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ORIGINAL RESEARCH

Therapeutic Effects of Exercise Training on Elderly Patients With Dementia: A Randomized Controlled Trial

I-Ting Liu, MD,[a] Wei-Ju Lee, PhD,[b] Shih-Yi Lin, PhD,[c] Shin-Tsu Chang, PhD,[a,d,e,f] Chung-Lan Kao, PhD,[g,h] Yuan-Yang Cheng, PhD[a,c,h]

From the [a]Department of Physical Medicine and Rehabilitation, Taichung Veterans General Hospital, Taichung; [b]Department of Neurology, Taichung Veterans General Hospital, Taichung; [c]Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung; [d]Department of Physical Medicine and Rehabilitation, Tri-Service General Hospital, Taipei; [e]School of Medicine, National Defense Medical Center, Taipei; [f]School of Medicine, Chung Shan Medical University, Taichung; [g]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, Taipei; and [h]School of Medicine, National Yang-Ming University, Taipei, Taiwan.

Abstract

Objective: To investigate whether strength or aerobic training can offer significantly more benefits with regarding the activities of daily living of elderly patients with dementia as well as to determine the effects of exercise on cognition, depression, and biochemical markers.

Design: Single-blind randomized controlled trial.

Setting: A nursing home for veterans.

Participants: A volunteer sample of participants (N=80) whose scores on the Mini-Mental State Examination were between 15 and 26 were included. Because of cardiopulmonary or orthopedic conditions that prohibit exercise training, along with any cognitive problems that may impede answering the contents of our questionnaires, 11 participants were excluded. During the exercise training period, 8 participants voluntarily dropped out of the study.

Interventions: The participants were randomly assigned to perform either strength or aerobic training for a total of 4 weeks.

Main Outcome Measures: The main outcome measure was the Barthel Index. Other outcome measures included the Mini-Mental State Examination, Montreal Cognitive Assessment, Geriatric Depression Scale, plasma monocyte chemotactic protein-1 levels, insulin-like growth factor-1 levels, and serum brain-derived neurotrophic factor levels.

Results: After completion of the program, we discovered a significant improvement in the patients' Barthel Index, Mini-Mental State Examination, Montreal Cognitive Assessment, and plasma monocyte chemotactic protein-1 levels in the strength-training group. For the patients who had received aerobic training, their serum brain-derived neurotrophic factor also improved significantly. However, the degree of improvement regarding these outcome measures did not achieve significant statistical difference between the 2 groups.

Conclusions: Through our study, an intensive 4-week exercise program, whether it be strength or aerobic training, is evidenced to bring significant benefits to elderly patients with dementia, while the serum brain-derived neurotrophic factor was additionally improved through aerobic training.

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Dementia is a mental disorder that can influence cognitive functions involving naming, orientation, calculation, and recent or even remote memory.[1] It can have a huge effect on a patient's quality of life, along with eventually causing a loss of both function and self-care ability. Furthermore, the behavioral and psychological symptoms of dementia may bring about enormous mental distress and burden to a patient's family and caregiver. Caring for this group of patients is certainly more difficult than it is for those who have other chronic diseases. In addition, the financial burden surrounding dementia is also tremendous because more than 818 billion US dollars globally are spent on managing

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this distressing disorder each year.[2] Therefore, methods regarding the best way to deal with dementia have already become a major public issue worldwide.

Among the various treatments available for patients with dementia, physical activity and exercise are both essential components that health care providers should never ignore. Exercise brings about a variety of benefits to the human body, including improved mood, a decrease in feelings of depression, less anxiety and stress, prevention of obesity, improved vitality, a reduced feeling of fatigue, alleviation of the risk of chronic diseases, improved brain function, relaxation and an improved quality of sleep, chronic pain reduction, and even a reduced risk of falling.[3] In past literature, exercise has also been proven to be beneficial to patients with dementia, whether it involves strength or aerobic training. Strength training emphasizes muscle building, which has been shown to improve both the ability of self-care in daily activities[4] and the psychological well-being of patients with dementia.[5] As for aerobic training, it can deliver enhanced cardiopulmonary endurance, which has been evidenced to slow the rate of cognitive decline,[6] enhance cognition and mobility,[7] and improve the basic[6] and instrumental activities of daily life (ADLs)[7] in patients with dementia. There have been many additional studies regarding exercises that combine strength and aerobic training that have also revealed their ability to slow the rate of decline in ADLs,[8] reduce depression,[9] and improve hand function and lower limb strength[10] as well as balance,[11] self-care function,[12] and cognition.[13] Because of the results of the studies mentioned above, we can be convinced that exercise is beneficial for patients with dementia. However, until now there have been very few studies that have directly compared the beneficial effects of different modes of exercise training. One study revealed that an exercise program combining both aerobic and strength training is more effective than an aerobic-only training regimen in slowing cognitive and motor decline in patients with dementia.[14] Additionally, another review article concluded that a combined exercise program is better than strength-only training in improving gait speed, functional mobility, and balance.[15] On the other hand, several biochemical markers related to dementia and exercise have been studied and written about in past literature, including brain-derived neurotrophic factor (BDNF),[16] monocyte chemotactic protein-1 (MCP-1),[17] and insulin-like growth factor-1 (IGF-1),[18] but information regarding the different effects of both strength and aerobic training on these biochemical markers has been limited. Therefore, we designed this prospective study to elucidate whether there are significant differences regarding self-care ability, cognition, depression, and biochemical markers of dementia between patients receiving strength training and those receiving aerobic training. We hypothesized that strength training could bring about more benefits in self-care ability and provide a greater reduction in depression than aerobic training, while aerobic training could bring about more benefits in cognitive functions, according to past published literature.[4-7]

List of abbreviations:

ADL	**activities of daily living**
BDNF	**brain-derived neurotrophic factor**
CCI	**Charlson Comorbidity Index**
GDS	**Geriatric Depression Scale**
IGF-1	**insulin-like growth factor-1**
MCP-1	**monocyte chemotactic protein-1**
MMSE	**Mini-Mental State Examination**
MoCA	**Montreal Cognitive Assessment**

Methods

Study design

The study was a simple randomized, parallel-group, observer-blinded clinical trial, which received approval from the institutional review committee of a tertiary medical center in Taiwan (No. CE18010B). Each patient was asked to sign an informed consent form prior to participating in the study.

Recruitment of participants

Inhabitants of a veterans' nursing home who were older than 65 years with scores on the Mini-Mental State Examination (MMSE) between 15 and 26 were recruited. The study protocol was announced with a poster on the bulletin board of the nursing home, and the inhabitants made the decision on whether to join the study by their own will. The exclusion criteria included any cardiopulmonary disease or orthopedic conditions that would prohibit the patient from undertaking exercise training during the program, along with any cognitive problems that could impede the patient from understanding and answering the content of the informed consent and questionnaires. To determine the sample size of this study, we used G*power 3.1.3[a] and set $\alpha=0.05$ with a power $(1-\beta)=0.8$.[19] Using MMSE in a past study[7] as the target outcome, with a standard deviation estimate as 5 and 7.7 in the treatment and control groups, respectively, the effect size difference was 0.75, and it was determined that at least 58 participants needed to be included in our study to achieve sufficient statistical power.

Protocol of intervention

The participants were then randomly assigned to either the strength training program or the aerobic training program for a total of 4 weeks. A randomized method that simply involved the participant tossing a coin was used to generate the random allocation sequence in our study. The strength training program involved the use of isotonic weight training machines targeting the biceps, triceps, and pectoralis major over the course of 1 day and the gluteus and quadriceps muscles the following day. The weight used during this training was 40%-50% of 1-repetition maximum, with the program constituting 2 sets of 12 repetitions in 1 day, 5 days a week. The aerobic training program, on the other hand, involved stationary bicycle training. Participants were asked to keep their pedaling rate at an intensity level of 5-6 on a 0-10 scale of rated perceived exertion during their 30-minute sessions on the stationary bicycle. This program was also executed five days a week. The exercise programs of the study were designed according to recommendations from the American College of Sports Medicine[20] and were executed under the supervision of a certified fitness trainer. The flowchart of the participants recruited for this study is shown in fig 1.

Outcome measures

The outcome measures of the study include the Barthel Index, MMSE, Montreal Cognitive Assessment (MoCA), Geriatric

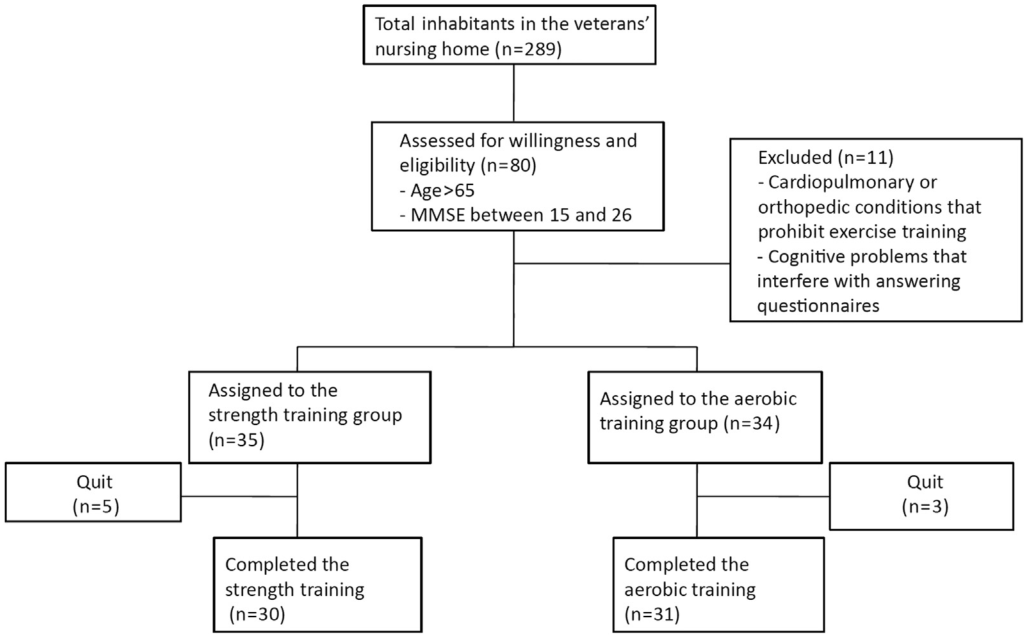

Fig 1 Flowchart of participant recruitment in our study.

Depression Scale (GDS), serum BDNF, plasma MCP-1, and plasma IGF-1. The Barthel Index is an ordinal scale used to measure performance in the basic ADLs, and the Chinese version has been tested for validity and reliability in the past.[21] The MMSE is a 30-point questionnaire that is used extensively in both clinical and research settings to measure cognitive function because it has the advantage of a short administration time and ease of use. However, the MMSE possesses a significant ceiling effect and cannot distinguish patients with very mild dementia from persons without dementia.[22] MoCA, on the other hand, is better suited than MMSE for detecting mild cognitive impairment among people older than 60 years.[23] Furthermore, the Chinese version of MoCA has been validated in the past.[24] The GDS was originally a 30-item self-report assessment used to identify depression in elderly persons, which has also been validated in its Chinese version.[25] Because it was time consuming to administer the original version of the GDS, shorter versions of it were developed. Among them, the 5-item GDS has demonstrated itself to be as effective as the 15-item GDS in screening depression in a community-dwelling older population,[26] with a significant reduction in administration time. Therefore, we used the GDS-5 as one of our outcome measures. BDNF can support the survival of existing neurons in a certain region of the central and peripheral nerve system, while furthermore promoting the growth and differentiation of new neurons and synapses.[27] Moreover, BDNF has been found to promote the survival of neurons affected in Alzheimer disease.[28] Hence, the response of this novel protein to physical exercise was checked in the study. MCP-1 is a member of the chemokine family and regulates the movement of monocytes to inflamed tissue in response to inflammatory signals. Because inflammation is considered to be one of the central mechanisms in the development of dementia,[29] the response of MCP-1 to exercise training was also of interest in our study. Recent studies have suggested that IGF-1 is essential for neurogenesis in the brain, and the reduction of IGF-1 with aging may contribute to cognitive decline.[30] Therefore, IGF-1 was also included as one of our outcome measures.

The Charlson Comorbidity Index (CCI) was calculated for each participant after a thorough chart review. Prior to the commencement of the exercise training programs, the outcome measures mentioned above were all examined by an assistant who was blind to the group allocations. A total of 10 mL of blood was drawn from each participant to analyze the biochemical markers of dementia. Serum or plasma was collected from each patient's whole blood after centrifugation at 1000 *g* at 4°C for 10 minutes and was then assayed for BDNF, MCP-1, and IGF-1 using commercial enzyme-linked immunosorbent assay kits[b] according to the instruction manuals. After 4 weeks of exercise training, the outcome measures mentioned above were examined once again by the same assistant and recorded.

Statistical analysis

SPSS 17.0[c] was used for data analysis in the study. The Kolmogorov-Smirnov test was performed to examine the degree of normal distribution. A paired *t* test was performed to analyze whether there was any significant improvement in the Barthel Index, MMSE, MoCA, GDS, serum BDNF, plasma MCP-1, and IGF-1 after the subjects had completed 4 weeks of the 2 different exercise training programs. The levels of improvement were also compared using the Student *t* test between the aerobic and the strength training groups. If the data were not normally distributed in the Kolmogorov-Smirnov test, the nonparametric Mann-Whitney *U* test and Wilcoxon signed-rank test would replace the Student *t* test and paired *t* test in our study, respectively. To further analyze the relationship between the changes of outcome measures over time and the different types of exercise training, a multivariate regression analysis incorporating the generalized estimating equation was applied, adjusting for age and CCI. A *P* value $<.05$ was considered to be statistically significant in the study.

Table 1 Baseline characteristics of the participants in the strength and aerobic groups

Variables	Strength Group (n=30)	Aerobic Group (n=31)
Age (y), mean ± SD	86.77±6.99	84.68±6.74
>85, n (%)	22 (73.33)	16 (51.61)
≤85, n (%)	8 (26.67)	15 (48.39)
Sex, n (%)		
Male	24 (80)	26 (83.87)
Female	6 (20)	5 (16.13)
CCI, mean ± SD	6.47±1.17	6.55±1.23
Barthel Index, mean ± SD	89.33±10.65	90.81±12.85
MMSE, mean ± SD	22.7±4.28	23.87±4.65
GDS, mean ± SD	0.4±0.68	0.48±0.57
MoCA, mean ± SD	19.12±3.79	19.78±4.69
BDNF(pg/mL), mean ± SD	23458.35±5418.26	19253.6±7008.84
IGF-1(ng/mL), mean ± SD	48.02±17.13	44.44±14.31
MCP-1(pg/mL), mean ± SD	291.12±42.07	311.29±110.15

Results

As depicted in fig 1, a total of 69 nursing home inhabitants initially joined the study, but 8 opted out during the training period on account of exercise intolerance. In the end, 61 participants completed the exercise programs, consisting of 50 men and 11 women. The youngest participant was 66 years old, and the oldest was 95. The average age of the participants was 85.7±6.9 years. A total of 30 subjects were randomly assigned to the strength training group, while the other 31 were assigned to the aerobic training group. The baseline data of the outcome measures of both groups are shown in table 1.

After 4 weeks of undergoing these intensive training programs, the outcome measures were reexamined (tables 2 and 3). For the patients receiving strength training, their Barthel index, MMSE, MoCA, and plasma MCP-1 improved significantly after 4 weeks. As for the patients receiving aerobic training, serum BDNF also improved significantly in addition to the improved parameters previously mentioned for the strength training group.

The degree of improvements was then statistically compared (table 4). The amount of change in the Barthel Index, MMSE, MoCA, GDS, and biochemical markers between the strength and aerobic training groups did not achieve statistical significance. Furthermore, the results were validated by multivariate regression analysis incorporating the generalized estimating equation, adjusting for age and CCI, which showed significant improvement in the Barthel Index, MMSE, MoCA, BDNF, and plasma MCP-1 after exercise training (table 5). The only outcome measure that was significantly influenced by the exercise mode was BDNF ($P=.02$).

Discussion

Our study directly compared the beneficial effects for patients with dementia between strength and aerobic training. The results clearly indicate that both strength and aerobic training programs over the course of 4 weeks can bring about significant benefits for patients with dementia in both their ADLs and cognitive performance. Furthermore, the difference in results between the 2 modes of exercise was not significant.

The participants in both training groups in our study displayed significant improvement in their basic ADLs, as measured by the Barthel Index, which is consistent with past findings. Littbrand et al[4] recruited patients with dementia with an MMSE score of 10 or greater and found that a high-intensity functional weight-bearing exercise program over the course of 3 months could prevent patients from experiencing a significant decline in their Barthel Index. Venturelli et al[6] also adopted the Barthel Index as their outcome measure and discovered that a 6-month aerobic walking program significantly improved the ADLs function in 21 patients with Alzheimer disease. Our study results are compatible with these 2 previous studies, and we have now further revealed that ADLs function can be improved even after only 1 month of intensive aerobic or strength training.

Our study adopted 2 types of outcome measures to evaluate the cognitive functions of our participants, and both improved

Table 2 Data for the outcome measures before and after 4 weeks of strength training

Outcome Measures, Mean ± SD	Before	After	*P* Value*	Effect Size
Barthel Index	89.33±10.65	94.5±7.92	<.001†	0.46
MMSE	22.7±4.28	24.2±4.87	.014†	0.32
GDS	0.4±0.68	0.63±0.77	.166	0.18
MoCA	19.12±3.79	20.76±5.39	.026†	0.38
BDNF (pg/mL)	23,458.35±5418.26	25,413.81±7504.38	.243	0.19
IGF-1 (ng/mL)	48.02±17.13	48.79±17.25	.717	0.06
MCP-1 (pg/mL)	291.12±42.07	262.54±95.57	.044†	0.33

* Wilcoxon signed-rank test.
† $P<.05$.

Table 3 Data for the outcome measures before and after 4 weeks of aerobic training

Outcome Measures, Mean ± SD	Before	After	*P* Value*	Effect Size
Barthel Index	90.81±12.85	95.65±9.19	.001†	0.41
MMSE	23.87±4.65	25.87±3.36	.001†	0.42
GDS	0.48±0.57	0.45±0.57	.813	0.03
MoCA	19.78±4.69	21.74±4.55	<.001†	0.52
BDNF (pg/mL)	19,253.6±7008.84	21,200.85±7406.38	.023†	0.34
IGF-1 (ng/mL)	44.44±14.31	44.23±13.92	.897	0.02
MCP-1 (pg/mL)	311.29±110.15	260.16±106.5	.006†	0.40

* Wilcoxon signed-rank test.
† $P<.05$.

significantly after 4 weeks of intensive training, whether it be through strength or aerobic training. Past articles have also supported the belief that exercise training can improve cognitive functions.[6,7,31] However, 1 study did fail to reveal the beneficial effects in cognitive function of high-intensity functional exercise programs in patients with dementia.[32] The reason for this most likely lies in the fact that their study included patients with more severe dementia (an MMSE of at least 10) than those in our study, making it more difficult for them to improve through exercise. Furthermore, their training protocol was less frequent than ours in that it lasted for 4 months but only consisted of five 45-minute sessions per each 2-week period.

Although exercise has long been considered an effective tool for dealing with depression,[33] the results of our study failed to reproduce the same benefit in patients with dementia, whether it be through strength training or aerobic training. We used the GDS 5-point edition to evaluate the depression statuses of our participants. Similarly, Conradsson et al[5] adopted the GDS 15-point edition as their outcome measure to assess the effects of high-intensity functional exercise programs on patients with dementia, and they also failed to establish the benefits of exercise on depression in their study at the patients' 3- and 6-month follow-ups. Another study adopted more specific instruments to assess the depressive statuses of patients with dementia, including the Cornell Scale for Depression in Dementia, the Dementia Mood Assessment Scale, and the Alzheimer's Mood Scale,[9] and they did observe some superior benefits from exercise compared with what was seen in the control groups. Therefore, the reason for our study results may be that the outcome measure was not sensitive enough to detect trivial changes in depression. In addition, the very low depression scores at baseline (0.4±0.68 in the strength group and 0.48±0.57 in the aerobic group) also exerted significant ceiling effects on the outcome measure of GDS in our study.

In past literature, several biochemical markers have been shown to change after exercise training, including BDNF, cholesterol, testosterone, estradiol, dehydroepiandrosterone, and insulin.[34] Among them, BDNF is the biomarker that has drawn the most attention. Several meta-analyses have revealed the effects of aerobic training on the upregulation of BDNF in elderly persons,[35] those with Alzheimer disease,[16] and healthy young men.[36] In our study, significant upregulation of BDNF was also observed but only in the aerobic training group. The same result was obtained in a systematic review involving 32 articles, which concluded that strength training had no influence on peripheral BDNF but that BDNF can be elevated through acute and chronic aerobic exercise.[37]

In human bodies, the elevation of MCP-1 concentration usually indicates the progression of inflammation, such as cardiac ischemia reperfusion injury,[38] acute kidney injury,[39] and pelvic inflammatory disease.[40] Accumulating evidence supports the belief that exercise can reduce chronic inflammatory response in human bodies, thus preventing the development of chronic diseases.[41] Inflammation, on the other hand, has long been considered to be a central mechanism in the development of dementia, particularly Alzheimer disease.[42] Therefore, exercise may inhibit the progression of dementia via its anti-inflammatory effects, which is most likely the reason for the improvement of cognitive function in our study. Both groups of exercise participants in our study had significantly lower MCP-1 levels after 4 weeks of training, which may explain, at least in part, the reason for their improvement in both MMSE and MoCA. One animal study has also revealed a dose-dependent response of MCP-1 levels being lowered after exercise in an Alzheimer disease mouse model,[17] which is compatible to the results of our study.

IGF-1 is a protein similar in molecular structure to insulin, which plays an important role in both childhood growth and anabolic functions in adults. A lower plasma level of IGF-1

Table 4 Comparison in the amount of change in the outcome measures between the strength and aerobic training groups

Outcome Measures, Mean ± SD	Strength Group	Aerobic Group	*P* Value*	Effect Size
Barthel Index	5.17±7.25	4.84±7.8	.738	0.04
MMSE	1.5±3.15	2±2.8	.441	0.10
GDS	0.23±0.9	−0.03±0.75	.203	0.16
MoCA	1.65±2.78	1.96±2.08	.922	0.01
BDNF (pg/mL)	1955.46±5471.86	1947.25±4184.54	.604	0.08
IGF-1 (ng/mL)	0.77±7.37	−0.21±7.54	.752	0.05
MCP-1 (pg/mL)	−28.58±76.18	−51.13±73.27	.604	0.08

* Mann-Whitney *U* test.

Table 5 Comparison of the outcome measures between the aerobic and strength training groups after 4 weeks of training

Outcome Measures	Coefficient β (95% CI)	*P* Value
Barthel Index		
Group (strength vs aerobic)	−0.75 (−5.46 to 3.96)	.755
Time (post vs pre)	5.00 (3.14 to 6.86)	<.001*
MMSE		
Group (strength vs aerobic)	−1.20 (−3.10 to 0.71)	.217
Time (post vs pre)	1.75 (1.02 to 2.49)	<.001*
GDS		
Group (strength vs aerobic)	0.04 (−0.20 to 0.28)	.722
Time (post vs pre)	0.10 (−0.11 to 0.31)	.351
MoCA		
Group (strength vs aerobic)	−0.33 (−2.61 to 1.94)	.774
Time (post vs pre)	1.84 (1.15 to 2.53)	<.001*
BDNF		
Group (strength vs aerobic)	4525.01 (724.89 to 8325.14)	.020*
Time (post vs pre)	1950.96 (532.31 to 3369.61)	.007*
IGF-1		
Group (strength vs aerobic)	5.18 (−3.38 to 13.74)	.236
Time (post vs pre)	0.24 (−1.97 to 2.44)	.834
MCP-1		
Group (strength vs aerobic)	−9.90 (−57.26 to 37.46)	.682
Time (post vs pre)	−40.93 (−63.21 to −18.66)	<.001*

NOTE. Coefficient β: the adjusted mean difference between strength and aerobic training or before and after exercise training.
* $P<.05$.

is associated with an increased risk of developing Alzheimer dementia, and higher levels of it may protect against neurodegeneration.[43] In our study, we attempted to examine the effects of exercise training on the plasma level of IGF-1. However, neither type of exercise mode had a significant effect on IGF-1 levels, which is similar to the results of a previous study.[18]

Study limitations

There were at least 4 limitations in our study. First, we did not monitor the participants' daily physical activities that may have coincided with our exercise training programs. Some participants may have spent either more or less time involved in exercise after joining our study. We were only able to encourage them to continue their typical daily activities without making any intentional abrupt changes to their routines. Second, because we recruited our participants from a nursing home for veterans, our participants were far older than those outside of the nursing home. Additionally, most of our subjects were male, implying that the results of our study may not be suitable when applying them to general populations. However, these results can still provide valuable information and offer useful recommendations for older men. Third, the questionnaire regarding depression that we adopted may have been too simplified to reflect any minor changes in a patient's depression status after exercise, which may be the reason for the statistical insignificance in our study. Finally, a patient's rated perceived exertion, rather than their target heart rate, was used to define the intensity of aerobic training in our study, which may have been confounded by each participant's mood status, their medical conditions, or the environmental factors during exercise training. However, the rated perceived exertion scale is still recommended by the American College of Sports Medicine[20] to define exercise intensity for older people, which after deliberate consideration, is the reason why we adopted this method.

Conclusions

Our study disclosed the significant benefits in cognitive function, ADLs, and several biochemical markers after merely 4 weeks of intensive exercise training, wherein the difference between aerobic and strength training was not significant. Therefore, we recommend that elderly patients with dementia choose the types of exercise they prefer to obtain the benefits that are brought on by exercise and physical activity.

Suppliers

a. G∗power 3.1.3; Heinrich-Heine-Universität.
b. ELISA; R&D Systems Inc.
c. SPSS 17.0; IBM.

Keywords

Aged; Dementia; Exercise; Rehabilitation; Resistance training

Corresponding author

Yuan-Yang Cheng, PhD, Department of Physical Medicine and Rehabilitation, Taichung Veterans General Hospital, No. 1650, Sect. 4, Taiwan Blvd, Taichung 40705, Taiwan. *E-mail address:* rifampin@gmail.com.

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