered in this study.

In conclusion, changes in MMSE score were positively and independently associated with changes in BMI and cerebral rSO₂ in this longitudinal study. Further prospective studies, with a larger number of CKD patients and a longer observational period, are needed to clarify whether maintaining BMI and cerebral oxygenation improves or prevents deterioration of cognitive function in CKD patients without dialysis therapy.

Materials and methods

Study design. This study was approved by the institutional review board of Saitama Medical Center, Jichi Medical University (Saitama, Japan: approval numbers, RIN 15-104 and RINS19-HEN007), and was conducted in accordance with the Declaration of Helsinki (2004 Tokyo revision). All patients signed informed consent forms before participation. This study was performed during routine visits to the outpatient department of our hospital. The patients enrolled in this prospective cohort study underwent clinical assessments at study initiation and again 1 year later. Patient recruitment was performed from July 5, 2018 to July 16, 2020, and the study was conducted between July 5, 2018 and September 2, 2021 in our medical center.

Patients. In this single-center longitudinal observational study, CKD patients who met the following criteria were enrolled: (1) all-stage CKD patients not yet requiring dialysis, who were followed up with by our Division of Nephrology; (2) patients who were older than 20 years; (3) patients who received dietary education and nutritional assessment for CKD management; and (4) patients who underwent 24-h urine collection for the evaluation of salt and protein intake. Patients diagnosed with the following comorbidities were excluded: congestive heart failure, chronic obstructive pulmonary disease, and apparent neurological disorder.

Of the 102 patients screened, 88 met the inclusion criteria and were enrolled for the study. Overall, 20 patients were excluded from the analysis due to lack of data. Ultimately, 68 patients (49 men, 19 women; mean age, 68.8 ± 11.6 years) were included and patients' data were analyzed in the present study. The patients' general

Characteristics	Total	Male	Female
n	68 (100)	49 (72)	19 (28)
Age (year)	68.8 ± 11.6	70.4 ± 10.1	64.7 ± 14.6
CKD stages G3a/3b/4/5	6(9)/20(29)/35(52)/7(10)	6(12)/13(27)/28(57)/2(4)	0(0)/7(37)/7(37)/5(26)
Systolic BP (mmHg)	136.2 ± 21.1	136.1 ± 22.6	136.6 ± 17.3
Diastolic BP (mmHg)	77.6 ± 13.9	76.8 ± 12.9	79.8 ± 16.5
Mean BP (mmHg)	97.2 ± 14.0	96.5 ± 14.9	98.8 ± 11.7
Causes of CKD			
Diabetes mellitus	27 (40)	23 (47)	4 (21)
Nephrosclerosis	23 (34)	18 (37)	5 (26)
Chronic glomerulonephritis	7 (10)	1 (2)	6 (32)
Others	11 (16)	7 (14)	4 (21)
Comorbidities			
Cerebrovascular disease	3 (4)	2 (4)	1 (5)
Cardiovascular disease	6 (9)	3 (6)	3 (16)
CKD-associated laboratory findings			
BUN (mg/dL)	29.0 (21.0–41.0)	29.0 (20.5–41.0)	32.0 (21.0–41.0)
Serum creatinine (mg/dL)	1.9 (1.4–2.5)	2.1 (1.5–2.5)	1.6 (1.3–2.8)
eGFR (mL/min/1.73m ²)	27.6 ± 10.7	28.8 ± 10.7	24.6 ± 10.4
Serum Na (mEq/L)	139 (138–141)	140 (138–141)	139 (137–141)
Serum K (mEq/L)	4.7 ± 0.5	4.7 ± 0.5	4.7 ± 0.7
Serum Cl (mEq/L)	106 ± 3	106 ± 3	107 ± 4
Serum Ca (mg/dL)	9.1 (8.8–9.4)	9.0 (8.8–9.3)	9.2 (8.9–9.4)
Serum P (mg/dL)	3.6 (3.1–4.0)	3.4 (3.0–3.7)	4.0 (3.7–4.6)
Hb (g/dL)	12.3 ± 1.6	12.6 ± 1.5	11.6 ± 1.7
Antihypertensive medication			
Renin-angiotensin system blocker	37 (54)	26 (53)	11 (58)
Calcium channel blocker	38 (56)	28 (57)	10 (53)
Others			
Vitamin D analogue	9 (13)	6 (12)	3 (16)
Phosphate binder	5 (7)	3 (6)	2 (11)
Erythropoiesis-stimulating agent	9 (13)	6 (12)	3 (16)
Sedative agent	2 (3)	1 (2)	1 (5)

Table 4. Patient characteristics. Categorical data are presented as number (%), continuous data are presented as mean ± standard deviation or median and interquartile range. *BP* blood pressure, *BUN* blood urea nitrogen, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate.

characteristics at study initiation are summarized in Table 4. In CKD patients included in this study, the numbers of patients at each CKD stage were as follows: G3a, 6; G3b, 20; G4, 35; and G5, 7. Causes of CKD included type 2 diabetes mellitus (27 patients), nephrosclerosis (23 patients), chronic glomerulonephritis (7 patients), and other causes (11 patients).

Evaluation of patient's renal function. For the classification of CKD stages, renal function was evaluated using eGFR based on the serum creatinine concentration (S-Cr), and eGFR was calculated using Eq. (1)⁴⁴:

$$\begin{aligned} \text{eGFR (mL/min/1.73m}^2\text{)} &= 194 \times \text{S - Cr} - 1.094 \times \text{age} - 0.287 \text{ (for men)} \\ \text{eGFR (mL/min/1.73m}^2\text{)} &= 94 \times \text{S - Cr} - 1.094 \times \text{age} - 0.287 \times 0.793 \text{ (for women)}. \end{aligned} \quad (1)$$

Method of nutritional assessment. Patients included in this study were instructed to record the total quantity of food and beverages consumed either by weight or in household measures, and the methods of food preparation. Energy intake was evaluated by dietitians based on each patients 3-day meal record using the fifth edition of the Japanese Standard Tables of Food Composition, published by the Science and Technology Agency of Japan⁴⁵. Furthermore, 24-h urine collection was performed to enable evaluation of urinary protein excretion (g/day), urinary urea nitrogen (UUN) excretion, and urinary Na⁺ excretion. The urine collection method was as follows: collection began in the morning after the first voided urine was discarded. The entire volume of urine was collected in a disposable 3 L container. To avoid the possibility of inadequate urine collection, all patients were trained to properly collect their urine samples and it was emphasized that collection must be initiated at a

specific time and completed at the same time the next day. Daily protein and salt intakes were calculated based on the UUN and urinary Na⁺ excretion values obtained from the 24-h urine collection.

Protein intake was calculated using Maroni's equation⁴⁶, as described in Eq. (2):

$$\text{Protein intake (g/kg ideal BW/day)} = (\text{BW (kg)} \times 0.031 + \text{UUN (g/day)}) \times 6.25 \div \text{ideal BW (kg)}. \quad (2)$$

Salt intake was calculated using Eq. (3):

$$\text{Salt intake (g/day)} = \text{urinary Na}^+ \text{ excretion (mEq/day)} \div 17 \quad (3)$$

In addition, ideal BW was calculated using Eq. (4):

$$\text{ideal BW (kg)} = \text{body height (m)} \times \text{body height (m)} \times 22 (\text{kg/m}^2) \quad (4)$$

Patient baseline characteristics and clinical laboratory measurements. The patients baseline characteristics and clinical data were collected from their medical charts. Data on the primary disease leading to CKD and the coexistence of comorbid cardiovascular or cerebrovascular diseases were extracted from the patients' medical records.

Blood pressure (BP) was measured in the sitting position. Blood samples were obtained at ambient temperatures from each patient. Peripheral blood counts and biochemical parameters were evaluated.

Monitoring of cerebral oxygenation. Cerebral rSO₂, a marker of cerebral oxygenation, was monitored using an INVOS 5100c saturation monitor (Covidien Japan, Tokyo, Japan). The principles behind rSO₂ measurement using this monitor have been previously reported^{16,47,48}. Briefly, this instrument uses a light-emitting diode to transmit near-infrared light at two wavelengths (735 and 810 nm) and two silicon photodiodes that act as light detectors to measure oxygenated hemoglobin (Hb) and deoxygenated Hb. The ratio of oxygenated Hb signal strength to the total Hb (oxygenated Hb + deoxygenated Hb) signal strength was calculated, and the corresponding percentage was recorded as a single numerical value that represented the rSO₂^{49,50}. All data obtained with this instrument were immediately and automatically stored. Furthermore, the light paths leading from the emitter to the different detectors shared a common part: the 30-mm detector assessed superficial tissue, whereas the 40-mm detector assessed deep tissue. By analyzing the differential signals collected by the two detectors, cerebral rSO₂ values in the deep tissue were obtained from a distance of 20–30 mm from the body surface^{51,52}. These measurements were performed at 6-s intervals.

Before measurement, patients were asked to sit in the chair for at least 5 min, and an rSO₂ measurement sensor was attached to the patient's forehead. Thereafter, rSO₂ was measured at 6-s intervals for 5 min, and the mean value was calculated.

Cognitive assessment method. Cognitive impairment was confirmed using the mini-mental state examination (MMSE)⁵³. This test has been widely used to evaluate global cognitive function in the clinical setting, including CKD patients^{23,25,26,54}. The maximum score was 30, and cognitive impairment was defined as a score ≤ 23 in keeping with standard practice^{26,55}. In this study, MMSE was conducted simultaneously with the evaluation of cerebral rSO₂.

Statistical analyses. Data are expressed as mean ± standard deviation, or median and interquartile range. First, it was determined whether the data showed normal distribution or not. Using the Shapiro–Wilk Test to evaluate each variable, normally distributed or non-normally distributed results were obtained. Paired Student's t test was used for values showing normal distribution, and Wilcoxon signed-rank test was used for values that did not show normal distribution when comparing clinical parameters between the study initiation and second measurements. The chi-square test was used to assess the differences in the prevalence of cognitive impairment at study initiation and second measurement complemented by an adjusted residual analysis. Correlations between changes in MMSE score and clinical parameters in CKD patients were evaluated using Pearson's correlation or Spearman's rank correlation for data with normal and skewed distribution, respectively. Multivariate linear regression analysis was performed to extract independent factors of changes in MMSE score. All analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM, Armonk, NY, USA). P values < 0.05 were considered statistically significant.

Data availability

All data analyzed during this study are available within the paper.

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Author contributions

Research idea and study design: S.O., K.I.; data acquisition: S.O., K.I., T.M., N.T., C.N., S.N., Y.H., N.I., M.M., M.S., K.H.; data analysis: S.O., K.I., Y.S.; statistical analysis: S.O., K.I., Y.S.; supervision: Y.M.; manuscript draft: S.O., K.I.; each author contributed important intellectual content during manuscript drafting, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Competing interests

The authors declare no competing interests.

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