Physical Exercise Improves Cognitive Function in Older Adults with Stage 3-4 Chronic Kidney Disease: A Randomized Controlled Trial

Research Article

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Abstract

Introduction: Patients with chronic kidney disease (CKD) exhibit a higher probability of having cognitive impairment or dementia than do those without CKD. The beneficial effects of physical exercise on cognitive function are known in the general older population, but more research is required in older adults with CKD.

Methods: Eighty-one outpatients (aged ≥ 65 years) with CKD stage G3–G4 were assessed for eligibility. Among them, 60 were randomized (single center, unblinded, stratified) and 53 received the allocated intervention (exercise n=27, control n=26). Patients in the exercise group undertook group-exercise training at our facility once weekly and independent exercises at home twice weekly or more, for 24 weeks. Patients in the control group received general care. General and specific cognitive functions (memory, attention, executive, and verbal) were measured, and differences in their scores at baseline and at the 24-week follow-up visit were assessed between the two groups.

Results: Forty-four patients completed the follow-up at 24 weeks (exercise n=23, control n=21). As compared to the patients in the control group, those in the exercise group showed significantly greater changes in Wechsler Memory Scale-Revised Logical Memory delayed recall (exercise effect: 2.82, 95% CI: 0.46 to 5.19, $p = 0.03$) and immediate and delayed recall (exercise effect: 5.97, 95% CI: 1.13 to 10.81, $p = 0.02$) scores.

Conclusions: The 24-week exercise intervention significantly improved the memory function in older adults with pre-dialysis CKD. This randomized controlled trial suggests that physical exercise is a useful non-pharmacological strategy for preventing cognitive decline in these patients.

Introduction

Older adults with chronic kidney disease (CKD) often have cognitive impairment, which is a major public-health issue. Recent reports show that patients with CKD have lower cognitive function scores and a higher probability of having cognitive impairment or dementia than those without CKD [1-4]. Furthermore, the risk of subsequent cognitive decline increases as renal function decreases [5-8], leading to poor health literacy, poor adherence to medical treatment, and difficulty in making appropriate choices regarding modalities of renal replacement therapy (RRT) [9, 10]. Additionally, cardiovascular disease and mortality risks are greater in older adults with CKD [11, 12].

Older adults are recommended to perform regular physical activity to enjoy substantial health benefits, including cognitive benefits [13]. Physical inactivity is a serious risk factor for Alzheimer's disease (AD) [14], and a high level of daily physical activity plays a protective role against it [15, 16]. The benefits of exercise on cognitive function and the size of the hippocampus have also been reported [17, 18].

Importantly, there is a difference in the trend of pathological changes related to cognitive decline between patients with CKD and those without. In the general older population, the main cause of dementia is AD. However, the major cause of cognitive decline in patients with CKD is vascular-type dementia (VaD) [5], as cases of CKD are often complicated not only by vascular risk factors, such as hypertension, diabetes, dyslipidemia, smoking, chronic inflammation, oxidative stress, and endothelial dysfunction, but also by non-vascular and central nervous system–affecting factors, such as anemia, malnutrition, and uremic neurotoxicity [19-21]. Due to the different etiologies of cognitive impairment, the effectiveness of exercise in preventing cognitive decline in patients with CKD remains unknown. Hence, this randomized controlled trial

was designed to clinically investigate the effects of physical exercise on the cognitive function of older adults with pre-dialysis CKD.

Materials and Methods

Trial design and participants

This single-center randomized controlled trial included patients aged ≥ 65 years with CKD stages G3 to G4 (estimated glomerular filtration rate [eGFR] 15–59.9 mL/min/1.73 m^2) treated on an outpatient basis at our Nephrology and Hypertension Clinic in Kawasaki Municipal Tama Hospital from July 1 to September 27, 2019 [22]. The exclusion criteria were as follows: inability to walk independently, undergoing RRT, anticipated time to RRT < 6 months, poorly controlled diabetes, unstable angina, and arteriosclerosis obliterans with a Fontaine classification of grade 2 or higher and exercise restriction. Participants meeting all criteria were randomly assigned to the exercise group (who received intervention) or control group (who did not).

Randomization and blinding

Patients were stratified by age (< 75 or ≥ 75 years) and CKD stage (G3 or G4) and randomized to either the exercise or control group using an interactive web response system (HOPE eACReSS, Fujitsu Ltd., Tokyo). Both groups received feedback on the baseline physical and cognitive function measurement results (first time point) and continued to receive general care from our nephrologists at the outpatient clinic. Furthermore, exercise training at the rehabilitation center and solo exercise at home were performed by those in the exercise group for 24 weeks (second time point). The outcome measure evaluators were blinded to patient allocation at both time-points.

Intervention

Patients in the exercise group undertook 60 min of the physical therapist–supervised group-exercise training once a week for 24 weeks (from October 2019 to March 2020) at our rehabilitation center. The group-exercise training consisted of 10 min of stretching, 20 min of resistance training (upper limb elevation, shoulder abduction, elbow flexion, grip strength, hip flexion, knee extension, and ankle dorsiflexion in a sitting position; and squats, calf raises, and hip abduction in a standing position), 5 min of balance exercises, 20 min of aerobic exercises, and 5 min of cool-down activities based on the clinical guidelines [23, 24]. Patients performed one set of 20 repetitions for each exercise at a slow speed using bodyweight, a hand gripper, and a resistance band. The balance exercises were tandem standing and one-leg standing. The aerobic exercise was performed on a cycling ergometer. Patients performed all exercises with moderate intensity, with perceived exertion of 11–13 on the 20-point Borg scale [25].

Moreover, patients were instructed to perform solo exercises at home according to a pamphlet (resistance training and walking) twice a week or more and record their adherence. Patients were requested to submit the calendar once a week to receive feedback.

Demographic and clinical characteristics

We investigated demographic and clinical characteristics at baseline. Demographic variables included age, sex, height, weight, body mass index (BMI), body fat, blood pressure (BP), frequency of drinking (categorized as every day, 5–6 times/week, 3–4 times/week, 1–2 times/week, 1–3 times/month, past, or none), smoking history (categorized as current use, past use, or none), Brinkman Index, living status (alone or otherwise), and educational background. Clinical characteristics included comorbidities, Charlson Comorbidity Index (CCI), medications, CKD stage, and primary kidney disease.

Outcomes

We defined changes in cognitive function as the primary outcome and changes in other measurements, including physical function, endothelial function, and laboratory measurements, as the secondary outcome. All measures were obtained before and after 24 weeks in both groups. Cognitive and physical functions were measured by physical and occupational therapists. Before the study commenced, participants were trained by the investigators and the assessment method was introduced and demonstrated before the tests were performed.

Cognitive function

The Mini-Mental State Examination (MMSE) was used as a measure for general cognitive function (total score=30) [26]. The Wechsler Memory Scale-Revised Logical Memory (WMS-R LM) immediate and delayed recall tests were used to assess memory function [27, 28]. In the WMS-R LM, two short stories (story A and B) were read aloud to the patients who were subsequently instructed to recall details of the stories immediately (WMS-R LM immediate recall) and after 30 min (WMS-R LM delayed recall) (total recall score=50) [27, 28]. The Trail Making Test Part A (TMT-A) and Part B (TMT-B) were used to measure attention and executive functions, respectively [29]. The TMT-A required patients to draw lines connecting 25 randomly ordered numbers in circles distributed across a sheet of paper into the correct ascending order (i.e., 1, 2, 3…25). In the TMT-B, the circles included both numbers (1–13) and letters (A–L), and patients were required to perform the additional task of connecting alternating numbers and letters in ascending order using lines as rapidly as possible (e.g., 1, A, 2, B, 3, C, …13; the letters were written in *Hiragana* in the Japanese version of the tool). The turnaround time was measured in seconds. Verbal function was measured using the verbal fluency test (VFT) [30]. The participants listed words beginning with a letter composed of characters for the "*ka*-words" (VFT "ka" words) and words belonging to the animal category (VFT "animals"). The number of

words listed in 60-second trials was noted [30]. Better performance is represented by lower values in the TMT-A and B and higher values in the other tests.

Depressive symptoms

Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS), with a maximal score of 15 [31].

Physical function

Single-leg standing time and 4-meter comfortable walking time were obtained. To determine gait speed, patients performed a 4-meter gait test twice at their usual pace (m/s) on a flat surface, with the highest speed from the two trials used in the analysis. To evaluate the single-leg standing time, patients were asked to maintain this position for as long as possible, with their eyes open. Two trials were completed for each leg, with a maximum possible total time of 60 s, with the maximal time used for analysis.

Endothelial function

Endothelial function was evaluated by using the reactive hyperemia index (RHI) on the Endo-PAT2000® (Itamar Medical Ltd., Caesarea, Israel) [32]. After a 5-minute equilibration period, the BP cuff on the test arm was inflated to 60 mmHg above the baseline systolic BP, or a maximum of 200 mmHg, for 5 minutes. After 5 minutes of occlusion, the cuff was deflated and the peripheral arterial tonometry tracing was recorded automatically by an online computer for another 5 minutes. We calculated the natural logarithmic transformation of the RHI (Ln-RHI) for use in the analyses, as reported previously [33]. Patients were instructed to avoid alcohol, caffeinated beverages, smoking, oral intake of foods, and physical exercise for 12 hours before the measurements [34].

Physical activity

The daily number of steps was assessed as the indicator of physical activity using the Kenz Lifecorder Ex 1 axial accelerometer (Suzuken Co Ltd., Nagoya, Japan) for 14 days before both time-points.

Laboratory measurements

For all patients, the following biochemical measurements were performed: hemoglobin, blood urea nitrogen, serum creatinine, serum cystatin C (cysC), albumin, hemoglobin A1c, high-sensitivity C-reactive protein, phosphorus, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum asymmetric dimethylarginine (ADMA), plasma brain-derived neurotrophic factor (BDNF), and urine protein/creatinine ratio. The estimated glomerular filtration rates based on creatinine (eGFRCr) and cystatin C (eGFRcysC) were calculated using an equation incorporating age, sex, and measured creatinine or cysC levels [22, 35]. Blood samples were drawn between 10:00 and 11:00 or 13:30 and 14:30 in the fasting state. Urine protein and urea-creatinine were measured by a spot urine test early morning on the measurement day.

Serum ADMA and plasma BDNF concentrations were measured using enzyme-linked immunosorbent assay (Immundiagnostik AG, Bensheim, Germany, and R&D Systems, Minneapolis, MN, USA, respectively). For measuring ADMA, blood samples were immediately centrifuged at 3000 rpm and 4 °C for 5 min after being drawn and stored at −80 °C until analyzed. For the BDNF assay, the blood sample was transferred to ice water for 15 min, after which the sample was centrifuged at 4700 rpm at 2–8 °C for 20 min and stored at −20 °C until analysis.

Power analysis for sample size calculation

We calculated the necessary sample size considering an 0.8-point increase (effect size=0.8) in the MMSE score (measurement of general cognitive function) in the exercise group

compared with the control group would be clinically significant. This was detected using a two-sided statistical test with an alpha and beta error of 0.05 and 0.20, respectively, at 26 patients per group. Allowing for a potential 15% attrition due to withdrawal, a total of 60 patients (30 patients per group) were finally recruited for this study.

Adherence and adverse events

We defined adherence as the rate of intervention performed in the exercise group. For calculating the adherence, we used the mean of the intervention rate of the center- and home-based exercises.

Statistical analysis

The outcome measures were analyzed according to an intention-to-treat principle; missing values were not imputed. Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) and categorical values as percentages. The chi-square test, non-paired t-test, and Mann–Whitney U test were used to compare the two groups in terms of baseline patient characteristics.

Differences in the primary and secondary outcome scores for examining the exercise effects at follow-up for both groups were assessed using analysis of covariance (ANCOVA) with baseline variables as covariates. All statistical analyses were performed using R version 4.0.0 (https://cran.r-project.org). *P*-values < 0.05 were considered statistically significant.

Results

Patient characteristics (participant flow diagram included)

Eighty-one patients were assessed for eligibility, and 21 were excluded as they were ineligible or lacked interest in study participation (Figure 1). Of the 60 randomized patients, 1 in the exercise group and 6 in the control group did not receive the allocated intervention, as they

withdrew consent after randomization. Finally, the study included 53 patients: 27 and 26 in the exercise group and the control group, respectively. The percentage of men significantly differed between the exercise and control groups (P = 0.03). The groups did not differ significantly in terms of any other parameter. Lastly, 4 patients (14.8%) in the exercise group and 5 patients (19.2%) in the control group could not complete the follow-up evaluation. Therefore, follow-up evaluations were completed in 44 patients (23 in the exercise group and 21 in the control group). The baseline characteristics of both groups are summarized in Table 1. In the exercise and control group, the mean age (SD) was 78.8 (6.0) and 78.1 (6.9) years, percentage of men was 43.5% and 76.2%, and mean eGFRCr (SD) was 38.0 (13.7) and 34.5 (13.2) mL/min/1.73 m^2, respectively.

Adherence and safety

The median adherence rate (IQR) was 95.2% (83.4%, 100%) and 91.3% (82.6%, 100%) in the supervised group for exercising at our facility and at home, respectively. No fall incidents or severe health problems caused by the intervention (i.e., harms) occurred during the study period.

Effect of exercise on cognitive function as the primary outcome

Figure 2 shows the results of the cognitive function at baseline and the changes from baseline. Significant differences were observed between the groups for changes in the WMS-R LM delayed recall (exercise effect: 2.82, 95% CI: 0.46 to 5.19, P = 0.03; Figure 2A) and WMS-R LM immediate and delayed recall (exercise effect: 5.97, 95% CI: 1.13 to 10.81, P = 0.02; Figure 2A). There were no significant differences between the groups for changes in MMSE (exercise effect: 0.74, 95% CI: −0.52 to 1.99, P = 0.26; Figure 2B), WMS-R LM immediate recall (exercise effect: 3.04, 95% CI: 0.08 to 5.99, P = 0.05; Figure 2A), TMT-A (exercise effect: 3.17, 95% CI: −11.61 to 17.95, P = 0.68; Figure 2C), TMT-B (exercise effect: 17.10, 95% CI: −37.98 to 71.18, P =

212 0.55; Figure 2C), VFT "*ka*-words" (exercise effect: 1.84, 95% CI: −0.30 to 3.98, *P* = 0.10; Figure
213 2C), or VFT "animals" (exercise effect: 0.72, 95% CI: −1.92 to 3.37, *P* = 0.60; Figure 2C).

214 Effect of exercise on secondary outcome measures

215 Table 2 shows changes in the secondary outcome measures. There were no significant
216 differences in any parameters of physical function. The change in single-leg standing time in the
217 exercise group showed an improving trend, although not significant (exercise effect: 9.56, 95%
218 CI: −0.15 to 18.97, *P* = 0.05). Changes in Ln-RHI, a measure of endothelial function, did not show
219 significant differences between the groups (exercise effect: 0.07, 95% CI: −0.28 to 0.45, *P* = 0.70).
220 Similarly, the number of steps as a physical activity (exercise effect: 389.49, 95% CI: −986.12 to
221 1765.10, *P* = 0.58) and depression scale (exercise effect: −0.11, 95% CI: −1.37 to 1.14, *P* = 0.86)
222 did not exhibit significant differences between the groups. Moreover, there were no significant
223 differences in any laboratory measurements, including serum ADMA and plasma BDNF
224 concentrations ($p > 0.05$).

225

226 ## Discussion/Conclusion

227 The main finding of this study was that memory function significantly improved in the
228 exercise group compared to the control group, which is consistent with results of previous
229 reports that examined the effects of exercise intervention on memory function in community-
230 dwelling older adults without CKD [36, 37]. Contrary to our hypothesis, there were no significant
231 differences in vascular factors such as endothelial function and ADMA. The benefits of exercise
232 on cognitive function might be difficult to correlate with the improvement in endothelial
233 function in patients with CKD due to them being complicated by advanced endothelial
234 dysfunction (the average Ln-RHI was 0.46 and 0.41 at baseline in the exercise and control group,

235 respectively). Thus, other mechanisms might have influenced the memory function
236 improvements in CKD in this study.

237 There are two hypotheses regarding the mechanisms of improvement of memory
238 function in our cohort of older patients with CKD. First, exercise may have improved memory
239 function through the increased volume of the hippocampus [18, 38]. Second, social interaction
240 through the supervised group exercise may have benefited memory function [39, 40].

241 Contrary to previous studies, there were no significant improvements in general
242 cognitive function or other cognitive domains, except for memory function in this study. Several
243 studies have reported that renal function is associated with executive function [41, 42], and
244 physical exercise can prevent patients on hemodialysis from experiencing a decline in executive
245 function [43]. However, the patients in this study were approximately 30 years older than those
246 in the previously mentioned study [43], leading to speculation that, in older patients, physical
247 exercise may be less effective in improving both executive and other cognitive functions than in
248 middle-aged patients. In addition, the effect of physical exercise on executive function and other
249 cognitive domains in previous studies targeting older adults without CKD differs from the effect
250 noted in this study [17, 44]. As mentioned above, the main cause of dementia in patients with
251 CKD differs from that in older adults without CKD. Ideally, we should have explored the most
252 effective exercise and its target patient age range for improving cognitive function in CKD by
253 dividing the patients into multiple sub-groups based on age, pathology, and the frequency,
254 intensity, time, and duration of exercise.

255 This study has several limitations. First, during the examination period, the coronavirus
256 disease (COVID-19) pandemic broke out. This trial was conducted between October 2019 and
257 March 2020, and the COVID-19 pandemic worsened around February 2020 in Japan. A previous
258 study reported that the time performing physical activity during the pandemic was significantly

shorter than that prior to the pandemic [45]. Therefore, COVID-19-related safety concerns may have restricted physical activity levels in the final month of the intervention period (from February to March 2020). Decreased physical and social activities due to the pandemic might have affected the results related to physical function, the amount of physical activity, and other factors in this study. Therefore, the results of this study need to be verified under normal circumstances and/or after the pandemic to be generalized. Second, the sample size was reduced before the final evaluation because of the withdrawals in the follow-up and allocation period, which necessitates future studies to have a larger number of patients. Third, as this trial was performed at a single center, the findings may not be generalizable to all older adults with pre-dialysis CKD. Therefore, it is not sufficient for clarifying the firm evidence of the effects of physical exercise on memory function and the other cognitive domains, and attention should be paid to interpreting this as pilot data that warrants additional studies. Fourth, there was a significant difference in the percentage of men between the exercise and control group at baseline. Randomization in this study using an interactive web response system; therefore, group allocation was not controllable. Coincidentally, however, a significant difference in the percentage of men was found due to the small sample size. Clinical trial reports require a clearly defined policy on the use of baseline data as covariates—single unadjusted analyses that compare a treatment group with a control group should be performed prior to the start of the randomized controlled trial [46]. In this study, we did not indicate the intention to use baseline characteristics as covariates prior to analyses. Therefore, the difference found in the percentage of men between the groups was not used in the ANCOVA. Nevertheless, a higher percentage of men in the exercise group might have affected the results. Fifth, the intervention period may have been insufficient for patients with CKD. We employed a 24-week intervention, which is typical in studies that investigate the effect of physical exercise on cognitive function among

283 community-dwelling older people [48]. A longer intervention period may be required for
284 improving not only memory but also other cognitive functions in patients with stage 3–4 CKD,
285 given the many vascular and non-vascular risks of dementia in these patients. Finally, based on
286 mean age, the patients in this study were much older than those in other studies that conducted
287 physical exercise in patients with CKD [49-50]. Therefore, there is a possibility that the intensity
288 of the physical exercise might not have been enough leading to challenges in obtaining an effect
289 not only on cognitive function but also on physical function and other indicators.

290 In conclusion, the 24-week combined exercise intervention might be effective in
291 improving memory function in older adults with pre-dialysis CKD. This result suggests that
292 physical exercise is a useful non-pharmacological strategy for preventing cognitive decline in
293 older adults with pre-dialysis CKD.

Statements

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Statement of Ethics

The study protocol was approved by the Institutional Committee on Human Research of St. Marianna University School of Medicine (IRB approval number: 4424) and has been registered with the UMIN Clinical Trials Registry on December 5, 2018 (Registration number: UMIN000035150), in compliance with the ethical guidelines of the 1975 Declaration of Helsinki.

Written informed consent was obtained from all patients prior to their enrolment in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

YO, MY, KH, and NT designed the study; YO, KH, SO, YT, HS, RH, WH, SK, HM, and NT carried out evaluations and/or interventions; MT analyzed the data; YO, MY, KH, SO, YT, HS, RH, WH, MS, YK, SK, HM, YS, and NT drafted and revised the paper; and all authors approved the final version of the manuscript.

Data Availability Statement

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

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Figure

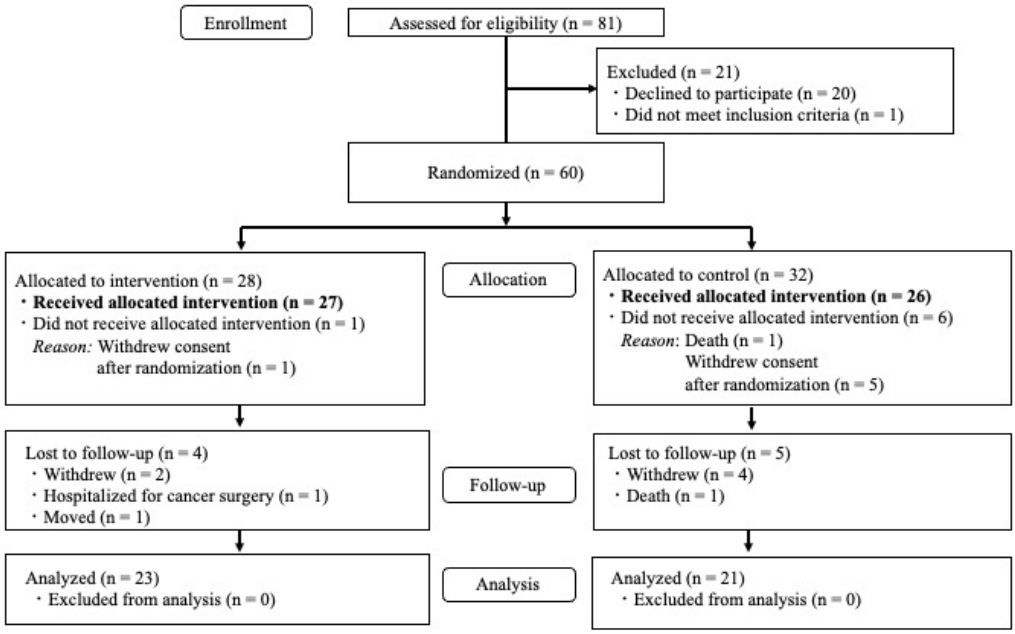
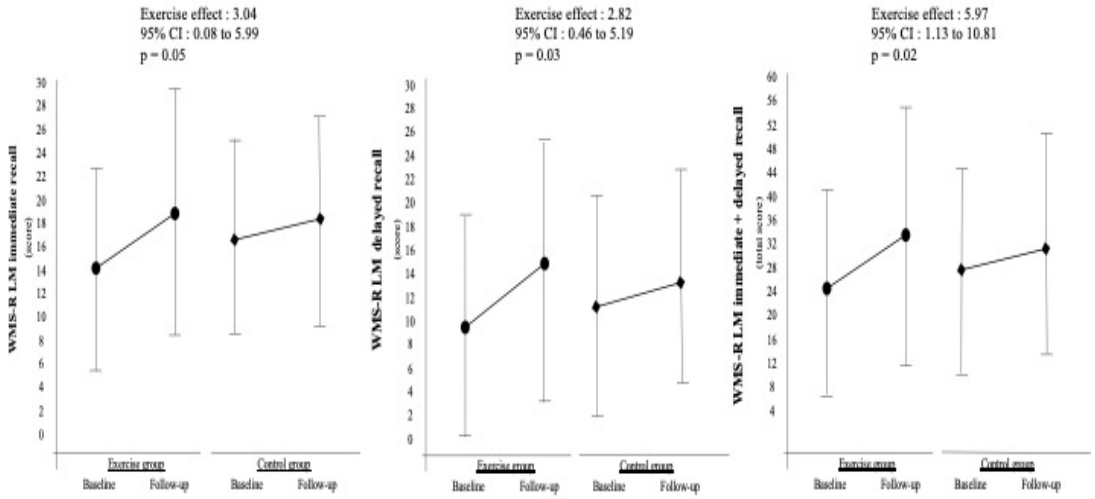
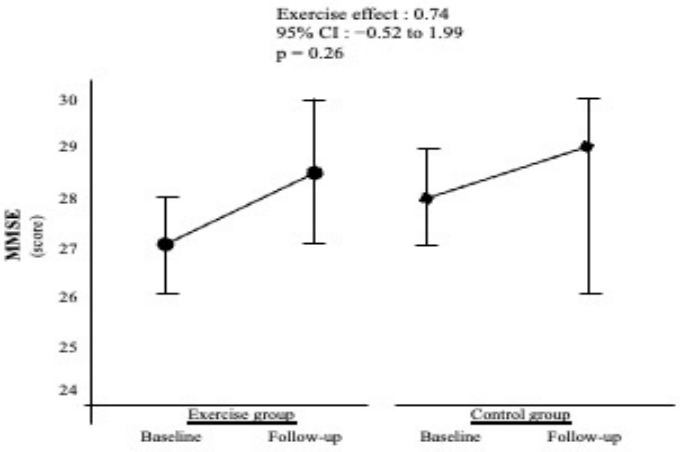


Figure 1. Participant flow diagram

Distribution of patients from assessment for eligibility to completion of the study period.


Exercise effect : 3.04
95% CI : 0.08 to 5.99
p = 0.05
WMS-R LM immediate recall (score)
Exercise group
Control group
Baseline
Follow-up
Exercise effect : 2.82
95% CI : 0.46 to 5.19
p = 0.03
WMS-R LM delayed recall (score)
Exercise effect : 5.97
95% CI : 1.13 to 10.81
p = 0.02
WMS-R LM immediate + delayed recall (total score)


Exercise effect : 0.74
95% CI : −0.52 to 1.99
p = 0.26
MMSE (score)
Exercise group
Control group
Baseline
Follow-up

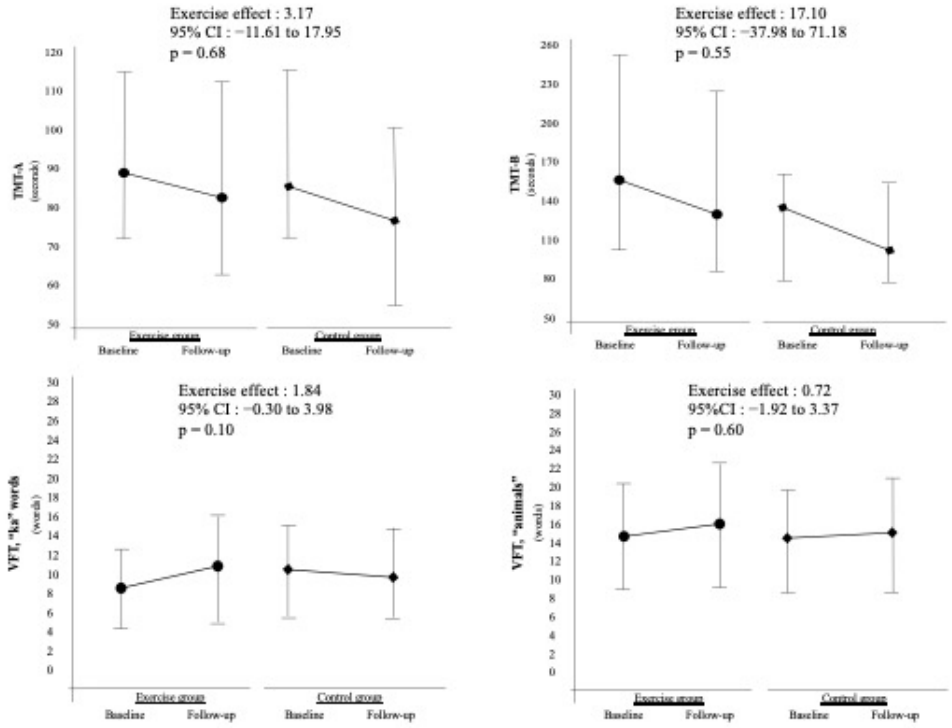


Figure 2. Changes in cognitive functions in response to the 24-week intervention

(a) WMS-R LM immediate recall, WMS-R LM delayed recall, WMS-R LM immediate recall and delayed recall; (b) MMSE; (c) TMT-A, TMT-B, VFT, "*ka*-words," VFT, "animals"

Abbreviations: WMS-R LM, Wechsler Memory Scale-Revised Logical Memory; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VFT, verbal fluency test; CI, confidence interval

Values are presented as mean ± standard deviation for WMS-R LM immediate recall, WMS-R LM delayed recall, WMS-R LM immediate recall and delayed recall, VFT "*ka*-words," and VFT "animals," and as median with 25–75% interquartile range for MMSE, TMT-A, and TMT-B.

The ANCOVA was used for revealing the differences in cognitive change between the groups and was adjusted for cognitive function at baseline.

Table 1. Baseline characteristics by study group

	Exercise Group (n= 27)	Control Group (n= 26)	*p*
Age (yr)*	78.4±6.4	78.1±7.4	0.86
Sex, *n* (% men)	12 (44.4)	19 (73.1)	0.03
Height (cm)*	158.3±8.2	161.4±8.8	0.19
Weight (kg)*	60.3±14.2	62.9±11.2	0.48
BMI (kg/m^2)*	23.8±4.1	24.1±3.7	0.82
Body fat (%)*	30.7±7.5	28.4±9.2	0.35
BP (mmHg)*			
Systolic	141.4±15.8	143.2±21.6	0.84
Diastolic	79.2±12.3	82.2±10.8	0.36
Drinking, *n* (%)			0.06
Every day	1 (3.7)	4 (15.4)	
5–6 times/week	1 (3.7)	3 (11.5)	
3–4 times/week	3 (11.1)	1 (3.8)	
1–2 times/week	2 (7.4)	1 (3.8)	
1–3 times/month	4 (14.8)	1 (3.8)	
Past	1 (3.7)	7 (26.9)	
None	15 (55.6)	9 (34.6)	
Smoking, *n* (%)			0.23
None	15 (55.6)	12 (46.2)	
Past	10 (37.0)	14 (53.8)	
Current	2 (7.4)	0 (0)	
Brinkman Index (points)†	0 (0–325)	0 (0–200)	0.47
Living alone, *n* (%)	12 (44.4)	7 (26.9)	0.18
Educational level (yr)†	15 (12–16)	12 (12–16)	0.16
Comorbidities, *n* (%)			
Cerebrovascular disease	2 (7.4)	3 (11.5)	0.61
Ischemic heart disease	2 (7.4)	2 (7.7)	0.97
Diabetes	7 (25.9)	4 (15.4)	0.34
Hypertension	20 (74.1)	22 (84.6)	0.34

Dyslipidemia	17 (63.0)	12 (46.2)	0.22
Neurological disorder	0 (0)	1 (3.8)	0.30
Orthopedic disease	4 (14.8)	4 (15.4)	0.95
Arteriosclerosis obliterans	0 (0)	0 (0)	—
Others	8 (29.6)	6 (23.1)	0.59
CCI (points)†	1 (0–2)	1 (0–1)	0.18
Medications, *n* (%)			
Antihypertensive agents	17 (63.0)	21 (80.8)	0.15
Statins	14 (51.9)	13 (50.0)	0.89
Oral hypoglycemic agents	6 (22.2)	4 (15.4)	0.53
Antiplatelet drugs	3 (11.1)	8 (30.8)	0.08
Diuretics	3 (11.1)	7 (26.9)	0.14
Sleep-inducing drugs	1 (3.7)	4 (15.4)	0.15
Psychotropic drugs	0 (0)	0 (0)	—
eGFRCr (mL/min/1.73m^2)*	33.0±12.9	36.6±14.1	0.33
CKD stage, *n* (%)			0.90
G3	15 (55.6)	14 (53.8)	
G4	12 (44.4)	12 (46.2)	
Primary kidney disease, *n* (%)			0.07
Diabetic nephropathy	1 (3.7)	2 (7.7)	
Nephrosclerosis	9 (33.3)	17 (65.4)	
Diabetic nephropathy + Nephrosclerosis	2 (7.4)	0 (0)	
Chronic glomerulonephritis	1 (3.7)	1 (3.8)	
Others	4 (14.8)	4 (15.4)	
Unknown	10 (37.0)	2 (7.7)	

BMI, Body Mass Index; BP, blood pressure; CCI, Charlson Comorbidity Index; CKD, Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; Cr, creatinine

*Mean ± Standard deviation; †Median (25–75% interquartile range)

Table 2. Changes in secondary outcome measures

	Exercise group		Control group		ANCOVA		
	Baseline	Follow-up	Baseline	Follow-up	Exercise effect	95% CI	*p*
Single-leg standing time (s)†	8.8 (3.5–29.4)	7.6 (4.3–56.5)	20.8 (8.6–60.0)	17.7 (10.0–34.7)	9.56	−0.15 to 18.97	0.05
Gait speed (m/s)*	1.04±0.26	1.15±0.30	1.16±0.20	1.20±0.21	0.05	−0.07 to 0.16	0.46
Ln-RHI*	0.46±0.23	0.51±0.31	0.41±0.21	0.45±0.33	0.07	−0.28 to 0.45	0.70
Number of steps (steps/day)†	3540 (2061–6089)	3757 (2324–6477)	4171 (2688–6287)	3575 (1923–5986)	389.49	−986.12 to 1765.10	0.58
GDS (score)†	3 (2–6)	4 (1–5)	3 (1–5)	3 (1–5)	−0.11	−1.37 to 1.14	0.86
BUN (mg/dL)*	24.8±10.6	26.9±8.9	29.2±11.2	31.5±13.3	−0.82	−4.79 to 3.16	0.68
Cr (mg/dL)*	1.67±0.64	1.71±0.79	1.39±0.57	1.46±0.69	0.08	−0.050 to 0.21	0.22
cysC (mg/L)†	1.75±0.61	1.74±0.74	1.56±0.53	1.62±0.63	0.09	−0.02 to 0.19	0.10
eGFRCr (mL/min/1.73m^2)*	38.0±13.7	37.2±14.5	34.5±13.2	34.7±13.7	−0.95	−3.34 to 1.45	0.43
eGFRcysC (mL/min/1.73m^2)*	43.3±15.9	43.0±17.5	40.6±19.1	42.2±20.1	−2.11	−5.17 to 0.94	0.17
Alb (g/dL)*	4.1±0.4	4.2±0.3	4.0±0.6	4.1±0.3	0.09	−0.07 to 0.24	0.28

hsCRP (mg/dL)†	0.06 (0.04–0.11)	0.07 (0.03–0.17)	0.04 (0.03–0.07)	0.03 (0.01–0.08)	−0.02	−0.09 to 0.050	0.53
P (mg/dL)*	3.6±0.6	3.8±0.5	3.2±0.6	3.5±0.6	0.14	−0.19 to 0.48	0.40
HDL-cho (mg/dL)*	56.8±17.4	62.1±18.8	60.9±20.5	65.3±21.6	0.40	−6.64 to 7.44	0.91
LDL-cho (mg/dL)*	109.7±33.8	116.2±37.9	112.8±50.4	107.7±25.8	9.85	−6.83 to 26.54	0.24
ADMA (mcmol/L)*	0.50±0.08	0.52±0.05	0.51±0.09	0.55±0.08	−0.02	−0.05 to 0.01	0.16
BNP (pg/mL)†	41.4 (28.8–68.8)	33.3 (23.7–48.6)	31.3 (9.6–65.4)	21.0 (10.6–52.2)	−2.98	−30.01 to 24.05	0.83
Hb (g/dL)*	12.6±1.8	12.8±1.6	12.7±1.8	12.7±1.8	−0.48	1.85 to 0.89	0.49
HbA1c (%)†	5.8 (5.5–6.5)	5.9 (5.7–6.2)	5.5 (5.4–5.9)	5.4 (5.2–5.9)	0.17	−0.003 to 0.35	0.05
BDNF (pg/mL)†	209 (123–243)	86 (71–158)	114 (84–216)	78 (63–125)	−39.99	−225.65 to 145.65	0.67
UPCR (g/gCr)†	0.18 (0.07–0.64)	0.14 (0.07–0.52)	0.15 (0.08–0.71)	0.29 (0.08–0.45)	−0.12	−0.57 to 0.33	0.60

*Mean ± standard deviation, †Median (25–75% interquartile range). Abbreviations: SPPB, Short Physical Performance Battery; RHI, Reactive Hyperemia Index; GDS, Geriatric Depression Scale; BUN, blood urea nitrogen; Cr, creatinine; cysC, cystatin C; eGFR, estimated glomerular filtration rate; Alb, Albumin, hsCRP, high-sensitivity C-reactive protein; P, phosphorus; HDL-cho, high density lipoprotein cholesterol; LDL-cho, low density lipoprotein cholesterol; ADMA, asymmetric dimethylarginine; BNP, brain natriuretic peptide; Hb, hemoglobin; BDFN, brain derived neurotrophic factor; UPCR, urine protein/creatinine ratio; CI, confidence interval

The ANCOVA was used for revealing differences between groups regarding the secondary outcome measures changes and has been adjusted for secondary outcome measures at baseline.