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Article

Circuit Training Improves the Levels of A β and BDNF Related to Cognitive Impairment Risk Factors in Obese Elderly Korean Women

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Abstract: The purpose of this study was to investigate the effect of circuit training on β -amyloid, BDNF, and cognitive function in untrained obese elderly Korean women. The subjects for the study were aged 65–70 years, composed of the circuit training group (n=12) and control group (n=11). The 60-minute combined exercise was performed 3 times per week for 16 weeks. Exercise intensity was progressively increased from 40% HRR to 70% HRR. The test data were analyzed by paired t-test, independent t-test, and two-way repeated measures ANOVA, and the alpha level of .05 was set for all tests of significance. The findings of this study were as follows: β -amyloid significantly decreased after the exercise group had compared to before the exercise and BDNF and cognitive function significantly increased after the exercise group had compared to before the exercise. However, there were no significant changes in β -amyloid, BDNF, and cognitive function in the control group. Therefore, it is suggested that the circuit training used in this study could be an effective exercise method for improving the risk factors of cognitive impairment in obese elderly Korean women.

Keywords: circuit training; β -amyloid; BDNF; cognitive function; obese elderly women

1. Introduction

The global average life expectancy has been increasing, leading to a rapid progression of aging worldwide and the prevalence of dementia is rapidly increasing worldwide [1].

Dementia is the loss of cognitive functioning and ability to lead one's daily life. It is the most prevalent neurodegenerative disease among the elderly, and such cognitive dysfunction is a primary cause of poor quality of life [2].

The types of dementia include Alzheimer's Disease (AD), vascular dementia, Parkinson's Disease, and other types of dementia caused by various underlying factors. AD, which accounts for approximately 70% of dementia cases [3], causes dysfunction of the synapses as nerve cells die [4] due to deposition of β -amyloid (A β) [5] and reduction of brain-derived neurotrophic factor (BDNF) [6]. It negatively affects cognitive and neurodegenerative processes and causes a state of cognitive dysfunction in perception, logic, reasoning, and awareness [7].

According to a report by Seoul National University Hospital [8], the neuropathology of AD begins 15 to 20 years prior to the appearance of such symptoms as problems with memory and spatiotemporal abilities, loss of linguistic abilities, and loss of identity, and the decline in cognitive function begins in the 50s and accelerates after the age of 65 [9]. In addition, the prevalence of dementia is higher among females than males [3], and females aged 60 to 74 are at a higher risk of cognitive decline than females aged 50 to 59 [10]. Therefore, to prevent AD, it is important to manage the pathological factors that cause dementia, and the pathological risk factors include A β and BDNF [11].

A β is generated in the brain when the amyloid precursor protein (APP) is metabolized by β -secretase and γ -secretase, which are enzymes located in the hippocampus, the most crucial area of the brain for memory and cognitive function. A β then aggregates to form amyloid plaques in the brain [12]. The accumulated A β induces neuronal cell death through the formation of amyloid

plaques [13], leading to oxidative damage, blood-brain barrier (BBB) dysfunction, and the development of neurofibrillary tangles in nerve fibers [14]. This, in turn, causes AD by impairing learning and memory formation abilities, disturbing the processing of new information, and causing behavioral dysfunctions [15].

In this respect, reducing or inhibiting A β has been proposed as a primary treatment method for AD, but most treatments depend on existing medications. However, it is possible to lower plasma A β concentrations through exercise [16], and the greater the amount of physical activity, the lower the A β concentration that has been observed [17].

BDNF concentration in the body, on the other hand, becomes lower with increasing age. Because its concentration in elderly females is lower than in elderly males, it serves as an indicator of memory and cognitive impairment in older females [18]. Thus, a decrease in plasma BDNF levels increases the probability of AD onset [6], but it is possible to delay the progression of dementia by increasing BDNF levels through exercise (Nagahara et al., 2009).

Cognitive function is critical in determining quality of life in old age, so managing cognitive decline is necessary to maintain and improve quality of life [19]. Regular exercise in old age can reduce the occurrence of dementia by up to 60%, while low levels of physical activity increase the prevalence of AD by 25% [20].

Regular exercise can promote cognitive function and act as a major factor in the prevention of AD by increasing the expression of proteins involved in neuroregeneration in the brain, such as BDNF, and decreasing the expression of A β , a key component of AD [21].

While exercise can maintain and improve cognitive function, social distancing, as well as limited operations and closures of exercise facilities due to COVID-19, has changed existing patterns of daily life. This has led to decreased time spent on physical activities [22] and lower rates of participation in regular exercise compared to the pre-pandemic period [23]. This decline in physical activities has reduced energy consumption, leading to an increase in the probability of sarcopenic obesity [24].

Furthermore, obesity causes functional and structural changes in the brain by reducing the expression of neurotrophic factors such as BDNF, which plays a vital role in neuroplasticity and neurogenesis, and by damaging cerebral vessels and BBB, leading to reduced cognitive functions and cognitive impairments [25]. Obese elderly individuals are less cognitively capable than elderly persons with normal body weight [26].

Those newly participating in or continuing physical exercises require easy accessibility in terms of time and location and generation of internal motivation. Exercising with others is more effective than exercising alone, and combinations of two or more safe exercises are more effective in improving motor functions in the elderly than performing a single type of exercise [27].

Among physical exercises, circuit training using weight load alternates between aerobic and resistance exercises and allows for engaging in various exercises within a short period of time and continued participation with interest. Additionally, circuit training is an enjoyable exercise method for anyone because of its low risk of injury, limited spatial restrictions, and flexibility to be performed with a group rather than alone.

Therefore, the present study aims to investigate the effect of circuit training on β -amyloid, BDNF, and cognitive function in untrained obese elderly Korean women aged 65 to 70, who are at a higher risk of developing dementia and accelerated cognitive decline than elderly males. It also aims to provide baseline data to be used in programs for preventing AD and improving physical functions and quality of life in the future.

2. Materials and Methods

2.1. Subjects

Twenty-three obese elderly women (living in Busan, Korea) who did not exercise regularly (defined as < 20 min of exercise twice a week) and had not taken drugs for obesity treatment in the previous six months were recruited for the current study. The participants were between the ages of 65 and 70 and had body fat percentages of 30% and over. Simple random sampling was used to assign

16 to the control group and 16 to the exercise group. Before the experiment, this study was approved by the Institutional Human Research Committee (This study was a study derived from the PNU IRB/2017_68_HR), and the subjects were fully informed regarding the purpose of the study; only those who were willing to participate in the experiment submitted their consent for participation. Both the measurement and analysis of test results were conducted on 11 cases in the control group and 12 cases in the exercise group after excluding withdrawals from the experiment due to personal circumstances. The physical characteristics of the participants and the procedures of the study are shown in Table 1 and Figure 1.

Table 1. Changes in body composition after 16 weeks of circuit training.

	CG(n=11)		EG(n=12)	
	Pre	Post	Pre	Post
Age(yr)	67.97±1.73		66.97±1.63	
Height(cm)	154.73±3.69		152.55±4.19	
Weight(kg)	55.49±4.44	55.75±4.72	57.33±6.61	57.24±6.59
BMI(kg/m ²)	24.45±1.70	24.58±2.00	24.67±2.38	24.62±2.31
SMM(kg/m ²)	19.09±1.40	18.99±1.34	19.68±1.85	19.98±1.87**
BFM(kg/m ²)	19.82±2.79	19.95±2.71	20.35±4.12	19.79±3.96
%BF(%)	35.55±3.12	35.65±2.45	35.37±3.31	34.33±3.45**

Values are $M \pm SD$; BMI: body mass index, SMM: skeletal muscle mass, BFM: body fat mass, %BF: percentage of body fat; CG: control group, EG: exercise group, ** $p < .01$: pre vs post intra-group.

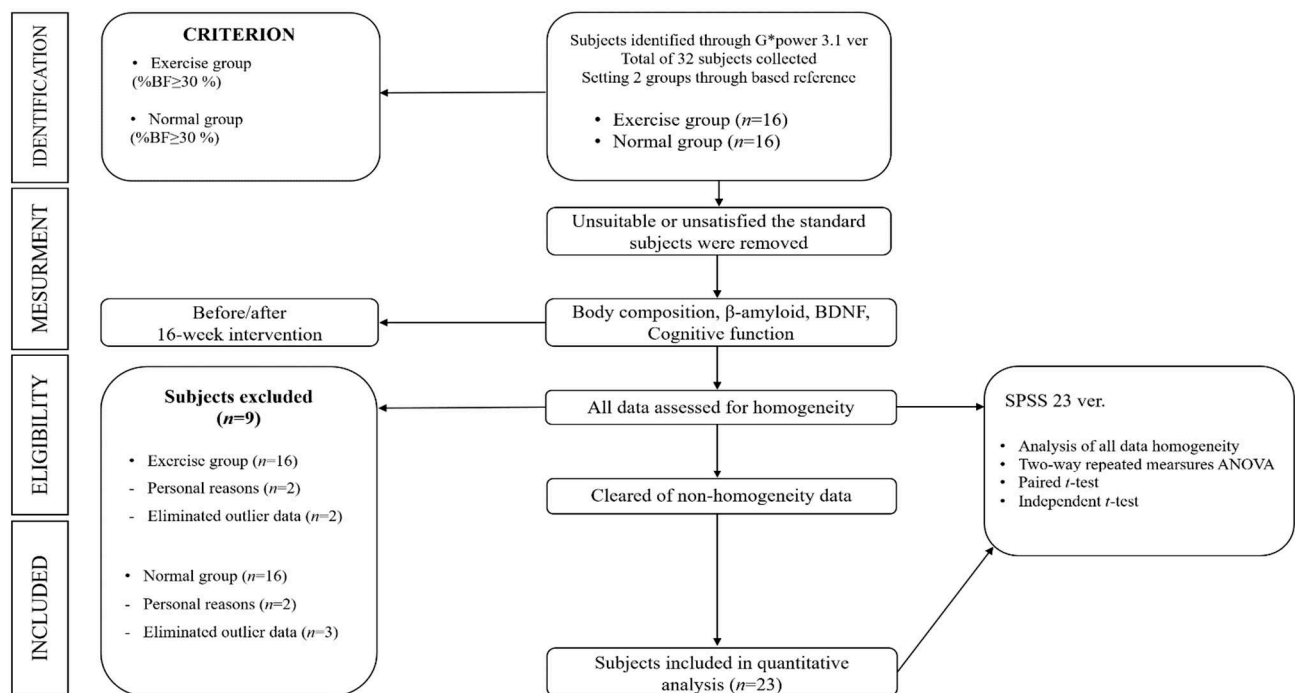


Figure 1. Procedures of this study.

2.2. Circuit Training Program

The exercise program was a modified and supplemented version of Ha et al.'s [28] program, consisting of 10 minutes of warm-up, 40 minutes of the main exercise, and 10 minutes of cool-down. The 60-minute program was conducted three times a week for 16 weeks. This exercise routine includes a variety of exercises such as standing low jump & shake, modified push-up, jogging in place, squats, high knee, crunch, step box, lunges, and jumping jacks.

The target heart rate was checked using wireless heart rate monitors (Polar RS400sd, USA), and ratings of perceived exertion (RPE) were used to maintain the exercise intensity. Heart rate reserve (HRR) was gradually increased throughout the exercise period from 40% to 50% (RPE 12–13) for weeks 1 through 4, 50% to 60% (RPE 13–14) for weeks 5 through 8, 60% to 65% (RPE 14–15) for weeks 9 through 12, and 65% to 70% (RPE 14–15) for weeks 13 through 16 to ensure the safety of the participants [29]. The progression of circuit exercises is shown in Figure 2.

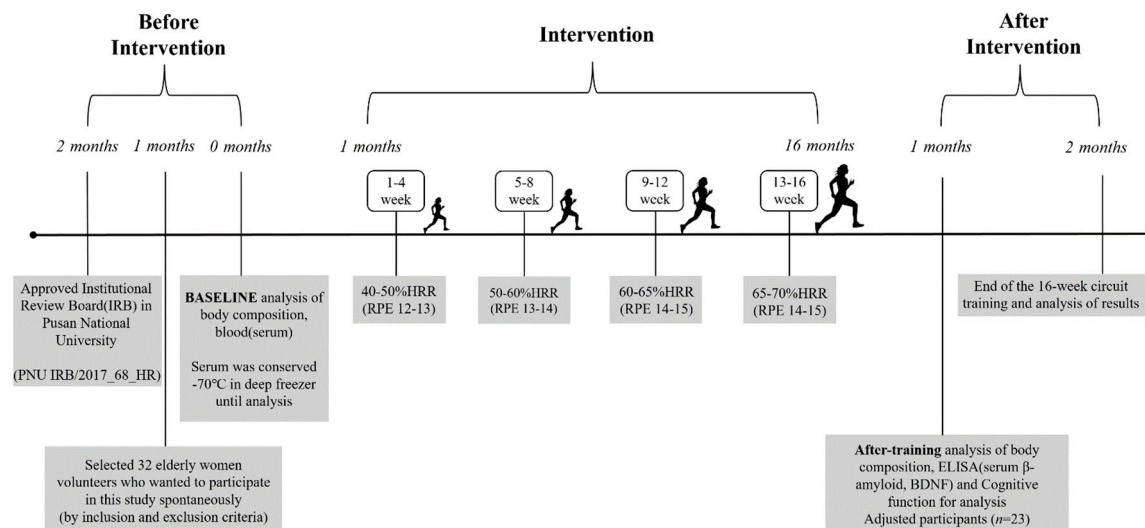


Figure 2. Flowchart of exercise intervention.

2.3. Measurement Items and Analytical Method

2.3.1. Body Composition

For the measurement of body composition, height was measured using a DS-103 automatic extensometer (Jenix Co., Korea) after all metals participants were carrying on their body had been removed, and weight (kg), body fat mass (kg), skeletal muscle mass (kg), and body fat percentage (%) were measured using an Inbody 770 body composition analyzer (Biospace Co., Korea).

2.3.2. Blood Analysis

All pre- and post-experiment tests for measuring β -amyloid, brain-derived neurotrophic factor (BDNF), and cognitive functions were performed under the same conditions using the same method. Participants arrived at the laboratory between 8 and 9 a.m., 60 minutes before the blood collection, while maintaining a 12-hour fasting state.

Medical technologists collected 10 ml of blood from the antebachial vein using vacutainer tubes and single-use syringes. The collected blood was put in a serum-separating tube (SST) and separated at 3,000 rpm for 20 minutes using a Combi-514R centrifuge (Hanil, Korea). After the serum was separated, the supernatant was transferred to a 1.5 ml microtube and stored at -70°C for analysis.

An enzyme-linked immunosorbent assay (ELISA) technique was employed for the analysis of A β using the human amyloid beta (aa1-42) Quantikine ELISA Kit (R&D Systems, USA) and Thermo Scientific Multiskan Go spectrophotometer (Thermo Scientific, Waltham, MA, USA).

BDNF was also analyzed using the ELISA method with Total BDNF Quantikine ELISA Kit (R&D Systems, USA) and Thermo Scientific Multiskan Go spectrophotometer (Thermo Scientific, Waltham, MA, USA).

2.3.3. Cognitive Function

Cognitive functions were measured using the Mini-Mental State Examination – Korean (MMSE-K), the modified and supplemented version of the Mini-Mental State Examination for the elderly in

Korea. The MMSE-K has a total of 12 items and a total score of 30. Scores of 24 and above indicate definitive normal, 20 to 23 suspected dementia, and 19 and below definitive dementia. The examination was conducted through one-on-one interviews, and the total score was calculated by adding the score of each item. The study was conducted on normal individuals who did not have suspected or confirmed dementia, which is why all 23 participants scored 24 points or higher.

2.3.4. Data Analysis

Regarding descriptive statistics, the means (M) and standard deviations (SD) were calculated for each measurement item using SPSS ver.23.0 (SPSS Inc., Chicago, IL, USA). Inter-group heterogeneity of the variables was tested using Levene's F-test. The mean difference tests for comparison before and after 16 weeks within each group were conducted using the paired t-test, and the between-group differences were tested using the independent t-test and the time interactions using a two-way ANOVA. The significance level was 0.05 for all statistical tests. A repeated test number (sample size) of 23 was derived from a priori sample size estimation using commercial software (G*Power, Version 3.0.1, Universitat, Kiel, Germany) based on a repeated measures ANOVA F-statistic at $p < .05$, $\beta = 0.2$, and an effect size of 0.5.

3. Results

3.1. β -amyloid

3.1.1. The Results for Intra-Group and Inter-Group Analysis of Changes and Interactions of β -amyloid are Shown in Figure 3 and Figure 4.

A significant group \times time interaction was found ($F=7.077$, $p < .05$). The exercise group showed a significant decrease in β -amyloid over time ($t=-3.086$, $p < .05$), and the inter-group comparison showed a significant difference in the after ($t=2.902$, $p < .05$), and amount of change ($t=2.660$, $p < .05$).

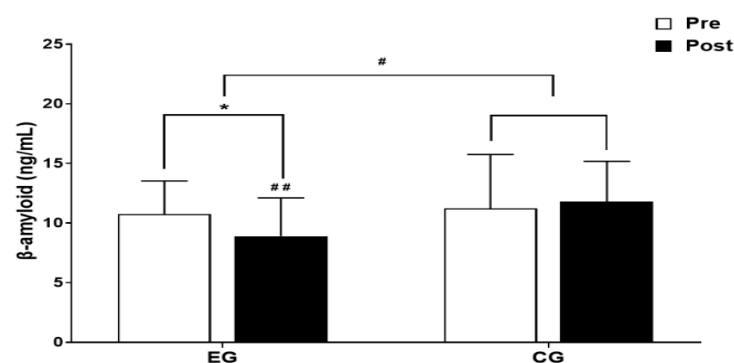


Figure 3. Comparisons of β -amyloid after 16-week circuit training. * $p < .05$: Pre vs Post; # $p < .05$: Exercise vs Control.

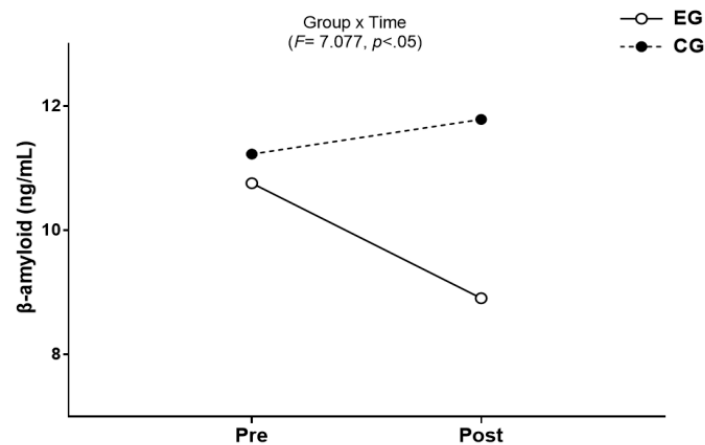


Figure 4. Result of two-way repeated measures ANOVA of β -amyloid after 16-week circuit training.

3.2. BDNF

3.2.1. The results for Intra-Group and Inter-Group Analysis of Changes and Interactions of BDNF are Shown in Figure 5 and Figure 6.

A significant group \times time interaction was found ($F=9.654, p<.01$). The exercise group showed a significant increase in BDNF over time ($t=4.910, p<.001$), and the inter-group comparison showed a significant difference in the amount of change ($t=-3.107, p<.01$).

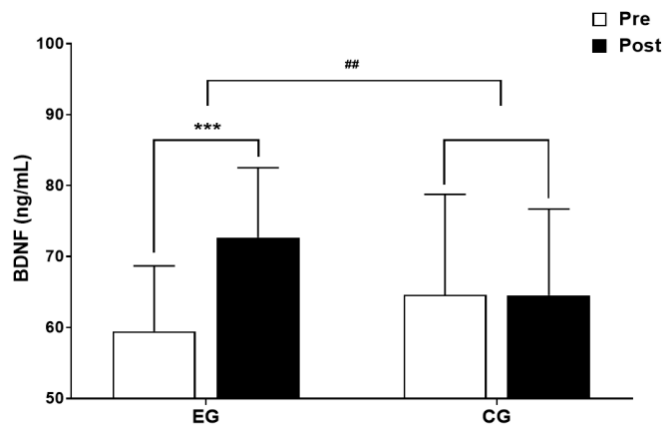


Figure 5. Comparisons of BDNF after 16-week circuit training. *** $p<.001$: Pre vs Post; ## $p<.01$: Exercise vs Control.

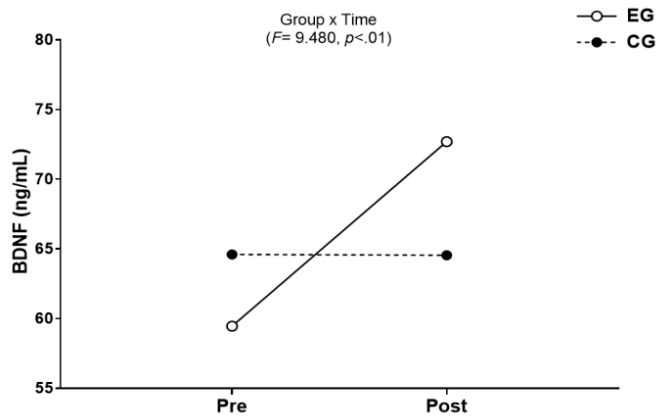


Figure 6. Result of two-way repeated measures ANOVA of BDNF after 16-week circuit training.

3.3. Cognitive Function

3.3.1. The Results for Intra-Group and Inter-Group Analysis of Changes and Interactions of Cognitive Function are Shown in Figure 7 and Figure 8.

A significant group \times time interaction was found ($F=4.738, p<.05$). The exercise group showed a significant increase in cognitive function over time ($t=2.727, p<.05$), and the inter-group comparison showed a significant difference in the amount of change ($t=-2.177, p<.05$).

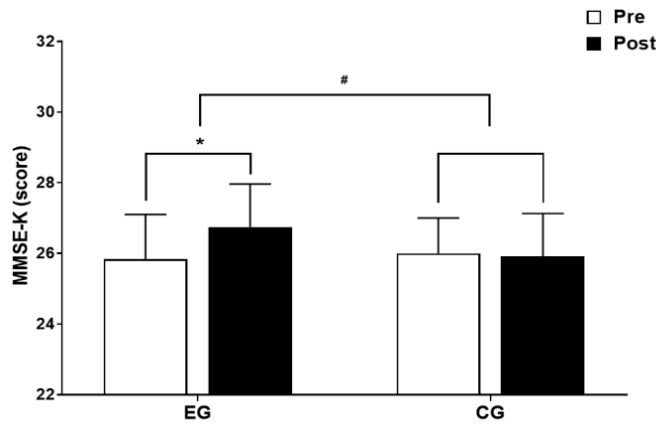


Figure 7. Comparisons of MMSE-K after 16-week circuit training. * $p<.05$: Pre vs Post; # $p<.05$: Exercise vs Control.

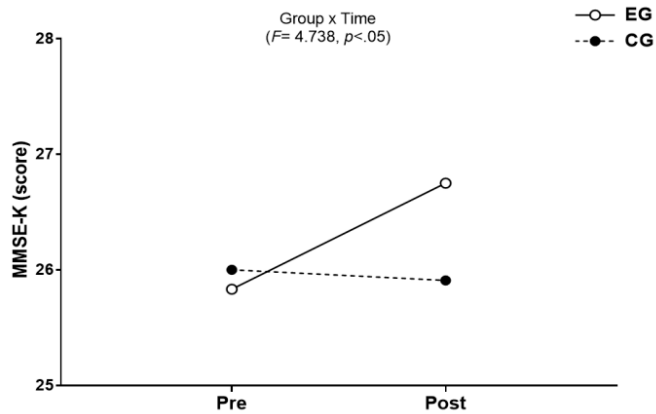


Figure 8. Result of two-way repeated measures ANOVA of MMSE-K after 16-week circuit training.

4. Discussion

Because hippocampal neurons are produced even after a person has reached adulthood [30], long-term exercises of appropriate intensity have a positive effect on preventing AD [31] and improving cognitive functions through enhancing cognitive performance, short-term memory, and long-term memory [32].

Therefore, exercise in the elderly at the onset of aging can improve cognitive function by affecting the reduction of $A\beta$ and increase of BDNF, which are risk factors for AD [21].

$A\beta$ decreased in elderly females after the intervention of 60-minute sessions of aerobic and anaerobic exercises three times a week for 12 weeks [21]. A decrease in $A\beta$ was also observed in elderly females who engaged in 8quarobics exercises for 50 minutes per session three times a week for 24 weeks [33], as well as in elderly females who performed a combination of elastic band and 8quarobics exercises for 90 minutes per session three times a week for 16 weeks [16].

Prior studies on $A\beta$ and exercise intensity in elderly females reported a significant decrease in $A\beta$ after participants performed Taekwondo Poomsae at 50–75% HRR for 60 minutes per session three times a week for 12 weeks [34], a decrease in the $A\beta$ index after participants performed a combination of physical stimulation and walking exercises at 60–70% of maximum heart rate for 45–60 minutes per session for 24 weeks [35], and a decrease in $A\beta$ after participants performed combined aerobic and anaerobic exercises at 50–70% intensity of target heart rate for 60 minutes per session three times a week for 12 weeks [21].

The mechanism of $A\beta$ decrease can generally be explained as follows: α -secretase metabolizes APP when blood flow to the brain is increased during exercise and inhibits the formation of plaques in the brain [36].

Therefore, the reason for the decrease in $A\beta$ in the present study appears to be the choice of 40–70% HRR as an appropriate exercise intensity for elderly females whose overall strength has been reduced due to aging. Regular circuit training increased the blood flow to and stable oxygenation of the brain, causing a rise in BDNF concentration, which is essential for the survival of nerve cells. The increased BDNF concentration activated non-amyloidogenic pathways with α -secretase and γ -secretase, leading to enhanced amyloid metabolism and a decrease in $A\beta$.

Serum and plasma BDNF in circulation can be indicators of BDNF in the central nervous system because BDNF is a myokine that is released by skeletal muscle cells and can cross the BBB in both directions [37], and the elevated plasma BDNF concentration is influenced by the type and intensity of exercise [38].

Prior studies on BDNF expression according to types of exercises showed that, for myokinetic BDNF, muscular resistance exercises that directly stimulate muscles could increase plasma BDNF concentration [39]. However, aerobic exercises were more effective than resistance exercises [40], and concurrent exercises were more effective than single resistance exercises in increasing plasma BDNF concentration [41].

As BDNF is affected by the exercise intensity, the increase of BDNF concentration was higher for mid- and high-intensity exercises (70% oxygen uptake reserve; %VO₂R) than for low-intensity exercises (40% VO₂R) [42], and only exercising with an intensity of 60% HRR or higher makes that increase possible [43]. Choi and Yoon [44] reported a significant increase in BDNF as a result of performing concurrent exercises of RPE 11–15.

Therefore, the increase in BDNF in the current study is most likely due to the application of aerobic-type circuit exercises with 65–70% intensity, which could provide more nutrition and oxygen to the brain cells by increasing the flow of blood and its speed to the brain. In addition, resistance exercises involving repeated contractions of skeletal muscles are likely more effective than a single movement.

The general characteristics of BDNF changes are the decrease of plasma BDNF levels with increased age [45], lower levels for ill or diseased persons [46], and lower levels in females than in males [18]. However, adults without existing medical conditions who have stable BDNF

concentrations can no longer significantly increase BDNF concentrations due to the ceiling effect [47]. Additionally, reduced body fat through exercise increases the rate of BDNF expression in obese persons [48], and the sensitivity of BDNF change is higher in obese females than in obese males [49].

Therefore, the higher sensitivity to BDNF of the participants, who were obese elderly females, and the improvement in body fat percentage from positive changes in body composition through exercise are suspected to be additional factors explaining a significant increase in BDNF concentration in the current study.

Cognitive functions are enhanced by regenerating damaged neurons and peripheral nerves and generating cerebral neurons through the expression of neurotropic factors [50,51].

The MMSE-K index improved in elderly females after they performed 60 minutes of circuit exercises three times a week for 12 weeks [28], and the MMSE-K score increased from 25.14 to 26.86 after 12 weeks of concurrent exercise among women with a mean age of 65 [52]. In addition, an improvement in physical and psychological abilities was observed after participation in exercises; as a result of performing combination exercises including 15-to-30-minute walks, strength exercises, and aquarobic exercises three or more times per week, elderly persons aged 65 and above showed enhanced memory, problem-solving abilities, linguistic abilities, attention, concentration, and mind and body stability [53].

Exercise must be of appropriate duration, intensity, and frequency to improve cognitive function [54], and cognitive decline cannot be prevented when the duration and intensity of exercises are reduced [55].

Analysis of cognitive function and the duration of exercise intervention showed that the effect was prominent in the order of 16 weeks or more, 12 weeks, 8 weeks, and 4 weeks, with the most significant effect of exercise observed for 16 weeks, followed by 12 weeks [56,57]. Mid- and high-intensity physical activities correlated highly with cognitive function [58]. The group that participated the least in mid- and high-intensity exercises was 0.65 times more likely to be at risk of cognitive dysfunction than the group that participated the most [59]. Those who were more active, especially those who exercised more than three times a week, were at a lower risk of developing dementia [60].

The results of these prior studies collectively show that exercises are effective in maintaining cognitive functions or slowing cognitive decline only when mid- and high-intensity exercises are performed more than three times a week for 16 weeks.

Therefore, the improvement in cognitive function in the current study seems to have resulted from continuous and regular exercise participation three times a week for 16 weeks, while increasing HRR and RPE every four weeks to mid- to high-intensity exercise with 65–70% HRR during the final weeks. The expression of BDNF, a myokine released during the contraction of skeletal muscles, is increased due to repeated muscle contraction in the upper and lower extremities, and cognitive functions are enhanced by the mechanism of inhibiting the α -secretase activity in the non-amyloidogenic pathway that results in the production of A β , which causes toxicity.

People who have been physically active or participated in regular exercise programs before becoming elderly delay cognitive decline, have lower A β expression, are at less risk of cognitive impairment when elderly [61], and have increased BDNF [62] compared to those who have not. A 10-year follow-up study of 295 males revealed that the cognitive function of the group of elderly persons with reduced physical activity decreased 2.6 times more than the group that maintained physical activity, and the delay of cognitive decline was only possible when engaging in exercises of moderate intensity or higher [63]. An analysis of the relationship between walking and cognitive function among women aged 65 years or older showed that the group that walked effectively prevented the decline of cognitive functions after six to eight years [64].

Therefore, when elderly females begin to age, they must exercise regularly and continuously to avoid an increase in A β and decrease in BDNF, risk factors of AD, thereby preventing cognitive decline and maintaining and improving their quality of life.

5. Conclusions and Suggestions

Our findings indicate that regular and continuous circuit training is effective in improving A β , BDNF, and cognitive function in obese elderly Korean women. Taken together, the results indicate that circuit training with sequential aerobic and anaerobic exercises conducted in the present study can be an effective method for preventing dementia by improving the levels of A β and BDNF, which are risk factors for cognitive impairment in obese elderly females, as well as hindering cognitive decline.

However, although the assessment of cognitive function was performed by an expert, it was difficult to derive the exact mechanism for improving cognitive function because the examination was simple, and the scores were determined by a single summation. It is recommended that future studies measure cognitive function in a manner that combines questionnaires and imaging tests. Furthermore, as the subjects of the current study were obese elderly females and the duration of the exercise program was limited to 16 weeks, comparative studies of males and females, obese and normal individuals, and various program durations are deemed necessary in subsequent research. Finally, as this study did not take into account the potential impact of cerebrovascular diseases such as brain damage or stroke that may occur in obese individuals, future research should include a range of studies that consider cardiovascular risk factors.

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