ORIGINAL ARTICLE

Effect of 3-month exercise and soy peptide intake on mild cognitive impairment: semi-randomized controlled trial

Masakazu IMAOKA,[1,2,3,4] Hidetoshi NAKAO,[5] Misa NAKAMURA,[1,2] Fumie TAZAKI,[1,2] Mitsumasa HIDA,[1,2] Ryota IMAI,[1,2] Masahisa IBUKI,[6] Motohiro MAEBUCHI,[7] Masatoshi TAKEDA[1,2]

[1]Department of Rehabilitation, Osaka Kawasaki Rehabilitation University, [2]Cognitive Reserve Research Center, [3]Graduate School, Department of Comprehensive Rehabilitation, Osaka Prefecture University, [4]Department of Preventive Gerontology, National Center for Geriatrics and Gerontology, [5]Josai International University, Department of Physical Therapy, Faculty of Welfare, [6]Japan Nutrition Co.,Ltd, [7]Strategy Planning Department, R&D Division, Fuji Oil Co., Ltd.

Correspondence: Masakazu Imaoka PT, PhD, Department of Rehabilitation, Osaka Kawasaki Rehabilitation University, 158 Mizuma, Kaizuka, Osaka 597-0104, Japan. Tel: +81-72-446-6700 E-mail: imaokamasakazu@gmail.com

ORCID: 0000-0002-5849-7107

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Abstract

Soy peptide, when consumed as a functional food, has been reported to improve cognitive function. The combined effects of soy peptide intake and exercise on cognitive function have been demonstrated. This study was intended to verify this effect in community-dwelling older adults with mild cognitive impairment (MCI). In this population-based, non-blinded randomized controlled trial, 27 old adults with MCI who were independent in activities of daily living, were randomly assigned to an exercise plus nutrition program (Ex + Nt group, n = 14) or to an exercise program (Ex group, n = 13). For three months, both groups received an exercise regimen once a week, but the Ex + Nt group received a soy supplement every day. Pre- and post-intervention measurements included grip strength, gait speed, skeletal muscle mass index, Mini-Mental State Examination (MMSE), Trail-making Test A, and Geriatric Depression Scale scores. The study participants were found that exercise training had an increased skeletal muscle mass index and gait speed in both groups. Those in the Ex + Nt and Ex groups showed a significant time effect on MMSE composite score ($p < 0.05$), with increases of 2.2 points and 0.9 points, respectively. A three-month exercise class for old adult persons with MCI was suggested to improve cognitive function, muscle mass and walking speed. It was suggested that ingestion of soy peptides could improve the MMSE composite score.

Key words: *Mild cognitive impairment, exercise, soy peptide, community-dwelling old adults*

INTRODUCTION

The number of old adult persons with dementia in Japan was estimated to be 4.62 million in 2012. One in seven old adult persons with dementia is ≥ 65 years old. The number of old adult persons with dementia will reach 7 million in 2025. That number is expected to increase to one in five old adult persons aged ≥ 65 years in the subsequent four years (Ministry of Health Law, 2016). The Dementia Policy Promotion Charter (Ministry of Health Law, 2019) is aimed at delaying or preventing the onset of dementia as well as emphasizing the perspectives of persons with dementia and their families, with an objective to establish a society where persons with dementia can experience a good quality of life. The Charter has made some progress towards these goals. To establish a concrete and effective approach is necessary.

Dementia is irreversible; hence, to take measures is important before it develops. In recent years, attention has been focused on mild cognitive impairment (MCI) (Winblad, 2004), which is an intermediate condition between normal cognition and dementia. MCI is defined as having a concern regarding a change in cognition or impairment in one or more cognitive domains but with preserved independence in functional abilities and without dementia (Alber, 2011). But the conversion rate from MCI to Alzheimer's disease increases to about 5%-10%, which is extremely high compared with the 1%-2% incidence rate of Alzheimer's disease in normal old adult persons (Mitchell, 2009; Peterson, 2004). The rate of MCI among community-dwelling old adult persons has been reported to range from 10% to 20% (Langa, 2014); therefore, they are considered to be a target population for an intervention strategy (Rose, 1985, 2001).

Although persons with MCI are at an increased

risk of developing dementia in the future, it has also been reported that cognitive function in persons with MCI improves and reverts back to normal (Brodaty, 2014). MCI has four types based on the number of cognitively impaired domains and the incidence of amnesia. In a two-year follow-up study, 31%-44% of those with cognitive impairment in a single domain are returned to normal, whereas only 5%-11% of those with cognitive impairment in multiple domains are returned to normal.

In addition, reversal is possible for participants without arthritis. Reversal is more likely for community dwelling older adults with higher complex mental activity, greater openness to experience, better vision, better smelling ability, or a larger combined volume of the left hippocampus and left amygdala (Sachdev, 2014). Shimada in 2018 also reported that regular active exercise and cognitive tasks improve cognitive function.

There have been varying durations of the exercise intervention period in previous study, ranging from 6 to 12 months (Devenney, 2017). To be able to produce effects in a shorter period of time is important. We have confirmed the effect of ingesting soy peptides to improve part of cognitive function through a relatively short three-month exercise class for old adult people living in the community, and the combination of exercise and nutrition in cognitive function. We believe that this is an effective initiative to make improvements in a short period of time (Imaoka, 2019). In this study, we intended to verify the effect of soy peptides and short exercises for three months on improving part of cognitive function in community-dwelling older adults with MCI.

METHODS

Trial design and participants

Two semi-randomized controlled trials were targeted at the entire population of old adult persons in a community-dwelling in Kaizuka City. The studies included those without MCI, and we examined the effects of a combination of exercise and nutrition (soy peptide) for three months on the improvement of cognitive function.

The inclusion criteria were community-dwelling old adults (aged ≥ 60 years) living in Kaizuka City, Osaka, Japan, who could independently perform activities of daily living and with a Mini-Mental State Examination (MMSE) score of 24–27 points, which is considered a mild cognitive decline (Sugisita, 2018).

The exclusion criteria were (a) old adults with an MMSE score of < 23 or ≥ 27 points, (b) those who dropped out of the class, and (c) those having missing data. Of 164 persons, 145 participated in the study, 27 persons with an MMSE score of 24–27 points were included (Figure 1). The reason for targeting the entire population is that, with an applicable rate of 10% to 20%, if only 8–16 persons were recruited from an exercise class of about 80 persons, statistical examination would be difficult. In this non-blinded randomized controlled trial, a targeted analysis was done in recruited 27 persons with MCI from the two semi-randomized controlled trials. The effects on cognitive function of a multicomponent exercise program (using different exercises performed with music and cognitive training) supplemented with soy peptide (Ex + Nt group, n = 14) were compared with those of an exercise program without the supplement (Ex group, n = 13).

The Ethics Committee of the Osaka Kawasaki Rehabilitation University approved the trial protocol (reference no = OKRU29-A021 and date of approval = January 31, 2018), requiring to obtain signed written informed consents from all the study participants without any compensation. Two trials were previously registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030404 and UMIN000034984).

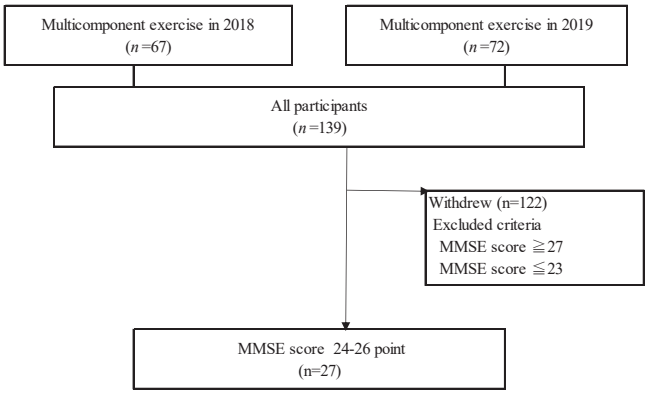

Figure 1. Study flowchart

Intervention: multicomponent exercise

We conducted a multicomponent exercise at the Kaizuka City Welfare Center. As shown in previous study (Imaoka, 2019), participants did a 15-minute memory training exercise and a 45-min aerobic exercise session once a week for three months. During the memory training session, participants listened to a novel, participated in word recall, and did two tasks (stepping on the spot and clapping their hands in multiples of 3 and 5). In aerobic exercise, participants

did a 10-minute self-stretching in a standing position. Next, they did a 15-minute musical exercise. The aerobic exercise included gymnastics according to the music of a popular local musician named Tsugesan. A total of 45 minutes of aerobic exercise sessions were provided with breaks along the way. The gymnastics were done on a yoga mat measuring 60 × 173 cm. The regimen included lower limb steps, upper limb rhythmic movements, skillful finger movements, and a 10-minute mindfulness exercise in the recumbent position. All exercises were taught by two physiotherapists and a few volunteer staff. Participants were instructed to self-monitored and recorded their daily steps in a notebook. Participants in the Ex +Nt group ingested commercially available soy peptide supplements (Peptide Athleeta 4000, Fuji Oil Co., Ltd., Osaka, Japan; see Table S1 for the nutrition label). The net weight of Peptide Athleeta 4000 with 4 g of soy peptide was 190 g. There was no time limit set for drinking the soy peptide supplements (Imaoka, 2019).

Table S1. Composition of the soy peptide supplement

Total calories (kcal)	48
Protein (g)	4.4
Fat (g)	0
Carbohydrate (g)	8.9
Sodium (mg)	112
Valine (mg)	184
Leucine (mg)	300
Isoleucine (mg)	177
Soybean peptide (mg)	4000

Measurement of outcomes

The cognitive status of the participants was measured using the Japanese version of the MMSE (Folstein, 1975). Body composition was assessed through bioelectrical impedance analysis (InBody270; InBody, Tokyo, Japan) (Nakamura, 2017). Muscle strength was calculated through measuring handgrip strength using a hand dynamometer (Grip-D; Takei, Niigata, Japan) (Makizako, 2017). Gait speed was measured through walking 6.4 m at a comfortable speed (Shimada, 2013). Depression trend was determined using the Japanese version of the Geriatric Depression Scale 15, which is a self-reported evaluation questionnaire (Burke, 1991).

Procedures

The MMSE is a simple cognitive function test that evaluates five cognitive areas: attention and orientation, memory, verbal fluency, language, and visuospatial cognition. It can be evaluated in 5 to 10 minutes, and the score is out of 30. In the Japanese version, a score of 27 points or more is considered normal, a score of 24-26 points corresponds with mild cognitive impairment, and a score of 23 points or less corresponds with dementia. Physiological parameters measured using bioelectrical impedance analysis (InBody270; InBody, Tokyo, Japan) were obtained from the participants' electronic medical records. The limb SMI was calculated as the limb skeletal muscle mass (kg) divided by the height squared (m^2). Grip strength was measured by handgrip strength, which has been reported to be significantly associated with whole-body muscle strength. The maximum voluntary isometric strength of the handgrip was measured using a grip-D hand dynamometer (Takei, Niigata, Japan) for the dominant hand while in a standing position. For gait speed, participants were instructed to walk 6.4 m (divided into two 2-m zones at each end and a 2.4-m zone in the middle) at a speed they found comfortable. The time needed (s) to pass the 2.4-m middle zone was measured to calculate the gait speed (m/s). We used the average of five gait trials. GDS-15 is the most frequently used screening test for depression worldwide. It consists of 15 short questions, and the subject answers "yes" or "no," so it is easy to answer, easy to score, and the enforcement time was 5 to 7 minutes. A score of 5 or higher is rated as a depressive trend, and a score of 10 or higher is rated as depressed.

Statistical analysis

Analysis of variance (ANOVA) was used for within- and between-group comparisons of continuous variables, and a Chi-square test was used for between-group comparisons of categorical variables at baseline. The effect of each intervention on outcome measurements was analyzed using a mixed 2 × 2 group (Ex and Ex + Nt groups) × time (pre- and post-intervention) two-way ANOVA.

In the sub-analysis, the sub-items of the MMSE (orientation time and place, registration, attention and calculation, recall, language, and copy) were analyzed separately in the Ex and Ex + Nt groups using a two-way ANOVA.

All statistical analyses were done using International Business Machine Statistical Package for Social Science version 27.0 for Windows, (IBM SPSS Corp., Armonk, New York, USA). The differences between groups were considered significant if p-values were smaller than 0.05.

RESULTS

All 27 individuals selected for the study completed the three-month intervention. The baseline characteristics of the participants were matched and found to be comparable (Table 1). The median relative adherence rate for nutritional supplementation was 90%. During the study period, participants recorded no health problems, musculoskeletal complications, muscle pains, or fall incidents.

Table 2 presents the comparison of cognitive function and physical function test values before and after the intervention and group × time interactions. The MMSE composite score, gait speed, and skeletal muscle mass index had significant time effects in both groups. Table 3 presents the comparisons of the MMSE subscale changes in the Ex and Ex + Nt groups. The attention and calculation item showed significant time-specific effects ($p < 0.05$).

Table 1. Baseline characteristics of the study participants

Items	Ex + Nt group (n = 14)	Ex group (n = 13)	F-value
	M ± SD	M ± SD	
Age (years)	75.8 ± 4.3	76.5 ± 4.4	0.04*
Sex, female, n (%)	9 (64.3)	7 (53.8)	
Height (cm)	154.1 ± 6.7	155.7 ± 9.7	4.11
Weight (kg)	53.8 ± 7.0	56.8 ± 9.4	1.30

*$p < 0.05$, significant differenct using t-test or chi square test
Ex + Ex, exercise + nutrition; cercit M ± SD, mean standard deviation
Except the age, the demographic characteristics are comparable between two groups

Table 2. Pre- and post-intervention outcome measurements in the two groups

	Pre-intervention	Post-intervention	Two-way ANOVA	
			Time effect	Time × group interaction
			F-value	F-value
MMSE score				
Ex + Nt	25.9 ± 1.1	28.1 ± 1.7	11.60*	4.38
Ex	26.0 ± 0.8	26.9 ± 2.4		
TMT-A (sec)				
Ex + Nt	119.4 ± 49.1	109.5 ± 51.4	3.42	0.18
Ex	109.1 ± 32.7	100.9 ± 33.1		
Gait speed (m/sec)				
Ex + Nt	1.25 ± 0.16	1.34 ± 0.14	8.93*	0.08
Ex	1.18 ± 0.21	1.30 ± 0.25		
Grip strength (kg)				
Ex + Nt	22.9 ± 8.6	25.2 ± 5.8	7.13*	0.19
Ex	23.5 ± 6.6	25.8 ± 6.3		
SMI (kg/m^2)				
Ex + Nt	6.06 ± 0.90	6.18 ± 0.88	11.93*	0.13
Ex	6.15 ± 0.89	6.26 ± 0.94		
GDS-15 score				
Ex + Nt	2.8 ± 2.1	2.0 ± 1.8	1.29	0.34
Ex	3.0 ± 1.9	2.7 ± 3.2		

*$p < 0.05$, significantly different using *t*-test
ANOVA, analysis of variance; Ex, exercise; Ex + N, exercise and soy peptide intake; MMSE, Mini Mental State examination; TMT, Trail-making Test; SMI, skeletal muscle mass index; GDS-15, Geriatric Depression Scale 15.

Table 3. Pre- and post-intervention cognitive domain, task, and subtotal scores on the MMSE

	Pre-intervention	Post-intervention	Δ-Value	Two-way ANOVA	
				Time effect	Time × group interaction
				F-value	F-value
Orientation score					
Ex + Nt	9.6 ± 0.6	9.7 ± 0.6	0.1	0.59	2.79
Ex	9.7 ± 0.5	9.3 ± 0.9	–0.4		
Registration score					
Ex + Nt	2.9 ± 0.3	3.0 ± 0.0	0.1	0.00	2.00
Ex	3.0 ± 0.0	2.9 ± 0.3	–0.1		
Attention and calculation score					
Ex + Nt	2.5 ± 1.1	3.9 ± 1.7	1.4	11.04*	3.1
Ex	3.2 ± 1.6	3.8 ± 1.7	0.6		
Recall score					
Ex + Nt	2.6 ± 0.5	2.7 ± 0.6	0.1	1.70	0.09
Ex	1.6 ± 1.3	1.8 ± 1.3	0.2		
Language score					
Ex + Nt	7.6 ± 0.6	7.8 ± 0.4	0.2	1.08	0.24
Ex	7.7 ± 0.5	7.8 ± 0.4	0.1		
Copy score					
Ex + Nt	0.9 ± 0.3	1.0 ± 0.0	0.1	3.1	0.28
Ex	0.9 ± 0.4	1.0 ± 0.0	0.1		

*$p < 0.05$, significantly different using *t*-test
ANOVA, analysis of variance; Ex, exercise; Ex + N, exercise and soy peptide intake; MMSE, Mini Mental State Examination; TMT, Trail-making Test; SMI, skeletal muscle mass index; GDS-15, Geriatric Depression Scale 15.

DISCUSSION

We examined the effects of an exercise program and the ingestion of soy peptide dietary supplements on 27 MCI individuals in two randomized controlled trials over a period of three months. During this time, the MMSE composite score improved significantly in both the Ex and Ex + Nt groups. The Ex + Nt group had a higher degree of improvement in the MMSE composite score. In addition, multicomponent exercise led to improved walking speed, grip strength, and increased muscle mass in both groups.

Previous studies (Meng, 2021; Zhou, 2020) on the effects of multicomponent exercise on MCI have shown improvements in general function, memory, language ability, executive function, and visuospatial ability. This study (Table 2) showed that both groups had significant MMSE composite scores ($p < 0.05$). The score and calculation items of the subscale items were significantly improved (data not shown). This findings re-confirm and support our previous suggestions that multicomponent exercise have improved cognitive function (Imaoka, 2019).

An overview of previous studies of older adult persons with MCI showed that the effectiveness of cognitive function assessment items in improving cognitive function is dependent on the type of exercise. Many studies that promote aerobic exercise and physical activity show that they have effects on executive function (Baker, 2010; Suzuki, 2012), language function (Suzuki, 2012), memory (Suzuki, 2013) and general cognitive function (Lautenschlager, 2008). Other reports observed that the effect is localized or that there is no effect on memory (Lam, 2015; Scherder, 2005). Meanwhile, strength training has been reported to have an effect on executive function (Nagamatsu, 2012), memory (Fiatarone, 2014; Shimada, 2018), and general cognitive function (Nagamatsu, 2012). In this study, attention and calculation domains improved significantly ($p < 0.05$). This was due to the participants imitating the exercises done by instructors and the program using counting exercises. Similarly, we suggest that logging the daily number of steps taken and calculating the difference with the previous day's steps may have motivated participants to reach their goals.

The MMSE composite score improved by 0.9

points in the Ex group and by 2.2 points in the Ex +Nt group which showed a large improvement in the group receiving daily soy peptide supplementation. This mechanism may be triggered by physiologically functional peptides in soy, such as Ser-Tyr and Gly-Arg, that upregulate noradrenaline and brain-derived neurotrophic factor in the brain (Ichinose, 2015).

Study limitations

The readers are cautioned not to over-interpret the study findings because this study has five study limitations: —

- This study is a study in which MCI applicable persons were extracted from Semi RCTs conducted separately.
- The total calorie intake of the Ex+Nt group was not adjusted. At baseline of this study, a 0.7-point difference existed between the two groups in the attention and calculation score, and although there was no significant difference, the possibility of bias cannot be ruled out.
- Open-label randomization in this study may have led to selection bias.
- Because of the small sample size in this study, a Type II error may have occurred.
- In this study, 5 points was the perfect score for the attention and calculation items, and both groups had almost perfect scores post trial, so it is possible that a ceiling effect occurred.

A randomized controlled trial is being planned, which will involve a cross-sectional survey of 1,000 persons from which 100 old adult persons with MCI will be extracted, with complete examination of sample size and effect size.

Summary

In this study, we found that multicomponent exercise for three months in patients with MCI had significant improvement in cognitive function. We suggest that ingestion of soy peptides may enhance cognitive improvement of old adult patients with MCI.

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